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Original Research

The impact of severe mental illness on lung cancer mortality of patients with lung cancer in Finland in 1990–2013: a register-based cohort study

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Abstract ***Background:*** Although the link between severe mental illness (SMI) and elevated cancer mortality is well established, few studies have examined lung cancer survival and SMI in detail. Our study compared cancer-specific mortality in patients with lung cancer with and without a history of SMI and analysed whether mortality differences could be explained by cancer stage at presentation, comorbidity or differences in cancer treatment.
Methods: We identified patients with their first lung cancer diagnosis in 1990–2013 from the Finnish Cancer Registry, their preceding hospital admissions due to SMI from the Hospital Discharge Register and deaths from the Causes of Death statistics. Competing risk analyses were used to estimate hazard ratios (HRs) for the impact of SMI on mortality.
Results: Of the 37,852 lung cancer cases, 12% had a history of SMI. Cancer-specific mortality differences were found between patient groups in some cancer types after controlling for stage at representation and treatment. Men with a history of psychosis had excess mortality risk (HR = 1.24, 1.06–1.45) in squamous cell carcinoma. Similar excess risk was found among women with psychosis in small-cell carcinoma (HR = 1.76, 1.41–2.19) and in squamous cell carcinoma (HR = 1.67, 1.26–2.20) and among women with mood disorders in

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adenocarcinoma (HR = 1.37, 1.08–1.74). Patient group differences in HRs in five-year mortality did not markedly change from the 1990s.
Conclusions: We found elevated cancer-specific mortality among persons with a history of SMI. Collaboration between patients, mental healthcare professionals and oncological teams is needed to reduce the mortality gap between patients with cancer with and without SMI.

1. Introduction

Lung cancer remains the most common cancer worldwide, the most common cancer among men and the leading cause of cancer-related death [1,2]. In Finland, lung cancer ranked the third most common cancer during our study period among men and seventh among women [3]. In 2015, the age-standardised incidence of lung cancer in Finland was 26.2 for men and 22.6 for women per 100,000. The five-year relative survival was 11% among men and 18% among women [3]. Smoking is the ultimate risk factor of lung cancer with 80–90% of incident cases attributed to it [4,5]. Its effect is lower in adenocarcinoma [6]. Risk factors for poor prognosis include advanced age, comorbidity, smoking, late stage at diagnosis and non-optimal treatment [7].

There is mounting evidence of elevated all-cause mortality among people with severe mental illness (SMI) [8]. In addition, in a meta-analysis, Catts et al [9] observed increased lung cancer incidence among patients with schizophrenia, which, however, disappeared after adjusting for smoking prevalence.

Most studies have found increased all-cause [2,8,10–17] and cancer-specific mortality [18,19] among lung cancer patients with SMI, whereas some have reported difference in neither of them [16,20,21]. These conflicting results may reflect differences in study populations, designs and definitions. Most studies examine lung cancer as a single mortality category and do not allow for closer look at comorbidity, cancer stage or treatment. Furthermore, most studies do not distinguish between morphological types of lung cancer and focus exclusively on schizophrenia.

The aim of our study was to examine whether cancer-specific mortality in lung cancer patients with a history of SMI was higher than in lung cancer patients without SMI and whether mortality differences could be explained by comorbidity, cancer stage at presentation or differences in cancer treatment. We also examined potential change in these outcomes during the study period.

2. Materials and methods

2.1. The study population

Data on patients with their first lung cancer diagnosis in 1990–2013 were obtained from the Finnish Cancer Registry containing nationwide data on virtually all cancers diagnosed in Finland since 1953 [22]. We examined the data back until 1953 to exclude patients with any prior cancer diagnoses. Lung cancer was defined based on ICD-O-3 topography codes C33 and C34 as cancer located in the trachea, bronchus or lung. Cancers defined morphologically as lymphoma (ICD-O-3 morphology codes M959-973, n = 221) were excluded. Cancers first diagnosed in autopsy (n = 8329) were also excluded. Lung cancers first diagnosed in autopsy represented 19% of original data among men and 14% among women. Among men, cases first diagnosed in autopsy varied from 19% in those without history of SMI to 21% in persons with non-affective psychotic disorder (NAPD). Differences in proportions found in autopsy were somewhat higher among women. Patients were allocated into four groups on the basis of morphology: (1) adenocarcinoma (ICD-O-3 codes M814-838), (2) small-cell lung carcinoma (SCLC; M8041-8045), (3) squamous cell carcinoma (SCC; M805-808) and (4) other.

Data on SMI in 1969–2013 were identified from the Hospital Discharge Register and individually linked to the cancer data. Hospital admissions due to SMI were only taken into account if they were recorded as main diagnoses and occurred at least one year before cancer diagnosis to exclude incident psychiatric disorders linked to cancer [23]. Information concerning history of SMI was classified into four main categories: non-affective psychotic disorder (NAPD (ICD-10 codes F20, F22–29 and the corresponding ICD-8 and ICD-9 codes), substance use disorder (SUD; ICD-10 codes F10–19), mood disorder (MD; ICD-10 codes F30–33 and F38–39) and no SMI. Owing to the long natural course of SMI, patients remained in the SMI population until the end of the follow-up. If patients had admissions in several SMI categories, they were classified hierarchically into NAPD, SUD and MD groups.

Causes of death for the cohort were obtained from the Causes of Death statistics of Statistics Finland until the end of 2014, from which the coding experts of the Cancer Registry had further determined whether they were cancer specific by examining the cause-of-death records together with other data on the cancer in question. Ethical approval for the study was received from the Research Ethics Committee of the National Institute for Health and Welfare.

2.2. Covariates

Cancer stage at the time of diagnosis was classified into three groups: (1) localised, (2) metastasised (regional or distant) and (3) unknown. Cancer treatment was classified into six categories: (1) surgical treatment, (2) radiotherapy, (3) chemotherapy, (4) surgical treatment and chemotherapy, (5) radiotherapy and chemotherapy and (6) other or no treatment or unknown.

A modified Charlson comorbidity index [24] was calculated for each patient using the Hospital Discharge Register records to mark the burden of comorbidity. Several diseases (congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, liver disease, diabetes with or without chronic complications, hemiplegia or paraplegia and renal disease) within five years preceding cancer diagnosis were used in the calculation.

Age at lung cancer diagnosis was stratified as younger than 45 years, subsequent 5-year groups and those 85 years or older. Other variates included the year of cancer diagnosis and sex. Cause-specific death was the main outcome event, and deaths of other causes were considered as competing outcome events. The patients were followed up from the date of cancer diagnosis until the end of 2014 or earlier death or emigration. Those alive at the end of the follow-up were censored at emigration or on 31st December 2014.

2.3. Statistical methods

We cross-tabulated the distributions of covariates by the SMI group. Pearson's chi-squared test was used to test differences in cancer type distribution among patient groups. We then calculated Kaplan–Meier estimates to describe survival differences between patient groups. In graphs, Kaplan–Meier curves were cut at 10 years of follow-up. Analyses were conducted separately for men and women and by the type of lung cancer.

Proportional subdistribution hazards regression models with other causes of death as competing risk events were conducted in three steps to assess differences in case-specific mortality in patient groups and to study the impact of covariates on patient group differences during the whole study period [25,26]. In the first step, we estimated hazard ratios (HRs) for patient groups adjusting for age, year of cancer diagnosis since 1990, cancer type and Charlson comorbidity index as well as interaction of the cancer type and patient group. In the second step, we further adjusted for cancer stage at presentation. In the third step, cancer treatment was added to the model. In each model, we calculated contrasts for differences for patient groups in lung cancer categories. We used generalised R^2 to assess how well each set of covariates predicted mortality [27].

To study if differences between patient groups altered during the study period, we adjusted competing risk models with 5-year follow-up in three cancer incidence periods (1990–1994, 1997–2001 and 2004–2008) to ensure equivalent potential follow-up. We used age group, incidence period, cancer type, Charlson comorbidity index, cancer stage at presentation and cancer treatment as covariates and calculated second- and third-degree interaction terms for the patient group, cancer type and incidence period. Interaction terms were examined to assess possible changes in time in mortality between patient groups in lung cancer categories.

For sensitivity analysis, we conducted similar models for cause-specific mortality with Cox regression models. The R statistical software version 3.5.1 was used for statistical analyses [28].

3. Results

In our study data, there were 37,852 incident lung cancer cases diagnosed between 1990 and 2013; of whom, 27,557 were men. A total of 35,299 patients died (including 31,900 case fatalities) during the total follow-up time of 60,177 person-years. Table 1 shows basic background characteristics of the study population. Among men, 13% of patients with lung cancer had a history of SMI, with SUD being the largest group. Among women, 10% of the lung cancer population had a history of SMI, with NAPD as the largest group. The average duration of SMI until cancer incidence varied from 15.9 years among men with MD to 24.9 years among men with NAPD. The proportion of adenocarcinoma was higher among female patients with cancer, whereas SCC was higher among male patients with cancer. Cancer type distributions differed in patient groups among men and women (both $p < 0.001$).

Kaplan–Meier curves (Fig. 1) showed lower survival in the NAPD group for SCLC among women and for SCC among both men and women. Survival was also lower in the MD group for adenocarcinoma among women.

Table 2 presents the HRs of cancer-specific mortality with other causes of death as the competing risk event in patient groups by sex and cancer type in three steps, with those without SMI as the reference category. Overall, our results showed that while stage at presentation (model II) and cancer treatment (model III) did explain a fair share of variation in mortality as indicated by the generalised R^2 values, some statistically significant differences remained between patient groups. Among men, patients with NAPD had a HR of 1.24 in SCC in model III. Among women, similar and even larger relative risks of lung cancer mortality were found among patients with NAPD with a HR of 1.76 in SCLC and 1.67 in SCC. The MD group among women with adenocarcinoma had an elevated risk (HR = 1.37) in

Table 1
Baseline characteristics of the population with first lung cancer in 1990–2013 in Finland by sex and the SMI category.

Variable	Category	Men				Women			
		NAPD	SUD	MD	No SMI	NAPD	SUD	MD	No SMI
Cases	N	955	2222	452	23928	405	288	318	9284
	(%)	(3)	(8)	(2)	(87)	(4)	(3)	(3)	(90)
Cancer type	Adenocarcinoma	12	16	14	18	17	25	21	30
(%)	Small-cell lung carcinoma	10	13	13	13	20	16	14	13
	Squamous cell carcinoma	26	25	24	25	12	17	14	12
	Other	52	46	50	45	51	43	51	45
Age at presentation	Mean	64.5	65.5	68.6	69.4	65.8	64.1	69.0	69.5
Charlson index	Mean	0.19	0.20	0.22	0.22	0.15	0.14	0.17	0.17
Stage at presentation	Local	13	15	17	15	11	18	14	15
%	Metastasised	62	63	63	64	64	60	60	63
	Unknown	25	22	21	21	25	22	26	22
Treatment	Operative	9	11	10	12	6	13	8	12
%	Operative + chemotherapy	1	3	4	3	3	3	5	4
	Chemotherapy	7	11	11	11	11	12	9	13
	Radiotherapy	24	19	19	22	16	18	16	17
	Chemotherapy + radiotherapy	7	11	11	13	10	13	16	14
	Other/none/unknown	51	45	44	39	54	41	47	41

NAPD, non-affective psychotic disorder; SUD, substance use disorder; MD, mood disorder; SMI, severe mental illness.

model III. In the 'other' type of lung cancer, HRs were elevated among men in the NAPD and SUD groups (1.19 and 1.18, respectively) and among women in the NAPD group (1.18) after adjusting for all covariates.

HRs for SMI groups from models estimated in three periods for 5-year follow-up did not change markedly in any of the cancer types.

Sensitivity analyses produced largely similar results. In full models, although the NAPD group in SCLC had similar risk to the results presented, it was, however, statistically significant among men, whereas statistical significance of difference between the MD group and those without history of SMI among women in adenocarcinoma disappeared.

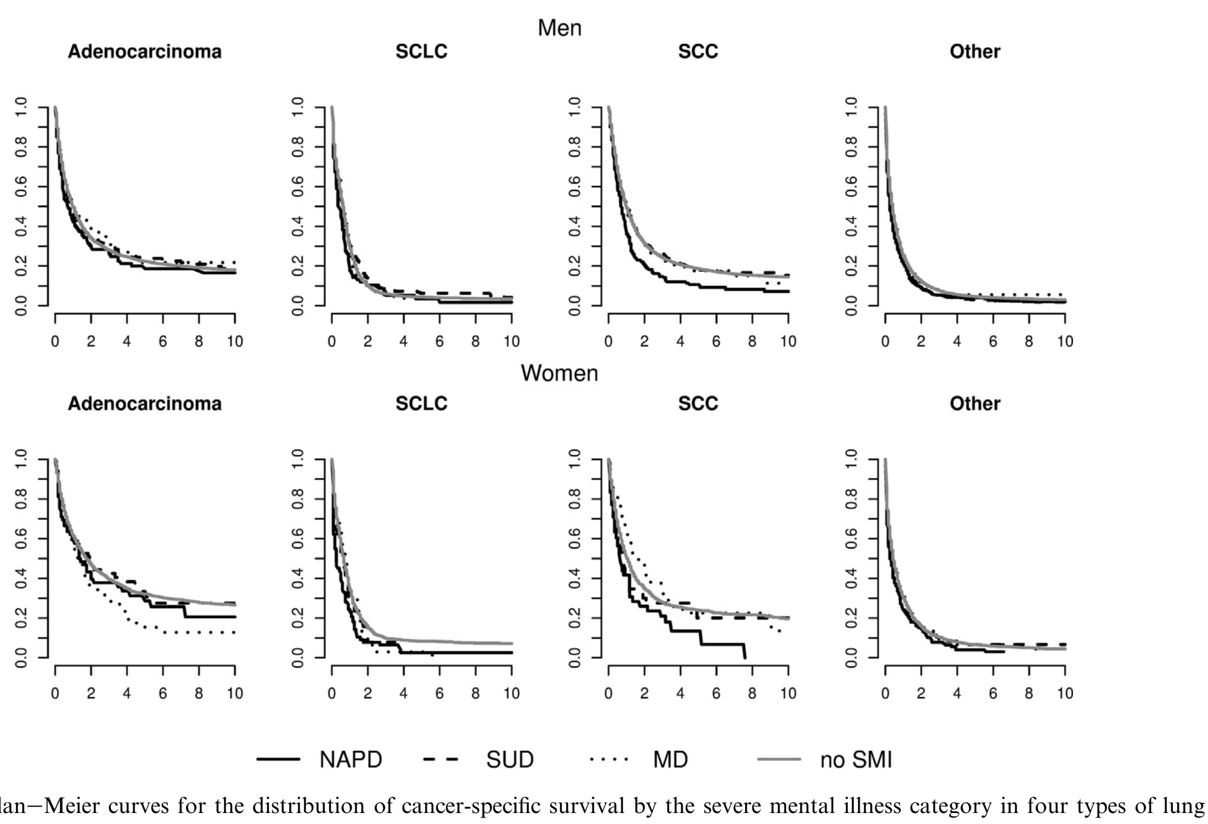

Fig. 1. Kaplan–Meier curves for the distribution of cancer-specific survival by the severe mental illness category in four types of lung cancer among Finnish men and women diagnosed with lung cancer in 1990–2013.

Table 2
Effect of history of severe mental illness to lung cancer mortality among Finnish men and women with lung cancer by the cancer type in 1990–2013: hazard ratios (HRs) and their 95% confidence intervals (CIs).

		Men						Women					
		Model I		Model II		Model III		Model I		Model II		Model III	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Adenocarcinoma	NAPD	1.13	0.90–1.42	1.14	0.91–1.42	1.08	0.83–1.41	1.19	0.88–1.60	1.21	0.91–1.61	1.08	0.81–1.42
	SUD	1.10	0.97–1.26	1.14	0.98–1.31	1.14	0.98–1.32	1.07	0.78–1.45	1.33	0.95–1.85	1.28	0.91–1.82
	MD	0.89	0.66–1.22	0.95	0.68–1.32	1.04	0.76–1.42	1.42	1.12–1.80	1.35	1.05–1.73	1.37	1.08–1.74
	No SMI	1.00		1.00		1.00		1.00		1.00		1.00	
Small-cell lung carcinoma	NAPD	1.26	0.98–1.61	1.28	0.99–1.65	1.25	0.96–1.62	1.82	1.43–2.31	1.83	1.44–2.32	1.76	1.41–2.19
	SUD	1.01	0.88–1.15	1.04	0.91–1.18	1.02	0.89–1.18	1.13	0.78–1.64	1.14	0.78–1.66	1.13	0.74–1.72
	MD	1.12	0.87–1.43	1.17	0.94–1.47	1.08	0.81–1.44	1.01	0.76–1.35	0.95	0.71–1.29	0.98	0.74–1.30
	No SMI	1.00		1.00		1.00		1.00		1.00		1.00	
Squamous cell carcinoma	NAPD	1.49	1.29–1.71	1.50	1.30–1.73	1.24	1.06–1.45	1.69	1.23–2.33	1.78	1.34–2.36	1.67	1.26–2.20
	SUD	1.09	0.98–1.20	1.14	1.03–1.26	1.06	0.95–1.17	1.24	0.87–1.77	1.33	0.94–1.89	1.34	0.95–1.88
	MD	1.06	0.85–1.32	1.11	0.89–1.39	1.10	0.88–1.37	0.93	0.70–1.25	1.05	0.78–1.42	1.01	0.73–1.40
	No SMI	1.00		1.00		1.00		1.00		1.00		1.00	
Other	NAPD	1.27	1.15–1.40	1.31	1.18–1.44	1.19	1.07–1.32	1.19	1.02–1.40	1.25	1.06–1.46	1.18	1.00–1.38
	SUD	1.23	1.15–1.32	1.26	1.18–1.35	1.18	1.11–1.27	1.12	0.92–1.37	1.18	0.96–1.44	1.13	0.91–1.39
	MD	0.99	0.86–1.15	1.00	0.87–1.16	0.96	0.83–1.12	0.99	0.82–1.19	1.03	0.86–1.22	1.02	0.86–1.22
	No SMI	1.00		1.00		1.00		1.00		1.00		1.00	
	Generalised R^2	0.0829		0.1771		0.2308		0.1232		0.2365		0.2774	

HR, hazard ratio; CI, confidence interval; NAPD, non-affective psychotic disorder; SUD, substance use disorder; MD, mood disorder; SMI, severe mental illness.
Model I: adjusting for age group, year of incidence and Charlson comorbidity index. Model II: model I + cancer stage at presentation. Model III: model II + cancer treatment.

4. Discussion

4.1. Overview of main findings

This registry-based study covering years 1990–2014 found elevated cancer-specific mortality risk among lung cancer patients with a history of NAPD and SUD compared with lung cancer patients without SMI history even after controlling for stage at presentation, comorbidity and cancer treatment. More specifically, we found elevated risk of cancer-specific mortality among both male and female patients with a history of NAPD in SCC, among female patients with a history of NAPD in SCC and among female patients with MDs in adenocarcinoma. According to our results, differences in cancer-specific mortality did not change during the study period between persons with or without SMI history.

Earlier evidence of increased lung cancer mortality among lung cancer patients with SMI is mixed [12,17,19]. Our result of elevated cancer-specific mortality among lung cancer patients with NAPD differs from that of Lawrence *et al.* [21] who did not find elevated case fatality among patients with lung cancer in the psychiatric patient population compared with the general population in a study in Western Australia in 1982–1995. Comorbidity and stage at presentation were not adjusted in their study.

Delayed diagnosis and lower likelihood of receiving adequate cancer care among psychiatric patients along with higher incidence of adverse treatment outcomes have been suggested to be possible reasons behind differences in outcomes [12,20,29,30]. In line with our results, a recent study from the US found that poor survival among patients with non-SCLC with pre-existing SMI was not explained by delay in diagnosis or inadequate cancer treatment [11]. Our results also remained after controlling for stage at presentation and cancer treatment. While there were patient group differences in cancer treatment in our study, they are likely to be related to differences in the distribution of cancer types between patient groups.

As for patients with MDs, concurrent depression has been linked to poor lung cancer survival, and it has been suggested that patients with depression choose not to initiate or continue treatments [14,15]. However, evidence concerning depression is mixed [15]. In our study, the differences between SMI groups were more prominent among women. This is likely to be partly explained by larger prevalence of competing causes of death among men. In addition, there is evidence of better survival among women with SCLC in the general population [31].

Smoking has been found to be more prevalent among patients with NAPD and SUD compared with those with MD or no history of SMI [32], and smoking cessation has been linked to improved prognosis of lung cancer [33]. We did not have information on smoking or smoking cessation interventions, but it is possible that high rates of smoking contributed to the excess mortality in patients with SMI. Smoking cessation interventions are effective and well tolerated in patients with SMI [34–36], and they should be an integral component of lung cancer treatment.

4.2. Methodological considerations

Strengths of our study include a nationwide cohort enabling a 24-year follow-up. The Finnish Cancer Registry has been reported to have close to 100% coverage of incident cancer cases with the accuracy of the records found to be good [22]. It made it possible for us to distinguish between histological types of lung cancer, stages of cancer at presentation and cancer treatment for the whole study period. We were able to identify histories of SMIs and information on comorbidities since 1969 from the Hospital Discharge Register, the coverage and overall accuracy of which have been considered good [37]. Our data enabled us to distinguish between cancer-specific and other causes of death. The Finnish Causes of Death statistics has been reported to be reliable and valid by international standards [38]. In addition, the cause-of-death information among patients with lung cancer has been revised with records in the Finnish Cancer Registry, enhancing the quality of our mortality data compared with most studies and enabling us to use the competing risk approach to correctly estimate marginal probability of a cancer-specific death in the presence of competing events.

We were not able to study cancer treatment adherence, communication between oncological teams and patients, cooperation with patients' primary care or psychiatric team or health behaviour among patients with SMI, which have also been linked to poorer lung cancer prognosis [11,14,18,30,39]. Furthermore, comorbidity that has been linked to outcomes of lung cancer [11,40] may have been insufficiently controlled for with the Charlson comorbidity index used in the current study. Nor did we have data on health behaviour of patients with lung cancer, particularly on smoking status. The cancer data contained quite large proportions of patients with an unknown stage or treatment. Furthermore, the historical long-term coding nomenclatures of the stage and treatment in the cancer registry records did not enable us to classify these factors into more precise categories that may be optimal in modern clinical terminology. In our study, patients with lung cancer with the cancer type 'other' with a history of NAPD and SUD had a higher lung cancer mortality risk. As the proportion of the 'other' type was higher among patients with SMI, that may reflect worse accuracy in the diagnostic process among them. We were unable to include the duration of SMI in competing risk models. Our data only contained diagnoses for mental illness treated in a hospital setting, overlooking less severe cases, especially SUD and MD [41]. This reduces generalisability of our results.

5. Conclusions

We found persistent excess cancer-specific mortality in lung cancer patients with a history of SMI. Further studies are needed for understanding all factors contributing to mortality differences including physical comorbidity, help-seeking behaviour and adherence to treatment recommendations as well as problems concerning stigmatisation and poorer cancer care. Collaboration between the patients, their outpatient mental healthcare team, oncological team and primary care professionals is needed throughout the cancer episode to guarantee optimal treatment and increase survival among this patient group.

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Conflict of interest statement

The authors report no conflicts of interest that would have biased the work.

Data statement

Owing to data protection legislation in Finland, individual-level data on the study subjects cannot be released.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.06.018.

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