Educational level and management and outcomes in non-small cell lung cancer. A nationwide population-based study

Linda Willén[a,b,c,*], Anders Berglund[d], Stefan Bergström[a,c], Michael Bergqvist[a,b,c], Anna Öjdahl-Bodén[e], Gunnar Wagenius[f], Mats Lambe[g,h]

[a] *Center for Research and Development, Uppsala University/Region Gävleborg, Sweden*
[b] *Department of Radiation Sciences and Oncology, Umeå University Hospital, Umeå, Sweden*
[c] *Department of Oncology, Gävle Hospital, Gävle, Sweden*
[d] *EpiStat, Uppsala, Sweden*
[e] *Division of Respiratory Diseases, Department of Medical Sciences, Karolinska University Hospital Huddinge, Stockholm, Sweden*
[f] *Division of Oncology, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden*
[g] *Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden*
[h] *Regional Cancer Center Uppsala Örebro, Uppsala, Sweden*

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ABSTRACT

Objectives: We examined associations between educational level and clinical presentation, patterns of management and mortality in patients with non-small cell lung cancer (NSCLC) in Sweden, a country with a National Health Care System.

Materials and Methods: We identified 39,671 patients with a NSCLC diagnosis 2002–2016 in Lung Cancer Data Base Sweden (LCBaSe), a population-based research database. In analyses adjusted for comorbidity and other prognostic factors, odds Ratios (OR) and hazard Ratios (HR) were estimated to examine associations between patients' educational level and aspects of management and mortality.

Results: Stage at diagnosis and waiting times did not differ between educational groups. In multivariable analysis, the likelihood to undergo PET/CT and assessment in a multidisciplinary team setting were higher in patients with high compared to low education (aOR 1.14; CI 1.05–1.23 and aOR 1.22; CI 1.14–1.32, respectively). In patients with early stage IA-IIB disease, the likelihood to undergo stereotactic radiotherapy was elevated in patients with high education (aOR 1.40; CI 1.03–1.91). Both all-cause (aHR 0.86; CI 0.77-0.92) and cause-specific mortality (aHR 0.83; CI 0.74-0.92) was lower in patients with high compared to low education in early stage disease (IA-IIB). In higher stage NSCLC no differences were observed. Patterns were similar in separate assessments stratified by sex and histopathology.

Conclusions: While stage at diagnosis and waiting times did not differ between educational groups, we found socioeconomic differences in diagnostic intensity, multidisciplinary team assessment, stereotactic radiotherapy and mortality in patients with NSCLC. These findings may in part reflect social gradients in implementation and use of novel diagnostic and treatment modalities. Our findings underscore the need for improved adherence to national guidelines.

1. Introduction

Globally lung cancer is the second most common malignancy and the leading cause of cancer related deaths. [1] With about 4000 incident cases reported in Sweden each year of which more than 75% are non-small cell lung cancer (NSCLC), lung malignancies represent the fourth and the sixth most common type of cancer in women and men, respectively [2,3].

Possible associations between socioeconomic status (SES) and lung cancer incidence, stage at diagnosis, patterns of management and mortality have been the focus of several earlier studies. While socioeconomic indicators have been found to be associated with lung cancer incidence, treatment intensity and survival [4–6], a recent meta-analysis found no clear evidence of associations between SES and stage, or in waiting times from diagnosis to start of treatment [7].

The core reasons for socioeconomic gradients in cancer

management and outcomes remain unclear, but may reflect factors related to the patient, tumor characteristics, availability and quality of care, individual differences in demands and expectations, communication skills as well as acceptance of, and adherence to treatments. In Sweden, economic barriers should not be an issue since all residents are entitled to equal access and quality of care at low out-of-pocket cost through a tax-funded National Health Care System. However, earlier studies based in Sweden have found evidence of lower diagnostic and treatment intensity and poorer outcomes in low SES patients with breast, lung and prostate cancer [8–10].

Using information from a nationwide lung cancer research database, the aim of this population-based cohort study was to investigate whether SES, assessed by educational level, is associated with clinical presentation, patterns of management and mortality in patients with NSCLC in Sweden.

2. Material and methods

2.1. Data collection

For the purpose of the present study, we used data available in Lung Cancer Data Base Sweden (LCBaSe), a research database generated by record linkage between the National Lung Cancer Register (NLCR) and several other Swedish population-based registers. The NLCR includes more than 95% of all patients registered with a lung cancer diagnosis in the Swedish Cancer Register and contains detailed information on demographic and clinical characteristics as well as diagnostic methods and initial treatment [3].

Additional individual level information was retrieved from the National Patient Register (NPR), the Swedish Cancer Register (SCR), the social database Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) and the Cause of Death Register (CDR).

Information on co-morbidity was based on records of up to eight discharge diagnoses retrieved from the NPR, and from the SCR on malignancies other than lung cancer. Date and cause of death was available in the CDR, a register with high completeness [11].

For estimation of SES, data on educational level were retrieved from LISA, a nationwide register including continuously updated information on highest achieved educational level for all residents aged 16 and older [12]. Education was collapsed into three groups based on the total number of years of schooling: low ≤9 years, middle 10–12 years and high ≥13 years, corresponding to mandatory school, high school and post-high school (college and university).

Comorbidity burden was estimated by use of the Charlson Comorbidity Index (CCI) and categorized into three groups; no (CCI 0), mild (CCI 1–2), and severe comorbidity (CCI 3 +) [13]. Smoking history was based on self-reported information at time of diagnosis retrieved from the NLCR and recorded as smoker (current smoker), former smoker (no smoking during the last year) and non-smoker (never smoked on a regular basis). Performance status (PS) was assessed by the treating physician based on the ECOG/WHO performance scale [14].

In analyses of waiting times, cutoffs were based on recommendations from the Swedish Lung Cancer Study Group and from goals stated by standardized-care pathways for lung cancer. The goals are a) time from referral to diagnosis within 30 days and b) time from diagnosis to start of treatment within 14 days for surgery and radiotherapy, 10 days for start of chemotherapy and other drugs, and 0 days for start of palliative care. Calculations of when 50% and 80% of the patients reached the goals were used as measurements of quality of care.

2.2. Statistical methods

Descriptive statistics, including Chi2-tests, were used to examine associations between educational level and demographic and clinical characteristics. In logistic regression models, odds ratios (OR) with 95% confidence intervals (CIs) were calculated to assess whether the use of PET/CT, EGFR testing, and multidisciplinary conferences differed by education, adjusted for sex, age at diagnosis, stage at diagnosis, CCI, PS and region. In a subsequent step, logistic regression models were used to address whether initial treatment differed by educational level and clinical subgroups (stratified on stage at diagnosis and restricted to patients with PS 0–2), adjusted for sex, age at diagnosis, smoking history, stage at diagnosis, CCI, PS, histopathology, region and year of diagnosis. In a final step, cause-specific and overall mortality were compared between educational groups. Survival time was calculated as the time interval between the date of lung cancer diagnosis and date of death, or emigration or end of follow-up (December 31, 2016). The risk of death from lung cancer and all causes, respectively, were expressed as hazard ratios with 95% confidence intervals using univariable and multivariable Cox regression models. The multivariable models were adjusted for sex, age at diagnosis, smoking history, stage at diagnosis, CCI, PS, histopathology, initial treatment, region and year of diagnosis. The assumption of proportional hazards in the Cox regression models were not violated, and was verified visually and tested based on weighted residuals.

Waiting times in relation to educational background and stratified by stage at diagnosis, were estimated in number of days until 50% (median) and 80% of the patients, respectively, reached the goals for time a) from referral to diagnosis and b) time from diagnosis to treatment decision.

All tests were two-sided and a 5% level was considered statistically significant. Statistical analyses were performed using R version 3.5.0 [15].

2.3. Research ethics

The study was approved by the Research Ethics Board in Stockholm (2016/1137-32; 2017-445-32).

3. Results

3.1. Clinical presentation

We identified a total of 52,780 men and women diagnosed with lung cancer between 2002 and 2016 of which 40,427 were recorded with a diagnosis of NSCLC (adenocarcinoma, squamous cell carcinoma, large cell carcinoma or adenosquamous carcinoma). Following exclusion of 756 patients without information on educational level, the final study population encompassed of 39,671 men and women with NSCLC of whom 43.7% were classified as having low, 40.6% middle and 15.6% high level of education.

A higher proportion of men compared to women were classified as having a low education (54.5% vs 45.5%). There were statistically significant differences between educational groups in the distribution of age at diagnosis, smoking history, comorbidity burden, performance status and histopathology (Table 1). Compared to patients with high education, a higher proportion of patients with low education were smokers (45.3% vs 34.2%), had a high comorbidity burden (CCI 1 or higher in 48.8% vs 39.8%) and a lower ECOG/performance status (PS 2 or lower in 43.6% vs 28.9%) and were more often diagnosed with squamous cell carcinoma (29.1% vs 19.7%). Adenocarcinomas were more common in patients with high compared to low education (67.1% vs 55.1%). Stage at diagnosis did not differ between educational groups.

3.2. Patterns of management

3.2.1. Waiting times

For stage IA-IV, waiting times were longer than recommended until 80% of the patients reached the prespecified goals. Regardless of stage,

Table 1
Demographic and clinical characteristics among patients diagnosed with NSCLC 2002–2016, by level of education.

| | Level of Education | | | | | | | Total | |
| | Low | | Middle | | High | | | | |
	n	%	n	%	n	%	p-value	n	%
All cases	17359	100	16109	100	6203	100		39671	100
Sex									
Male	9467	54.5	7950	49.4	3050	49.2		20467	51.6
Female	7892	45.5	8159	50.6	3153	50.8	< 0.001	19204	48.4
Age at diagnosis									
0-59	1677	9.7	3013	18.7	1282	20.7		5972	15.1
60-69	5170	29.8	6060	37.6	2250	36.3		13480	34.0
70-79	7230	41.6	5212	32.4	1971	31.8		14413	36.3
80-89	3171	18.3	1763	10.9	673	10.8		5607	14.1
90 +	111	0.6	61	0.4	27	0.4	< 0.001	199	0.5
Charlson Comorbidity Index									
CCI 0	8878	51.1	8997	55.9	3731	60.1		21606	54.5
CCI 1-2	5545	31.9	4624	28.7	1603	25.8		11772	29.7
CCI 3 +	2936	16.9	2488	15.4	869	14.0	< 0.001	6293	15.9
Smoking history									
Smoker	7692	45.3	7389	46.6	2086	34.2		17167	44.1
Former smoker	7660	45.1	6894	43.5	2850	46.8		17404	44.7
Never smoker	1641	9.7	1560	9.8	1157	19.0	< 0.001	4358	11.2
WHO performance status									
0	2983	17.9	3871	24.9	1948	32.3		8802	23.0
1	6434	38.5	6252	40.1	2337	38.8		15023	39.2
2	3983	23.8	3195	20.5	1003	16.6		8181	21.4
3	2473	14.8	1651	10.6	542	9.0		4666	12.2
4	831	5.0	607	3.9	196	3.3	< 0.001	1634	4.3
Histopathology									
Adenocarcinoma	9558	55.1	9805	60.9	4160	67.1		23523	59.3
Squamous cell	5044	29.1	3916	24.3	1222	19.7		10182	25.7
Large cell	2576	14.8	2195	13.6	742	12.0		5513	13.9
Adenosquamous	181	1.0	193	1.2	79	1.3	< 0.001	453	1.1
Stage at diagnosis									
IA-IIB	4301	25.2	4095	25.8	1608	26.2		10004	25.6
IIIA	1636	9.6	1515	9.5	562	9.2		3713	9.5
IIIB-IV	11115	65.2	10281	64.7	3957	64.6	0.49	25353	64.9

Abbreviations: WHO = World Health Organization.

Table 2
Waiting times in relation to educational background and stratified by stage at diagnosis, estimated in number of days until 50% (median) and 80% of the patients respectively reached the goals of time from referral to diagnosis and time from diagnosis to treatment decision.

| | Level of Education | | | | Level of Education | | | |
| | Low | Middle | High | Total | Low | Middle | High | Total |
	50% of the patients				80% of the patients			
Referral - Diagnosis, days								
Stage IA-IIB	39	38	41	39	84	82	84	83
Stage IIIA	23	23	22	23	48	49	50	49
Stage IIIB-IV	14	13	12	13	33	31	30	32
Diagnosis - Treatment decisions, days								
Stage IIA-IIB	12	10	9	10	34	33	28	33
Stage IIIA	14	14	13	14	35	34	34	34
Stage IIIB-IV	12	11	11	11	26	25	24	25

there were no differences between educational groups neither regarding time between dates of referral and diagnosis, nor time between diagnosis and start of treatment (Table 2).

3.2.2. Diagnostic intensity and multidisciplinary team meeting

Computed tomography (CT) thorax, thoracocentesis and thoracoscopy were slightly more commonly performed in patients with high compared to low education. In contrast, patients with low education more often underwent transthoracic needle biopsy (Table 3). More pronounced differences were observed for PET/CT which was performed in 48.6% of patients with high education compared to 39.8% in those with low education, a finding that remained statistically significant following adjustment for sex, age at diagnosis, stage at diagnosis, CCI, PS and region (aOR 1.14; CI 1.05–1.23) (data available 2007–2016). For patients with adenocarcinoma, testing for EGFR was performed in 59.7% and 53.8% of patients with high and low education respectively (data available 2010–2016). However, following adjustments these differences were statistically non-significant (aOR 1.10; CI 0.84–1.43).

The likelihood to be discussed in a multidisciplinary team setting (MDT) was significantly higher in patients with high education, a finding that remained in adjusted analysis (aOR 1.22; CI 1.14–1.32).

3.2.3. Treatment intensity

In patients with stage IA-IIB disease and PS 0–2, the likelihood to undergo stereotactic radiotherapy was significantly elevated in the fully adjusted model in patients with a high education (aOR 1.40; CI 1.03–1.91). No significant socioeconomic differences were observed for other treatment options, including surgery (Table 4).

3.3. Mortality

3.3.1. Mortality (all patients)

In early stage disease (IA-IIB), high education was associated with lower overall (aHR 0.86; CI 0.77-0.92) and lower cause-specific mortality (aHR 0.83; CI 0.74-0.92) after adjustment for sex, age at

Table 3

Diagnostic intensity and multidisciplinary team meeting in patients diagnosed with NSCLC 2002–2016, by level of education.

| | Level of Education | | | | | | | Total | |
| | Low | | Middle | | High | | | | |
	n	%	n	%	n	%	p-value	n	%
Mode of detection									
Bronchoscopy	12689	73.4	11942	74.4	4610	74.5	0.06	29241	74.0
Bronchoscopy EBUS*	1097	14.2	1216	15.0	490	15.3	0.17	2803	14.7
CT Thorax	16894	97.6	15761	98.1	6065	98.0	0.01	38720	97.9
Mediastinoscopy	1109	6.4	1034	6.5	395	6.4	0.99	2538	6.4
US/CT upper abdomen	15484	89.8	14405	89.9	5573	90.2	0.64	35462	89.9
Thoracocentesis	2282	13.3	1950	12.2	840	13.6	< 0.001	5072	12.9
Thoracoscopy	195	1.1	228	1.4	112	1.8	< 0.001	535	1.4
Transthoracic needle biopsy	4744	27.6	4472	28	1617	26.2	0.03	10833	27.5
CT/MRI brain**	2841	24.5	2994	25.5	1203	25.9	0.09	7038	25.2
Other	3649	21.5	3505	22.2	1402	22.9	0.07	8556	22
PET/CT **	4691	39.8	5426	45.5	2281	48.6	< 0.001	12398	43.6
EGFR testing***	2636	53.8	3297	58.1	1475	59.7	< 0.001	7408	56.8
Multidisciplinary team meeting	10498	60.5	10635	66.0	4323	69.7	< 0.001	25456	64.2

* Available for.2008–2016

** Available for.2007–2016

*** Available for 2010–2016, adenocarcinomas.

Abbreviations:

EBUS = endobronchial ultrasound.

CT = computer tomography.

US = ultrasound.

MRI = magnetic resonance imaging.

PET = positron emission tomography.

EGFR = epidermal growth factor receptor.

diagnosis, smoking history, stage at diagnosis, CCI, PS, histopathology, initial treatment, region and year of diagnosis. In more advanced stage disease (IIIA-IV), there were no socioeconomic differences in mortality (Table 5).

3.3.2. Mortality stratified by sex

In early stage disease (IA-IIB), similar patterns were found in adjusted analyses stratified by gender with little or no difference between sexes (**data not shown**). In men, but not women with stage IIIA

disease, both overall (aHR 1.24; CI 1.05–1.46) and cause specific mortality (aHR 1.28; CI 1.07–1.53) were higher in those with high education.

3.3.3. Mortality stratified by histopathology

In analyses stratified by histopathology, high education was associated with a lower overall and cause-specific mortality in patients with early stage (IA-IIB) adenocarcinomas, large cell and adenosquamous carcinomas (**data not shown**). A similar, but not statistically significant

Table 4

Initial treatments in patients with NSCLC 2002–2016, by stage and level of education. Binary logistic regression with odds ratios (OR) and 95% confidence intervals (CI).

| | Low | | | | Middle | | | | High | | | | Total | |
	n	%	aOR**	95% CI	n	%	aOR**	95% CI	n	%	aOR**	95% CI	n	%
Stage IA-IIB, WHO PS 0-2														
Planned surgery	2688	68.1	1.00	ref.	2942	75.6	0.95	0.84-1.08	1243	80.5	1.06	0.89-1.26	6873	73.3
Stereotactic radiotherapy*	374	35.6	1.00	ref.	344	34.0	1.24	0.99-1.54	116	32.0	1.4	1.03-1.91	834	34.4
Stage IIIA, WHO PS 0-2														
Planned surgery	228	16.1	1.00	ref.	249	18.3	0.86	0.70-1.07	113	22.1	0.88	0.67-1.16	590	17.9
Chemo/radiotherapy*	406	39.8	1.00	ref.	532	49.1	1.16	0.96-1.40	213	52.9	1.17	0.90-1.50	1151	45.9
Radiotherapy	629	45.8	1.00	ref.	615	47.3	1.12	0.96-1.32	219	44.8	1.02	0.82-1.27	1463	46.3
Stage IIIB, WHO PS 0-2														
Chemotherapy***	1562	72.4	1.00	ref.	1482	76.0	1.1	0.94-1.28	528	76.5	1.18	0.94-1.47	3572	74.4
Radiotherapy	858	39.8	1.00	ref.	786	40.3	1.04	0.91-1.19	267	38.7	1.07	0.88-1.29	1911	39.8
Chemo/radiotherapy*	371	30.9	1.00	ref.	436	36.0	1.03	0.86-1.24	155	36.6	0.97	0.75-1.26	962	34.0
Stage IV, WHO PS 0-2														
Chemotherapy***	4492	79.3	1.00	ref.	4956	83.4	0.99	0.89-1.10	2111	85.6	1.08	0.94-1.25	11559	82.2
Radiotherapy	683	12.1	1.00	ref.	693	11.7	1.01	0.90-1.14	266	10.8	1.04	0.89-1.22	1642	11.7

* Available from.2007–2016

** Adjusted odds ratios; adjusted for sex, age at diagnosis, smoking history, stage at diagnosis, Charlson Comorbidity Index, performance status, histopathology, region and year of diagnosis.

*** Also including other medical therapies such as tyrosine kinase inhibitors and checkpoint inhibitors.

Abbreviations:

WHO = World Health Organization.

PS = performance status.

Table 5
Overall and Cause-specific mortality expressed as crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) in patients diagnosed with NSCLC.2002–2016.

	Overall mortality				Cause-specific mortality			
	HR	95% CI	aHR*	95% CI	HR	95% CI	aHR*	95% CI
Stage IA-IIB								
Low education	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
Middle education	0.77	0.71-0.83	0.96	0.90-1.02	0.77	0.71-0.84	0.96	0.89-1.03
High education	0.62	0.55-0.69	0.86	0.77-0.92	0.61	0.54-0.70	0.83	0.74-0.92
Stage IIIA								
Low education	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
Middle education	0.86	0.78-0.96	1.01	0.93-1.10	0.90	0.80-1.01	1.02	0.93-1.12
High education	0.85	0.73-0.98	1.12	0.99-1.26	0.91	0.77-1.06	1.13	0.99-1.29
Stage IIIB-IV								
Low education	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
Middle education	0.91	0.87-0.94	1.03	0.99-1.06	0.92	0.89-0.95	1.03	0.99-1.06
High education	0.81	0.77-0.85	0.99	0.95-1.03	0.82	0.78-0.86	0.99	0.95-1.04

*adjusted hazard ratios; adjusted for sex, age at diagnosis, smoking history, stage at diagnosis, Charlson Comorbidity Index, performance status, histopathology, initial treatment, region and year of diagnosis.

lower mortality was observed in patients with squamous cell carcinomas. In stage IIIA squamous cell carcinoma, however, both overall (aHR 1.25; CI 1.04–1.53) and cause-specific mortality (aHR 1.28; CI 1.04–1.58) were higher in patients with high compared to low education.

4. Discussion

4.1. Summary of results

In this nationwide study of patients with non-small-cell lung cancer, we found evidence of socioeconomic differences in diagnostic intensity; a high educational level was associated with an increased likelihood to undergo PET/CT. There was also evidence of an increased likelihood for patients with high education to be discussed in a multidisciplinary setting. Furthermore, the likelihood to undergo stereotactic radiotherapy was elevated in patients with high education compared to those with low education. In early, but not late stage disease, high education was associated with a lower all-cause and cause specific mortality both overall and in analyses stratified by sex and histopathology. There were no differences between educational groups in stage at diagnosis or in waiting times.

4.2. Methodological strengths and limitations

Strengths of our study included the use of information from a population-based research database generated by record linkage between several high-quality registers. In contrast to many previous studies where SES has been assessed by residential area, our study was based on individual level educational achievement, which is considered to represent a good indicator of socioeconomic status in relation to health and longevity. In addition, the data at hand included information on smoking history, performance status and comorbidity reducing the potential confounding influences of co-existing disease. To our knowledge, only one previous study to date has examined aspects of diagnostic intensity in lung cancer in relation to socioeconomic status [[9]].

Limitations included the absence of information on patient related factors such as lifestyle, health awareness and beliefs as well as health care seeking behavior. Information on smoking history was based on self-report and thus subject to misclassification due to misreporting or recall bias. Also, no data were available on treatments beyond first line. While educational achievement assessed by years in school may not adequately reflect quality of schooling, it represents a likely marker of health awareness and knowledge needed to navigate the health care system. In the oldest birth cohorts, educational level might represent a

less ideal indicator of socioeconomic standing because of changes in the Swedish school system over time. The data used to determine CCI were restricted to medical conditions requiring hospital care. Thus, the co-morbidity burden is likely to have been underestimated. A revision of the TNM Classification of Malignant Tumors in use from 2010 is likely to have affected classification of tumor stage in all patients in a similar way. It cannot be excluded that socioeconomic gradients in cancer management and outcomes in part reflect differences in patient-doctor communication and interactions, resulting in unequal provision of care. However, any such differences could not be assessed based on data at hand. Also, no data were available to correctly characterize patients dying shortly after diagnosis or start of treatment.

4.3. Comparisons to previous studies

4.3.1. SES and clinical presentation

Stage represents an important prognostic factor and several studies have focused on the role of severity of disease at diagnosis as an explanation for socioeconomic differences in cancer outcomes. We found no association between educational level and stage, corroborating results from several previous studies conducted in Scotland, Canada, Denmark and England, all countries with Uniform Health Care Systems (UHCS), that found no or weak associations between socioeconomic status and tumor stage at presentation in patients with lung cancer and other malignancies. [16–19] On the other hand, results from the US, a country with a non-UHCS, showed that the likelihood to present with advanced-stage cancers was elevated in uninsured or Medicaid-insured patients [20]. Another US study reported higher rates of stage I and lower rates of stage IV lung cancer in disabled patients with insurance coverage compared to an uninsured control group, suggesting that costs represent a barrier for seeking health care in the US setting [21]. Similarly, results from a recent meta-analysis based on data from 23 studies indicated the presence of inequalities in stage at diagnosis in non-UHCS countries, but not in UHCS settings [7]. Thus, the results of our study conducted in a UHCS setting, corroborate these findings.

Our findings of a higher proportion of adenocarcinomas in patients with high education confirm results from earlier studies and are likely to reflect socioeconomic differences in smoking prevalence [22,23].

4.3.2. SES and patterns of management
4.3.2.1. Waiting times. In contrast to a previous study set in central Sweden [9], we found no differences in waiting times between educational groups. Also, a Danish nationwide study has reported an association between low education and longer than recommended waiting times between referral and diagnosis [18]. However, similar

to our findings, a recent meta-analysis found no evidence of socioeconomic differences in waiting time from diagnosis to treatment [7].

4.3.2.2. SES, diagnostic intensity and multidisciplinary team assessment. Few studies to date have examined possible associations between SES and diagnostic intensity. Berglund et al found evidence of higher diagnostic intensity in patients with high education [9]. In our study differences in diagnostic intensity was primarily observed for PET/CT that was more commonly performed in patients with high education. In the tumor staging phase, PET/CT is important since the method has a high sensitivity and high negative prognostic value in differentiating between malign and benign lymph nodes, enabling correct assessment of prognosis and choice of optimal treatment [24]. Compared to initial treatment plans for radiotherapy of lung cancer, pretreatment PET/CT is associated with major alterations in 20% of the plans [25]. We also observed small differences between educational groups in the use of CT thorax, thoracocentesis and thoracoscopy.

In our study, a high educational level was associated with an increased likelihood to be discussed in a MDT setting. It has previously been shown that MDT assessment represents an independent predictor of receiving radiotherapy, chemotherapy and referral to palliative care [26]. Also, discussion in a MDT is associated with a change in initial management plans for more than 50% of the patients [27]. If the MDT is held in a center where thoracic surgery is available, patients have been estimated to be 51% more likely to have surgery. [28] While multidisciplinary assessments have not been shown to be associated with lung cancer survival, it may improve quality of life [26].

4.3.2.3. SES and treatment intensity. Our study found statistically significant socioeconomic disparities in treatment with stereotactic radiotherapy, but not for other treatment modalities, including surgery. Earlier studies have reported more pronounced socioeconomic differences in treatment intensity in patients with lung cancer. In a systematic review and meta-analysis, low SES was associated with a reduced likelihood both in UHCS and non-UHCS countries of receiving any type of treatment, including surgery and chemotherapy [29]. A recent nationwide Danish study reported similar findings; patients with low socioeconomic status were less likely to receive treatment [30]. Socioeconomic inequalities in treatment have been suggested as an explanation of observed social differences in lung cancer outcomes [31].

4.3.3. SES and mortality

Results from several earlier studies have found socioeconomic differences in both over-all and cause-specific mortality in lung cancer [6,9,17,19,30–34]. In the present study, we found evidence of socioeconomic gradients in outcomes in early stage disease. Similar patterns in mortality were also found in analyses stratified by sex and histopathology. Similarly, an English study found differences in early stage NSCLC with a 3-year survival of 50% in affluent groups compared to 39% in the most deprived group. [19] Several studies have reported that socioeconomic disparities in survival are most pronounced soon after a cancer diagnosis [30,34]. While not the focus or explored in our study, marital status has been suggested to be associated with lung cancer mortality [35]. A Belgian study reported a lower lung cancer mortality in men with a highly educated partner. However, the results for women with lung cancer were less uniform [36].

4.3.4. SES and use of new diagnostic methods and treatments

We found evidence of social gradients in MDT and use of PET/CT and stereotactic radiotherapy. In recent years, the need of management decisions based on MDT discussions has been a focus point in the Swedish Cancer Strategy aiming to improve provision of quality of care. In the early part of the period under study, both PET/CT and stereotactic radiotherapy were not yet extensively available in Sweden. PET/

CT is today implemented nationwide, guideline based and available in all diagnostic centers. Stereotactic radiotherapy is becoming more readily available as an option for patients deemed unfit for surgery. Also, novel treatments introduced during the last decade such as tyrosine kinase inhibitors, bevacizumab and pemetrexed have mainly targeted adenocarcinomas, which are more common in patients with high education.

Taken together, it cannot be excluded that our findings of socioeconomic differences in mortality in part reflects differences in the clinical implementation and use of new diagnostic methods and treatments.

5. Conclusions

In conclusion, while we found no differences in stage at diagnosis or waiting times between educational groups, we found evidence of socioeconomic gradients not only in diagnostic intensity and MDT assessment, but also in outcomes in patients managed within a National Health Care System aiming to provide equal care. While the core reasons for these differences remain incompletely understood, the observed inequalities warrants an increased awareness and underscores the need for stricter adherence to national guidelines to optimize outcomes for all patients with lung cancer.

Conflict of interest

None declared.

References

[1] Europe PMC Funders Group, The global burden of Cancer 2013, JAMA Oncol. 1 (July (4)) (2015) 505–527, https://doi.org/10.1001/jamaoncol.2015.0735.
[2] Statistics on Cancer Incidence 2016, The Swedish National Board of Health and Welfare, 2017 (Accessed 17 March 2018), http://www.socialstyrelsen.se/publikationer2017/2017-12-31.
[3] The Swedish National Lung Cancer registry, Lung Cancer in Sweden, Accounting the Years 2012-2016, (2017), pp. 1–53 November:https://www.cancercentrum.se/globalassets/cancerdiagnoser/lunga-och-lungsack/kvalitetsregister/rapport/nlcr_rapport_tom2016_171120_publicera.pdf (Accessed 17 March 2018).
[4] A. Sidorchuk, E.E. Agardh, O. Aremu, et al., Socioeconomic differences in lung cancer incidence: a systematic review and meta-analysis. Cancer Causes Control. 20 (May (4)) (2009) 459–471, https://doi.org/10.1007/s10552-009-9300-8.
[5] S.M. Crawford, V. Saurezpaf, Haynes, et al., Social and geographical factors affecting access to treatment of lung cancer, Br. J. Cancer 101 (6) (2009) 897–901, https://doi.org/10.1038/sj.bjc.6605257 Epub 2009 Aug 18.
[6] M.P. Coleman, P. Babb, A. Sloggett, et al., Socioeconomic inequalities in cancer survival in England and Wales, Cancer 91 (January (1 suppl)) (2001) 208–216.
[7] L. Forrest, S. Sowden, G. Rubin, et al., Socio-economic inequalities in stage at diagnosis, and in time intervals on the lung cancer pathway from first symptom to treatment: systematic review and meta-analysis, Thorax 72 (May (5)) (2017) 430–436, https://doi.org/10.1136/thoraxjnl-2016-209013 Epub 2016 Sep 28.
[8] S. Eaker, M. Halmin, R. Bellocco, et al., Social differences in breast cancer survival in relation to patient management within a National Health Care System (Sweden), Int. J. Cancer 124 (January (1)) (2009) 180–187, https://doi.org/10.1002/ijc.23875.

[9] A. Berglund, L. Holmberg, C. Tishelman, et al., Social inequalities in non-small cell lung cancer management and survival: a population-based study in central Sweden, Thorax. 65 (April (4)) (2010) 327–333, https://doi.org/10.1136/thx.2009.125914.

[10] K. Tomic, E. Ventimiglia, D. Robinson, et al., Socioeconomic status and diagnosis, treatment, and mortality in men with prostate cancer. Nationwide population-based study, Int. J. Cancer (January) (2018), https://doi.org/10.1002/ijc.31272 [Epub ahead of print].

[11] The Swedish National Board of Health and Welfare, Cause of Death Register, (2011) Accessed 18 January 2018 http://www.scb.se/Statistik/HS/HS0301/_dokument/HS0301_BS_2009.pdf.

[12] Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA), Statistics Sweden, Stockholm, Sweden, 2019 Accessed 18 January 2018 http://www.scb.se/vara-tjanster/bestalla-mikrodata/vilka-mikrodata-finns/longitudinella-register/longitudinell-integrationsdatabas-for-sjukforsakrings–och-arbetsmarknadsstudier-lisa/.

[13] H. Quan, B. Li, C.M. Couris, et al., Updating and validating the Charlson co-morbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries, Am. J. Epidemiol. 173 (March (6)) (2011) 676–682, https://doi.org/10.1093/aje/kwq433 Epub 2011 Feb 17.

[14] M.M. Oken, R.H. Creech, D.C. Tormey, et al., Toxicity and response criteria of the eastern cooperative oncology group, Am. J. Clin. Oncol. 5 (December (6)) (1982) 649–655.

[15] R Foundation for Statistical Computing V, Austria. R Core Team, R: a Language and Environment for Statistical Computing 2014, (2014) http://www.R-project.org/.

[16] Brewster, Thomson, Hole, et al., Relation between socioeconomic status and tumour stage in patients with breast, colorectal, ovarian, and lungcancer: results from four national, population based studies, BMJ 322 (April (7290) (2001) 830–831.

[17] C.M. Booth, G. Li, J. Zhang-Salomons, W.J. Mackillop, The Impact of socioeconomic status on stage of cancer at diagnosis and survival: a population-based study in Ontario, Canada, Cancer 116 (September (17)) (2010) 4160–4167, https://doi.org/10.1002/cncr.25427.

[18] S.I. Dalton, B.L. Frederiksen, E. Jacobsen, et al., Socioeconomic position, stage of lung cancer and time between referral and diagnosis in Denmark, 2001-2008, Br. J. Cancer 105 (September (7)) (2011) 1042–10428, https://doi.org/10.1038/bjc.2011.342 Epub 2011 Sep 6.

[19] A. Berglund, M. Lambe, Lüchtenborg, et al., Social differences in lung cancer management and survival in South East England: a cohort study, BMJ Open 2 (May (3)) (2012), https://doi.org/10.1136/bmjopen-2012-001048 pjj:e001048, Print 2012.

[20] M.T. Halpern, E.M. Ward, A.L. Pavluck, et al., Association of insurance status and ethnicity with cancer stage at diagnosis for 12 cancer sites: a retrospective analysis, Lancet Oncol. 9 (March (3)) (2008) 222–231, https://doi.org/10.1016/S1470-2045(8)70032-9 Epub 2008 Feb 20.

[21] E.P. McCarthy, L.H. Ngo, Chirikos Tn, et al., Cancer Stage at diagnosis and survival among persons with Social Security Disability Insurance on medicare, Health Serv. Res. 42 (April (2)) (2007) 611–628.

[22] M.J. Thun, C.A. Lally, J.T. Flannery, et al., Cigarette smoking and changes in the histopathology of lung cancer, J. Natl. Cancer Inst. 89 (November (21)) (1997) 1580–1586.

[23] G. Menvielle, J.E. Franck, Radoï, et al., Quantifying the mediating effects of

[24] P. De Leyn, Clinical value of ESTS guidelines on preoperative lymph node staging for NSCLC, Eur. J. Cardiothorac. Surg. 40 (August (2)) (2011) 280–281, https://doi.org/10.1016/j.ejcts.2010.12.002 Epub 2011 Jan 13.

[25] C. Birk Christensen, A. Loft-Jakobsen, P. Munck Af Rosenschöld, 18F-FDG PET/CT for planning external beam radiotherapy alters therapy in 11% of 581 patients, Clin. Physiol. Funct. Imaging (Febuary) (2017), https://doi.org/10.1111/cpf.12411.

[26] M.M. Boxer, S.K. Vinod, J. Shafig, et al., Do multidisciplinary team meetings make a difference in the management of lung cancer? Cancer 117 (November (22)) (2011) 5112–5120, https://doi.org/10.1002/cncr.26149 Epub 2011 Apr 2.

[27] K.A. Ung, B.A. Campbell, D. Duplan, et al., Impact of the lung oncology multi-disciplinary team meetings on the management of patients with cancer, Asia. J. Clin. Oncol. 12 (June (2)) (2016) e298–304, https://doi.org/10.1111/ajco.12192 Epub 2014 Mar 27.

[28] A.L. Rich, L.J. Tata, C.M. Free, et al., Inequalities in outcomes for non-small cell lung cancer: the influence of clinical characteristics and features of the local lung cancer service, Thorax 66 (December (12)) (2011) 1078–1084, https://doi.org/10.1136/thx.2011.158972 Epub 2011 Jul 23.

[29] L.F. Forrest, J. Adams, H. Wareham, et al., Socioeconomic inequalities in lung Cancer treatment: systematic review and meta-analysis, PLoS Med. 10 (2) (2013) e1001376, https://doi.org/10.1371/journal.pmed.1001376 Epub 2013 Feb 5.

[30] S.O. Dalton, M. Steding-Jessen, E. Jakobsen, et al., Socioeconomic position and survival after lung cancer: influence of stage, treatment and comorbidity among Danish patients with lung cancer diagnosed in 2004-2010, Acta Oncol. 54 (May (5)) (2015) 797–804, https://doi.org/10.3109/0284186X.2014.1001037 Epub 2015 Mar 12.

[31] L. Forrest, J. Adams, G. Rubin, et al., The role of receipt and timeliness of treatment in socioeconomic inequalities in lung cancer survival: population-based, data-linkage study, Thorax 70 (Febuary (2)) (2015) 138–145, https://doi.org/10.1136/thoraxjnl-2014-205517 Epub 2014 Jun 12.

[32] L.G. Shack, B. Rachet, D.H. Brewster, et al., Socioeconomic inequalities in cancer survival in Scotland 1986-2000, Br. J. Cancer 97 (October (7)) (2007) 999–1004 Epub 2007 Sep 18.

[33] J.H. Van der Heyden, M.M. Schaap, A.E. Kunst, et al., Socioeconomic inequalities in lung cancer mortality in 16 European populations, Lung Cancer 63 (March (3)) (2009) 322–330, https://doi.org/10.1016/j.lungcan.2008.06.006 Epub 2008 Jul 25.

[34] B. Rachet, L. Ellis, C. Maringe, et al., Socioeconomic inequalities in cancer survival in England after the NHS cancer plan, Br. J. Cancer 103 (August (4)) (2010) 446–453, https://doi.org/10.1038/sj.bjc.6605752 Epub 2010 Jun 29.

[35] J.M. Varlotto, R. Voland, K. McKie, et al., Population-based differences in the outcome and presentation of lung cancer patients based upon racial, histologic, and economic factors in all lung patients and those with metastatic disease, Cancer Med. 7 (4) (2018) 1211–1220, https://doi.org/10.1002/cam4.1430 Epub 2018 Mar 13.

[36] K. Vanthomme, H. Vandenheede, Hagedoorn, et al., Socioeconomic disparities in lung cancer mortality in Belgian men and women (2001-2011): does it matter who you live with? BMC Public Health 16 (June) (2016) 493.