

# Forecasting lung cancer incidence, mortality, and prevalence to year 2030

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## Research Article

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# Abstract

**Background** Lung cancer incidence and prevalence is increasing worldwide and there is a focus on prevention, early detection, and development of new treatments which will impact the epidemiological patterns of lung cancer. The clinical characteristics and the trends in incidence, mortality, and prevalence of lung cancer in Denmark from 2006 through 2015 is described and a model for predicting the future epidemiological profile of lung cancer through 2030 is introduced.

**Methods** The study population comprised all cases of lung cancer, registered in the Danish Cancer Registry, who were alive on January 1, 2006 or had a first-time ever diagnosis of lung cancer during 2006 through 2015. Information on morphology, stage of the disease, comorbidity and survival was obtained from other Danish health registers. Based on NORDCAN data and estimated patient mortality rates as well as prevalence proportions for the period 2006 through 2015, future case numbers of annual incidence, deaths, and resulting prevalence were projected.

**Results** A total of 44,291 patients were included in the study. A shift towards more patients diagnosed with lower stages and with adenocarcinoma was observed. The incidence increased and the patient mortality rate decreased significantly, with a doubling of the prevalence during the observation period. We project that the numbers of prevalent cases of lung cancer in Denmark most likely will increase from about 10,000 at the end of 2015 to about 23,000 at the end of 2030.

**Conclusions** Our findings support that lung cancer is being diagnosed at an earlier stage, that incidence will stop increasing, that mortality will decrease further, and that the prevalence will continue to increase substantially. Projections of cancer incidence, mortality, and prevalence are important for planning health services and should be updated at regular intervals.

## Introduction

Worldwide, the incidence of lung cancer has been described as an epidemic with variabilities across countries according to socio-economic, historical, and cultural characteristics<sup>1</sup>. This also applies to the Western European countries where different trends in incidence have been attributed to differences in smoking patterns and socio-economic prerequisites<sup>2</sup>.

Lung cancer is associated with huge costs for patients and society, and there is an increasing focus on prevention, early detection with screening, and development of new treatments<sup>3</sup>. When introduced, such new modalities will impact the future epidemiological patterns of lung cancer. This dynamic scenario calls for tools to monitor a comprehensive description of the current and future trends in the epidemiology of lung cancer.

In this paper we describe the clinical characteristics and the trends in incidence, mortality, and prevalence of lung cancer in Denmark from 2006 through 2015. Based on these observations we introduce a model for predicting the future epidemiological profile of lung cancer through 2030.

# Material And Methods

## *Data sources*

The study population comprised all patients with lung cancer in Denmark from 2006 through 2015. The study is a part of the CEDAR Study (Cancer Impact in Denmark Study). The CEDAR Study is a nationwide, observational study on patient populations with cancer of the lung, breast, bladder, ovary, and prostate.

Patients have been ascertained from the Danish Cancer Registry<sup>4</sup>, and by record linkage at person-level information from the Danish Civil Person Register<sup>5</sup>, the Danish Cancer Registry, the Danish National Patient Register<sup>6</sup>, the Danish Register of Causes of Death<sup>7</sup>, and the Pathology Register<sup>8</sup>, cancer trajectories have been established with profiles of the patients by stage, tumour morphology and comorbidity at diagnosis. Furthermore, milestones on the introduction of relevant new cancer treatments and other interventions were established.

## *Study population and data*

The study population comprised patients with a diagnosis of lung cancer registered in the Cancer Registry [ICD10 code C33-C34]. We included all prevalent patients resident in Denmark and alive on January 1, 2006, and all patients with a first-time ever diagnosis of lung cancer from January 1, 2006 through December 31, 2015.

For each case of cancer in the Danish Cancer Registry there is one tumour morphology SNOMED code recorded. The codes were grouped in accordance with the morphology classification in the Danish Lung cancer Register<sup>9</sup>. In the Danish Cancer Registry, cases of lung cancer is registered with codes in the TNM classification system for disease stage. These data were converted to disease stage based on TNM UICC version 7<sup>10</sup>. Based on hospital diagnoses registered during the 10 years period prior to the diagnosis of lung cancer, we established a Charlson Comorbidity Index score<sup>11</sup> for each patient. Patients were followed based on data from the Danish Civil Registration System until death, emigration, or December 31, 2016, whatever came first. Annual population counts by sex and age was obtained from national census data at Statistic Denmark and used as denominator when calculating descriptive numbers.

## *Methods of analysis*

Incidence rates were estimated annually (per 10,000) as the number of new cases divided by the estimated person-time at risk in the background population and expressed per 10.000. The data were grouped by sex and age in the intervals 40-59, 60-69, 70-79, and  $\geq 80$  years, respectively, thereby truncating the risk population at 40 years as the lower level. The very few cases of lung cancer with diagnosis below age 40 years were allocated to the age group 40-60 years. Prevalence proportions were estimated (per 10.000) as the number of patients alive divided by the total population size on an annual basis with reference to December 31 each year. Patient mortality rates were estimated annually (per 100

person-years at risk in the patient population) as the number of deaths (regardless of cause of death) divided by the estimated patient-time at risk.

The projection of the future numbers of annual incident cases, deaths, and resulting prevalent case numbers was made for the period 2016 through 2030 and was based on the principles in a 'stock and flow' model for a closed population<sup>12</sup>. For the incidence rates, we used data and forecasts as published for lung cancer in Denmark by NORDCAN, a database on cancer statistics in the Nordic countries<sup>13</sup>. Since NORDCAN does not publish mortality rates in a form usable for the present purpose, we used an exponential model applied to the present observed mortality rates for the period. For reference purposes we have established the hypothetical scenario with all incidence and mortality rates kept constant at the levels of year 2015. For the projection analyses data were stratified for sex and age groups 40-59, 60-69, 70-79, and  $\geq 80$  years. We quantified the individual components driving the change in incidence and prevalence over calendar time.

Poisson regression analysis (Stata version 15.0) was applied to assess potential determinants of the incidence and mortality rates. Chi-square analyses were used to test for trends in proportions.

### *Ethical approval*

**Ethical Approval statement:** All experimental protocols were approved by the Danish Data Protection Agency under j.nr. 2008-58-0035.

**Informed Consent:** Due to Danish legislation on register-based research, no further permissions were required, including informed consent, waived by the Danish Protection Agency.

**Guidelines/Accordance:** all methods were carried out in accordance to relevant guidelines and regulations.

## Results

### *Epidemiological characteristics*

Over time, the incidence increased in case numbers, with a trend towards gender balance from a predominance of men. The prevalence doubled in the observed period, from 5.967 patients by end of year 2005 to 10.394 patients by the end of 2015. The annual number of deaths was higher for males than for females, with a stable total number around 4,000 annually in spite of the increasing prevalence (Table 1).

### *Stage, pathology and comorbidity*

Of the 44,291 patients diagnosed from 2006 through 2015 a detailed TNM stage was not reported for 8%. The stage distribution is presented in (Figure 1) where it is seen that the relative numbers of patients in stage classes IV and IIIB declined weakly whereas a relative increase in patients in stage classes 0 – IIIA,

was observed. The increasing trend in the proportion of patients diagnosed with stage classes 0-III A was statistically significant ( $P<0.0001$ ).

The number of patients without a specific morphology diagnosis decreased from 14% in 2006 to 8% in 2015. The proportion of patients diagnosed with adenocarcinoma increased statistically significant ( $P<0.0001$ ) with a corresponding decrease in the number of patients with large cell carcinoma and other primary lung cancer (Figure 2). At high level morphology classification, the proportions of patients with squamous cell and small cell carcinomas have been relatively stable

The proportion of patients with comorbidity (CCI score $>0$ ) increased over time (Table 2). Thus, the proportion of patients without comorbidity (CCI score=0) decreased from 64 % in 2006 to 59 % in 2015. This trend was statistically significant ( $P<0.0001$ ).

The statistical analysis of the incidence and mortality rates is summarized in (Table 3). During the study period, the incidence rate for females was 20% lower ( $P<0.0001$ ) compared with the rate for males. For both sexes, the incidence rates increased statistically significantly ( $P<0.0001$ ) for the age groups 60-69 and 70-79 years using the age group  $<60$  years as the reference. The incidence rate level for the age group  $\geq 80$  years was interposed between those by the age groups 60-69 and 70-79 years. With the inclusion of age groups and sex as covariates the incidence rate decreased statistically significantly by 0.5% annually ( $P=0.005$ ).

During the study period, the mortality rate for females was reduced by 19% ( $P<0.0001$ ) compared with the rate for males. Compared with the age group  $<60$  years, the mortality rate was not different for the age group 60-79 (6% increase,  $P=0.242$ ), but was statistically significantly increased for the age groups 70-79 and  $>80$  years by 21% ( $P<0.001$ ) and 76% ( $P<0.0001$ ), respectively. The mortality rate decreased significantly over time by 6%, ( $P<0.000$ ). Compared with no comorbidity (CCI=0) the mortality rate increased with increasing comorbidity by 44%, 34% and 86% ( $P<0.0001$  for all) for CCI=1, CCI=2, and CCI $>2$ , respectively.

### *Epidemiological projections*

The age-standardized summary rate is predicted to decrease slightly, but due to the ageing population the crude rate is modestly increasing (Figure 3 -top). The mortality in lung cancer is decreasing for all age-specific rates as well as for the crude (unadjusted) rate, and this trend is predicted to continue according to an exponential forecasting model (Figure 3 - bottom).

The observed and projected annual case numbers of incidence and mortality are showed in (Figure 4), with the corresponding annual growth. The age-standardized summary rate is predicted to decrease slightly, but due to the ageing population the crude rate is modestly increasing. The mortality in lung cancer is decreasing for all age-specific rates as well as for the crude rate, and this trend is predicted to continue according to an exponential forecasting model.

Using the annual numbers of new cases and deaths together with the number of prevalent cases by the end of 2005 as inputs to the 'stock and flow' model, annual prevalence numbers are estimated as shown in (Figure 5) together with the observed values for the period from the end of 2005 to the end of 2015. The modelled trend in prevalence numbers follows closely the observations. According to the model, the numbers of prevalent cases of lung cancer in Denmark will more than double from about 10,000 at the end of 2015 to about 23,000 at the end of 2030. In the reference scenario with constant sex and age specific incidence and mortality rates, the increase in prevalence is less marked with an estimated number of prevalent cases at about 12,500 at the end of 2030.

Using the modelled NORDCAN data from the core model of projection, the annual absolute number of incident cases increased by 13% from year 2006 through year 2015. Demographical changes would have increased the annual case number by 17%, but this is reduced by 4% due to the slight decreasing trend in the general incidence level. According to the core model, the annual number of incident cases will increase by 7% from 2016 through 2030. The expected demographic changes considered isolated would lead to an increase at 22%, but this is impaired negatively by 15% due to the expected decreasing trend in the incidence level.

During the period end of 2005 through end of 2015 the absolute number of prevalent cases increased by 76% according to the core model. The effect of epidemiological disequilibrium at the end of 2005 account for an increase at 8% and demographical changes account for additional 14%. However, the decreasing trend in incidence level has reduced the increase in prevalence by 6%. The remaining contribution to the increase in prevalence amounts to 60% and is accounted for by decreasing mortality level during the 10-years period.

For the period from the end of 2015 through the end of 2030, the core model predicts an increase in the absolute prevalent case number at 119%. The attributions to this increase are estimated as follows: Effect of epidemiological disequilibrium: 9%; demographical changes: 14%; changes in incidence level: -12%; changes in mortality level: 107%.

## Discussion

This study reports an analysis of the clinical characteristics together with current and future epidemiological trends of lung cancer in Denmark.

Stage distribution of lung cancer has shifted towards lower stages at diagnosis. Stages IV and IIIB that today primarily indicate oncological treatment with palliative intent and, optionally, in combination with targeted therapy or immune therapy, continue to be the dominant stage classifications albeit with a slight decrease from 2006 through 2015. At the same time, diagnosis in the stage classifications I to IIIA has increased from 25% in 2006 to 36% in 2015. The trend towards detecting lung cancer at an earlier stage provides a potential for offering curative treatment at an increasing rate, leading to improved prognosis.

However, this trend is partly opposed by trends towards increasing age at diagnosis and a heavier load of comorbidity<sup>14</sup>.

Apparently, the proportion of patients diagnosed with adenocarcinoma of the lung has increased markedly from 27% in 2006 to 45% in 2015. It is, however, questionable if this represents an actual change in the morphology pattern or whether the changes may be explained by increasing need for precise morphology classification and/or better diagnostic tools, including improved biopsy techniques. In the same period new guidelines on the classification of adenocarcinoma has been implemented worldwide and this probably has been of major impact for classifying large cell carcinomas and other primary lung cancers<sup>15</sup>.

This analysis indicates that lung cancer in Denmark undergoes significant changes in the epidemiological profile. The incidence level is expected to decrease further, but the demographical changes will result in a modest increase in the annual absolute number of incident cases. In contrast, we expect a continuous reduction in the overall mortality rate, thereby increasing the annual growth in the prevalence to about 1000 in 2030 (Figure 5).

Our results support that the epidemiology of lung cancer changes differently between the sexes. The incidence level is increasing for females in certain age groups, but the overall incidence level is still lower for females than for males. Yet, the background population at risk is growing relatively most for females in the higher age groups resulting in a trend towards an overweight of females among the new cases. This, combined with the substantially lower mortality in females than in males, results in a trend towards an increasing overweight of females in the prevalent population.

We estimate the prevalence of lung cancer in Denmark to more than double from the end of 2015 to the end of 2030. In the alternative scenario with constant incidence and mortality rates since 2015, the prevalence increase is much lower, due to the assumption of no further improvements in the prognosis of lung cancer. Since we find it more likely with a continued improvement in the prognosis in lung cancer, the projections in the core model with the marked increasing prevalence is considered realistic.

Whereas the demographic evolution towards a relative increase in people of high age is a major driver of the increasing number of incident cases of lung cancer, our analysis demonstrates that the improvements in prognosis (as reflected in decreasing patient mortality rates) is by far the most important driver of the increasing prevalence of lung cancer.

The major strengths of this study are the validity of the data sources. The Cancer Registry, the Danish National Patient Register, and the Pathology Register are all believed to be complete and valid and as mentioned, the projected incidence and mortality rates follow the observed.

The limitations include the uncertainties associated with assumptions regarding the future levels of incidence and mortality. Changes in annual incident case numbers are driven by changes in the size and composition of the background population at risk of disease together with changes in the sex and age

specific incidence rates. In addition to changes in demography and incidence rates, the changes over time in the annual number of prevalent cases are driven by changes in prognosis (here quantified as changes in the patient mortality rates) plus the effect of epidemiological disequilibrium, if present at the start of the projection period. Epidemiological disequilibrium exists if the annual number of new cases is not in balance with the number of deaths /regardless of cause) in the patient population. Under epidemiological disequilibrium, prevalence will change towards achieving a state of equilibrium. The model is well suited for changing assumptions, for example, implementation of screening programmes and new treatments.

Data on TNM and comorbidity are from the Cancer Registry and the Danish National Patient Register and are not validated by clinicians and they are associated with some degree of uncertainty. It is estimated that this uncertainty is of a minor magnitude and do not have a significant impact on the result. The effects of CCI must be interpreted with caution because resection status has not been included in the analysis and because of potential interaction with age.

The worldwide lung cancer epidemic goes on. Years of focus on prevention and intervention against tobacco consumption has so far only had a modest effect on the incidence of lung cancer. Attempts over many years to develop more effective treatment methods have only marginally changed the prognosis of this deadly disease. In the light of the development of new treatment options and implementation of screening for lung cancer, a new optimism can be traced in the professional environment. Our data support that lung cancer is being diagnosed at an earlier stage, that incidence will stop increasing, and that mortality will decrease further. But these positive changes have implications in terms of a substantially increasing prevalence, with resources allocated to an increased demand for treatment, follow-up, and aftercare.

Projections of cancer incidence, mortality and prevalence are important for planning health services and to provide a baseline for assessing the impact of public health interventions. We present a dynamic model to predict these changes and provide a comprehensive description of the current and future trends in the clinical characteristics and epidemiological profile of lung cancer. If implemented and updated periodically, this could be an important tool in planning of lung cancer health care. Realizing that forecasting models heavily depend on the assumed trends in incidence and mortality that drive the future prevalence, our simple and transparent tool makes it easy to establish alternative forecasting scenarios.

## **Declarations**

### **Ethical approval**

Ethical Approval statement: All experimental protocols were approved by the Danish Data Protection Agency under j.nr. 2008-58-0035.

### **Informed Consent:**

Due to Danish legislation on register-based research, no further permissions were required, including informed consent, waived by the Danish Protection Agency.

### **Guidelines/Accordance**

all methods were carried out in accordance to relevant guidelines and regulations.

### **Consent for publication:**

All authors consent publication. Due to Danish legislation on register-based research, no further permissions were required, including informed consent, waived by the Danish Protection Agency.

### **Authors' contributions:**

E.J. and A.G. wrote the main manuscript text, and interpreted and discussed the findings and critically reviewed the manuscript.. A.G. conducted statistical analysis and prepared tables and figures. MB interpreted and discussed the findings and critically reviewed the manuscript. MH interpreted and discussed the findings and critically reviewed the manuscript. KEO interpreted and discussed the findings and critically reviewed the manuscript. GP interpreted and discussed the findings and critically reviewed the manuscript.

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### **Declaration of conflicts of interest:**

The authors have no conflicts of interest to declare.

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## Tables

**Table 1. Epidemiological key numbers of lung cancer in Denmark 2006 to 2015**

Year	New cases			Deaths			Prevalence (end of year)		
	Males	Females	Total	Males	Females	Total	Males	Females	Total
2005	-	-	-	-	-	-	3,071	2,896	5,967
2006	2,168	1,929	4,097	2,158	1,752	3,910	3,080	3,073	6,153
2007	2,273	2,018	4,291	2,065	1,755	3,820	3,284	3,334	6,618
2008	2,226	2,021	4,247	2,118	1,809	3,927	3,396	3,546	6,942
2009	2,261	2,044	4,305	2,119	1,855	3,974	3,537	3,736	7,273
2010	2,294	2,218	4,512	2,133	1,900	4,033	3,698	4,052	7,750
2011	2,277	2,214	4,491	2,068	1,883	3,951	3,908	4,385	8,293
2012	2,359	2,182	4,541	2,140	1,880	4,020	4,124	4,687	8,811
2013	2,239	2,302	4,541	2,100	1,901	4,001	4,264	5,089	9,353
2014	2,417	2,247	4,664	2,193	1,935	4,128	4,489	5,400	9,889
2015	2,296	2,306	4,602	2,140	1,959	4,099	4,646	5,748	10,394
All years	22,810	21,481	44,291	21,234	18,629	39,863	-	-	-

**Table 2: Distribution of Charlson Comorbidity Index at diagnosis, LC patients diagnosed 2006-2015 (incl.)**

CCI	Year at diagnosis										Total
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	
0	64 %	63 %	63 %	63 %	62 %	61 %	62 %	60 %	60 %	59 %	27,292 (62%)
1	17 %	17 %	18 %	17 %	18 %	18 %	17 %	18 %	18 %	17 %	7,799 (18%)
2	11 %	11 %	11 %	12 %	12 %	12 %	12 %	13 %	13 %	13 %	5,348 (12%)
>2	8 %	8 %	8 %	8 %	9 %	9 %	9 %	9 %	9 %	10 %	3,852 (9%)

**Table 3. Statistical analysis of incidence and mortality**

INCIDENCE				
	Covariate	HR	95% C.I.	P value
	Sex			
	Male (ref.)	(1)	-	-
	Females	0.803	0.789 ; 0.819	<0.0001
	Year (ref.:2006)	0.995	0.992 ; 0.999	0.005
	AgeGrp			
	<60 (ref.)	(1)	-	-
	60-69	4.499	4.374 ; 4.628	<0.0001
	70-79	8.286	8.059 ; 8.520	<0.0001
	≥80	6.977	6.755; 7.207	<0.0001
MORTALITY				
	Covariate	HR	95% C.I. (a)	P value
	Sex			
	Male (ref.)	(1)	-	-
	Females	0.809	0.761 ; 0.859	<0.0001
	Year (ref.: 2006)	0.944	0.934 ; 0.954	<0.0001
	AgeGrp			
	<60	(1)	-	-
	60-69	1.058	0.963 ; 1.162	0.242
	70-79	1.208	1.102 ; 1.323	<0.0001
	≥80	1.756	1.606 ; 1.921	<0.0001
	CCI			
	0 (ref.)	1	-	-
	1	1.447	1.355 ; 1.501	<0.0001
	2	1.339	1.243 ; 1.435	<0.0001
	>2	1.857	1.735 ; 1.989	<0.0001

## Figures

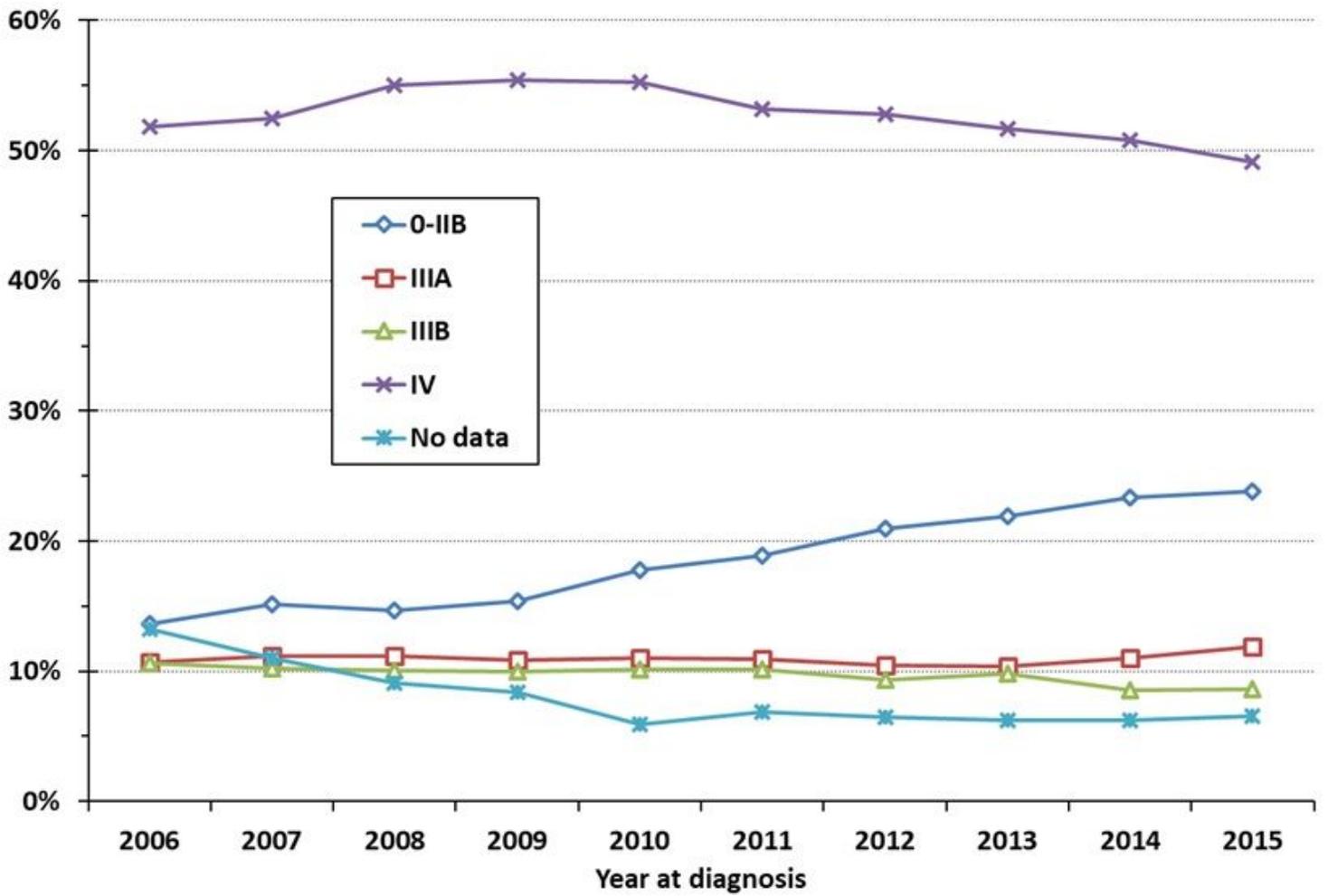


Figure 1

Trend in high-level stage distribution, LC patients diagnosed 2006-2015 (incl.)

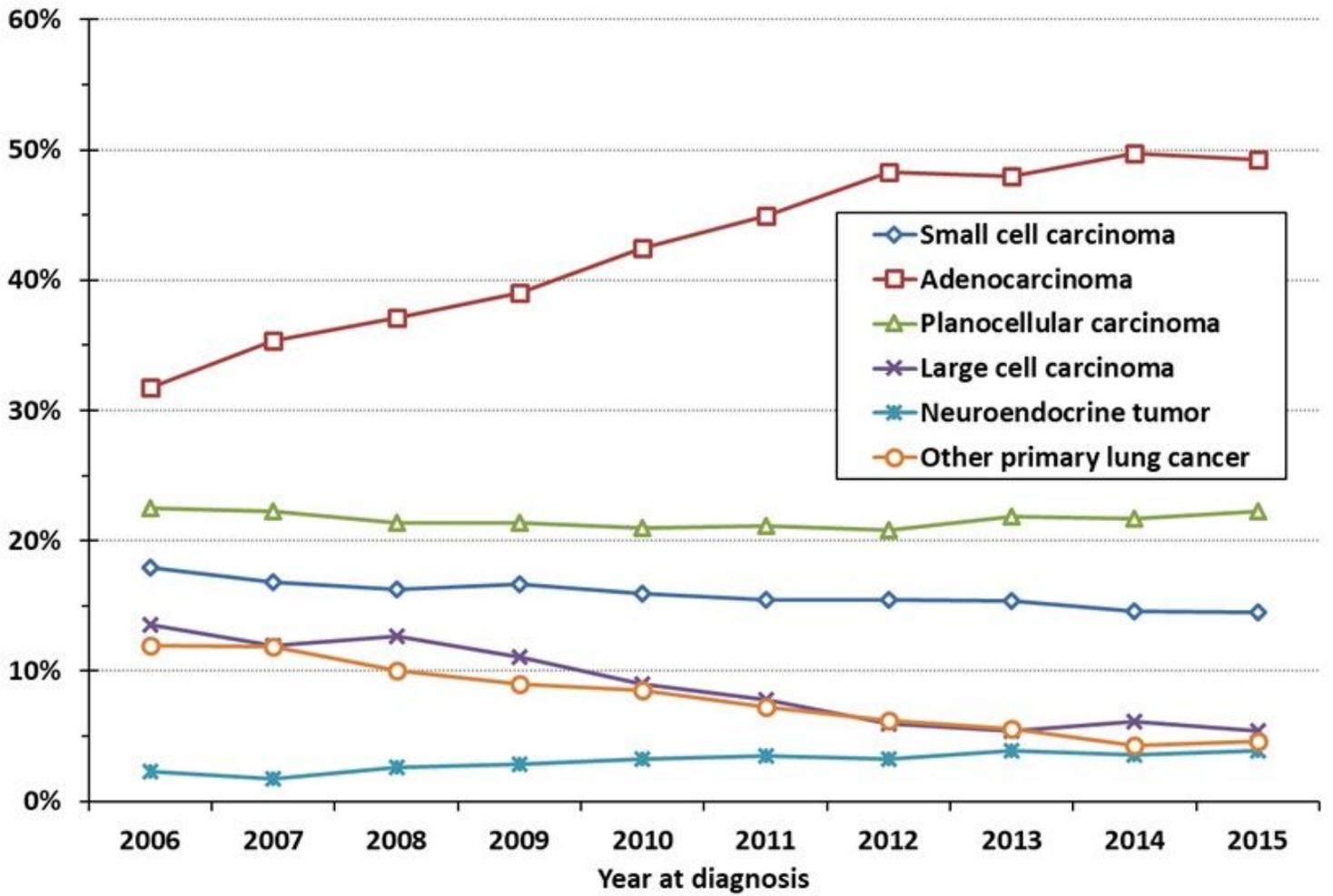
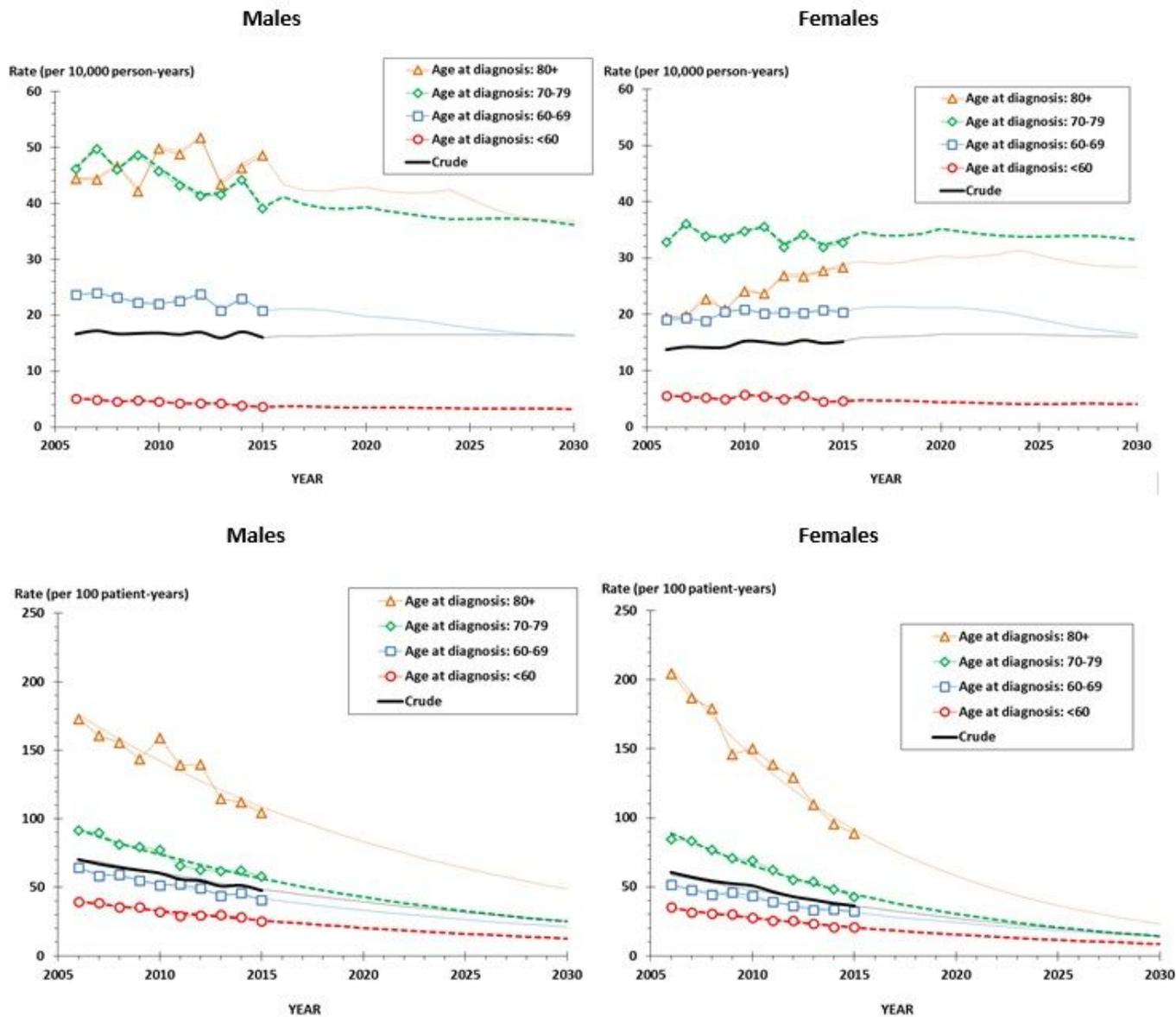


Figure 2

Trends in the distribution of high-level morphology categories, LC patients diagnosed 2006-2015 (incl.), with conclusive pathology (N=40,457)



**Figure 3**

Incidence (top) and mortality (bottom) rates of lung cancer: Observed (full lines, with symbols) and projected (dotted lines) rates

Case numbers

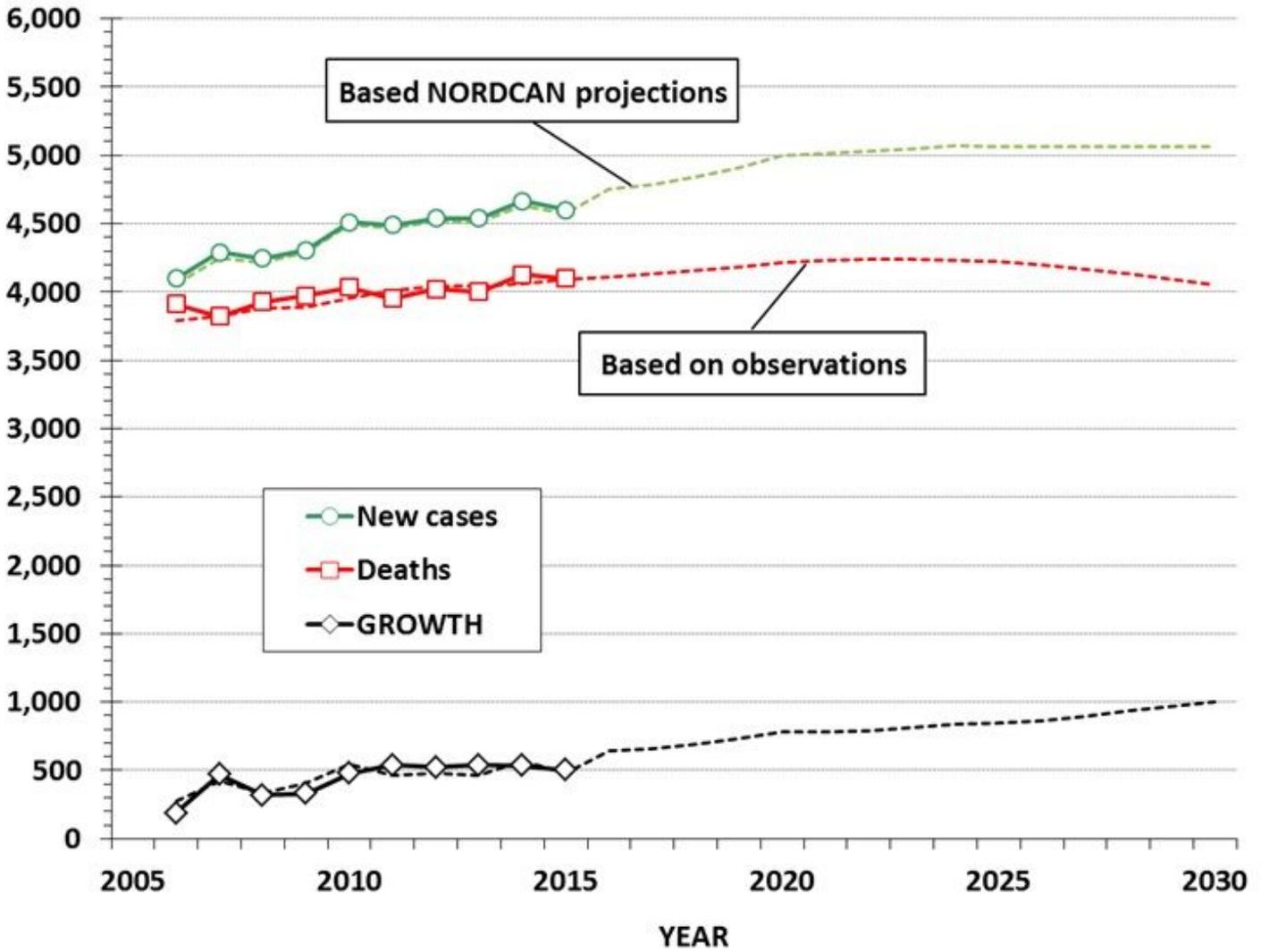


Figure 4

New cases and deaths in LC: Observed (full lines, with symbols) and projected (dotted lines) case numbers, with estimated annual growths

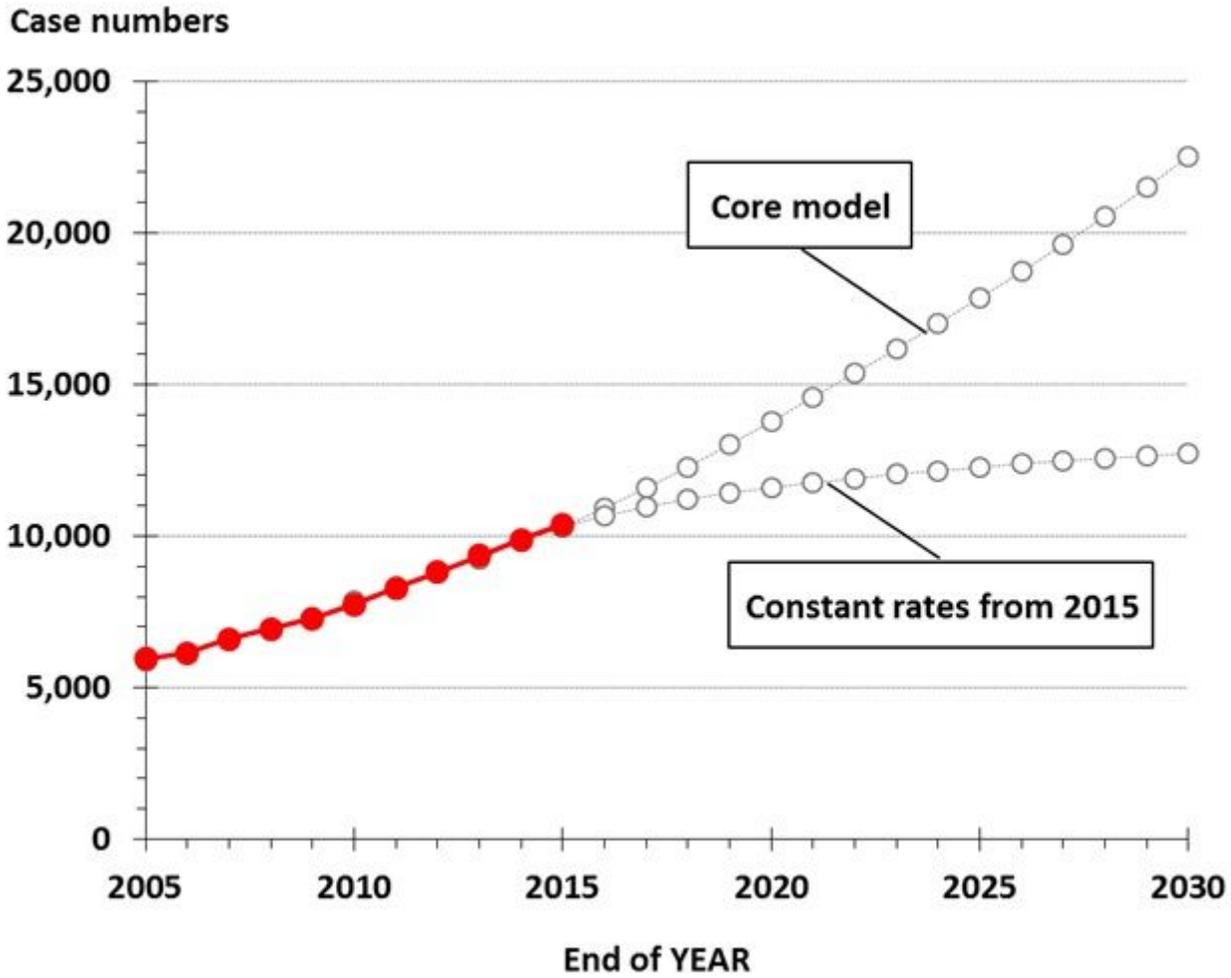


Figure 5

Observed and projected prevalence of LC: Observed (full lines, with filled symbols) and projected (dotted lines) number of prevalent cases