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# Long-term Effects of Targeted Therapies Launch on Survival and Mortality of Lung Cancer in Taiwan

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# Title Page

## Long-term Effects of Targeted Therapies Launch on Survival and Mortality of Lung Cancer in Taiwan

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**Abstract**

**Objectives:** Two oral targeted therapies, gefitinib and erlotinib, were firstly approved and then launched into the market for patients with later stages of non-small cell lung cancer (NSCLC) in Taiwan in 2003 and 2006, respectively. This study is aimed toward an examination of the trends of the lung cancer epidemic and the effects of the launch of new

drugs over the past 20 years.

**Setting:** Yearly lung cancer-related epidemic data (1994-2013) were retrieved from the Taiwan Cancer Registry Database.

**Design and Outcome Measures:** Using a time series design with autoregressive integrated moving average (ARIMA) model, we investigated and predicted trends in the incidence and early diagnosis of lung cancer in Taiwan. We also estimated the changes in survival rates and mortality following the launch of targeted therapies using interrupted time series and segmented regression models.

**Results:** The age-standardized incidence of lung cancer increased from 22.53 per 100,000 people in 1994 to 34.09 in 2013, and it has been predicted that it will reach 38.98 by 2020. The rate of early diagnosis of NSCLC increased from 12.63% in 2004 to 23.99% in 2013, and it was predicted to reach 32.95% by 2020. The two-year survival rate of lung cancer increased by 19.81% (95%CI: 14.90%, 24.71%) three years following the launch of gefitinib. There was a relative decrease of 5.97% (95%CI: -8.20%, -3.73%) in the mortality 3 years following the launch of gefitinib.

**Conclusions:** Targeted therapies have benefited lung cancer treatment by significantly increasing the survival rate and decreasing the mortality of lung cancer in Taiwan.

**Keywords:** targeted therapies; lung cancer; incidence; survival rate; mortality

**Category:** original study

**Running head:** Targeted therapies for lung cancer treatment

**Strengths and limitations of this study**

- This study examined the long-term trends in yearly incidence, the rate of early diagnosis, survival rate, and mortality of lung cancer.
- The changes in lung cancer-related survival rates and mortality following the launch of the targeted therapies were estimated.
- An interrupted time series design, a strong quasi-experimental method, was applied.
- This study confirmed the benefits of targeted therapies on the survival rate and mortality in respect to lung cancer treatment in Taiwan.
- This study did not use patient-level data to separate the patients by lung cancer sub-types and disease severity.

# Manuscript

## Introduction

Lung cancer is the leading cause of cancer deaths worldwide.[1] Globally, around 1.82 million new patients were diagnosed with lung cancer (12.9% of all cancer diagnoses), and around 1.59 million patients died (19.4% of all cancer mortalities) in 2012.[2] The incidence was 23.1 per 100,000 people, and the mortality was 19.7 per 100,000 people in 2012[2], which has increased over time.[1–3] In the United States, approximately 214,000 new cases (13.3% of all cancer diagnoses) of lung cancer are expected out of which 168,000 deaths (27.2% of all cancer mortalities) were estimated due to lung cancer in 2012.[3]

In Taiwan, lung cancer is also one of the most commonly diagnosed cancers as well as the leading cause of cancer deaths. Approximately 12,462 new cases of lung cancer (12.1% of all cancer diagnoses) and 9,167 deaths (19.9% of cancer deaths) were predicted to occur in Taiwan in 2014.[4] About 85% of all lung cancers are identified as non-small cell, and approximately 75% of these are metastatic or advanced at diagnosis, for which no curative treatment is available.[5-8] Given most patients are diagnosed with advanced stage diseases, it is considered a terminal illness with a five-year survival rate of less than 15%.[9-11]

Oral targeted therapies for non-small cell lung cancer (NSCLC) were launched into the market for epidermal growth factor receptor (EGFR) mutation patients in Taiwan in 2003. These EGFR molecular targeted drugs (MTD), gefitinib and erlotinib, were firstly approved as third-line or second-line therapy for advanced NSCLC patients because of their therapeutic benefits, as suggested by randomized clinical trials.[12-14] The recent National Comprehensive

Cancer Network guideline[15] further suggests MTD as the first-line therapy for EGFR mutation-positive, advanced NSCLC patients based on accumulating evidence showing a significant association between mutated EGFR and the clinical benefits of MTD.[16-18] In the light of rapid disease progression, the access to pharmaceutical innovations such as MTD on a timely basis is vital to NSCLC patients with the right indications who need it.

Little is known about the long-term epidemic trends of lung cancer and the effects of the introduction of new drugs being launched in Taiwan. This study is first intended to address these gaps by examining the trends in yearly incidence, the rate of early diagnosis, survival rate, and mortality over the past 20 years (1994-2013). In addition, the subsequent yearly incidence and early diagnosis stage rates are investigated and predicted until 2020, based on the past trends. We also estimate the changes in lung cancer-related survival rates and mortality following the launch of the targeted therapies under consideration in this work.

## Method

### *Data sources*

We obtained data from 1994-2013 (20 years) related to the lung cancer incidence in Taiwan from the Taiwan Cancer Registry Database, which was compiled by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan.[19] The data include yearly incidence and mortality for various cancer types by age, gender, and administrative division. Survival rates within several years of diagnosis of various cancer types are also available from the database. Use of this data for research purposes is exempt from review by the Institutional

Review Board (IRB) in Taiwan. All analyses were carried out with SAS software, version 9.4 (SAS Institute, Cary, NC).

***Measurements***

To examine the trends in lung cancer incidence, we collected the yearly number of new patients, crude incidence (per 100,000 people), and age-standardized incidence (per 100,000 people) of lung cancer by gender from 1994 to 2013. The global population in year 2000 was used to calculate the age-standardized incidence.[20] In addition, the yearly total of new lung cancer patients (small cell lung cancer and non-small cell lung cancer) according to diagnostic stages were collected, and we calculated the rates of early diagnosis over time. Diagnostic stages from 0 to 2 were considered the early diagnostic stage, and stages from 3 to 4 were considered the late diagnostic stage.

To evaluate the impacts of the launch of the targeted therapies, yearly 1 year-, 2 year-, and 3 year- lung cancer survival rates by gender from 1994-2013 were collected. Furthermore, we collected the yearly number of deaths, the crude mortality (per 100,000 people), and the age-standardized mortality (per 100,000 people) for lung cancer by gender from 1994 to 2013.

***Statistical Analysis***

To assess the yearly changes in lung cancer epidemiology using the age-standardized incidence and early diagnosis rates as defined above, we used a time series design with the autoregressive integrated moving average (ARIMA) model, which was developed by Box and Jenkins.[21] The model is generally referred to as an ARIMA(p,d,q) model, where

parameters p, d, and q are non-negative integers that refer to the order of the autoregressive, integrated, and moving average parts of the model, respectively. These models are fitted to time series data either to better understand the data or to determine points in the series.[22] We used the estimated rates from the ARIMA model for time series graphs.

To determine the effects of the launch of the targeted therapies on clinical outcomes for lung cancer treatment, we also estimated the changes in the lung cancer-related 1 year- and 2 year-survival rates by gender and the changes in the age-standardized mortality following the launches of the targeted therapies using interrupted time series and segmented regression models, a strong quasi-experimental method.[23-25] The method can provide strong evidence of causal effects because it takes into consideration the question of whether an intervention causes abrupt and measurable interruptions in a preexisting trend.[23,26] We used segmented linear regression models to estimate the post-new targeted therapy drug launch effects on changes in both the level and trend of both survival rates and age-standardized mortality.[27] All analyses were carried out with SAS software, Version 9.4 (SAS Institute, Cary, NC).

## Results

Table 1 presents the past trends (1994-2013) and future predictions (2014-2020) of the age-standardized incidence of lung cancer by gender in Taiwan over time. The overall age-standardized incidence of lung cancer increased from 22.53 (per 100,000) in 1994 to 34.09 in 2013, and it was predicted to reach 38.98 by 2020 based on the trend of the previous 20 years. By gender, the age-standardized incidence for males increased from 30.11 (per

100,000) in 1994 to 43.01 in 2013, and it was predicted to reach 48.11 by 2020; the age-standardized incidence for females increased from 13.82 (per 100,000) in 1994 to 26.16 in 2013, and it was predicted to reach 31.57 by 2020.

[Table 1]

Table 2 shows the past trends (1994-2013) and future predictions (2014-2020) of the rate of the early diagnosis of lung cancer by type of lung cancer in Taiwan. The rate of NSCLC grew rapidly from 12.63% in 2004 to 23.99% 2013, and it was predicted to reach 32.95%, based on the trend for the past 10 years, while the rate of SCLC slightly reduced from 4.78% in 2004 to 4.10% 2013 and was predicted to reach 3.11% by 2020.

[Table 2]

**Effects of the launch of gefitinib (2003) on survival rate**

Table 3 details the parameter estimates from the segmented regression models of changes in the lung cancer survival rate following the launch of the targeted therapies. Overall, the 1-year and 2-year survival rates increased relatively by 10.18% (95% CI: 6.77%, 13.59%) and 19.81% (95% CI: 14.90%, 24.71%) 3 years following gefitinib's launch in 2003. In the case of men, the 1-year and 2-year survival rates increased relatively by 10.70% (95% CI: 9.34%, 12.06%) and 14.25% (95% CI: 3.27%, 25.24%); in the case of women, the 1-year and 2-year survival rates increased relatively by 14.82% (95% CI: 6.92%, 22.71%) and 31.12% (95% CI: 15.64%, 46.60%).

[Table 3]

**Effects of erlotinib's launch (2006) on survival rate**

Overall, there were no significant changes in the 1-year and 2-year survival rates 3 years following erlotinib's launch in 2006. In the case of men, the 1-year and 2-year survival rates did not change either; however, there were relative reductions of 13.34% (95%CI: -20.48%, -6.20%) and 11.77% (-22.36%, -1.18%) in the 1-year and 2-year survival rates for women. Figure 1 shows the 1-year and 2-year survival rates of lung cancer in Taiwan over time.

[Figure 1]

**Effects of the launch of gefitinib (2003) on mortality**

Table 4 presents the parameter estimates from the segmented regression models of changes in the lung cancer mortality following the launch of the targeted therapies. Overall, the mortality decreased relatively by 5.97% (95% CI: -8.20%, 3.73%) 3 years following gefitinib's launch in 2003. In the case of men, it reduced relatively by 5.40% (95% CI: -10.08%, -0.73%), and in the case of women, it decreased relatively by 4.38% (95% CI: -7.50%, -1.25%).

[Table 4]

**Effects of the launch of erlotinib (2006) on mortality**

Overall, there were no significant changes in the mortality 3 years following the launch of erlotinib in 2006. There were relative reductions of 7.20% (95%CI: -9.69%, -4.71%) in the mortality for men. The rate of mortality did not, however, change significantly for women. Figure 2 shows the overall lung cancer mortality in Taiwan over time.

[Figure 2]

## Discussion

In this study, 7 year (2014-2020) lung cancer incidence trends in Taiwan were analyzed and projected based on the observed incidence from 1994 to 2013 (20 years), using a time series design. Then, the trends in the rates of early diagnosis of cancer were also predicted for 7 years (2014-2020) based on the past early diagnosis rates from 2004 to 2013 (10 years). Furthermore, the present study is the first study to examine the national trend in lung cancer survival rates and mortality following the introduction of targeted therapies in Taiwan using interrupted time series and segmented regression models.

This study predicted an ongoing gradual increase in the age-standardized incidence of lung cancer for both men and women in Taiwan. According to our results, the overall incidence of lung cancer in Taiwan (35.4 per 100,000) was lower than that in the United States (38.4) and Canada (37.9) in 2012, but it was higher than that in the United Kingdom (30.0), Australia (27.0), Japan (24.6) and South Korea (28.7).[28] Between 1994 and 2013, the age-standardized rate steadily increased by 42.84% for men and by 89.29% for women, and there was an estimated overall 51.31% growth rate (Table 1). According to these trends, incidence will rise continuously to 48.11 per 100,000 for men and 31.57 per 100,000 for women by 2020. Our findings showing these increasing trends are similar to those of previous studies[29,30] investigating earlier trends (up to 2008) in Taiwan. However, decreasing trends for both men and women in other countries have been observed. For example, lung cancer incidence decreased for both men and women in the United States (2004-2009)[31], China (1997-2005 for men and 2001-2005 for women)[32], Hong Kong (1983-2000)[33] and

Singapore (1980-2007)[34]. The incidence decreased for men but increased for women in the Czech Republic (1984-1998)[35]. Previous studies have provided evidence of a reduction in the prevalence of smoking following smoking bans.[36-38] Lung cancer in non-smokers can be caused by exposure to radon, secondhand smoke, air pollution, or other factors in addition to workplace exposure to asbestos, diesel exhaust, or specific other chemicals that can also cause lung cancers in some people who don't smoke.[39,40] It is important to find the main reasons (other than smoking) causing these increasing trends in Taiwan.

Even though the incidence of lung cancer in Taiwan has increased over time, the rate of early diagnosis has also gradually increased. The rate of incidence of NSCLC grew from 14.27% to 23.99% (2-fold) from 2004-2013, and it is expected to increase to one third (32.95%) by 2020. However, the early diagnosis rate of SCLC has remained very low (less than 5%) without a significant increase. There are almost no symptoms at the initial stage of lung cancer, so, it is difficult to detect it early.[41] However, the National Lung Screening Trial (NLST)[42] conducted by the National Health Institute in the United States found that the use of low-dose computed tomography in high risk groups for lung cancer could detect tumors earlier and reduce mortality by 20%. Hence, the National Comprehensive Cancer Network (NCCN) guideline recommends screening for people who smoke more than one pack of cigarettes a day, have smoked for more than 30 years, have quit smoking for less than 15 years, or are 55-74 years old.[43] The Taiwan Lung Cancer Society refers to the NCCN guideline and also announced an expert consensus to continue to improve the early diagnosis rate in 2015.

Originally, only chemotherapies were used as drug therapy for lung cancer treatment. Then, the first targeted therapy, gefitinib, was approved for market in 2003, followed by the second target therapy, erlotinib, which became available in 2006. Compared with standard chemotherapies, most clinical trials have shown that when these two target drugs were used as the first line of treatment for advanced NSCLC with EGFR mutations, overall survival did not increase significantly. However, progression-free survival was significantly increased by round 3-8 months.[16,44-47] This study confirms that since the first targeted therapy (gefitinib) was approved for the market, the one-year survival rate increased by about 10%, and the two-year survival rate increased by about 20% 3 years after the new drug was launched in the case of both men and women. However, the subsequent survival rate did not change markedly after the launch of the second targeted therapy (erlotinib) because the second drug is not a so-called "breakthrough innovation," as was the case for the first targeted therapy.

This study also estimated the age-standardized mortality of lung cancer for both men and women in Taiwan. We found that the overall mortality of lung cancer in Taiwan (25.0 per 100,000) is lower than that in the United States (28.6), Canada (28.4) and the United Kingdom (25.4) in 2012, but it is higher than that in South Korea (21.3), Australia (18.5) and Japan (17.4).[28]

The present study also confirmed that after the gefitinib's launch, the mortality for both men and women was approximately 5% lower than expected 3 years following the launch. However, only the mortality for men was 7% lower than expected 3 years following the launch of the second drug, erlotinib. Therefore, Taiwan's lung cancer treatment capacity

needs to be strengthened in the future.

There are some limitations to this study. Instead of overall lung cancer types, targeted therapies are only appropriate for advanced NSCLC patients with EGFR mutation. Advanced NSCLC patients account for about 64% of overall lung cancer patients in Taiwan.[5-8] Among them, approximately 40-50% patients have EGFR mutation. This study found that targeted therapies (especially gefitinib) have benefited lung cancer treatment by significantly increasing the survival rate and decreasing the mortality of lung cancer in Taiwan. However, the launch of gefitinib is not the only explanation for the improvement in survival and mortality related to lung cancer. Other diagnosis and treatment factors, including better diagnostic tools (such as molecular testing), earlier diagnosis, treatment sequencing strategies, personalized care, multimodality care, palliative care support, and psychological support have roles in outcome improvements. Furthermore, other factors, including patient's living habits and the global management of cancer patients, have also contributed the improvement in outcomes. In addition, using the data from the Taiwan Cancer Registry Database, this study was aimed toward an analysis of the aggregated data to estimate the two diagnostic indicators of lung cancer (incidences and early diagnosis rates) for the past and the future, as well as to evaluate changes in the two clinical indicators (survival rates and mortality) before and after the launch of the target therapies. Unfortunately, due to restrictions in the database, in addition to the early diagnosis rate, this study did not use patient-level data to separate the patients by lung cancer sub-types (NSCLC or SCLC) and disease severity (cancer stages). This study should provide a descriptive basis for additional research. There is a continuing

need for an adequate data sources for the practical application of the trends in lung cancer epidemiology.

## Conclusion

To conclude, this study focused on the epidemic trends of lung cancer, and the major findings suggest that the incidence of overall lung cancer and NSCLC early diagnosis rate increased in the past and that this trend is likely to continue in the future. On the other hand, this study confirmed the benefits of targeted therapies (especially the initial one, gefitinib) on the survival rate and mortality in respect to lung cancer treatment in Taiwan. However, whether these results will also apply to specific types and stages of lung cancer cannot be determined based on this study. Further research is therefore warranted.

## List of abbreviations

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; ARIMA: Autoregressive Integrated Moving Average; EGFR: epidermal growth factor receptor; MTD: molecular targeted drugs; IRB: Institutional Review Board.

## Author Contributions

JCH, CFW and SCY conceptualized and designed the study. PCL and YCL provided suggestions for the research design from a clinical perspective. CFW collected data, performed the analyses, and drafted the manuscript. JCH reviewed all data and revised the manuscript critically for intellectual content. All authors approved the final version for submission.

## Competing Interests

The authors have no competing interests.

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## Data Sharing Statement

The authors obtained nationwide data from1994-2013 (20 years) related to the lung cancer incidence in Taiwan from the Taiwan Cancer Registry Database, compiled by the Health

Promotion Administration, Ministry of Health and Welfare, Taiwan.

## ■ Ethics approval and consent to participate

Use of data from the online Taiwan Cancer Registry Database for research purposes is exempt from review by the Institutional Review Board (IRB) in Taiwan because the data used is public and aggregated population-level information.

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**Table 1. 1994-2013 Trends and 2014-2020 Forecast of Incidence of Lung Cancer in Taiwan**

| | Standardized Incidence_all (per 100,000) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All | | | | Male | | | | Female | | | |
| | Real value | Forecast (ARIMA) | Low 95% | Up 95% | Real value | Forecast (ARIMA) | Low 95% | Up 95% | Real value | Forecast (ARIMA) | Low 95% | Up 95% |
| 1994 | 22.53 | NA | | | 30.11 | NA | | | 13.82 | NA | | |
| 1995 | 22.53 | 23.17 | | | 30.08 | 30.81 | | | 14.02 | 14.51 | | |
| 1996 | 25.88 | 23.35 | | | 34.61 | 30.86 | | | 16.04 | 14.98 | | |
| 1997 | 26.64 | 25.72 | | | 35.57 | 34.85 | | | 16.76 | 15.98 | | |
| 1998 | 28.85 | 27.24 | | | 38.49 | 36.23 | | | 18.29 | 17.43 | | |
| 1999 | 30.30 | 29.03 | | | 40.11 | 38.92 | | | 19.61 | 18.51 | | |
| 2000 | 30.74 | 30.70 | | | 41.42 | 40.69 | | | 19.36 | 19.94 | | |
| 2001 | 30.08 | 31.43 | | | 39.86 | 42.04 | | | 19.78 | 20.57 | | |
| 2002 | 30.31 | 31.10 | | | 39.81 | 40.83 | | | 20.47 | 20.62 | | |
| 2003 | 29.47 | 31.07 | | | 39.17 | 40.59 | | | 19.47 | 21.15 | | |
| 2004 | 32.31 | 30.54 | | | 43.36 | 40.02 | | | 21.03 | 21.10 | | |
| 2005 | 32.40 | 32.30 | | | 43.07 | 43.64 | | | 21.69 | 21.23 | | |
| 2006 | 32.51 | 33.20 | | | 42.82 | 43.88 | | | 22.36 | 22.39 | | |
| 2007 | 33.80 | 33.30 | | | 44.38 | 43.63 | | | 23.51 | 23.06 | | |
| 2008 | 33.40 | 34.25 | | | 44.07 | 44.97 | | | 23.21 | 23.94 | | |
| 2009 | 35.88 | 34.34 | | | 46.39 | 44.89 | | | 26.01 | 24.45 | | |
| 2010 | 34.52 | 35.98 | | | 44.98 | 46.89 | | | 24.83 | 25.52 | | |
| 2011 | 34.74 | 35.74 | | | 45.10 | 45.93 | | | 25.33 | 26.56 | | |
| 2012 | 35.37 | 35.50 | | | 44.53 | 45.86 | | | 27.13 | 26.12 | | |
| 2013 | 34.09 | 36.01 | | | 43.01 | 45.38 | | | 26.16 | 27.20 | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **2014** | **35.29** | **32.66** | **37.92** | **43.97** | **40.35** | **47.59** | **27.77** | **25.92** | **29.62** |
| **2015** | **35.76** | **32.54** | **38.98** | **44.63** | **39.82** | **49.45** | **27.94** | **25.91** | **29.97** |
| **2016** | **36.45** | **32.61** | **40.28** | **45.33** | **39.53** | **51.14** | **28.92** | **26.45** | **31.38** |
| **2017** | **37.07** | **32.73** | **41.41** | **46.03** | **39.39** | **52.67** | **29.44** | **26.75** | **32.13** |
| **2018** | **37.71** | **32.92** | **42.50** | **46.72** | **39.34** | **54.11** | **30.22** | **27.25** | **33.18** |
| **2019** | **38.35** | **33.14** | **43.55** | **47.42** | **39.36** | **55.48** | **30.85** | **27.67** | **34.04** |
| **2020** | **38.98** | **33.39** | **44.57** | **48.11** | **39.43** | **56.80** | **31.57** | **28.16** | **34.97** |

1. NSCLC = Non-small cell lung cancer; SCLC = Small cell lung cancer

2. NA = not available

**Table 2. 2004-2013 Trends and 2014-2020 Forecast of Rate of Early Diagnosis of Lung Cancer in Taiwan**

| | Early Diagnosis Stage Rate (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | NSCLC | | | | SCLC | | | |
| | Real value | Forecast (ARIMA) | Low 95% | Up 95% | Real value | Forecast (ARIMA) | Low 95% | Up 95% |
| 1994 | NA | NA | | | NA | NA | | |
| 1995 | NA | NA | | | NA | NA | | |
| 1996 | NA | NA | | | NA | NA | | |
| 1997 | NA | NA | | | NA | NA | | |
| 1998 | NA | NA | | | NA | NA | | |
| 1999 | NA | NA | | | NA | NA | | |
| 2000 | NA | NA | | | NA | NA | | |
| 2001 | NA | NA | | | NA | NA | | |
| 2002 | NA | NA | | | NA | NA | | |
| 2003 | NA | NA | | | NA | NA | | |
| 2004 | 12.63 | NA | | | 4.78 | NA | | |
| 2005 | 14.27 | 13.90 | | | 5.77 | 4.66 | | |
| 2006 | 14.37 | 15.43 | | | 4.09 | 4.92 | | |
| 2007 | 15.09 | 15.96 | | | 6.26 | 4.99 | | |
| 2008 | 15.66 | 16.51 | | | 3.13 | 4.64 | | |
| 2009 | 18.46 | 17.12 | | | 3.06 | 4.98 | | |
| 2010 | 20.23 | 19.29 | | | 3.91 | 2.90 | | |
| 2011 | 20.51 | 21.35 | | | 3.34 | 3.15 | | |
| 2012 | 23.16 | 22.05 | | | 3.87 | 3.51 | | |
| 2013 | 23.99 | 24.04 | | | 4.10 | 3.33 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **2014** | **25.38** | **23.36** | **27.39** | **3.75** | **1.26** | **6.24** |
| **2015** | **26.61** | **24.13** | **29.09** | **3.78** | **1.14** | **6.41** |
| **2016** | **27.89** | **24.93** | **30.84** | **3.56** | **0.30** | **6.83** |
| **2017** | **29.15** | **25.81** | **32.49** | **3.50** | **0.02** | **6.99** |
| **2018** | **30.42** | **26.72** | **34.11** | **3.34** | **NA** | **7.22** |
| **2019** | **31.68** | **27.66** | **35.70** | **3.25** | **NA** | **7.36** |
| **2020** | **32.95** | **28.63** | **37.26** | **3.11** | **NA** | **7.52** |

1. NSCLC = Non-small cell lung cancer; SCLC = Small cell lung cancer
2. NA = not available

**Table 3. Estimated Changes in Lung Cancer Survival Rates Following the Launch of Targeted Therapies (gefitinib and erlotinib) Using Interrupted Time Series and Segmented Regression Models**

| | | | 1. Effects of gefitinib's launch | | | | 2. Effects of erlotinib's launch | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Intercept | Baseline trend | Level change | Trend change | Absolute change (3 year later) | Relative change (3 year later) | Level change | Trend change | Absolute change (3 year later) | Relative change (3 year later) |
| 1-year survival rate (all) | 0.3478 | 0.0041 (0.0015, 0.0067) | NS | 0.0135 (0.0096, 0.0174) | 0.0404 (0.0286, 0.0522) | 10.18% (6.77%, 13.59%) | NS | NS | 0 | 0.00% |
| 2-year survival rate (all) | 0.2169 | NS | -0.0138 (-0.0272, -0.0004) | 0.0189 (0.0171, 0.0207) | 0.0430 (0.0331, 0.0528) | 19.81% (14.90%, 24.71%) | NS | NS | 0 | 0.00% |
| 1-year survival rate (male) | 0.3505 | NS | NS | 0.0125 (0.0111, 0.0139) | 0.0375 (0.0333, 0.0417) | 10.70% (9.34%, 12.06%) | NS | NS | 0 | 0.00% |
| 2-year survival rate (male) | 0.2165 | -0.0024 (-0.0046, -0.0001) | -0.0206 (-0.0363, -0.0049) | 0.0158 (0.0130, 0.0186) | 0.0268 (0.0084, 0.0452) | 14.25% (3.27%, 25.24%) | NS | NS | 0 | 0.00% |
| 1-year survival rate (female) | 0.3532 | 0.0110 (0.0071, 0.0149) | -0.0455 (-0.0929, 0.0019) | 0.0392 (0.0213, 0.0571) | 0.0720 (0.0374, 0.1065) | 14.82% (6.92%, 22.71%) | NS | 0.0315 (-0.0513, -0.0117) | -0.0945 (-0.1537, -0.0354) | -13.34% (-20.48%, -6.20%) |
| 2-year survival rate (female) | 0.2174 | 0.0056 (0.0030, 0.0083) | -0.0391 (-0.0795, -0.0013) | 0.0396 (0.0256, 0.0536) | 0.0861 (0.0514, 0.1208) | 31.12% (15.64%, 46.60%) | NS | 0.0227 (-0.0386, -0.0068) | -0.0576 (-0.1170, 0.0019) | -11.77% (-22.36%, -1.18%) |

1. 95%CI = estimate +/- (1.96*se); All terms p<0.1 retained in models

2. NS = non-significant

**Table 4. Estimated Changes in Lung Cancer Mortality Following the Launch of Targeted Therapies (gefitinib and erlotinib) Using Interrupted Time Series and Segmented Regression Models**

| | | | 1. Effects of gefitinib's launch | | | | 2. Effects of erlotinib's launch | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Intercept | Baseline trend | Level change | Trend change | Absolute change (3 years later) | Relative change (3 years later) | Level change | Trend change | Absolute change (3 years later) | Relative change (3 years later) |
| Mortality (all) | 25.75 | 0.26 (0.11, 0.42) | NS | -0.58 (-0.81, -0.34) | -1.73 (-2.43, -1.02) | -5.97% (-8.20%, 3.73%) | NS | NS | 0 | 0.00% |
| Mortality (male) | 34.48 | 0.45 (0.20, 0.70) | -2.15 (-4.11, -0.20) | NS | -2.15 (-4.11, -0.20) | -5.40% (-10.08%, -0.73%) | NS | -0.94 (-1.29, -0.59) | -2.81 (-3.87, -1.76) | -7.20% (-9.69%, -4.71%) |
| Mortality (female) | 15.80 | 0.17 (0.04, 0.30) | NS | -0.26 (-0.46, -0.06) | -0.78 (-1.38, -0.19) | -4.38% (-7.50%, -1.25%) | NS | NS | 0 | 0.00% |

1. 95%CI = estimate +/- (1.96*se); All terms p<0.1 retained in models

2. NS = non-significant

# Figures

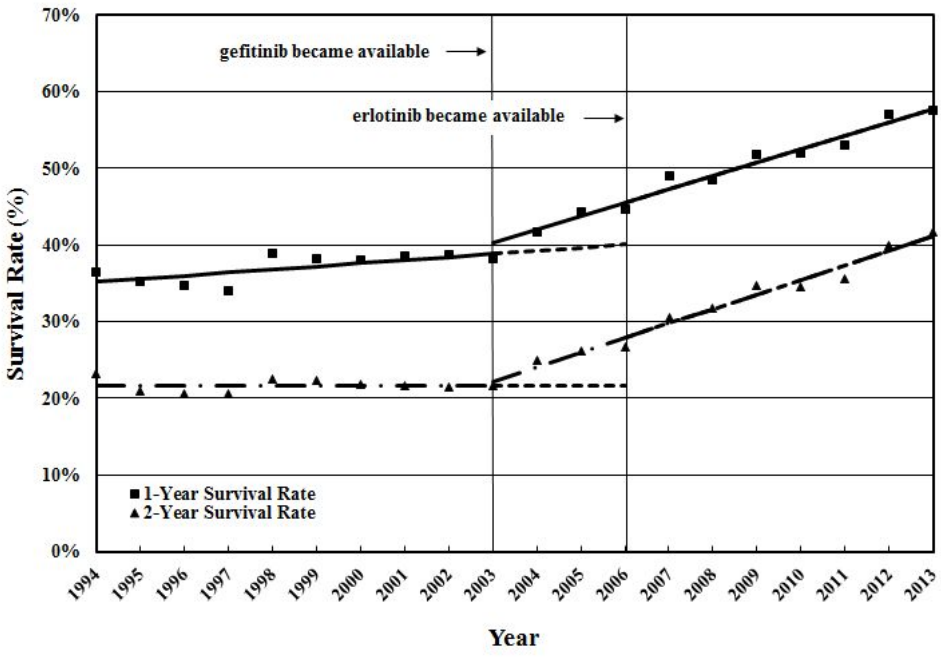


**Figure 1. Yearly Lung Cancer Survival Rates in Taiwan (1994-2013)**




**Figure 2. Yearly Lung Cancer Mortality in Taiwan (1994-2013)**

BMJ Open

# Lung Cancer Survival and Mortality in Taiwan following the Initial Launch of Targeted Therapies: An Interrupted Time Series Study

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# Title Page

## Lung Cancer Survival and Mortality in Taiwan following the Initial Launch of Targeted Therapies: An Interrupted Time Series Study

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## Abstract

**Objectives:** Two oral targeted therapies, gefitinib and erlotinib, were firstly approved and then launched into the market for patients with late-stage non-small cell lung cancer (NSCLC) in Taiwan in 2003 and 2006, respectively. The aim of this study was to exam the trends in lung cancer burden and the effects of the launch of new drugs on the survival and mortality of lung cancer during 1994-2013.

**Setting:** Yearly lung cancer-related data (1994-2013), including incidence, number of early diagnosis case, survival rate and mortality, were retrieved from the Taiwan Cancer Registry Database.

**Design and Outcome Measures:** Using a time series design with autoregressive integrated moving average (ARIMA) model, we investigated and projected trends in the incidence and early diagnosis of lung cancer in Taiwan. We also estimated the changes in survival rates and mortality following the launch of targeted therapies using interrupted time series and segmented regression models.

**Results:** The age-standardized incidence of lung cancer increased from 22.53 per 100,000 people in 1994 to 34.09 in 2013, and it was projected to reach 38.98 by 2020. The rate of early diagnosis of NSCLC increased from 12.63% in 2004 to 23.99% in 2013, and it was projected to reach 32.95% by 2020. The 2-year survival rate of lung cancer increased by 19.81% (95%CI: 14.90%, 24.71%) three years following the launch of gefitinib. There was a relative decrease of 5.97% (95%CI: -8.20%, -3.73%) in the mortality three years following the launch of gefitinib.

**Conclusions:** Lung cancer survival rate increased and mortality decreased significantly in following the launch of gefitinib and erlotinib in Taiwan.

**Keywords:** targeted therapies; lung cancer; incidence; cancer survival; cancer mortality; gefitinib; erlotinib

**Category:** original study

**Running head:** Targeted therapies for lung cancer treatment

**Strengths and limitations of this study**

- This study examined the long-term trends in yearly incidence, the rate of early diagnosis, survival rate, and mortality of lung cancer.
- Long term data from the Taiwan Cancer Registry Database was used in this study.
- A time series design was used to project the incidence and the rate of early diagnosis.
- An interrupted time series design was applied to estimate the changes in survival rates and mortality following the launch of targeted therapies.
- This study did not use patient-level data to separate the patients by lung cancer sub-types and disease severity.

# Manuscript

## Introduction

Lung cancer is the leading cause of cancer deaths worldwide.[1] Globally, around 1.82 million new patients were diagnosed with lung cancer (12.9% of all cancer diagnoses), and around 1.59 million patients died (19.4% of all cancer mortalities) in 2012.[2] The incidence was 23.1 per 100,000 people, and the mortality was 19.7 per 100,000 people in 2012[2], which has increased over time.[1–3] In the United States, approximately 214,000 new cases of lung cancer (13.3% of all cancer diagnoses) and 168,000 deaths due to lung cancer (27.2% of all cancer mortalities) were estimated in 2012.[3]

In Taiwan, lung cancer is also one of the most commonly diagnosed cancers as well as the leading cause of cancer deaths. Approximately 12,462 new cases of lung cancer (12.1% of all cancer diagnoses) and 9,167 deaths (19.9% of cancer deaths) were projected to occur in Taiwan in 2014.[4] About 85% of all lung cancers are identified as non-small cell, and approximately 75% of these are metastatic or advanced at diagnosis, for which no curative treatment is available.[5-8] Given most patients are diagnosed with advanced stage diseases, it is considered a terminal illness with a five-year survival rate of less than 15%.[9-11]

Oral targeted therapies for non-small cell lung cancer (NSCLC) were launched into the market for epidermal growth factor receptor (EGFR) mutation patients in Taiwan in 2003 (gefitinib) and in 2006 (erlotinib). These EGFR molecular targeted drugs, gefitinib and erlotinib, were initially approved as third-line or second-line therapy for advanced NSCLC patients because of their therapeutic benefits, as suggested by randomized clinical trials.[12-14]

The recent National Comprehensive Cancer Network guideline[15] recommends gefitinib and erlotinib as the first-line therapy for EGFR mutation-positive, advanced NSCLC patients based on accumulating evidence showing a significant association between mutated EGFR and the clinical benefits of gefitinib and erlotinib.[16-18] In light of rapid disease progression, timely access to pharmaceutical innovations such as targeted therapies is vital to NSCLC patients. The new targeted therapies, gefitinib and erlotinib have been reimbursed by Taiwan's national health insurance since 2004 and 2007, respectively, for NSCLC patients who meet the above requirements based on evidence and clinical need.

Little is known about the effects of the introduction of new targeted therapies in Taiwan. This study is one of the first to address the gap by examining the changes in lung cancer-related survival rates and mortality following the launch of gefitinib and erlotinib.

## Method

### *Data sources*

We obtained data from 1994-2013 related to the lung cancer incidence in Taiwan from the Taiwan Cancer Registry Database, which was compiled by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan.[19] The data include yearly incidence and mortality for various cancer types by age, gender, and administrative division. Survival rates within several years of diagnosis of various cancer types are also available from the database.

Through the routine cancer case notification reminders and collection procedures each

year, the sources of possible cancer cases and the cancer registration declaration database are combined. Health Promotion Administration calculates the completeness of cancer registration declarations in each year, approximately 98.44% in 2016.[20] In addition, in accordance with the practice of the International Agency for Research on Cancer (IARC), Percentage of Death Certificate Only Cases (DCO%) and Percentage of Morphologically Verified Cases (MV%) are used as quality indicators of the reporting data. In 2016, as a result of the data collection and comparison, the DCO% was 0.91%, indicating that the coverage of the registration system was complete and the data quality in the system was consistent. In the same year, the MV% of all cancer cases was 92.23%, that of men was 90.79%, and that of women was 93.89%, indicating that the diagnosis of cancer cases is accurate.[20] Use of this data for research purposes is exempt from review by the Institutional Review Board (IRB) in Taiwan.

***Measurements***

To examine the trends in lung cancer incidence, we collected the yearly number of new patients, crude incidence (per 100,000 people), and age-standardized incidence (per 100,000 people) of lung cancer by gender from 1994 to 2013. The global population in year 2000 was used to calculate the age-standardized incidence.[21] In addition, the yearly total of new lung cancer patients (small cell lung cancer and non-small cell lung cancer) according to diagnostic stages were collected, and we calculated the rates of early diagnosis over time. Diagnostic stages from 0 to 2 were considered as early-stage, and stages 3 and 4 were categorized as late-stage.

To evaluate the impacts of the launch of targeted therapies, 1 year- and 2 year- lung

cancer survival rates by gender from 1994-2013 were collected. Furthermore, we collected the yearly number of deaths, the crude mortality (per 100,000 people), and the age-standardized mortality (per 100,000 people) for lung cancer by gender from 1994 to 2013.

***Statistical Analysis***

To assess the yearly changes in lung cancer epidemiology using the age-standardized incidence and early diagnosis rates as defined above, we used a time series design with the autoregressive integrated moving average (ARIMA) model, which was developed by Box and Jenkins.[22] The model is generally referred to as an ARIMA(p,d,q) model, where parameters p, d, and q are non-negative integers that refer to the order of the autoregressive, integrated, and moving average parts of the model, respectively. These models are fitted to time series data either to better understand the data or to determine points in the series.[23] We used the estimated rates from the ARIMA model for time series graphs.

To determine the effects of the launch of the new targeted therapies for lung cancer on clinical outcomes, we also estimated the changes in the lung cancer-related 1 year- and 2 year-survival rates and age-standardized mortality following the launches of gefitinib and erlotinib using interrupted time series and segmented regression models, a strong quasi-experimental method.[24-26] The method can provide strong evidence of causal effects because it takes into consideration the question of whether an intervention causes abrupt and measurable interruptions in a preexisting trend.[24,27] We used segmented linear regression models to estimate effects of the launch of new targeted therapies on changes in the level and

trend of both survival rates and age-standardized mortality.[28] The basic model included terms to estimate the baseline level for each outcome (intercept) ($\beta_0$), baseline trend (slope) ($\beta_1$), changes in the level immediately after the drug launch ($\beta_2$), and changes in the trend after the drug launch ($\beta_3$) (see the following model).[24,29]

$$Y_t = \beta_0 + \beta_1 * time_t + \beta_2 * intervention_t + \beta_3 * time\_after\_intervention_{t+} e_t$$ [24]

The models also controlled for autocorrelation.[30] To identify the most parsimonious models, we used backward elimination and excluded non-significant terms (P>0.05).

All analyses were carried out with SAS software, Version 9.4 (SAS Institute, Cary, NC).

***Patient and Public Involvement***

No patients were involved in the study.

## Results

Table 1 presents the past trends (1994-2013) and future projections (2014-2020) of the age-standardized incidence of lung cancer by gender in Taiwan. The overall age-standardized incidence of lung cancer increased from 22.53 (per 100,000) in 1994 to 34.09 in 2013, and it was projected to reach 38.98 by 2020 based on the trend during 1994-2013. By gender, the age-standardized incidence for males increased from 30.11 (per 100,000) in 1994 to 43.01 in 2013, and it was projected to reach 48.11 by 2020; the age-standardized incidence for females increased from 13.82 (per 100,000) in 1994 to 26.16 in 2013, and it was projected to reach 31.57 by 2020.

[Table 1]

Table 2 shows the past trends (1994-2013) and future projections (2014-2020) of the rate of the early diagnosis of lung cancer by type of lung cancer in Taiwan. The rate of NSCLC grew rapidly from 12.63% in 2004 to 23.99% 2013, and it was projected to reach 32.95%, based on the trend during 1994-2013, while the rate of SCLC slightly reduced from 4.78% in 2004 to 4.10% 2013 and was projected to reach 3.11% by 2020.

[Table 2]

**Effects of the 2003 launch of gefitinib on survival rate**

Table 3 details the parameter estimates from the segmented regression models of changes in the lung cancer survival rate following the launch of targeted therapies. Overall, 1-year and 2-year survival rates increased by 10.18% (95% CI: 6.77%, 13.59%) and 19.81% (95% CI: 14.90%, 24.71%) three years following gefitinib's launch in 2003 (see Figure 1). Among men, 1-year and 2-year survival rates increased by 10.70% (95% CI: 9.34%, 12.06%) and 14.25% (95% CI: 3.27%, 25.24%); and among women, 1-year and 2-year survival rates increased by 14.82% (95% CI: 6.92%, 22.71%) and 31.12% (95% CI: 15.64%, 46.60%).

[Table 3] [Figure 1]

**Effects of the launch of gefitinib and erlotinib on survival rate**

Overall, there were no significant changes in 1-year and 2-year survival rates three years following gefitinib and erlotinib's launch. Figure 1 shows the 1-year and 2-year survival rates of lung cancer in Taiwan over time. Among men, 1-year and 2-year survival rates did not

change; however, there were relative reductions of 13.34% (95%CI: -20.48%, -6.20%) and 11.77% (-22.36%, -1.18%) in 1-year and 2-year survival rates for women.

**Effects of the 2003 launch of gefitinib on mortality**

Table 4 presents the parameter estimates from the segmented regression models of changes in the lung cancer mortality following the launch of targeted therapies. Overall, the mortality decreased relatively by 5.97% (95% CI: -8.20%, 3.73%) three years following gefitinib's launch in 2003 (see Figure 2). Among men, mortality reduced by 5.40% (95% CI: -10.08%, -0.73%), and among women, mortality decreased by 4.38% (95% CI: -7.50%, -1.25%).

[Table 4] [Figure 2]

**Effects of the launch of gefitinib and erlotinib (2006) on mortality**

Overall, there were no significant changes in mortality three years following the launch of gefitinib and erlotinib in 2006. Figure 2 shows the overall lung cancer mortality in Taiwan over time. There were relative reductions of 7.20% (95%CI: -9.69%, -4.71%) in the mortality for men. The rate of mortality did not, however, change significantly for women.

[Figure 2]

## Discussion

This study projected 7 years (2014-2020) lung cancer incidence in Taiwan based on the observed incidence from 1994 to 2013 (20 years). We also projected rates of early diagnosis of cancer for 2014 through 2020 based on the past trends. Furthermore, the present study is the first study to examine the national trend in lung cancer survival rates and mortality

following the introduction of targeted therapies in Taiwan using an interrupted time series design.

We estimated an ongoing gradual increase in the age-standardized incidence of lung cancer for both men and women in Taiwan. According to our results, the overall incidence of lung cancer in Taiwan (35.4 per 100,000) was lower than that in the United States (38.4) and Canada (37.9) in 2012, but it was higher than that in the United Kingdom (30.0), Australia (27.0), Japan (24.6) and South Korea (28.7).[31] Between 1994 and 2013, the age-standardized rate steadily increased by 42.84% for men and by 89.29% for women, and there was an estimated overall 51.31% growth rate (Table 1). According to these trends, incidence would reach 48.11 per 100,000 for men and 31.57 per 100,000 for women by 2020. Our findings showing these increasing trends are similar to those of previous studies[32,33] investigating earlier trends (up to 2008) in Taiwan. However, decreasing trends for both men and women in other countries have been observed. For example, lung cancer incidence decreased for both men and women in the United States (2004-2009)[34], China (1997-2005 for men and 2001-2005 for women)[35], Hong Kong (1983-2000)[36] and Singapore (1980-2007)[37]. The incidence decreased for men but increased for women in the Czech Republic (1984-1998)[38]. Previous studies have provided evidence of a reduction in the prevalence of smoking following smoking bans.[39-41] Lung cancer in non-smokers can be caused by exposure to radon, secondhand smoke, air pollution, or other factors in addition to workplace exposure to asbestos, diesel exhaust, or specific other chemicals that can also cause lung cancers in some people who don't smoke.[42,43] It is important to identify key drivers (other than smoking) of

these increasing trends in Taiwan.

The incidence of lung cancer in Taiwan has increased over time and the rate of early diagnosis of NSCLC gradually increased, but the ratio was still low (less than 25%) until 2013, and the early diagnosis rate of SCLC has remained very low (less than 5%) without a significant increase. There are almost no symptoms at the initial stage of lung cancer, thus, it is difficult to detect it early.[44] However, the National Lung Screening Trial (NLST)[45] conducted by the National Institutes of Health in the United States found that the use of low-dose computed tomography in high risk groups for lung cancer could detect tumors earlier and reduce mortality by 20%. Hence, the National Comprehensive Cancer Network (NCCN) guideline recommends screening for people who smoke more than one pack of cigarettes a day, have smoked for more than 30 years, have quit smoking for less than 15 years, or are 55-74 years old.[46] The Taiwan Lung Cancer Society followed the NCCN guidelines and announced, in 2015, an expert consensus to further improve the early diagnosis rate. Early diagnosis through lung cancer screening might improve in the upcoming years.

For many years only chemotherapies were available for treatment of lung cancer. Then, the first targeted therapy, gefitinib, was approved for market in 2003, followed by the second targeted therapy, erlotinib, which became available in 2006. Compared with chemotherapies, most clinical trials have shown that when these two targeted drugs were used as the first-line of treatment for advanced NSCLC with EGFR mutations, overall survival did not increase significantly, although progression-free survival increased significantly by 3-8 months.[16,47-50]

We used real-world data to examine changes in lung cancer survival and mortality following the launch of these two targeted therapies in Taiwan. Gefitinib and erlotinib were reimbursed by Taiwan's National Health Insurance soon after marketing approval and their utilization has increased rapidly over time. Our study of gefitinib and erlotinib prescribing trends during 2004-2013[51] found that the number of patients using gefitinib increased from 228 (5.48% of all patients using antineoplastic agents) in 2004 to 5558 (38.08%) in 2013; and the number of patients using erlotinib increased from 499 (8.44%) in 2007 to 2984 (20.44%) in 2013.

Using rigorous research methods, this study found that the 1-year survival rate increased by about 10%, and the 2-year survival rate increased by about 20% in both men and women three years after the first targeted therapy (gefitinib) was launched. However, the subsequent survival rate did not change markedly after the launch of the second targeted therapy (erlotinib) because it is not a so-called "breakthrough innovation," as was the case for the first targeted therapy. Together, findings from our prior and current studies suggest improved lung cancer survival and mortality following the launch of the first two targeted therapies and their increased use in Taiwan.

This study also estimated the age-standardized mortality of lung cancer for both men and women in Taiwan. We found that the overall mortality of lung cancer in Taiwan (25.0 per 100,000) is lower than that in the United States (28.6), Canada (28.4) and the United Kingdom (25.4) in 2012, but it is higher than that in South Korea (21.3), Australia (18.5) and Japan (17.4).[31] The mortality of lung cancer increased from 1994 to 2003 and decreased from

2003 to 2013 in Taiwan. However, it has gradually increased in Japan, has remained steady in Canada and Australia, and has decreased in the United States and the United Kingdom.[51,52]

The present study also found that after the gefitinib's launch, the mortality for both men and women was approximately 5% lower than expected three years following the launch. However, only the mortality for men was 7% lower than expected three years following the launch of the second drug, erlotinib. Before the molecular testing of EGFR was established, the indication of gefitinib was considered mainly by using four factors; adenocarcinoma, non-smoker, Asian and female. It is possible that male patients gained more benefits after the molecular testing become routine practice in the clinic.

There are some limitations to this study. First, targeted therapies are only appropriate for advanced NSCLC patients with EGFR mutation. Advanced NSCLC patients account for about 64% of overall lung cancer patients in Taiwan.[5-8] Among them, approximately 40-50% patients have EGFR mutation. This study found improved lung cancer survival and mortality following the launch of targeted therapies, gefitinib and erlotinib. However, improvements in survival and mortality related to lung cancer may be due to other factors. Other diagnosis and treatment factors, including the availability and use of diagnostic tools (such as molecular testing), earlier diagnosis, treatment sequencing strategies, personalized care, multimodality care, palliative care support, and psychological support have roles in outcome improvements. Other factors, including patient's living habits and the global management of cancer patients, may also contributed the improvement in outcomes. Further studies considering of these factors are needed. Second, pemetrexed, a cytotoxic chemotherapy, has been approved in

Taiwan since 2004. Pemetrexed is indicated for non-squamous NSCLC, broader than EGFR-mutated NSCLC, thus, it could affect the mortality of lung cancer specially after the approval of the platinum-pemetrexed combination therapy in 2008. We did not have data on pemetrexed in this study to examine the survival or mortality of lung cancer in Taiwan following the launch of pemetrexed. However, based on our previous study[53] of prescribing trends of antineoplastic agents in Taiwan, the prescription rate of folic acid analogues (including pemetrexed) during 2009-2012 remained steady (prescription rate from 16.7% to 17.13%; growth rate of market share: 0.43%). Finally, we did not examine survival and mortality by lung cancer sub-types following the launch of targeted therapies. We did not have patient-level data to separate the patients by lung cancer sub-types (NSCLC or SCLC) and disease severity (cancer stages). This study the data from the Taiwan Cancer Registry Database to estimate the two diagnostic indicators of lung cancer (incidences and early diagnosis rates) over time, and to evaluate changes in the two clinical indicators (survival rates and mortality) after the launch of targeted therapies. Notwithstanding these limitations, this study should provide an important basis for additional research.

## Conclusion

In summary, our findings suggest that the incidence of overall lung cancer and NSCLC early diagnosis rate increased in the past and that this trend is likely to continue in the future. Importantly, this study found that the survival rate and mortality of patients with lung cancer improved in Taiwan following the launch of targeted therapies (especially the initial one, gefitinib). However, further research is warranted to determine if these results are applicable

to specific sub-types and stages of lung cancer.

## List of abbreviations

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; ARIMA: Autoregressive Integrated Moving Average; EGFR: epidermal growth factor receptor; MTD: molecular targeted drugs; IRB: Institutional Review Board.

## Author Contributions

JCH, CFW and SCY conceptualized and designed the study. PCL and YCL provided suggestions for the research design from a clinical perspective. CFW collected data, performed the analyses, and drafted the manuscript. JCH reviewed all data and revised the manuscript critically for intellectual content. CYL reviewed all data and revised the manuscript critically for intellectual content. All authors approved the final version for submission.

## Competing Interests

The authors have no competing interests.

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## Data Sharing Statement

The authors obtained nationwide data from 1994-2013 (20 years) related to the lung cancer incidence in Taiwan from the Taiwan Cancer Registry Database, compiled by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan.

## ■ Ethics approval and consent to participate

Use of data from the online Taiwan Cancer Registry Database for research purposes is exempt from review by the Institutional Review Board (IRB) in Taiwan because the data used is public and aggregated population-level information.



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## Figure Legends

Figure 1. Yearly Lung Cancer Survival Rates in Taiwan (1994-2013)

Figure 2. Yearly Lung Cancer Mortality in Taiwan (1994-2013)

**Table 1. 1994-2013 Trends and 2014-2020 Forecast of Incidence of Lung Cancer in Taiwan**

| | Standardized Incidence all (per 100,000) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | All | | | | Male | | | | Female | | | |
| | Actual value | Forecast (ARIMA) | confidence intervals | | Actual value | Forecast (ARIMA) | confidence intervals | | Actual value | Forecast (ARIMA) | confidence intervals | |
| | | | Low 95% | Up 95% | | | Low 95% | Up 95% | | | Low 95% | Up 95% |
| 1994 | 22.53 | NA | | | 30.11 | NA | | | 13.82 | NA | | |
| 1995 | 22.53 | 23.17 | | | 30.08 | 30.81 | | | 14.02 | 14.51 | | |
| 1996 | 25.88 | 23.35 | | | 34.61 | 30.86 | | | 16.84 | 14.98 | | |
| 1997 | 26.64 | 25.72 | | | 35.57 | 34.85 | | | 16.76 | 15.98 | | |
| 1998 | 28.85 | 27.24 | | | 38.49 | 36.23 | | | 18.79 | 17.43 | | |
| 1999 | 30.3 | 29.03 | | | 40.11 | 38.92 | | | 19.61 | 18.51 | | |
| 2000 | 30.74 | 30.7 | | | 41.42 | 40.69 | | | 19.96 | 19.94 | | |
| 2001 | 30.08 | 31.43 | | | 39.86 | 42.04 | | | 19.78 | 20.57 | | |
| 2002 | 30.31 | 31.1 | | | 39.81 | 40.83 | | | 20.47 | 20.62 | | |
| 2003 | 29.47 | 31.07 | | | 39.17 | 40.59 | | | 19.47 | 21.15 | | |
| 2004 | 32.31 | 30.54 | | | 43.36 | 40.02 | | | 21.03 | 21.1 | | |
| 2005 | 32.4 | 32.3 | | | 43.07 | 43.64 | | | 21.49 | 21.23 | | |
| 2006 | 32.51 | 33.2 | | | 42.82 | 43.88 | | | 22.36 | 22.39 | | |
| 2007 | 33.8 | 33.3 | | | 44.38 | 43.63 | | | 23.71 | 23.06 | | |
| 2008 | 33.4 | 34.25 | | | 44.07 | 44.97 | | | 23.21 | 23.94 | | |
| 2009 | 35.88 | 34.34 | | | 46.39 | 44.89 | | | 26.01 | 24.45 | | |
| 2010 | 34.52 | 35.98 | | | 44.98 | 46.89 | | | 24.83 | 25.52 | | |
| 2011 | 34.74 | 35.74 | | | 45.1 | 45.93 | | | 25.63 | 26.56 | | |
| 2012 | 35.37 | 35.5 | | | 44.53 | 45.86 | | | 27.13 | 26.12 | | |
| 2013 | 34.09 | 36.01 | | | 43.01 | 45.38 | | | 26.16 | 27.2 | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 2014 | 35.29 | 32.66 | 37.92 | 43.97 | 40.35 | 47.59 | 27.77 | 25.92 | 29.62 |
| 2015 | 35.76 | 32.54 | 38.98 | 44.63 | 39.82 | 49.45 | 27.94 | 25.91 | 29.97 |
| 2016 | 36.45 | 32.61 | 40.28 | 45.33 | 39.53 | 51.14 | 28.92 | 26.45 | 31.38 |
| 2017 | 37.07 | 32.73 | 41.41 | 46.03 | 39.39 | 52.67 | 29.44 | 26.75 | 32.13 |
| 2018 | 37.71 | 32.92 | 42.5 | 46.72 | 39.34 | 54.11 | 30.22 | 27.25 | 33.18 |
| 2019 | 38.35 | 33.14 | 43.55 | 47.42 | 39.36 | 55.48 | 30.85 | 27.67 | 34.04 |
| 2020 | 38.98 | 33.39 | 44.57 | 48.11 | 39.43 | 56.8 | 31.57 | 28.16 | 34.97 |

1. NSCLC = Non-small cell lung cancer; SCLC = Small cell lung cancer

2. NA = not available

**Table 2. 2004-2013 Trends and 2014-2020 Forecast of Rate of Early Diagnosis of Lung Cancer in Taiwan**

| | Early Diagnosis Stage Rate (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | NSCLC | | | | SCLC | | | |
| | Actual value | Forecast (ARIMA) | confidence intervals | | Actual value | Forecast (ARIMA) | confidence intervals | |
| | | | Low 95% | Up 95% | | | Low 95% | Up 95% |
| 1994 | NA | NA | | | NA | NA | | |
| 1995 | NA | NA | | | NA | NA | | |
| 1996 | NA | NA | | | NA | NA | | |
| 1997 | NA | NA | | | NA | NA | | |
| 1998 | NA | NA | | | NA | NA | | |
| 1999 | NA | NA | | | NA | NA | | |
| 2000 | NA | NA | | | NA | NA | | |
| 2001 | NA | NA | | | NA | NA | | |
| 2002 | NA | NA | | | NA | NA | | |
| 2003 | NA | NA | | | NA | NA | | |
| 2004 | 12.63 | NA | | | 4.78 | NA | | |
| 2005 | 14.27 | 13.9 | | | 5.77 | 4.66 | | |
| 2006 | 14.37 | 15.43 | | | 4.09 | 4.92 | | |
| 2007 | 15.09 | 15.96 | | | 6.26 | 4.99 | | |
| 2008 | 15.66 | 16.51 | | | 3.13 | 4.64 | | |
| 2009 | 18.46 | 17.12 | | | 3.06 | 4.98 | | |
| 2010 | 20.23 | 19.29 | | | 3.91 | 2.9 | | |
| 2011 | 20.51 | 21.35 | | | 3.34 | 3.15 | | |
| 2012 | 23.16 | 22.05 | | | 3.87 | 3.51 | | |
| 2013 | 23.99 | 24.04 | | | 4.1 | 3.33 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 2014 | 25.38 | 23.36 | 27.39 | 3.75 | 1.26 | 6.24 |
| 2015 | 26.61 | 24.13 | 29.09 | 3.78 | 1.14 | 6.41 |
| 2016 | 27.89 | 24.93 | 30.84 | 3.56 | 0.3 | 6.83 |
| 2017 | 29.15 | 25.81 | 32.49 | 3.5 | 0.02 | 6.99 |
| 2018 | 30.42 | 26.72 | 34.11 | 3.34 | NA | 7.22 |
| 2019 | 31.68 | 27.66 | 35.7 | 3.25 | NA | 7.36 |
| 2020 | 32.95 | 28.63 | 37.26 | 3.11 | NA | 7.52 |

1. NSCLC = Non-small cell lung cancer; SCLC = Small cell lung cancer

2. NA = not available

**Table 3. Estimated Changes in Lung Cancer Survival Rates Following the Launch of Targeted Therapies (gefitinib and erlotinib) Using Interrupted Time Series and Segmented Regression Models**

| | | | 1. Effects of gefitinib's launch (2003) | | | | 2. Effects of gefitinib and erlotinib's launch (2006) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Intercept | Baseline trend (95% C.I.) | Level change (95% C.I.) | Trend change (95% C.I.) | Absolute change (3 year later) (95% C.I.) | Relative change (3 year later) (95% C.I.) | Level change (95% C.I.) | Trend change (95% C.I.) | Absolute change (3 year later) (95% C.I.) | Relative change (3 year later) (95% C.I.) |
| 1-year survival rate (all) | 0.3478 | 0.0041 (0.0015, 0.0067) | NS | 0.0135 (0.0096, 0.0174) | 0.0404 (0.0286, 0.0522) | 10.18% (6.77%, 13.59%) | NS | NS | 0 | 0.00% |
| 2-year survival rate (all) | 0.2169 | NS | -0.0138 (-0.0272, -0.0004) | 0.0189 (0.0171, 0.0207) | 0.0430 (0.0331, 0.0528) | 19.81% (14.90%, 24.71%) | NS | NS | 0 | 0.00% |
| 1-year survival rate (male) | 0.3505 | NS | NS | 0.0125 (0.0111, 0.0139) | 0.0375 (0.0333, 0.0417) | 10.70% (9.34%, 12.06%) | NS | NS | 0 | 0.00% |
| 2-year survival rate (male) | 0.2165 | -0.0024 (-0.0046, -0.0001) | -0.0206 (-0.0363, -0.0049) | 0.0158 (0.0130, 0.0186) | 0.0268 (0.0084, 0.0452) | 14.25% (3.27%, 25.24%) | NS | NS | 0 | 0.00% |
| 1-year survival rate (female) | 0.3532 | 0.0110 (0.0071, 0.0149) | -0.0455 (-0.0929, 0.0019) | 0.0392 (0.0213, 0.0571) | 0.0720 (0.0374, 0.1065) | 14.82% (6.92%, 22.71%) | NS | -0.0315 (-0.0513, -0.0117) | -0.0945 (-0.1537, -0.0354) | -13.34% (-20.48%, -6.20%) |
| 2-year survival rate (female) | 0.2174 | 0.0056 (0.0030, 0.0083) | -0.0391 (-0.0795, -0.0013) | 0.0396 (0.0256, 0.0536) | 0.0861 (0.0514, 0.1208) | 31.12% (15.64%, 46.60%) | NS | -0.0227 (-0.0386, -0.0068) | -0.0576 (-0.1170, 0.0019) | -11.77% (-22.36%, -1.18%) |

1. 95% C.I. = 95% confidence intervals = estimate +/- (1.96*standard error); All terms p<0.1 retained in models

2. NS = non-significant

**Table 4. Estimated Changes in Lung Cancer Mortality Following the Launch of Targeted Therapies (gefitinib and erlotinib) Using Interrupted Time Series and Segmented Regression Models**

| | | | 1. Effects of gefitinib's launch (2003) | | | | 2. Effects of gefitinib and erlotinib's launch (2006) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Intercept | Baseline trend (95% C.I.) | Level change (95% C.I.) | Trend change (95% C.I.) | Absolute change (3 years later) (95% C.I.) | Relative change (3 years later) (95% C.I.) | Level change (95% C.I.) | Trend change (95% C.I.) | Absolute change (3 years later) (95% C.I.) | Relative change (3 years later) (95% C.I.) |
| Mortality (all) | 25.75 | 0.26 (0.11, 0.42) | NS | -0.58 (-0.81, -0.34) | -1.73 (-2.43, -1.02) | -5.97% (-8.20%, 3.73%) | NS | NS | 0 | 0.00% |
| Mortality (male) | 34.48 | 0.45 (0.20, 0.70) | -2.15 (-4.11, -0.20) | NS | -2.15 (-4.11, -0.20) | -5.40% (-10.08%, -0.73%) | NS | -0.94 (-1.29, -0.59) | -2.81 (-3.87, -1.76) | -7.20% (-9.69%, -4.71%) |
| Mortality (female) | 15.80 | 0.17 (0.04, 0.30) | NS | -0.26 (-0.46, -0.06) | -0.78 (-1.38, -0.19) | -4.38% (-7.50%, -1.25%) | NS | NS | 0 | 0.00% |

1. 95% C.I. = 95% confidence intervals = estimate +/- (1.96*standard error); All terms p<0.1 retained in models

2. NS = non-significant


Figure 1. Yearly Lung Cancer Survival Rates in Taiwan (1994-2013)

173x119mm (300 x 300 DPI)

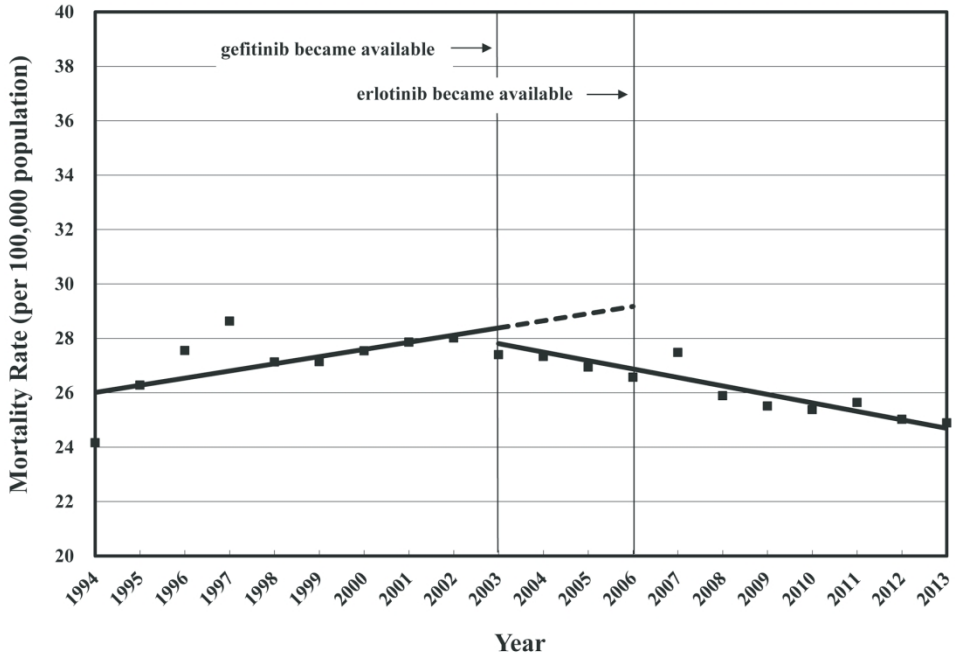


Figure 2. Yearly Lung Cancer Mortality in Taiwan (1994-2013)

173x118mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

| Page | | Item No | Recommendation |
|---|---|---|---|
| 2 | **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract |
| 2-3 | | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| | **Introduction** | | |
| 4-5 | Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported |
| 5 | Objectives | 3 | State specific objectives, including any prespecified hypotheses |
| | **Methods** | | |
| 5-7 | Study design | 4 | Present key elements of study design early in the paper |
| 5-7 | Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| NA | Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants |
| NA | | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case |
| 6-7 | Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| 5-7 | Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| 6 | Bias | 9 | Describe any efforts to address potential sources of bias |
| 5-7 | Study size | 10 | Explain how the study size was arrived at |
| 5-7 | Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| 7-8 | Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding |
| 7-8 | | | (*b*) Describe any methods used to examine subgroups and interactions |
| NA | | | (*c*) Explain how missing data were addressed |
| NA | | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy |
| NA | | | (*e*) Describe any sensitivity analyses |

Continued on next page

| | | | |
|---|---|---|---|
| | **Results** | | |
| NA | Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
| NA | | | (b) Give reasons for non-participation at each stage |
| NA | | | (c) Consider use of a flow diagram |
| 8-9 | Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders |
| NA | | | (b) Indicate number of participants with missing data for each variable of interest |
| NA | | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) |
| 9-10 | Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time |
| NA | | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure |
| 8-10 | | | *Cross-sectional study*—Report numbers of outcome events or summary measures |
| 9-10 | Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
| 9-10 | | | (*b*) Report category boundaries when continuous variables were categorized |
| 9-10 | | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| 8-10 | Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |
| | **Discussion** | | |
| 10-14 | Key results | 18 | Summarise key results with reference to study objectives |
| 14-15 | Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| 10-14 | Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| NA | Generalisability | 21 | Discuss the generalisability (external validity) of the study results |
| | **Other information** | | |
| 16 | Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

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

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

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# Lung Cancer Survival and Mortality in Taiwan following the Initial Launch of Targeted Therapies: An Interrupted Time Series Study

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# Title Page

## Lung Cancer Survival and Mortality in Taiwan following the Initial Launch of Targeted Therapies: An Interrupted Time Series Study

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## Abstract

**Objectives:** Two oral targeted therapies, gefitinib and erlotinib, were firstly approved and then launched into the market for patients with late-stage non-small cell lung cancer (NSCLC) in Taiwan in 2003 and 2006, respectively. The aim of this study was to examine the trends in lung cancer burden and changes in lung cancer-related survival rates and mortality following the launch of these new drugs.

**Setting:** Yearly lung cancer-related data (1994-2013), including incidence, number of early diagnosis case, survival rate and mortality, were retrieved from the Taiwan Cancer Registry Database.

**Design and Outcome Measures:** Using a time series design with autoregressive integrated moving average (ARIMA) model, we investigated and projected trends in the incidence and early diagnosis of lung cancer in Taiwan. We also estimated the changes in survival rates and mortality following the launch of targeted therapies using interrupted time series and segmented regression models.

**Results:** The age-standardized incidence of lung cancer increased from 22.53 per 100,000 people in 1994 to 34.09 in 2013, and it was projected to reach 38.98 by 2020. The rate of early diagnosis of NSCLC increased from 12.63% in 2004 to 23.99% in 2013, and it was projected to reach 32.95% by 2020. The 2-year lung cancer survival increased by 19.81% (95%CI: 14.90%, 24.71%) three years following the launch of gefitinib. Lung cancer mortality declined by 5.97% (95% CI: -8.20%, -3.73%) three years following the launch of gefitinib.

**Conclusions:** Lung cancer survival rate increased and mortality decreased significantly following the launch of gefitinib and erlotinib in Taiwan.

**Keywords:** targeted therapies; lung cancer; incidence; cancer survival; cancer mortality; gefitinib; erlotinib

**Category:** original study

**Running head:** Targeted therapies for lung cancer treatment

**Strengths and limitations of this study**

- This study examined the long-term trends in yearly incidence, the rate of early diagnosis, survival rate, and mortality of lung cancer.
- Long term data from the Taiwan Cancer Registry Database was used in this study.
- A time series design was used to project the incidence and the rate of early diagnosis.
- An interrupted time series design was applied to estimate the changes in survival rates and mortality following the launch of targeted therapies.
- This study did not use patient-level data to separate the patients by lung cancer sub-types and disease severity.

# Manuscript

## Introduction

Lung cancer is the leading cause of cancer deaths worldwide.[1] Globally, around 1.82 million new patients were diagnosed with lung cancer (12.9% of all cancer diagnoses), and around 1.59 million patients died (19.4% of all cancer mortalities) in 2012.[2] The incidence was 23.1 per 100,000 people, and mortality was 19.7 per 100,000 people in 2012[2], which has increased over time.[1–3] In the United States, approximately 214,000 new cases of lung cancer (13.3% of all cancer diagnoses) and 168,000 deaths due to lung cancer (27.2% of all cancer mortalities) were estimated in 2012.[3]

In Taiwan, lung cancer is also one of the most commonly diagnosed cancers as well as the leading cause of cancer deaths. Approximately 12,462 new cases of lung cancer (12.1% of all cancer diagnoses) and 9,167 deaths (19.9% of cancer deaths) were projected to occur in Taiwan in 2014.[4] About 85% of all lung cancers are identified as non-small cell, and approximately 75% of these are metastatic or advanced at diagnosis, for which no curative treatment is available.[5-8] Given most patients are diagnosed with advanced stage diseases, it is considered a terminal illness with a five-year survival rate of less than 15%.[9-11]

Oral targeted therapies for non-small cell lung cancer (NSCLC) were launched into the market for epidermal growth factor receptor (EGFR) mutation patients in Taiwan in 2003 (gefitinib) and in 2006 (erlotinib). These EGFR molecular targeted drugs, gefitinib and erlotinib, were initially approved as third-line or second-line therapy for advanced NSCLC patients because of their therapeutic benefits, as suggested by randomized clinical trials.[12-14]

The recent National Comprehensive Cancer Network guideline[15] recommends gefitinib and erlotinib as the first-line therapy for EGFR mutation-positive, advanced NSCLC patients based on accumulating evidence showing a significant association between mutated EGFR and the clinical benefits of gefitinib and erlotinib.[16-18] In light of rapid disease progression, timely access to pharmaceutical innovations such as targeted therapies is vital to NSCLC patients. The new targeted therapies, gefitinib and erlotinib have been reimbursed by Taiwan's national health insurance since 2004 and 2007, respectively, for NSCLC patients who meet the above requirements based on evidence and clinical need.

Little is known about the effects of the introduction of new targeted therapies in Taiwan. This study is one of the first to address the gap by examining the changes in lung cancer-related survival rates and mortality following the launch of gefitinib and erlotinib.

## Method

### *Data sources*

We obtained data from 1994-2013 related to the lung cancer incidence in Taiwan from the Taiwan Cancer Registry Database, which was compiled by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan.[19] The data include yearly incidence and mortality for various cancer types by age, gender, and administrative division. Survival rates within several years of diagnosis of various cancer types are also available from the database.

Through the routine cancer case notification reminders and collection procedures each

year, the sources of possible cancer cases and the cancer registration declaration database are combined. Health Promotion Administration calculates the completeness of cancer registration declarations in each year, approximately 98.44% in 2016.[20] In addition, in accordance with the practice of the International Agency for Research on Cancer (IARC), Percentage of Death Certificate Only Cases (DCO%) and Percentage of Morphologically Verified Cases (MV%) are used as quality indicators of the reporting data. In 2016, as a result of the data collection and comparison, the DCO% was 0.91%, indicating that the coverage of the registration system was complete and the data quality in the system was consistent. In the same year, the MV% of all cancer cases was 92.23%, that of men was 90.79%, and that of women was 93.89%, indicating that the diagnosis of cancer cases is accurate.[20] Use of this data for research purposes is exempt from review by the Institutional Review Board (IRB) of the National Cheng Kung University Hospital in Taiwan.

***Measurements***

To examine the trends in lung cancer incidence, we collected the yearly number of new patients, crude incidence (per 100,000 people), and age-standardized incidence (per 100,000 people) of lung cancer by gender from 1994 to 2013. The global population in year 2000 was used to calculate the age-standardized incidence.[21] In addition, the yearly total of new lung cancer patients (small cell lung cancer and non-small cell lung cancer) according to diagnostic stages were collected, and we calculated the rates of early diagnosis over time. Diagnostic stages from 0 to 2 were considered as early-stage, and stages 3 and 4 were categorized as late-stage.

To evaluate the impacts of the launch of targeted therapies, 1 year- and 2 year- lung cancer survival rates by gender from 1994-2013 were collected. Furthermore, we collected the yearly number of deaths, the crude mortality (per 100,000 people), and the age-standardized mortality (per 100,000 people) for lung cancer by gender from 1994 to 2013.

***Statistical Analysis***

To assess the yearly changes in lung cancer epidemiology using the age-standardized incidence and early diagnosis rates as defined above, we used a time series design with the autoregressive integrated moving average (ARIMA) model, which was developed by Box and Jenkins.[22] The model is generally referred to as an ARIMA(p,d,q) model, where parameters p, d, and q are non-negative integers that refer to the order of the autoregressive, integrated, and moving average parts of the model, respectively. These models are fitted to time series data either to better understand the data or to determine points in the series.[23] We used the estimated rates from the ARIMA model for time series graphs.

To determine the effects of the launch of new targeted therapies for lung cancer on clinical outcomes, we also estimated the changes in the lung cancer-related 1 year- and 2 year-survival rates and age-standardized mortality following the launches of gefitinib and erlotinib using interrupted time series and segmented regression models, a strong quasi-experimental method.[24-26] The method can provide strong evidence of causal effects because it takes into consideration the question of whether an intervention causes abrupt and measurable interruptions in a preexisting trend.[24,27] We used segmented linear regression

models to estimate effects of the launch of new targeted therapies on changes in the level and trend of both survival rates and age-standardized mortality.[28] The basic model included terms to estimate the baseline level for each outcome (intercept) ($\beta_0$), baseline trend (slope) ($\beta_1$), changes in the level immediately after the drug launch ($\beta_2$), and changes in the trend after the drug launch ($\beta_3$) (see the following model).[24,29]

$$Y_t = \beta_0 + \beta_1 * time_t + \beta_2 * intervention_t + \beta_3 * time\_after\_intervention_{t+} e_t$$ [24]

The models also controlled for autocorrelation.[30] To identify the most parsimonious models, we used backward elimination and excluded non-significant terms (P>0.05).

All analyses were carried out with SAS software, Version 9.4 (SAS Institute, Cary, NC).

### *Patient and Public Involvement*

Patients and the public were not involved in the design or planning of the study.

## Results

Table 1 presents the past trends (1994-2013) and future projections (2014-2020) of the age-standardized incidence of lung cancer by gender in Taiwan. The overall age-standardized incidence of lung cancer increased from 22.53 (per 100,000) in 1994 to 34.09 in 2013, and it was projected to reach 38.98 by 2020 based on the trend during 1994-2013. By gender, the age-standardized incidence for males increased from 30.11 (per 100,000) in 1994 to 43.01 in 2013, and it was projected to reach 48.11 by 2020; the age-standardized incidence for females increased from 13.82 (per 100,000) in 1994 to 26.16 in 2013, and it was projected to reach

31.57 by 2020.

[Table 1]

Table 2 shows the past trends (1994-2013) and future projections (2014-2020) of the rate of the early diagnosis of lung cancer by type of lung cancer in Taiwan. The rate of NSCLC grew rapidly from 12.63% in 2004 to 23.99% in 2013, and it was projected to reach 32.95%, based on the trend during 1994-2013, while the rate of SCLC slightly reduced from 4.78% in 2004 to 4.10% in 2013 and was projected to reach 3.11% by 2020.

[Table 2]

**Effects of the 2003 launch of gefitinib on survival rate**

Table 3 details the parameter estimates from the segmented regression models of changes in the lung cancer survival rate following the launch of targeted therapies. Overall, 1-year and 2-year survival rates increased by 10.18% (95% CI: 6.77%, 13.59%) and 19.81% (95% CI: 14.90%, 24.71%) three years following gefitinib's launch in 2003 (see Figure 1). Among men, 1-year and 2-year survival rates increased by 10.70% (95% CI: 9.34%, 12.06%) and 14.25% (95% CI: 3.27%, 25.24%); and among women, 1-year and 2-year survival rates increased by 14.82% (95% CI: 6.92%, 22.71%) and 31.12% (95% CI: 15.64%, 46.60%).

[Table 3] [Figure 1]

**Effects of the launch of gefitinib and erlotinib on survival rate**

Overall, there were no significant changes in 1-year and 2-year survival rates three years following gefitinib and erlotinib's launch. Figure 1 shows the 1-year and 2-year survival rates

of lung cancer in Taiwan over time. Among men, 1-year and 2-year survival rates did not change; however, 1-year and 2-year survival rates reduced by 13.34% (95% CI: -20.48%, -6.20%) and 11.77% (95% CI: -22.36%, -1.18%) among women.

**Effects of the 2003 launch of gefitinib on mortality**

Table 4 presents the parameter estimates from the segmented regression models of changes in the lung cancer mortality following the launch of targeted therapies. Overall, mortality decreased by 5.97% (95% CI: -8.20%, 3.73%) three years following gefitinib's launch in 2003 (see Figure 2). Among men, mortality reduced by 5.40% (95% CI: -10.08%, -0.73%), and among women, mortality decreased by 4.38% (95% CI: -7.50%, -1.25%).

[Table 4] [Figure 2]

**Effects of the launch of gefitinib and erlotinib (2006) on mortality**

Overall, there were no significant changes in lung cancer mortality three years following the launch of gefitinib and erlotinib in 2006. Figure 2 shows the overall lung cancer mortality in Taiwan over time. Among men, mortality reduced by 7.20% (95% CI: -9.69%, -4.71%) but mortality did not change significantly for women.

[Figure 2]

## Discussion

This study projected 7 years (2014-2020) lung cancer incidence in Taiwan based on the observed incidence from 1994 to 2013 (20 years). We also projected rates of early diagnosis of cancer for 2014 through 2020 based on the past trends. Furthermore, the present study is the first study to examine the national trend in lung cancer survival rates and mortality

following the introduction of targeted therapies in Taiwan using an interrupted time series design.

We estimated an ongoing gradual increase in the age-standardized incidence of lung cancer for both men and women in Taiwan. According to our results, the overall incidence of lung cancer in Taiwan (35.4 per 100,000) was lower than that in the United States (38.4) and Canada (37.9) in 2012, but it was higher than that in the United Kingdom (30.0), Australia (27.0), Japan (24.6) and South Korea (28.7).[31] Between 1994 and 2013, the age-standardized rate steadily increased by 42.84% for men and by 89.29% for women, and there was an estimated overall 51.31% growth rate (Table 1). According to these trends, incidence would reach 48.11 per 100,000 for men and 31.57 per 100,000 for women by 2020. Our findings showing these increasing trends are similar to those of previous studies[32,33] investigating earlier trends (up to 2008) in Taiwan. However, decreasing trends for both men and women in other countries have been observed. For example, lung cancer incidence decreased for both men and women in the United States (2004-2009)[34], China (1997-2005 for men and 2001-2005 for women)[35], Hong Kong (1983-2000)[36] and Singapore (1980-2007)[37]. The incidence decreased for men but increased for women in the Czech Republic (1984-1998)[38]. Previous studies have provided evidence of a reduction in the prevalence of smoking following smoking bans.[39-41] Lung cancer in non-smokers can be caused by exposure to radon, secondhand smoke, air pollution, or other factors in addition to workplace exposure to asbestos, diesel exhaust, or specific other chemicals that can also cause lung cancers in some people who don't smoke.[42,43] It is important to identify key drivers (other than smoking) of

these increasing trends in Taiwan.

The incidence of lung cancer in Taiwan has increased over time and the rate of early diagnosis of NSCLC gradually increased, but the ratio was still low (less than 25%) until 2013, and the early diagnosis rate of SCLC has remained very low (less than 5%) without a significant increase. There are almost no symptoms at the initial stage of lung cancer, thus, it is difficult to detect it early.[44] However, the National Lung Screening Trial (NLST)[45] conducted by the National Institutes of Health in the United States found that the use of low-dose computed tomography in high risk groups for lung cancer could detect tumors earlier and reduce mortality by 20%. Hence, the National Comprehensive Cancer Network (NCCN) guideline recommends screening for people who smoke more than one pack of cigarettes a day, have smoked for more than 30 years, have quit smoking for less than 15 years, or are 55-74 years old.[46] The Taiwan Lung Cancer Society followed the NCCN guidelines and announced, in 2015, an expert consensus to further improve the early diagnosis rate. Early diagnosis through lung cancer screening might improve in the upcoming years.

For many years only chemotherapies were available for treatment of lung cancer. Then, the first targeted therapy, gefitinib, was approved for market in 2003, followed by the second targeted therapy, erlotinib, which became available in 2006. Compared with chemotherapies, most clinical trials have shown that when these two targeted drugs were used as the first-line of treatment for advanced NSCLC with EGFR mutations, overall survival did not increase significantly, although progression-free survival increased significantly by 3-8 months.[16,47-50]

We used real-world data to examine changes in lung cancer survival and mortality following the launch of these two targeted therapies in Taiwan. Gefitinib and erlotinib were reimbursed by Taiwan's National Health Insurance soon after marketing approval and their utilization has increased rapidly over time. Our study of gefitinib and erlotinib prescribing trends during 2004-2013[51] found that the number of patients using gefitinib increased from 228 (5.48% of all patients using antineoplastic agents) in 2004 to 5558 (38.08%) in 2013; and the number of patients using erlotinib increased from 499 (8.44%) in 2007 to 2984 (20.44%) in 2013. Using rigorous research methods, the current study found that the 1-year survival rate increased by about 10%, and the 2-year survival rate increased by about 20% in both men and women three years after the first targeted therapy (gefitinib) was launched. However, the subsequent survival rate did not change markedly after the launch of the second targeted therapy (erlotinib) because it is not a so-called "breakthrough innovation," as was the case for the first targeted therapy. Together, findings from our prior and current studies suggest improved lung cancer survival and mortality following the launch of the first two targeted therapies and their increased use in Taiwan.

This study also estimated the age-standardized mortality of lung cancer for both men and women in Taiwan. We found that the overall mortality of lung cancer in Taiwan (25.0 per 100,000) is lower than that in the United States (28.6), Canada (28.4) and the United Kingdom (25.4) in 2012, but it is higher than that in South Korea (21.3), Australia (18.5) and Japan (17.4).[31] The mortality of lung cancer increased from 1994 to 2003 and decreased from 2003 to 2013 in Taiwan. However, it has gradually increased in Japan, has remained steady in

Canada and Australia, and has decreased in the United States and the United Kingdom.[51,52]

The present study also found that mortality for both men and women was approximately 5% lower than expected three years following the launch of gefitinib. However, mortality for men was 7% lower than expected three years following the launch of the second drug, erlotinib without changes in mortality detected for women. Before the molecular testing of EGFR was established, the indication of gefitinib was considered mainly by using four factors: adenocarcinoma, non-smoker, Asian and female. It is possible that male patients gained more benefits after the molecular testing become routine practice in the clinic.

There are some limitations to this study. First, targeted therapies are only appropriate for advanced NSCLC patients with EGFR mutation. Advanced NSCLC patients account for about 64% of overall lung cancer patients in Taiwan.[5-8] Among them, approximately 40-50% patients have EGFR mutation. This study found improved lung cancer survival and mortality following the launch of targeted therapies, gefitinib and erlotinib. However, improvements in survival and mortality related to lung cancer may be due to other factors. Other diagnosis and treatment factors, including the availability and use of diagnostic tools (such as molecular testing), earlier diagnosis, treatment sequencing strategies, personalized care, multimodality care, palliative care support, and psychological support have roles in outcome improvements. Other factors, including patient's living habits and the global management of cancer patients, may also contributed the improvement in outcomes. Further studies considering of these factors are needed. Second, pemetrexed, a cytotoxic chemotherapy, has been approved in Taiwan since 2004. Pemetrexed is indicated for non-squamous NSCLC, broader than

EGFR-mutated NSCLC, thus, it could affect the mortality of lung cancer specially after the approval of the platinum-pemetrexed combination therapy in 2008. We did not have data on pemetrexed in this study to examine the survival or mortality of lung cancer in Taiwan following the launch of pemetrexed. However, based on our previous study[53] of prescribing trends of antineoplastic agents in Taiwan, the prescription rate of folic acid analogues (including pemetrexed) during 2009-2012 remained steady (prescription rate from 16.7% to 17.13%; growth rate of market share: 0.43%). Finally, we did not examine survival and mortality by lung cancer sub-types following the launch of targeted therapies. We did not have patient-level data to separate patients by lung cancer sub-types (NSCLC or SCLC) and disease severity (cancer stages). This study used data from the Taiwan Cancer Registry Database to estimate the two diagnostic indicators of lung cancer (incidences and early diagnosis rates) over time, and to evaluate changes in the two clinical indicators (survival rates and mortality) after the launch of targeted therapies. Notwithstanding these limitations, this study should provide an important basis for additional research.

## Conclusion

In summary, our findings suggest that the incidence of overall lung cancer and NSCLC early diagnosis rate increased in the past and that this trend is likely to continue in the future. Importantly, this study found that the survival rate and mortality of patients with lung cancer improved in Taiwan following the launch of targeted therapies (especially the initial one, gefitinib). However, further research is warranted to determine if these results are applicable to specific sub-types and stages of lung cancer.

## List of abbreviations

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; ARIMA: Autoregressive Integrated Moving Average; EGFR: epidermal growth factor receptor; MTD: molecular targeted drugs; IRB: Institutional Review Board.

## Author Contributions

JCH, CFW and SCY conceptualized and designed the study. PCL and YCL provided suggestions for the research design from a clinical perspective. CFW collected data, performed the analyses, and drafted the manuscript. JCH reviewed all data and revised the manuscript critically for intellectual content. CYL reviewed all data and revised the manuscript critically for intellectual content. All authors approved the final version for submission.

## Competing Interests

The authors have no competing interests.

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## Data Sharing Statement

The authors obtained nationwide data from 1994-2013 (20 years) related to the lung cancer

incidence in Taiwan from the Taiwan Cancer Registry Database, compiled by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan.

## ■ Ethics approval and consent to participate

Use of data from the online Taiwan Cancer Registry Database for research purposes is exempt from review by the Institutional Review Board (IRB) in Taiwan because the data used is public and aggregated population-level information.



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## Figure Legends

Figure 1. Yearly Lung Cancer Survival Rates in Taiwan (1994-2013)

Figure 2. Yearly Lung Cancer Mortality in Taiwan (1994-2013)

**Table 1. 1994-2013 Trends and 2014-2020 Forecast of Incidence of Lung Cancer in Taiwan**

| | Standardized Incidence all (per 100,000) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | All | | | | Male | | | | Female | | | |
| | Actual value | Forecast (ARIMA) | confidence intervals | | Actual value | Forecast (ARIMA) | confidence intervals | | Actual value | Forecast (ARIMA) | confidence intervals | |
| | | | Low 95% | Up 95% | | | Low 95% | Up 95% | | | Low 95% | Up 95% |
| 1994 | 22.53 | NA | | | 30.11 | NA | | | 13.82 | NA | | |
| 1995 | 22.53 | 23.17 | | | 30.08 | 30.81 | | | 14.02 | 14.51 | | |
| 1996 | 25.88 | 23.35 | | | 34.61 | 30.86 | | | 16.84 | 14.98 | | |
| 1997 | 26.64 | 25.72 | | | 35.57 | 34.85 | | | 16.76 | 15.98 | | |
| 1998 | 28.85 | 27.24 | | | 38.49 | 36.23 | | | 18.79 | 17.43 | | |
| 1999 | 30.3 | 29.03 | | | 40.11 | 38.92 | | | 19.61 | 18.51 | | |
| 2000 | 30.74 | 30.7 | | | 41.42 | 40.69 | | | 19.96 | 19.94 | | |
| 2001 | 30.08 | 31.43 | | | 39.86 | 42.04 | | | 19.78 | 20.57 | | |
| 2002 | 30.31 | 31.1 | | | 39.81 | 40.83 | | | 20.47 | 20.62 | | |
| 2003 | 29.47 | 31.07 | | | 39.17 | 40.59 | | | 19.47 | 21.15 | | |
| 2004 | 32.31 | 30.54 | | | 43.36 | 40.02 | | | 21.03 | 21.1 | | |
| 2005 | 32.4 | 32.3 | | | 43.07 | 43.64 | | | 21.49 | 21.23 | | |
| 2006 | 32.51 | 33.2 | | | 42.82 | 43.88 | | | 22.36 | 22.39 | | |
| 2007 | 33.8 | 33.3 | | | 44.38 | 43.63 | | | 23.71 | 23.06 | | |
| 2008 | 33.4 | 34.25 | | | 44.07 | 44.97 | | | 23.21 | 23.94 | | |
| 2009 | 35.88 | 34.34 | | | 46.39 | 44.89 | | | 26.01 | 24.45 | | |
| 2010 | 34.52 | 35.98 | | | 44.98 | 46.89 | | | 24.83 | 25.52 | | |
| 2011 | 34.74 | 35.74 | | | 45.1 | 45.93 | | | 25.63 | 26.56 | | |
| 2012 | 35.37 | 35.5 | | | 44.53 | 45.86 | | | 27.13 | 26.12 | | |
| 2013 | 34.09 | 36.01 | | | 43.01 | 45.38 | | | 26.16 | 27.2 | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 2014 | 35.29 | 32.66 | 37.92 | 43.97 | 40.35 | 47.59 | 27.77 | 25.92 | 29.62 |
| 2015 | 35.76 | 32.54 | 38.98 | 44.63 | 39.82 | 49.45 | 27.94 | 25.91 | 29.97 |
| 2016 | 36.45 | 32.61 | 40.28 | 45.33 | 39.53 | 51.14 | 28.92 | 26.45 | 31.38 |
| 2017 | 37.07 | 32.73 | 41.41 | 46.03 | 39.39 | 52.67 | 29.44 | 26.75 | 32.13 |
| 2018 | 37.71 | 32.92 | 42.5 | 46.72 | 39.34 | 54.11 | 30.22 | 27.25 | 33.18 |
| 2019 | 38.35 | 33.14 | 43.55 | 47.42 | 39.36 | 55.48 | 30.85 | 27.67 | 34.04 |
| 2020 | 38.98 | 33.39 | 44.57 | 48.11 | 39.43 | 56.8 | 31.57 | 28.16 | 34.97 |

1. NSCLC = Non-small cell lung cancer; SCLC = Small cell lung cancer

2. NA = not available

**Table 2. 2004-2013 Trends and 2014-2020 Forecast of Rate of Early Diagnosis of Lung Cancer in Taiwan**

| | Early Diagnosis Stage Rate (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | NSCLC | | | | SCLC | | | |
| | Actual value | Forecast (ARIMA) | confidence intervals | | Actual value | Forecast (ARIMA) | confidence intervals | |
| | | | Low 95% | Up 95% | | | Low 95% | Up 95% |
| 1994 | NA | NA | | | NA | NA | | |
| 1995 | NA | NA | | | NA | NA | | |
| 1996 | NA | NA | | | NA | NA | | |
| 1997 | NA | NA | | | NA | NA | | |
| 1998 | NA | NA | | | NA | NA | | |
| 1999 | NA | NA | | | NA | NA | | |
| 2000 | NA | NA | | | NA | NA | | |
| 2001 | NA | NA | | | NA | NA | | |
| 2002 | NA | NA | | | NA | NA | | |
| 2003 | NA | NA | | | NA | NA | | |
| 2004 | 12.63 | NA | | | 4.78 | NA | | |
| 2005 | 14.27 | 13.9 | | | 5.77 | 4.66 | | |
| 2006 | 14.37 | 15.43 | | | 4.09 | 4.92 | | |
| 2007 | 15.09 | 15.96 | | | 6.26 | 4.99 | | |
| 2008 | 15.66 | 16.51 | | | 3.13 | 4.64 | | |
| 2009 | 18.46 | 17.12 | | | 3.06 | 4.98 | | |
| 2010 | 20.23 | 19.29 | | | 3.91 | 2.9 | | |
| 2011 | 20.51 | 21.35 | | | 3.34 | 3.15 | | |
| 2012 | 23.16 | 22.05 | | | 3.87 | 3.51 | | |
| 2013 | 23.99 | 24.04 | | | 4.1 | 3.33 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 2014 | 25.38 | 23.36 | 27.39 | 3.75 | 1.26 | 6.24 |
| 2015 | 26.61 | 24.13 | 29.09 | 3.78 | 1.14 | 6.41 |
| 2016 | 27.89 | 24.93 | 30.84 | 3.56 | 0.3 | 6.83 |
| 2017 | 29.15 | 25.81 | 32.49 | 3.5 | 0.02 | 6.99 |
| 2018 | 30.42 | 26.72 | 34.11 | 3.34 | NA | 7.22 |
| 2019 | 31.68 | 27.66 | 35.7 | 3.25 | NA | 7.36 |
| 2020 | 32.95 | 28.63 | 37.26 | 3.11 | NA | 7.52 |

1. NSCLC = Non-small cell lung cancer; SCLC = Small cell lung cancer

2. NA = not available

**Table 3. Estimated Changes in Lung Cancer Survival Rates Following the Launch of Targeted Therapies (gefitinib and erlotinib) Using Interrupted Time Series and Segmented Regression Models**

| | | | 1. Effects of gefitinib's launch (2003) | | | | 2. Effects of gefitinib and erlotinib's launch (2006) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Intercept | Baseline trend (95% C.I.) | Level change (95% C.I.) | Trend change (95% C.I.) | Absolute change (3 year later) (95% C.I.) | Relative change (3 year later) (95% C.I.) | Level change (95% C.I.) | Trend change (95% C.I.) | Absolute change (3 year later) (95% C.I.) | Relative change (3 year later) (95% C.I.) |
| 1-year survival rate (all) | 0.3478 | 0.0041 (0.0015, 0.0067) | NS | 0.0135 (0.0096, 0.0174) | 0.0404 (0.0286, 0.0522) | 10.18% (6.77%, 13.59%) | NS | NS | 0 | 0.00% |
| 2-year survival rate (all) | 0.2169 | NS | -0.0138 (-0.0272, -0.0004) | 0.0189 (0.0171, 0.0207) | 0.0430 (0.0331, 0.0528) | 19.81% (14.90%, 24.71%) | NS | NS | 0 | 0.00% |
| 1-year survival rate (male) | 0.3505 | NS | NS | 0.0125 (0.0111, 0.0139) | 0.0375 (0.0333, 0.0417) | 10.70% (9.34%, 12.06%) | NS | NS | 0 | 0.00% |
| 2-year survival rate (male) | 0.2165 | -0.0024 (-0.0046, -0.0001) | -0.0206 (-0.0363, -0.0049) | 0.0158 (0.0130, 0.0186) | 0.0268 (0.0084, 0.0452) | 14.25% (3.27%, 25.24%) | NS | NS | 0 | 0.00% |
| 1-year survival rate (female) | 0.3532 | 0.0110 (0.0071, 0.0149) | -0.0455 (-0.0929, 0.0019) | 0.0392 (0.0213, 0.0571) | 0.0720 (0.0374, 0.1065) | 14.82% (6.92%, 22.71%) | NS | -0.0315 (-0.0513, -0.0117) | -0.0945 (-0.1537, -0.0354) | -13.34% (-20.48%, -6.20%) |
| 2-year survival rate (female) | 0.2174 | 0.0056 (0.0030, 0.0083) | -0.0391 (-0.0795, -0.0013) | 0.0396 (0.0256, 0.0536) | 0.0861 (0.0514, 0.1208) | 31.12% (15.64%, 46.60%) | NS | -0.0227 (-0.0386, -0.0068) | -0.0576 (-0.1170, 0.0019) | -11.77% (-22.36%, -1.18%) |

1. 95% C.I. = 95% confidence intervals = estimate +/- (1.96*standard error); All terms p<0.1 retained in models

2. NS = non-significant

**Table 4. Estimated Changes in Lung Cancer Mortality Following the Launch of Targeted Therapies (gefitinib and erlotinib) Using Interrupted Time Series and Segmented Regression Models**

| | | | 1. Effects of gefitinib's launch (2003) | | | | 2. Effects of gefitinib and erlotinib's launch (2006) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Intercept | Baseline trend (95% C.I.) | Level change (95% C.I.) | Trend change (95% C.I.) | Absolute change (3 years later) (95% C.I.) | Relative change (3 years later) (95% C.I.) | Level change (95% C.I.) | Trend change (95% C.I.) | Absolute change (3 years later) (95% C.I.) | Relative change (3 years later) (95% C.I.) |
| Mortality (all) | 25.75 | 0.26 (0.11, 0.42) | NS | -0.58 (-0.81, -0.34) | -1.73 (-2.43, -1.02) | -5.97% (-8.20%, 3.73%) | NS | NS | 0 | 0.00% |
| Mortality (male) | 34.48 | 0.45 (0.20, 0.70) | -2.15 (-4.11, -0.20) | NS | -2.15 (-4.11, -0.20) | -5.40% (-10.08%, -0.73%) | NS | -0.94 (-1.29, -0.59) | -2.81 (-3.87, -1.76) | -7.20% (-9.69%, -4.71%) |
| Mortality (female) | 15.80 | 0.17 (0.04, 0.30) | NS | -0.26 (-0.46, -0.06) | -0.78 (-1.38, -0.19) | -4.38% (-7.50%, -1.25%) | NS | NS | 0 | 0.00% |

1. 95% C.I. = 95% confidence intervals = estimate +/- (1.96*standard error); All terms p<0.1 retained in models

2. NS = non-significant

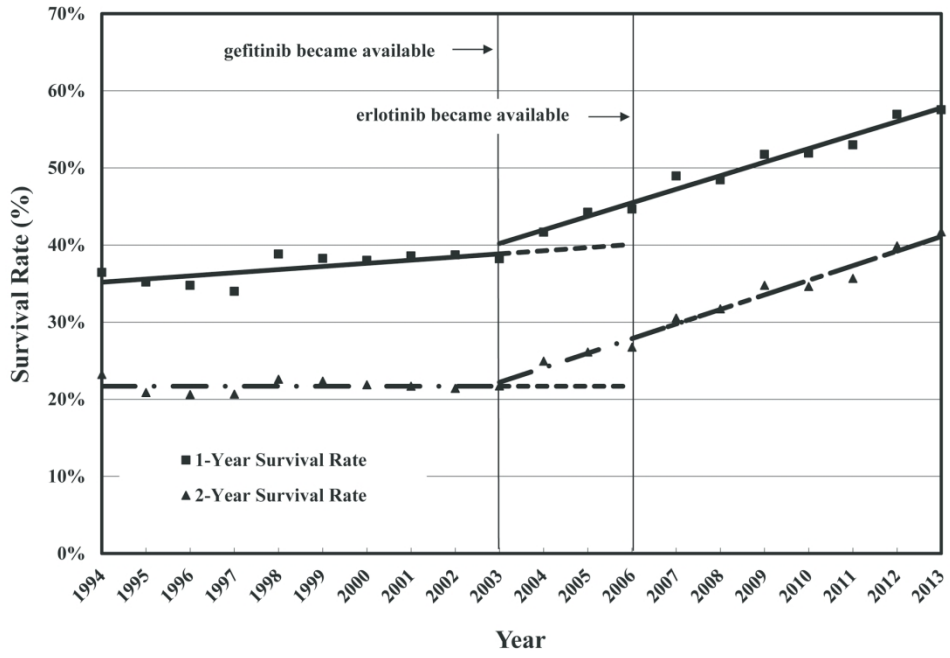


Figure 1. Yearly Lung Cancer Survival Rates in Taiwan (1994-2013)

173x120mm (300 x 300 DPI)

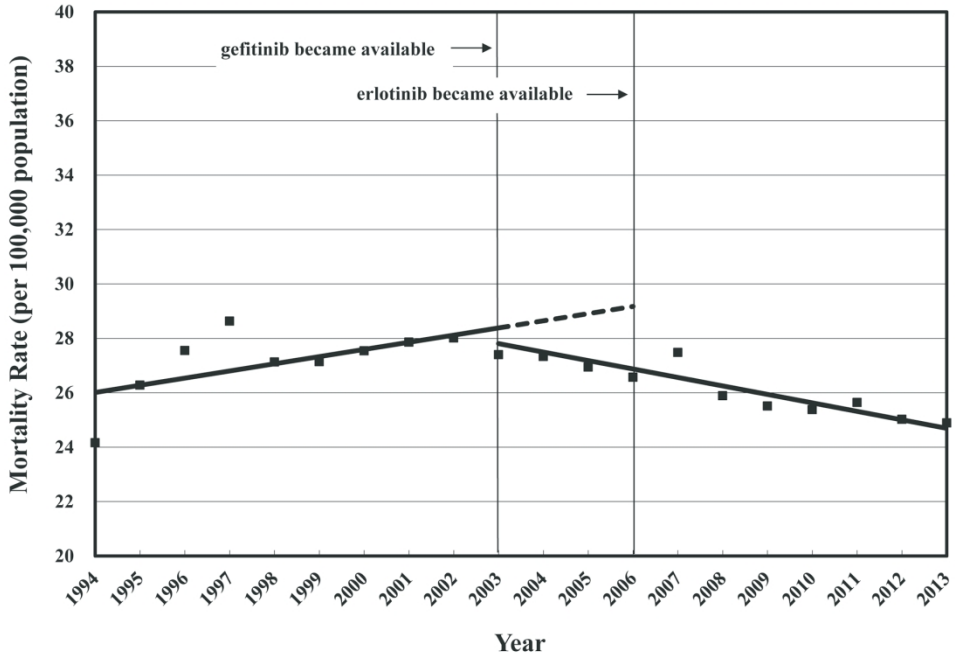


Figure 2. Yearly Lung Cancer Mortality in Taiwan (1994-2013)

173x118mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

| Page | | Item No | Recommendation |
|---|---|---|---|
| 2 | **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract |
| 2-3 | | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| | **Introduction** | | |
| 4-5 | Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported |
| 5 | Objectives | 3 | State specific objectives, including any prespecified hypotheses |
| | **Methods** | | |
| 5-7 | Study design | 4 | Present key elements of study design early in the paper |
| 5-7 | Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| NA | Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants |
| NA | | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case |
| 6-7 | Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| 5-7 | Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| 6 | Bias | 9 | Describe any efforts to address potential sources of bias |
| 5-7 | Study size | 10 | Explain how the study size was arrived at |
| 5-7 | Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| 7-8 | Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding |
| 7-8 | | | (*b*) Describe any methods used to examine subgroups and interactions |
| NA | | | (*c*) Explain how missing data were addressed |
| NA | | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy |
| NA | | | (*e*) Describe any sensitivity analyses |

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| | **Results** | | |
| NA | Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
| NA | | | (b) Give reasons for non-participation at each stage |
| NA | | | (c) Consider use of a flow diagram |
| 8-9 | Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders |
| NA | | | (b) Indicate number of participants with missing data for each variable of interest |
| NA | | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) |
| 9-10 | Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time |
| NA | | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure |
| 8-10 | | | *Cross-sectional study*—Report numbers of outcome events or summary measures |
| 9-10 | Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
| 9-10 | | | (*b*) Report category boundaries when continuous variables were categorized |
| 9-10 | | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| 8-10 | Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |
| | **Discussion** | | |
| 10-14 | Key results | 18 | Summarise key results with reference to study objectives |
| 14-15 | Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| 10-14 | Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| NA | Generalisability | 21 | Discuss the generalisability (external validity) of the study results |
| | **Other information** | | |
| 16 | Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

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

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