A Bayesian Model for Age, Period, and Cohort Effects on Mortality Trends for Lung Cancer, in Association with Gender-Specific Incidence and Case–Fatality Rates

Chun-Ru Chien, MD, PhD,* and Tony Hsui-Hsi Chen, PhD†

Introduction: To study time trends in lung cancer mortality by separating the incidence and case–fatality rates, in association with age, period, and cohort effects.

Methods: Lung cancer cases ($n = 44,139$) diagnosed between 1996 and 2002 in Taiwan were analyzed by decomposing the time trend in mortality into incidence and case–fatality rates. Descriptive data, together with periodical treatment distribution (surgery, chemotherapy, and others) were analyzed using a Bayesian age, period, and cohort (BAPC) model.

Results: Midterm mortality (2-year age-adjusted standardized mortality rate) has been decreasing for male lung cancer patients since about 2000, mainly because of a decrease in incidence during this period. For women, 2-year age-adjusted standardized mortality rate has been slightly increasing, mainly as a result of increasing incidence. There were small improvements (3–6%) in the short-term (1-year) case–fatality rate, possibly owing to increased utilization (15–18%) of chemotherapy. The midterm (2-year) case–fatality rate remained roughly the same, especially for men.

Conclusions: Using a new BAPC model, we found that the trends in mortality for lung cancer paralleled the changes in incidence, with opposite effects in men and women. Increased utilization of chemotherapy might have partly accounted for the small improvement in the case–fatality rate. The contributions of other unmeasured factors such as staging and histologic distribution remain to be clarified in future studies.

Key Words: Bayes Theorem, Lung Neoplasms, Treatment Utilization, Trends.

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ORIGINAL ARTICLE

Although time trends in lung cancer incidence and mortality have been studied previously,1–4 it is of interest to study these in a country such as Taiwan, with a low but rapidly increasing incidence rate for lung cancer. Lung cancer is the leading cancer in Taiwan1,2,4,5 and accounts for 19.6% of deaths from cancer, with the highest increase in mortality for both men and women worldwide.1–3,5

The advent of new treatments may contribute to the time trends in case–fatality rates, which in turn affect mortality. Although trend analyses of cancer incidence and mortality have been conducted based on cancer registry data, these analyses did not include etiological factors, and few studies have separated the time trend in case–fatality rates from that in the incidence by using a classic age–period–cohort (APC) analysis. The APC model is a Poisson regression model, in which the number of events (incidence or death) is analyzed according to age at each event (age), year of the event (period), and year of birth (cohort). The age effect accounts for the duration of the exposure to risk factors. The period effect represents factors that have an impact on all individuals at the same time, regardless of age. The cohort effect corresponds to an exposure that is specific to each generation.6,7

In this study, we developed a Bayesian APC (BAPC) effect model to study time trends in lung cancer incidence and mortality in Taiwan. The case–fatality time trend was separated from the time trend for incidence, to assess the influence of the contemporaneous trends of treatment utilization and treatment-specific mortality on the time trend in the case–fatality rate.

MATERIALS AND METHODS

Data Sources

Information on all newly diagnosed cases of lung cancer in Taiwan between 1979 and 2002 ($n = 91,811$) was taken from the Cancer Registry of the Bureau of Health, Department of Health, Taiwan. The median age at diagnosis was 66 (SD = 3.3) years. The male to female ratio was 2.44 (65,110/26,701). Lung cancer in this study was defined according to ICD code 162. Information on death (all-cause mortality) was obtained by linking these incident cases of lung cancer with the national mortality registry until the end of December 2004. The denominator of population size used to calculate the number of person-years during the contemporaneous period was obtained from the Ministry of the...
The Cancer and Death Registries were missing up to 20% of the data before 1985, but percentage has been gradually reduced to <0.1% since 1996; therefore, only data from 1996 to 2002 (n = 44,139) were included in the analysis of age at diagnosis between 20 and 89 years old.

The initial treatment was also recorded in the Cancer Registry. The percentage of missing data decreased gradually and was <5% after 1996. The treatments were classified as surgery (with/without other treatment), chemotherapy (without surgery, with/without other treatment), and other (modified from Ref. 9), and treatment-specific 1- and 2-year case-fatality rates were calculated. Staging information was not available in the National Cancer Registry by the end of 2007 and was therefore not included in our analysis. Tumor grading was also not included, as its prognostic significance was still elusive.10 Other clinical characteristics of these 44,139 patients are listed in Table 1.

### Relationships Between Incidence, Case–Fatality, and Mortality

The mortality rate in an underlying population is a function of the incidence and case–fatality rate, and thus the 1- or 2-year mortality rate was approximately decomposed by applying the following formula:

\[
\text{Mortality Rate} = \frac{\text{Incidence Rate (incident cases/person-years)}}{\text{t-year Case–Fatality Rate}}
\]

\[
= \frac{\text{(number of deaths/number of incident cases)}}{t}\text{-year Case–Fatality Rate}
\]

where \( t \)-year is 1- or 2-year. Note that the rare disease assumption was applied to the incidence and mortality rates.

### Statistical Analysis

We divided the observed cases into seven 1-year periods, between 1996 and 2002. Given that lung cancer is uncommon in younger populations and is not usually actively treated in elderly patients, 70 age bands between 20 and 89 years and 76 cohorts (first cohort born in 1908, 76th cohort born in 1983) were included in the model.

We used data from the seven periods to estimate crude age- and gender-specific incidence rates, as well as the age-adjusted standardized incidence rate (ASIR) and age-adjusted standardized mortality rate (ASMR). The 1-year mortality (death within 1 year after diagnosis) and 2-year mortality (death within 2 years after diagnosis) were predicted for comparison with the corresponding observed rates. The ASIR and ASMR were calculated using the 2002 population as a reference. The case–fatality rate was calculated as in the abovementioned formula.

We assumed that the number of incident cases or deaths in each age/period group followed a Poisson distribution with the rare disease assumption, which was appropriate in our study because the highest incidence was 0.5% (31/65640). A BAPC model with logarithm transformation was used to model the expected number of outcomes, including incidence and 1- and 2-year mortality, as a function of age, period, and cohort effects. The model form was as follows:

\[
\text{Events}(i) \sim \text{Poisson}(\mu(i))
\]

\[
\log(\mu(i)) = \log(\text{person-year}(i)) + \alpha_{\text{age}(i)} + \beta_{\text{period}(i)} + \gamma_{\text{cohort}(i)} + \text{Interaction}
\]

Log (person-year) is often called offset. In addition to age \((\alpha)\), the effects of period and cohort \((\beta\) and \(\gamma)\) were explicitly explained by the regression coefficients. For example, in the incidence model for 45-year-old men diagnosed in 1998, the median period and cohort coefficients were \(-0.038\) and \(0.07041\), respectively, reflecting the magnitudes of the effects of the period 1998 and the cohort born in 1953. We used the method proposed by Albert in 199611 for model selection of the interaction terms between 2 of the 3 components: age, period, and cohort effects. Although our model can be adapted to study the interactions among age, period, and cohort effects, we expected that the interaction between the age and period effects would be more significant than other interactions. Regarding the parameters for estimation, for the model without interaction, there were 153 parameters (70 for age, 7 for period, and 76 for cohort). For the final model in our analysis (with an age–period interaction), an additional 490 parameters \((70 \times 7\) were added, for a total of 643 parameters. A Gaussian autoregressive prior model was used to smooth the age, period, and cohort effects and to extrapolate the period and cohort effects from their second autoregressive order.

The program was implemented with WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) using Markov Chain Monte Carlo methods. Posterior distributions, from which we drew inferences on incidence/mortality and case–fatality rates, were generated from 5000 iterations, after discarding 500 burn-in iterations. We defined the median iterative value as an overall summary and defined the 95% credibility intervals (CI) using 2.5 and 97.5 percentiles of the 5000 iterated results. The program is available from the authors (Chen or Chien) upon request.

### RESULTS

#### Model Selection

Incidence was modeled as the outcome of interest for men, and the model with an age–period interaction was

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### TABLE 1. Clinical Characteristics of the Study Population (n = 44,139) by Calendar Year

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<tbody>
<tr>
<td>Number of cases</td>
<td>5,180</td>
<td>5,471</td>
<td>6,094</td>
<td>6,626</td>
<td>6,897</td>
<td>6,853</td>
<td>7,018</td>
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<tr>
<td>Median age (years)</td>
<td>68</td>
<td>68</td>
<td>69</td>
<td>69</td>
<td>70</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>71</td>
<td>70</td>
<td>70</td>
<td>69</td>
<td>70</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>Histology (% adenocarcinoma)</td>
<td>34</td>
<td>36</td>
<td>39</td>
<td>39</td>
<td>42</td>
<td>44</td>
<td>43</td>
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<tr>
<td>Surgery (%)</td>
<td>16</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>18</td>
<td>19</td>
<td>17</td>
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<tr>
<td>Chemotherapy (%)</td>
<td>20</td>
<td>22</td>
<td>29</td>
<td>29</td>
<td>35</td>
<td>35</td>
<td>38</td>
</tr>
<tr>
<td>Radiotherapy (%)</td>
<td>32</td>
<td>31</td>
<td>26</td>
<td>23</td>
<td>26</td>
<td>26</td>
<td>26</td>
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*Percentage receiving surgery, chemotherapy, or radiotherapy as part of their initial treatment.*

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statistically more significant than that in the absence of this interaction. Similarly, the age-period interaction was significant in the models of incidence and 1- and 2-year mortality in women. Accordingly, our subsequent estimations were based on models that included an age-period interaction.

**Gender- and Age-Specific Rates**

Figures 1–3 (A, men; B, women) show the observed (A) and estimated (E) gender-specific curves for incidence (ASIR) and 1- and 2-year mortality (ASMR), with the respective 95% CI. In general, the estimated values were close to the observed values, indicating the adequate fit of the model.

For men, the ASIR and the 1- and 2-year ASMRs showed a peak around the year 2000 and then gradually declined. For women, the ASIR increased rapidly from 1996 to 1999, after which the rate increase slowed. The 1-year ASMR was relatively steady during this same period, but the 2-year ASMR slowly increased.

**Case–Fatality**

Time trends for mortality may be influenced by those for incidence or case–fatality rate, as mentioned in the methods section. The time trends for 1- and 2-year case–fatality rates for men and women (Figure 4A, B) were studied to identify the relative contributions of incidence and case–fatality to mortality. For men, the 2-year case–fatality rate was stable during this period and the 1-year case–fatality rate fell by ~3% between 1997 and 1998. This implies that the improvement in male mortality after 2000 (Figures 2A and 3A) was attributable mainly to a reduction in incidence, which contributed to the reduction in the case–fatality rate (bottom of Figure 4A shows 1-year case–fatality rate). In women, the 1-year case–fatality rate fell markedly by ~6% between 1997 and 1999, but this improvement was counteracted by a large increase in the incidence, resulting in an increase in mortality, particularly 2-year ASMR.

**Trends in Treatment Utilization and Related Case–Fatality Rates**

The time trends for treatment utilization in conjunction with 1- and 2-year case–fatality rates by gender are displayed in Figure 5A–C. The 1-year case–fatality rate improved for both male and female patients who did not receive surgical treatment, and the 2-year case–fatality rate remained steady when chemotherapy was administered. For men, between 1996 and 2002, treatment utilization was stable for surgery
(average, 17%) and increased for chemotherapy (19–34%) compared with other treatments. The 1-year case–fatality rate was lower for those treated with chemotherapy (average, 62%) than for those treated with other modalities (average, 77%). There was also moderate improvement in the surgery-related 1-year case–fatality rate (39–33%) from 1996 to 2002. For women, between 1996 and 2002, treatment utilization was also stable for surgery (average, 18%) and increased for chemotherapy (15–33%) compared with other modalities, and the corresponding 1-year case–fatality rate was lower with chemotherapy (average, 51%) than with other modalities (average, 72%). There was also slight improvement in the surgery-related 1-year case–fatality rate (33–25%) from 1996 to 2002. These data are compatible with the improvement in the 1-year case–fatality rate and imply that the improvement was mainly the result of increased utilization of chemotherapy:

For men, \((34–19\%) \times (77–62\%) = 2.25\%\);

For women, \((33–15\%) \times (72–51\%) = 3.8\%\).

**DISCUSSION**

By using a BAPC model in conjunction with the decomposition of mortality into incidence and case–fatality rates, we demonstrated that in a country such as Taiwan with low incidence of lung cancer, the time trend in mortality for lung cancer was opposite in men and women. The midterm mortality (2-year ASMR) for male lung cancer patients decreased after about 2000, mainly as a result of decreased incidence (ASIR) during this period. In contrast, women showed a moderate increase in midterm (2-year) mortality, attributable primarily to increased incidence. Regarding case–fatality rates, there was a small improvement in the short-term (1-year) rate, which was possibly caused by increased utilization of chemotherapy, but the improvement in the midterm (2-year) case–fatality rate was still lacking, especially for men.

Our results are compatible with those in the literature, which have shown that most lung cancer patients are diagnosed at an advanced, incurable stage, given the currently available treatment options. Although chemotherapy can lead to modest gains in survival (e.g., 2–4 months in advanced non-small cell lung cancer [NSCLC]), the long-term outcome in lung cancer patients is still poor.\(^{12,13}\)

In contrast to previous studies,\(^{2,3,14}\) our study included some unique features. First, both incidence and mortality data were simultaneously analyzed. It is well known that using mortality data to make an inference has the drawback of not separating the effects of the case–fatality rate from real changes in the underlying incidence. The prognosis of lung cancer is poor, and the mortality is therefore approximately equal to the incidence rate. However, there have been major advances in treatments such as chemotherapy over the past 5 years, and a high response rate to biologic therapy has been demonstrated in Asian lung cancer patients.\(^{12,15}\) Accordingly, it is better to use the incidence and mortality, rather than either alone, to assess epidemiological long-term trends for lung cancer.

Second, we used a Bayesian, rather than classic, APC model.\(^{16}\) As in some previous studies,\(^{7,17}\) this approach provided more reliable and stable estimations. We also found that the estimations were highly accurate. Furthermore, the estimation of CI is not intractable, as has been seen previously.\(^{2,3}\)

There are several potential limitations in our study. The first is that the study period (1996–2002) was not very long, owing to the limited availability of information regarding treatment and survival status. Therefore, we did not investigate long-term mortality, as is usually assessed in other cancers such as breast cancer. However, given that lung cancer is a highly fatal disease with 5-year overall survival rates of <15% and a 2-year survival rate of 10–15% for the majority of patients with advanced NSCLC,\(^{13}\) we believe that our description of the trends for midterm mortality (2 years) may be sufficient for studying the time trend for lung cancer in association with age, period, and cohort effects. In addition, as most of the randomized controlled studies supporting the efficacy of chemotherapy versus best supportive care for advanced NSCLC patients were published between 1988 and 1999,\(^{18}\) we consider our study period to be appropriate for investigating the effect of chemotherapy. Nonetheless, more recent cohorts and longer follow-up periods will be needed in future studies, especially in view of recently published breakthrough studies on the treatment of NSCLC.\(^{19–22}\)
The second limitation is that cancer staging information was not available in our study. However, the trends in staging distribution in Taiwan have indicated an increase in the proportion of cancers at an advanced stage in the contemporaneous period, making the improved short-term case-fatality rate less likely to have been caused by an increase in early-stage cancer diagnosis.

A third limitation is that we did not measure survival according to histologic subtype (i.e., adenocarcinoma versus nonadenocarcinoma). In Taiwan, as in Western countries, the number of adenocarcinoma patients, who are supposed to have relatively good survival, has increased, and this may partly account for the improved short-term case-fatality rate. However, this is unlikely to have made a substantial contribution to the improved short-term fatality rate. The crude 1-year case-fatality rate was slightly better for adenocarcinoma patients (62% for men and 55% for women) than for nonadenocarcinoma patients (67% for men and 63% for women), and between 1996 and 2002, the proportion of adenocarcinoma patients has increased from 28 to 35% of men and from 47 to 61% of women. Therefore, the absolute contribution of the increased percentage of adenocarcinoma patients to the improvement in the 1-year case-fatality rate would have been 0.4% for men and 1.1% for women, which constitutes only a small part of our observed improvement (3% for men and 6% for women). However, it is still unclear whether the cell type is a prognostic factor in NSCLC.

In this study, we developed a Bayesian APC model to study time trends in lung cancer incidence and mortality in Taiwan, which has a low but rapidly increasing incidence of lung cancer. By applying this new BAPC model to time trend data from Taiwan and by decomposing mortality into the incidence and case-fatality rates, we demonstrated that midterm (2-year) mortality has been decreasing for male lung cancer patients since about the year 2000, whereas the opposite is true for female patients and that the change in mortality during this period paralleled the change in incidence, which was opposite in men and women. Increased utilization of chemotherapy might have partly accounted for the small (3–6%) improvement in the short-term (1-year) case-fatality rate. The contributions of other unmeasured factors such as staging and histologic distribution remain to be clarified in a future study.

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REFERENCES


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