# Bayesian Age-Period-Cohort Model of Lung Cancer Mortality

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## ABSTRACT

**OBJECTIVES:** Cancer is the second most common cause of death in the US. Lung cancer is the leading cause of cancer deaths. An analysis of the epidemiological situation, as a support tool for planning of public health, requires an understanding of lung cancer mortality rates. Mortality rate temporal trends may be assessed by using data derived from age (time between birth and death), period (Time of death) and birth – cohorts (time of birth) of patients with lung cancer.

**METHODS:** Data regarding lung cancer mortality and incidence rates in the US from 1971 to 2010 were used in the study and obtained from the National Cancer Institute. Age-period-cohort (APC) models are widely used for studying time trends of disease incidence or mortality. Model identifiability is less of a problem with the Bayesian APC models. Our study applied the Bayesian APC model fitted with histogram smoothing prior decomposing mortality rates into age, period, and birth-cohort.

**RESULTS:** Based on the data from the National Cancer Institute it was determined that as age increased, mortality rates from lung cancer increased more rapidly for individuals over the age of 52. The average annual lung cancer deaths for individuals over the age of 52 appear to be 28 deaths and, there were 47 deaths for individuals who were over 57 years old. There was a total of 157 deaths annually for individuals who were over 82 years old. The mortality of younger cohorts was lower than older cohorts. The relative risk of lung cancer lowered from period 1993 to recent periods.

**CONCLUSION:** The fitted Bayesian Age-Period-Cohort model, with histogram smoothing prior, is capable of explaining the mortality rate of lung cancer. The reduction in carcinogens in cigarettes and the increase in smoking cessation from around 1960 may have led to the decreasing trend of lung cancer mortality that has taken place, since period 1993.

*Key words: Histogram smoothing, Multinomial, Multivariate normal, Logit parameters, Mortality*

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## INTRODUCTION

Lung cancer (LC) is the leading cause of cancer deaths in the US, where cancer remains the second most common cause of deaths [1]. In 2011, 14% of all cancer diagnoses and 27% of all cancer deaths were due to LC. More people in the United States die from LC than any other type of cancers which is true for both men and women. After increasing for decades, LC death rates are decreasing nationally as fewer people smoke cigarettes [2]. However, it is still one of

the largest threats for public health to address. About 221,200 new cases and an estimated 158,040 deaths were reported in the American Cancer Society`s estimates for LC in the United States for 2015. It is of strong public interest to predict the trend, number of LC deaths, and the corresponding mortality rates for planning by public health and for demographical reasons.

The analysis of trends in epidemiology is an important method of monitoring the behaviour of diseases. The analysis can be used to monitor etiology of disease and assess the effect of public health policies in the form of prevention, improve treatment, and cost assessment. Age-period-cohort (APC) modelling has been a well-known issue in epidemiology [3-9]. The unidentifiability problem for parameters estimation has been drawing the attention of many researchers. It exists because of the relationship among age, period, and cohort. To resolve this problem, several approaches have been suggested by researchers to analyze the trend and make predictions in cancer epidemiology [7,10-12]. This study applied Holford approach[7] to analyze the effects.

In our study, we analyze LC mortality of individuals residing in the USA based on age at death, period at death, and birth-cohort through Bayesian APC model with histogram smoothing priors. The Bayesian method extracts the necessary information from the data to describe the trend observed by exploring the uncertainty associated with functions of parameters. Various studies have been carried out through Bayesian APC analysis [13-15] with different smoothing priors. But, to the best of our knowledge, histogram smoothing prior has not been considered in Bayesian statistical modelling. We have assumed that the densities of APC possess similar property of smoothness to adapt histogram smoothing prior. The analysis has been executed with the statistical package R and WinBUGS.

## METHODS

### Data and Population

The data for this study was from the Surveillance, Epidemiology, and End Results (SEER) Program of National Cancer Institute (NCI), USA. The data contained incidence and mortality due to LC in the USA from 1971 to 2010. We have grouped incidence and mortality into thirteen 5-year age groups (20-24 years old through 80-84 years old) and eight 5-year periods (1971-1975 years through 2006-2010 years). These age groups and calendar periods involved 20 (13 age groups+8 periods -1) possibly overlapping 5-year cohorts [5]. We have considered those age groups in our study because SEERStat does not give the counts for less than 10 numbers of observations and the study had many such cases especially below the age of 20 years old for mortality counts. The same was true for age groups above 84 years old. Also, a further factor which was taken into account which was that cigarette smoking is the most common cause of lung cancer and this habit is likely to develop in adult ages. Ages, periods, and cohorts were represented by their medians during our study.

Age specific LC mortality rates seem stable for age groups 40 years and lower. Within every period, it can be noticed that mortality rate is increasing until age groups 77 years and decreasing afterwards (Fig. 1). Age specific mortality rates are lower for lower age in all birth cohorts. Similarly, it is significantly high for older birth cohorts. Older people of all birth-cohorts might be at high risk of ending up as lung cancer patients (Fig. 2). Period specific mortality rates for lung cancer are lower for lower age groups for every period. The greater the age, the more mortality rates seem to be for each period. The mortality rate for age group 82 years was lower than age groups 67, 72, and 77 in early periods. However, it seems to be greater in 1993 and recent periods (Fig. 3). Cohort specific mortality rates due to lung cancer are higher for age groups in early birth-cohorts. However, it seems to be decreasing for lower age groups for recent birth-cohorts. We have noticed that older people are at more risk of dying due to lung cancer than younger people throughout the birth-cohorts. Within the same age group, the mortality rate of younger birth-cohort is relatively lower than older birth-cohort (Fig. 4).

We have plotted mortality rates as an initial exploration whether rates are proportional between periods or cohorts. These plots might help to have preliminary idea that model possibly includes as contributing factors. Log scale rate plots of Fig. 1 and Fig. 3 will exhibit almost parallel lines if age specific rates are proportional between periods which might indicate age-period model. Similarly,

log scale rate plots of Fig. 2 and Fig. 4 will exhibit parallel lines if age specific rates are proportional between cohorts which possibly indicates age-cohort model [16].

FIGURE 1

AGE-SPECIFIC LUNG CANCER MORTALITY RATES PER 100,000 IN THE USA BY 5-YEAR PERIOD

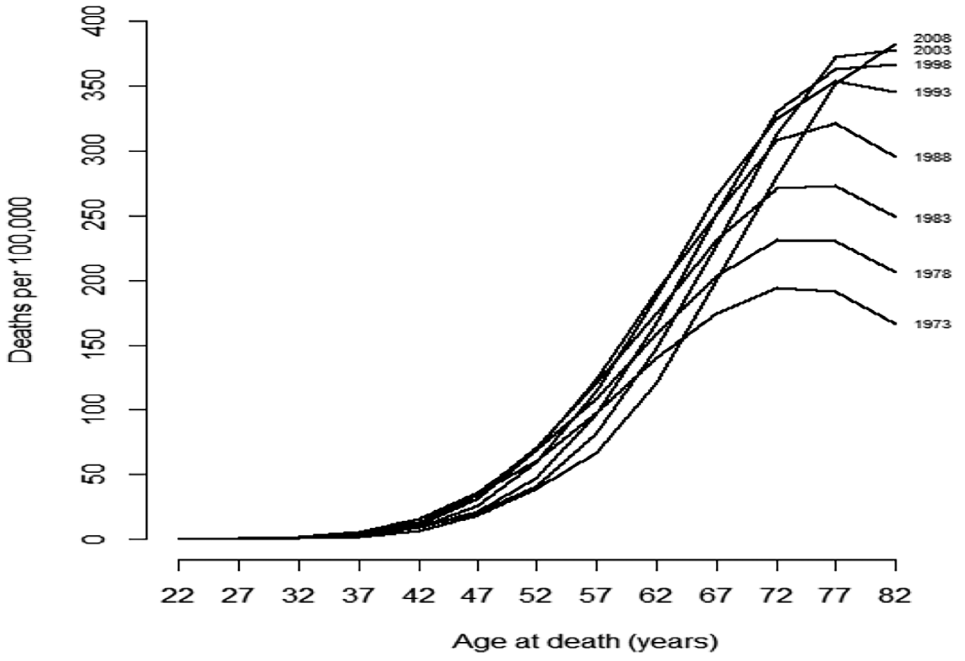



FIGURE 2

AGE-SPECIFIC LUNG CANCER MORTALITY RATES PER 100,000 IN THE USA BY 5-YEAR BIRTH-COHORT

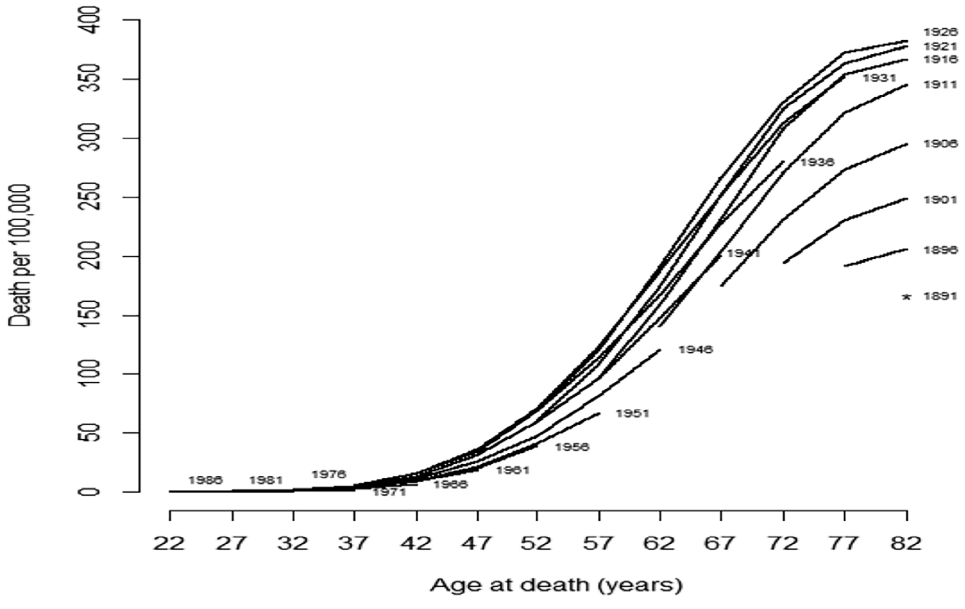


FIGURE 3

PERIOD-SPECIFIC LUNG CANCER MORTALITY RATES PER 100,000 IN THE USA BY 5-YEAR AGE GROUP

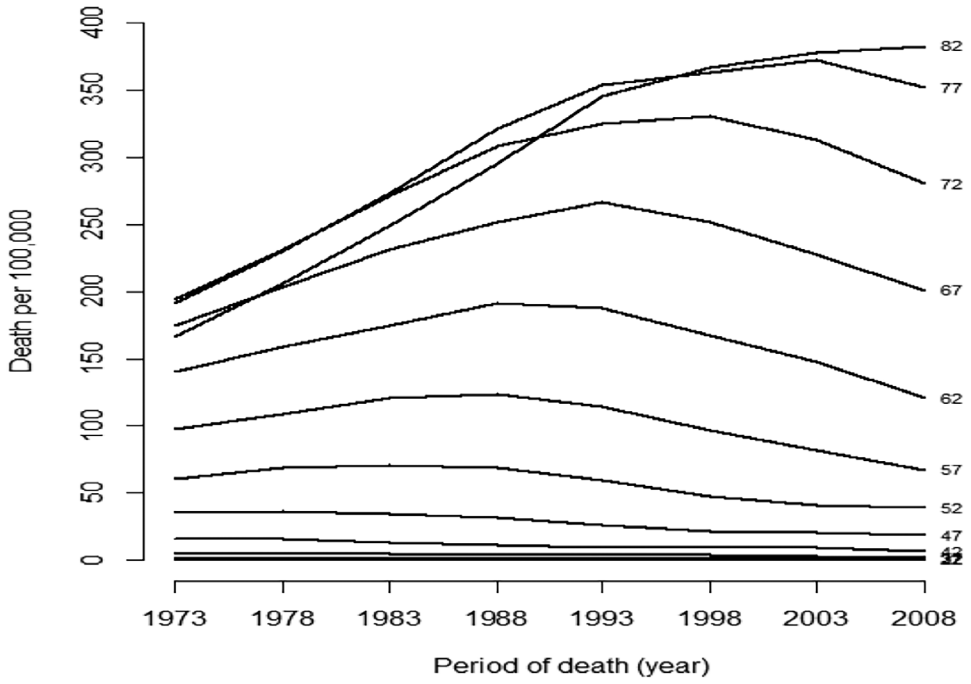
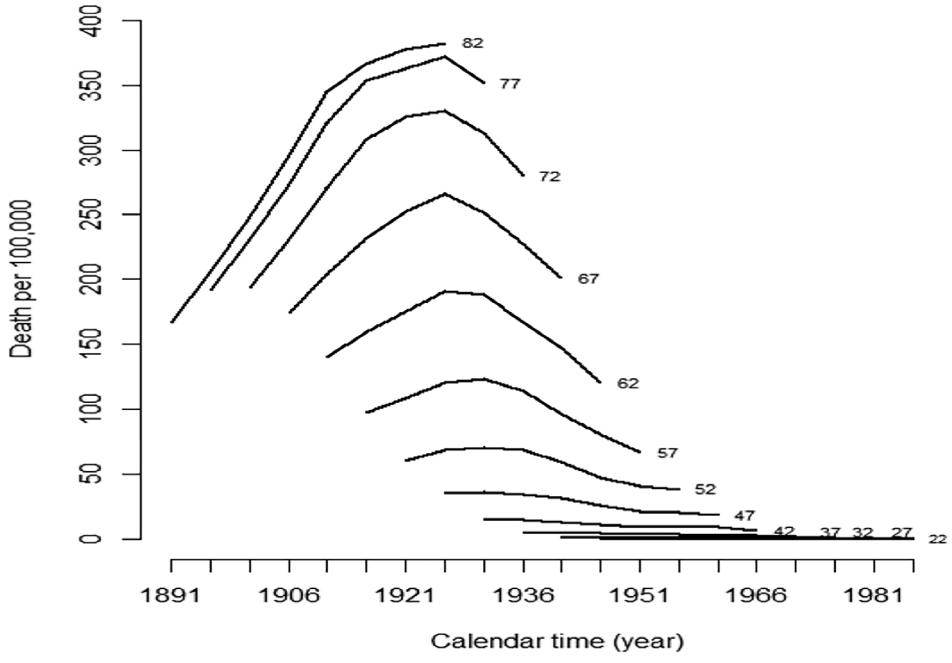



FIGURE 4

COHORT-SPECIFIC LUNG CANCER MORTALITY RATES PER 100,000 IN THE USA BY 5-YEAR AGE GROUP



## Modeling

Let $d_{ij}$ be the observed deaths for age group i in time period j. We have assumed that these followed a Poisson distribution with mean $d_{ij} \sim Poisson(\lambda_{ij})$ i.e.

The mean of age-specific and period-specific death counts $\lambda_{ij}$ is regressed on the effects of age, period, and birth-cohort using the corresponding person-years at risk $n_{ij}$ as the offset. More specifically, let $\alpha_1$ is age effect *(i=1,2, ..., I)*, $\beta_j$ is period effect *(j=1,2, ..., J)*, and $Y_k$ is cohort effect *(k=1,2, ..., K)* with relations *K=I+J-1* and *K=I+j-i*. The mortality rate may be described through: $log(\lambda_{ij})=log(n_{ij})+\alpha_i+\beta_j+Y_k$

The choice of prior is always an important issue in Bayesian Statistical Analysis. Normality is common assumption for time effect-specific (age, period, and cohort) smoothing prior formulations in most of the smoothing approaches including power link model[17]. Our assumptions regarding APC are not restricted to any particular family of distributions. Histogram smoothing is a technique for the analysis of independent and identically distributed (iid) observations with unknown density which is concentrated on a finite interval of the real line [18]. A histogram helps to visualize the data since it adapts and replaces a large point set with a compact approximation of the underlying distribution. It eliminates the random fluctuation that usually occurs with the estimate of parameters and prevents instability in a situation where there are very few counts of deaths, as is the case in the younger age groups. The variance parameters (APC variances) provide information about the degree of smoothness. The larger the values, the greater the degree of smoothing [19]. The trends corresponding to age, period, and cohort were smoothed using the histogram smoothing prior. The prior issues having been addressed, it remains crucial to take into account the fact that the model did not appear to be sensitive to the prior of variance (roughness) parameters.

The relation *cohort=period-age*, leads to a non-identifiability problem for which a constraint should be introduced [20,21]. We have adopted the Holford approach to represent the effects [6,7]. It offers to use models that incorporate effects due to the risk factors by introducing a constraint. To consider slope of an effect zero is one of the suggested approaches. It has been observed that the age-cohort model with an unstructured error term is enough to describe the extra Poisson variation [22]. Therefore, we estimated age and cohort effects while assuming that the slope of period was zero and considering 1941 as a reference cohort. Thereafter, the fitted values were introduced to the model which included only period effects, while considering 1998 as a reference period. In this way, we obtained the independent effects of age, period, and cohort. A similar approach with respect to choice of effect has been previously adopted [14,15].

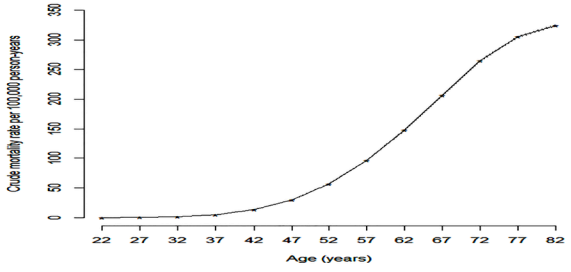
The parameter estimates for the model are obtained from posterior distribution. Median is the point estimate. The model goodness-of-fit was measured by the posterior mean deviance [23]. The deviance information criterion (DIC) has been considered to compare the models which adjusts the posterior mean deviance for the number of parameters in the model [23]. A smaller DIC indicates the better fit. 95% credible intervals were obtained using 2.5th and 97.5th percentiles of the Monte Carlo Markov Chain run.

## Results

We fitted partial as well as full models and compared the different models based on the DICs that were obtained. The full model, which contained the age at death, period at death, and birth-cohort, displayed the best fit with the lowest DIC in comparison with the partial models (Table 1). We further investigated age, period, and birth-cohort models with their different possible interactions. Having done so, we observed no evidence of significant interactions as indicated by DICs. The estimated parameter values of age, relative risks of period, and cohort components with their 95% credible intervals are presented in Table 2.

FIGURE 5

ESTIMATED AGE-SPECIFIC ANNUAL MORTALITY RATES (AGE EFFECTS) IN 5-YEAR AGE GROUPS



We observed that the mortality rate is stable at around 1 or 2 deaths per 100,000 for age groups who are 32 years old and under, and approximately 5 deaths for individuals who are 37 (Fig. 5; Table 2). However, the mortality rate by age had an upward inflection with individuals who were age 42 and above. The upward inflection of mortality rate is consistent with older ages. We have observed that it reaches the peak of 325 (95% CI: 323-326) deaths per 100,000 person-year for the age group of individuals who were 82 years old. The 95% point wise credible intervals are the intervals of the mean function which appears narrower in our model. This might be due to the scale of model which has substantially broader and greater variability.

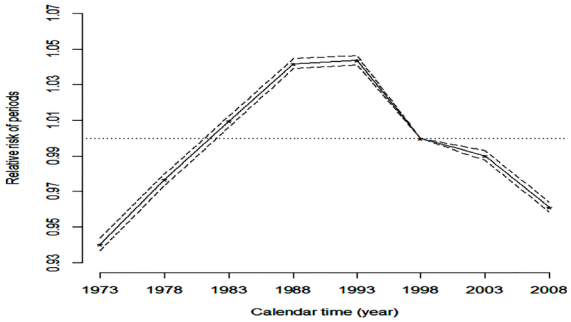
FIGURE 6

ESTIMATED RELATIVE RISKS FOR 5-YEAR BIRTH COHORTS (COHORT EFFECTS) WITH 95% CREDIBLE INTERVAL WITH RESPECT TO REFERENCE COHORT 1941


It should be noted that the risk of birth-cohort increased sharply among cohorts from the late 1800s into the early 1900s before reaching a plateau and then declining (Fig. 6). The curvature of cohort effect depicts an increase in peak risk at birth cohort 1926 and declines continuously until 1950 as it was observed in Fig. 4. The risk of LC mortality peaked in birth-cohort 1926-1931and that is supported by similar research [24-26]. We have observed an increase in birth-cohort slope in 1950, indicating a deterioration of birth-cohort trend in LC mortality after 1950. These results have strongly agreed with a similar research [26]. Cohort effect can be seen in a slowing of decline in risk after cohort 1950 in almost all age intervals, which indicates that the worsening birth-cohort risk is not an artefact of the model fitting (Fig. 4). We have noticed declining birth-cohort risk after 1960. The relative risk due to LC mortality by birth-cohort reflects upward inflection for people born around 1975 which is consistent with mortality rates by cohort. A wider 95% credible interval was observed in the latest cohorts because of fewer LC death points leading to greater uncertainty.

FIGURE 7

ESTIMATED RELATIVE RISKS FOR 5-YEAR CALENDAR PERIODS (PERIOD EFFECTS) WITH 95% CREDIBLE INTERVAL WITH RESPECT TO REFERENCE PERIOD 1998




We have witnessed a continuous increase in the relative risk in period effects peaking in period 1991through 1995. Thereafter there has been a downward inflection (Fig. 7) consistent with Fig. 3. This observation would indicate that the risk of LC mortality rate has been decreasing after the 1991 - 1995 calendar period. The result has been well underlined by research [26]. We have observed that the risk of mortality rate decreased most rapidly during the 2003-2008 time periods, which has been reinforced in similar research [26,27].

## DISCUSSION

The data supports strong evidence of significant changes in risk from LC by birth cohorts. An initial increase of risk of mortality trend is observed in the early 19th century. There could be many possible etiologic factors, such factors include but are not limited to increased air pollution by gases and dust caused by industries, the asphalting of roads, the increase in automobile traffic, exposure to gas in World War I, the influenza pandemic of 1918, working with benzene or gasoline [28,29]. LC can be caused by environmental exposures as well. However, 80-90% of LCs are attributed to cigarette smoking and second-hand smoke [27]. Tobacco use has been identified as the greatest contributing risk factor for LC in developed countries and is approaching the same status in developing countries [30]. The peak of birth-cohort risk occurred in 1926, which may have been

caused by the earlier use of cigarettes [25,31,32]. These cohorts had the highest prevalence of cigarette smoking during World War II [32], when half of the young population smoked cigarettes. Mortality rate is observed to be higher for age groups 60 years old and above. People, who were born around 1926, reached the age of 60 and above after 1980, that is where the higher risk has been observed in the period effect. The fact that the risk of LC increased with increasing age might be due to the number of cigarettes consumed in a lifetime. An increase in age as a risk can be interpreted as a reflection of past smoking [33-35].

There has been no significant breakthrough in lung cancer treatment that explains the decrease in mortality rates after the calendar period of 1993 [36]. However, we have witnessed a decrease in slopes of incidence rate curves after 1993. The lack of a breakthrough in treatment, while a decrease in mortality rate, might suggest that the decrease in mortality rates is caused by a decrease in risk of LC instead of an improvement in survival. The impact on the initiation of a decrease in tobacco carcinogen exposure by cigarette manufacturers and an increase in smoking cessation, which began around 1960, might have caused the substantial decline in the calendar-period risk that took place after 1993. Because of the lower risk in mortality from period 1993, as can be observed in fig 3 and similarly, a lower risk in mortality from period 1961 as observed in fig 2, the decreasing slope of risk to birth-cohort 1961-1971 might have been observed. A reduction in risk of death in the USA due to LC is observed through the periods 1991-2010 from period-specific trend depicted in Fig. 3. Older people are relatively more at risk than younger people. A similar conclusion has been discussed in the study [1].

A decreasing mortality trend was observed during cohorts 1926-1951 which was attributed to the prevalence of smoking filter cigarettes and manufacture of low-tar cigarettes [25]. The overall risk of death due to LC slightly increased in 1951-1961, possibly because of the promotion of deeper inhalation of smoke [29]. The decrease may also reflect a failure of widespread tobacco control efforts by private and public health agencies in the 1960s [31] to break through social and cultural aspects which influenced teenage-smoking [37,38]. Marijuana contains the same carcinogen as is found in cigarettes [39]. It is possible that the increased smoking of marijuana by teenagers and young adults in the 1960s and 1970s contributed to the increase in risk of birth-cohort around 1950.

Since 1964 when the first Surgeon General's report on the health consequences of smoking was published, cigarette smoking cessation rates increased and cigarette smoking initiation rates decreased more rapidly among men than women [29]. The increase of use of cigarettes and marijuana among teenagers since 1991 most likely is reflected by an increase in birth-cohort risk for people born around 1975. Increased smoking from 1971 may have increased the relative risk of death from LC in birth-cohort around the 1980 and contemporary cohorts [29]. People born during 1880-90 had a relatively high prevalence of cigarette smoking with mixed tobacco and tar that could have led to an increase in risk. However, insufficient data earlier than the 1971 period prevented precise estimation of the risk trend among older periods.

The proposed model fits mortality data

TABLE 1

DIC VALUES FOR DIFFERENT COMBINATIONS FOR AGE, PERIOD, AND COHORT MODELS FOR DEATHS DUE TO LC IN THE USA

| COMPONENTS IN MODELS | DIC |
|---|---|
| Age | 165,722 |
| Period | 1,923,440,000 |
| Cohort | 1,041,650,000 |
| Age, period | 116,025 |
| Period, cohort | 233,250,000 |
| Period, cohort, period*cohort | 850,328,000 |
| Age, period, age*period | 120,595 |
| Age, period, cohort, age*period | 11,924 |
| Age, cohort, age*cohort | 8,021.3 |
| Age, cohort | 7,171.17 |
| Age, period, cohort | 2,119.65 |

well in general. Therefore, it is reasonable to argue that our approach extracts the necessary information from the data which was used to explain a possible trend. In a summary, the previously described Bayesian approach resulted in one flexible model that can be adapted to incidence and mortality data.

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TABLE 2

| RESULTS OF THE AGE-PERIOD-COHORT MODEL | | |
|---|---|---|
| COMPONENTS OF MODEL | ESTIMATOR | 95% CI |
| AGE | | |
| 20-24 | 0.164 | 0.155, 0.173 |
| 25-29 | 0.429 | 0.412, 0.442 |
| 30-34 | 1.481 | 1.452, 1.496 |
| 35-39 | 4.918 | 4.869, 4.963 |
| 40-44 | 13.342 | 13.262, 13.436 |
| 45-49 | 29.962 | 29.812, 30.112 |
| 50-54 | 56.936 | 56.709, 57.107 |
| 55-59 | 96.248 | 95.864, 96.537 |
| 60-64 | 148.254 | 147.662, 148.699 |
| 65-69 | 206.629 | 206.010, 207.250 |
| 70-74 | 264.522 | 263.730, 265.317 |
| 75-79 | 305.187 | 303.969, 306.410 |
| 80-84 | 324.059 | 322.765, 325.358 |
| PERIOD | | |
| 1971-1975 | 0.940 | 0.937, 0.944 |
| 1976-1980 | 0.977 | 0.973, 0.980 |
| 1981-1985 | 1.010 | 1.007, 1.012 |
| 1986-1990 | 1.042 | 1.039, 1.045 |
| 1991-1995 | 1.044 | 1.041, 1.046 |
| 1996-2000 | 1 | Reference |
| 2001-2005 | 0.990 | 0.988, 0.993 |
| 2006-2010 | 0.961 | 0.958, 0.964 |
| COHORT | | |
| 1889-1893 | 0.529 | 0.524, 0.536 |
| 1894-1898 | 0.646 | 0.641, 0.650 |
| 1899-1903 | 0.761 | 0.757, 0.765 |
| 1904-1908 | 0.884 | 0.881, 0.889 |
| 1909-1913 | 1.013 | 1.010, 1.018 |
| 1914-1918 | 1.115 | 1.111, 1.120 |
| 1919-1923 | 1.178 | 1.174, 1.182 |
| 1924-1928 | 1.238 | 1.234, 1.243 |
| 1929-1933 | 1.209 | 1.206, 1.214 |
| 1934-1938 | 1.117 | 1.114, 1.121 |
| 1939-1943 | 1 | Reference |
| 1944-1948 | 0.835 | 0.832, 0.839 |
| 1949-1953 | 0.708 | 0.705, 0.712 |
| 1954-1958 | 0.688 | 0.684, 0.692 |
| 1959-1963 | 0.637 | 0.631, 0.642 |
| 1964-1968 | 0.483 | 0.476, 0.490 |
| 1969-1973 | 0.376 | 0.366, 0.387 |
| 1974-1978 | 0.402 | 0.381, 0.423 |
| 1979-1983 | 0.473 | 0.432, 0.515 |
| 1984-1988 | 0.545 | 0.467, 0.633 |

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