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The Estimation Of Age, Period And Cohort Effects For Lung Cancer

Yijie Li
316446007@qq.com

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Name: Yijie Li

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Department: Epidemiology of Microbial Diseases

Advisor/Committee Chair: Theodore Holford

Committee Members: Yawei Zhang

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Abstract:

Lung cancer is one of the most fatal diseases in the world, so it is important to understand the pattern of lung cancer trends at population level. The age-period-cohort model (APC model) is used in this article to analyze the effects of age, year at diagnosis and year at birth on lung cancer in the U.S. The results suggest the age, period and cohort curvature effects are all significant on the lung cancer incidence and mortality. By looking at the plot of the age, period and cohort effects, we found historical events of interest like world war, sales strategies by tobacco companies and lung cancer screening technology may drive the period and cohort effects on the lung cancer in the U.S. The methodology used in this paper will be helpful for public health interventions evaluation and predicting the outcomes the future disease fluctuation driven by those interventions.

Introduction:

The death rates of lung and bronchus cancer is much higher than other cancer in 2015, so it is critical to analyze the lung cancer trends at a population level and evaluate the effects of public interventions. The trends of lung cancer incidence and mortality rates provides important clues for its etiology. The temporal factors in lung cancer trend analysis include: (i) age at diagnosis; (ii) period, which is year at diagnosis; (iii) cohort, which is the year of birth. The period effect on lung cancer could result from the date of the event of interest, such as changes in lung cancer screening. On the other hand, the cohort effects on lung cancer may reveal generational exposures, which could be the change of smoking habits by promotional activities that influenced people at a young age. A classic example of the generational exposure is the distribution of free cigarettes to military recruits during the World War II. Also, during 1960s and 1970s, women in the United States were strongly targeted by tobacco companies, which was suggested as a manifestation of women's rights[1].

APC models estimate the age, period and cohort effects in a generalize linear model and provide an interpretation of the temporal trends for lung cancer incidence rate and mortality rates. The APC model suffers from the identifiability problem because of the linear dependence between the age, period and cohort, which is cohort = period - age. To overcome the identifiability problem, a potential solution is to partition the age, period and cohort effects into the overall linear trend and the corresponding curvature (the deviation from the linear trend) and to set arbitrary constraints on the parameters. It is commonly known that curvature of the age, period and cohort effects are estimable regardless the constraint that is applied. The curvature effects of age, period and cohort are helpful for detection of major fluctuations around the general linear trends.

The disease data is tabulated into a form that divides age and period into the corresponding intervals. This analysis uses equal age and period interval widths. However, for research purpose sometimes the interval widths of age and period may not be equal, which may bring another identifiability problem. The additional identifiability problem usually results in saw-toothed micro-trend, which is biologically implausible.

In this paper, the age, period and cohort effects on lung cancer incidence and mortality rates will be analyzed by the APC model and the smoothing spline function will be used to solve the micro-identifiability problem due to the unequal age and period interval widths[2].

Methods:

The data of interest is lung cancer incidence and mortality in the cancer registry of Surveillance Epidemiology and End Results (SEER) Program (www.seer.cancer.gov) and the vital statistics in the U.S from the National Bureau of

Economic Research(http://www.nber.org/data/vital-statistics-mortality-data-multiple-cause-of-death.html). The population of interest is people aged 35 to 84 who were diagnosed with lung cancer between 1973 to 2014. In SEER, lung cancer is defined as diagnosis of malignant neoplasms of trachea, bronchus and lung while the lung cancer mortality is defined as the SEER specific-cause of death. In data tabulation for the overall lung cancer trend, the age is divided into 5-year intervals while year is a single-year interval, for a better visualization of the trend. For the APC model fitting, we employ single age intervals with age index i (i=1,2,3, ...85), for period j (j = 1973, 1974,...2014) and for cohort k = j-i The response variables are $\widehat{\lambda}_{ijk} = n_{ijk} / p_{ijk}$, where the n_{ijk} represents the lung cancer incidence or lung cancer mortality in SEER and the U.S with a Poisson distribution and p_{ijk} represents the population corresponding to the lung cancer incidence and mortality.

The format of the APC model on lung cancer is:

$$\phi(\lambda_{ijk}) = \mu + \alpha_i + \pi_j + \gamma_k$$

$\phi(\lambda_{ijk})$ is the link function, i.e., the log function, μ is the intercept, α_i is the age effect, π_j is the period effect and γ_k is the cohort effect. To avoid adding constraints, we could partition the effects into linear trend and curvature trends. For example, for age effects: $\alpha i = i^* \beta_\alpha + \alpha_{Ci}$, where i* is the normalized index for age ($i^* = i - (I+1)/2$). Similarly, we have the curvature effects for period and cohort as well. The format of APC model will be:

$$\phi(\lambda_{ijk}) = \mu + \alpha_i + \pi_j + \gamma_k + i^* \beta_\alpha + \alpha_{Ci} + j^* \beta_\gamma + \pi_{Cj} + k^* \beta_\lambda + \gamma_{Ck}$$

One way to obtain curvature is by using the orthogonal method, where the set of regressors can be found by making the analysis-of-variance design matrix that orthogonal to the linear term. Meanwhile, the linear period trends are forced to be zero, with the slopes of age and cohort added to the curvature terms. In this way, the estimates of slopes become the estimate ($\beta_\alpha + \beta_\pi$) for age and ($\beta_\gamma + \beta_\pi$) for cohort.

To obtain the curvature effects, the response variables are the lung cancer incidence and lung cancer death rate in SEER and the U.S, with the period slope (?) variable excluded in the model[1].

On the other hand, the smoothing spline function is applied to solve the micro-trend identifiability problem because it puts a reduction in the magnitude of the serrated pattern which can have arbitrarily large amplitude, which depends on the constraint used to find a set of parameter estimates. In the analysis, the knots are set depending on the interval width of age, period and cohort. The number of knots for the age spline function are set as 5, which are: 40, 50, 60, 70 and 80. The number of knots for period spline function are set as 7, which are: 1980, 1985, 1990, 1995, 2000, 2005 and 2010. The number of knots for cohort spline function are set as 8, which are: 1900, 1910, 1920, 1930, 1940, 1950, 1960 and 1970[2].

Also, the lung cancer incidence and mortality in the U.S are plotted by period and cohort with different age group, which provides an overview of the trend of lung cancer incidence and mortality.

The model comparison is used to test the significance of the curvature effects of age, period and cohort. The reduced models will be an APC model without age, period and cohort curvature effects individually and null hypothesis is that there is no difference between full model (with age, period and cohort model) and reduced model.

Result:

1. Lung cancer mortality trend

The lung cancer mortality trend shows that people with higher age have increasing lung cancer mortality rate in both SEER lung cancer registry and the U.S. By looking at the mortality trend by period, the lung cancer mortality in different age groups are relatively steady in the SEER cancer registry compared to those in the U.S population. In detail, people who are older than 70 have their lung cancer mortality increased during the year at diagnosis in the U.S population, while the rest reached peaks around 1995 (Figure.1). Lung cancer mortality trend was also analyzed in different by sex. For females, the both SEER and U.S population shows a similar pattern to the overall trend (Figure.2.). In contrast, the lung cancer mortality rate in males increased by period until 1990 then decreased (Figure.3.).

In contrast, the overall lung cancer mortality rate peaked for people born 1920-1930 in SEER and U.S population among different age group. For females, the pattern of lung cancer mortality rates among cohorts is similar to the one in overall lung cancer mortality rate trend (Figure.5.). However, people born around 1910 had the highest lung cancer mortality rate (Figure.6.).

Overall, the lung cancer mortality rate is much higher in males compare to females.

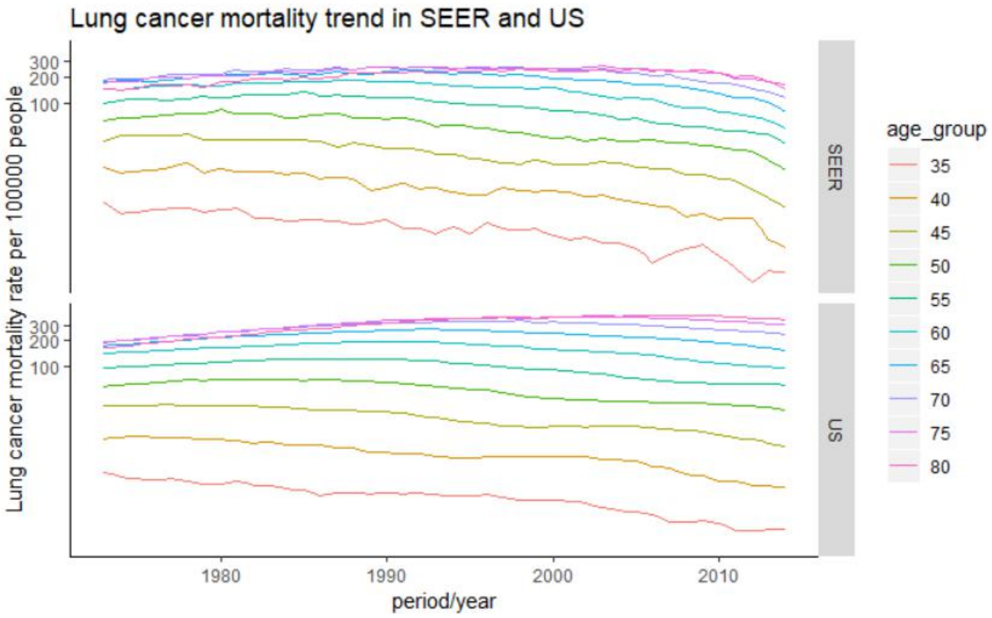

Figure.1. The crude lung cancer mortality trend by year in SEER lung cancer registry and the U.S

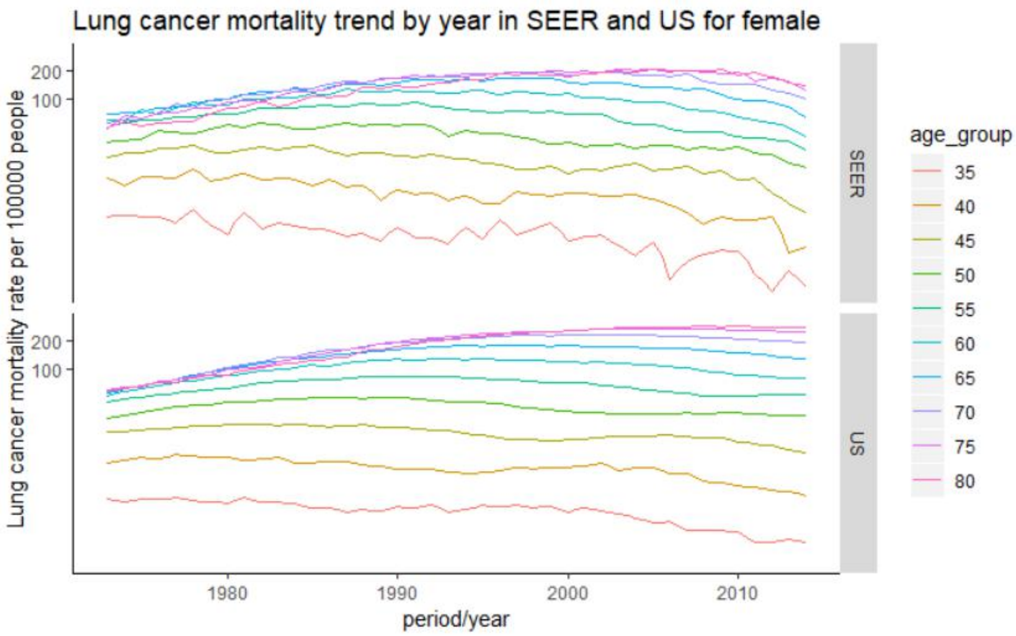

Figure.2. The lung cancer mortality trend in female by period in SEER lung cancer registry and the U.S

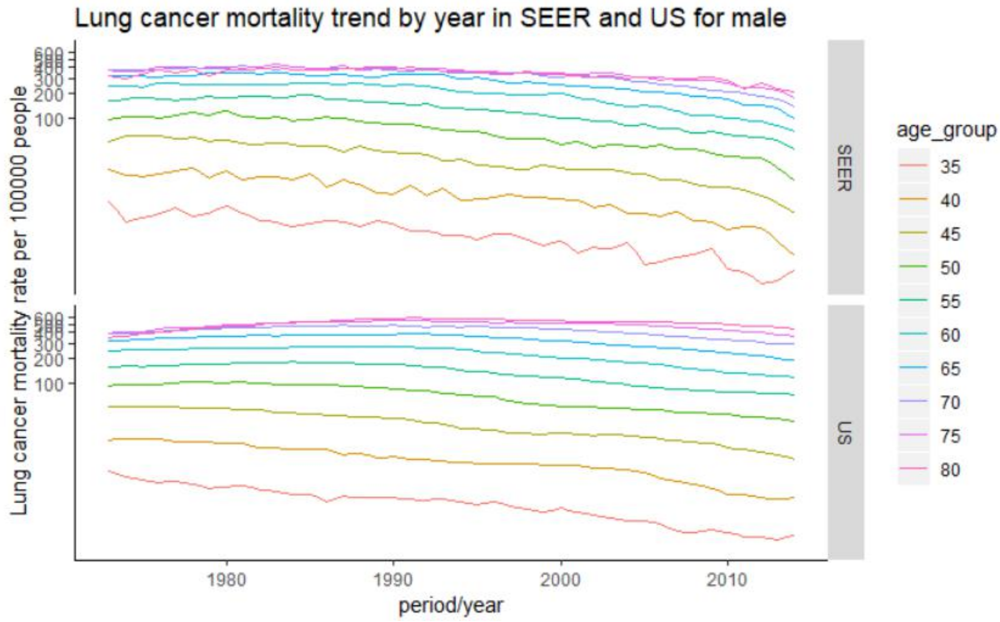

Figure.3. The lung cancer mortality trend in female by period in SEER lung cancer registry and the U.S

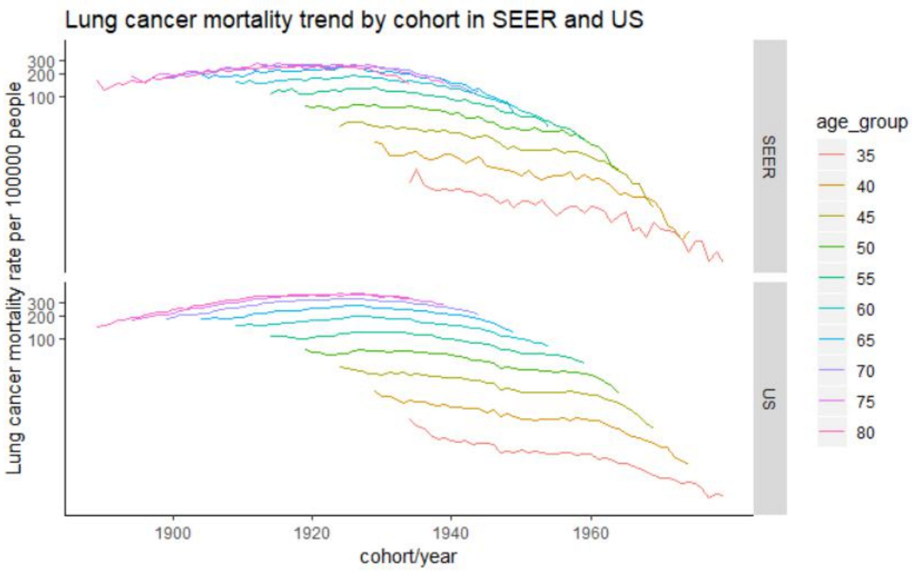

Figure.4. The lung cancer mortality trend by cohort in SEER lung cancer registry and the U.S

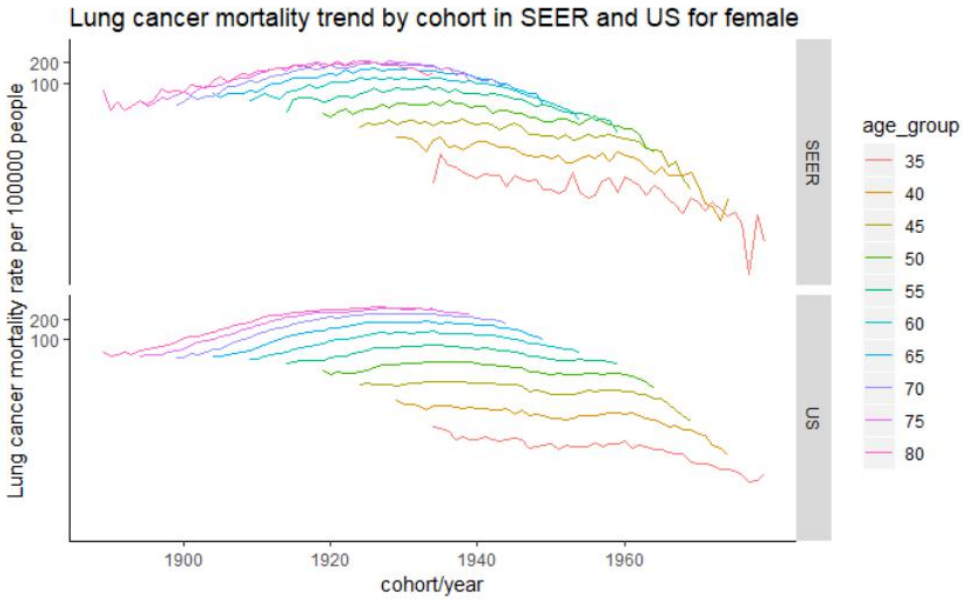

Figure.5. The lung cancer mortality trend in female by cohort in SEER lung cancer registry and the U.S

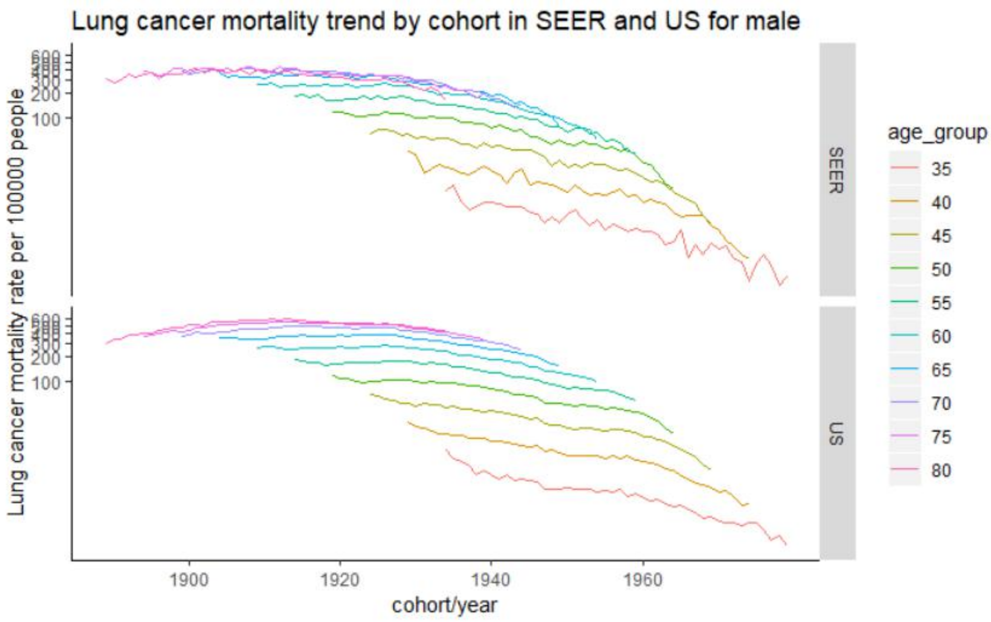

Figure.6. The lung cancer mortality trend in male by cohort in SEER lung cancer registry and the U.S

2. Temporal curvature effects on lung cancer on incidence and mortality.

The curvature effects of age, period and cohort were calculated from the full model and spline function. These linear predictors are plotted on a graph and analyzed for their impact on the linear trend of age, period and cohort. For the crude curvature effects of age on lung cancer incidence in SEER registries, Figure.7 suggests that the crude age effect decreases in negative departure direction for people who were younger than 55 years old. However, the crude curvature effects increase for people aged more than 55 years and peaks around 75 years and remains at a similar level thereafter. The age curvature effects on lung cancer incidence in SEER lung cancer registries are analyzed as well. Figure 8 shows that the age curvature effects on lung cancer incidence is similar between male and female in SEER cancer registries. The female group shows a higher extent of positive curvature effects of age than male. Similar patterns are observed for age curvature effects on lung cancer mortality in SEER registries and the U.S.

For period effects, Figure 9 shows that crude period curvature effect on SEER lung cancer incidence decreases in negative departure direction until 1980. However, it increases subsequently reaching peaks around 1985. After 1985, the period effect decreases again along the year at diagnosis and reaches the lowest level around 2000, Then the period effect again rises started to have increasing rate in the decreasing direction and becomes relatively constant. According to Figure 10, both males and females in SEER cancer registries have curvature effects of period that decreases before 1980. Then, their curvature effects increase reaching peaks around 1985 for males and 1990 for females. Then the curvature effects decrease. For males, the curvature effects decrease and reach a valley around 2000 after which it increases slightly. In contrast, the curvature effects for female decreases after 2000. In contrast, the pattern of period curvature effects on lung cancer mortality is quite different. In detail, Figure 15 shows that curvature effects of period on lung cancer mortality in SEER registries decreases from 1973 to 1980 (negative departure) but increases in adverse direction after 1980 and peaked around 1990 and 2005, which is different from the pattern of period curvature effects on lung cancer incidence. Then, the period curvature increases in negative departure direction after 2008. Compared to the crude effects, the curvature effects of period in male and female shows similar pattern. The difference is that the extent of curvature period effect in female is lower than male before 1980 and after 2007 but remains higher in the rest of time (Figure 16.).

The crude curvature effects of period on mortality shows similar pattern to those effects on the lung cancer incidence, where a concave shape could be observed. Specifically, the period effect declines from 1973 to 1980 and from 1990 to 2005. The period effect increases from 1980 to 1990 and from 2005 to 2014. This curvature effect peaks around 1990 (Figure 21.). The curvature effect of period on the lung cancer mortality in the U.S for male and female shows similar pattern compare to the crude period effects. However, the extent of the curvature period effects is higher in females than males (Figure 22.).

The crude cohort effect in Figure.11 shows that the departure from the cohort linear trend peaks around 1930 and the cohort effect decreases along the year of birth finally have increasingly negative departure on the cohort linear trend after 1950

(Figure 11.). Looking by sex, the curvature effects of year of birth on males remain relatively positive until 1920, when the effect starts to decrease. For females, however, the curvature effects decrease in negative departure direction but increases in positive departure direction and finally peaks around 1940 and had 2nd peak around 1960. Then, the departure of cohort starts to decline after 1960. (Figure 12.). Compare to the curvature effects on incidence, Figure 17 suggests that the cohort curvature effects on SEER lung cancer mortality increases since 1900 on positive departure direction and peaks around 1930. Then it declines until 1950. Then, it increases in negative departure direction. More specifically, Figure 18 shows that the cohort curvature effects on SEER lung cancer mortality shows similar patterns compare to these effects on lung cancer incidence for male and female. The crude curvature effects of cohort on lung cancer mortality in the U.S peaks around 1930 and then the departure decreases until 1950. Then the cohort effect had adverse effects and constantly increase since 1950 (Figure 23.). If look at the difference of cohort effects by sex,the cohort curvature effects on the lung cancer mortality in male follows the crude curvature effects. On the other hand, the curvature cohort effects on female decreases in negative direction but increases after 1910, and peaks around 1940 and 1960. After 1970, the cohort curvature again decreases and back to the negative direction (Figure 24.).

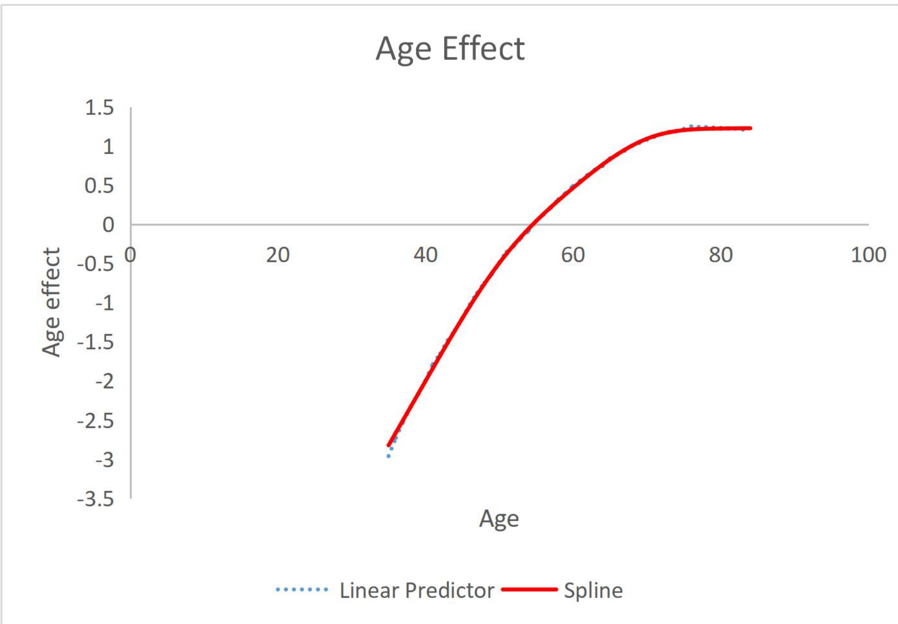

Figure 7. The crude a effects on lung cancer incidence in SEER registries.

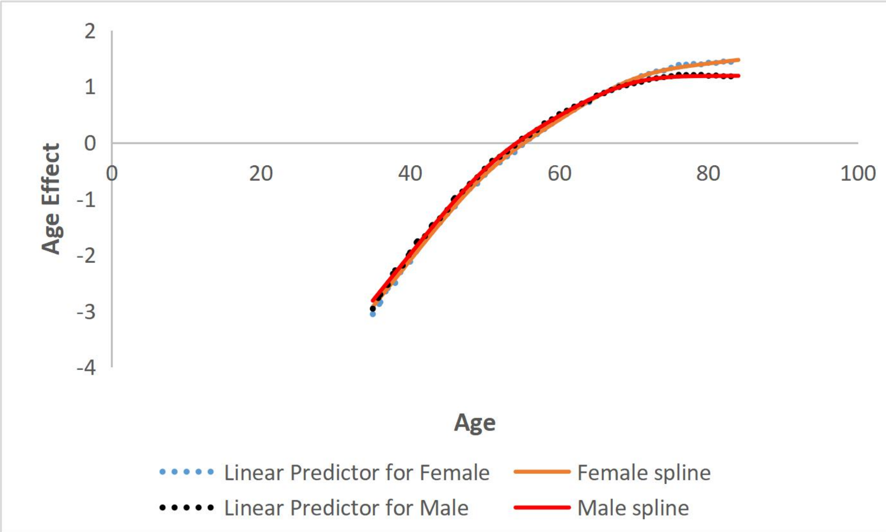

Figure 8. Age effects on lung cancer incidence for male and female in SEER registries.

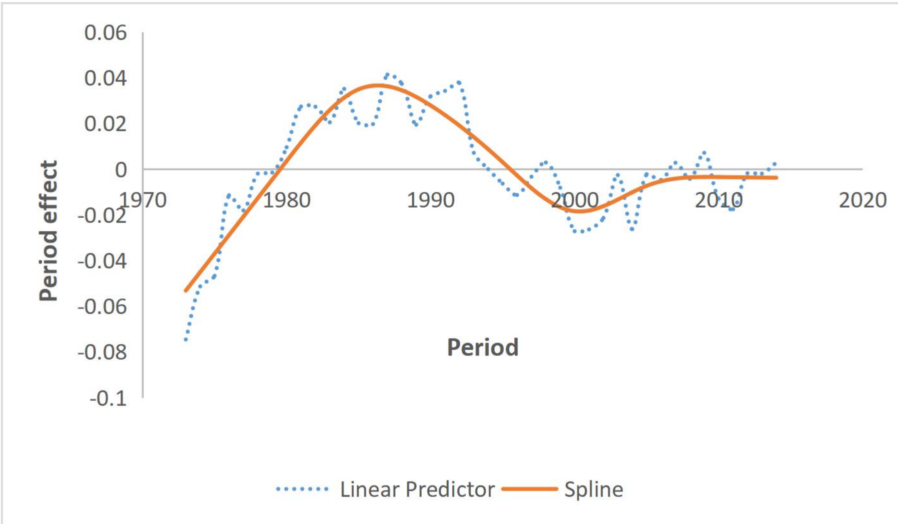

Figure 9. Period effects on lung cancer incidence in SEER lung cancer registries.

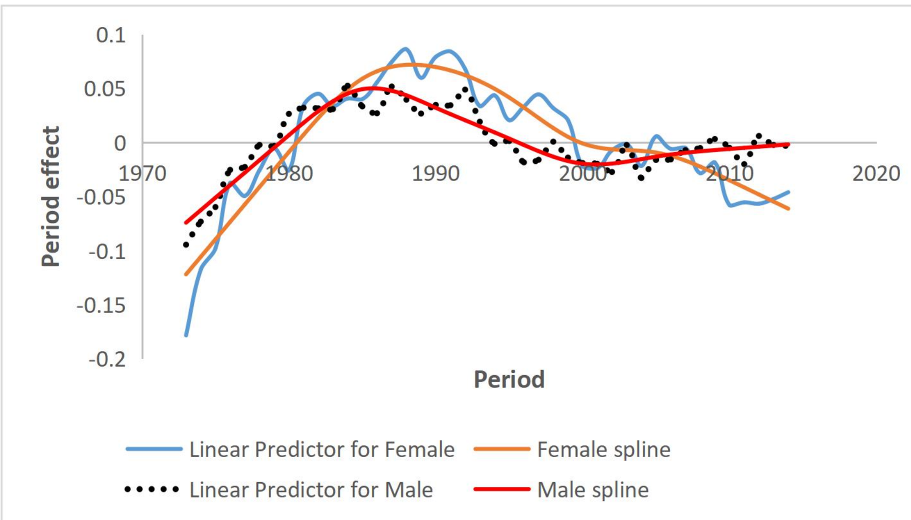

Figure 10. Period effects on lung cancer incidence in SEER lung cancer registries

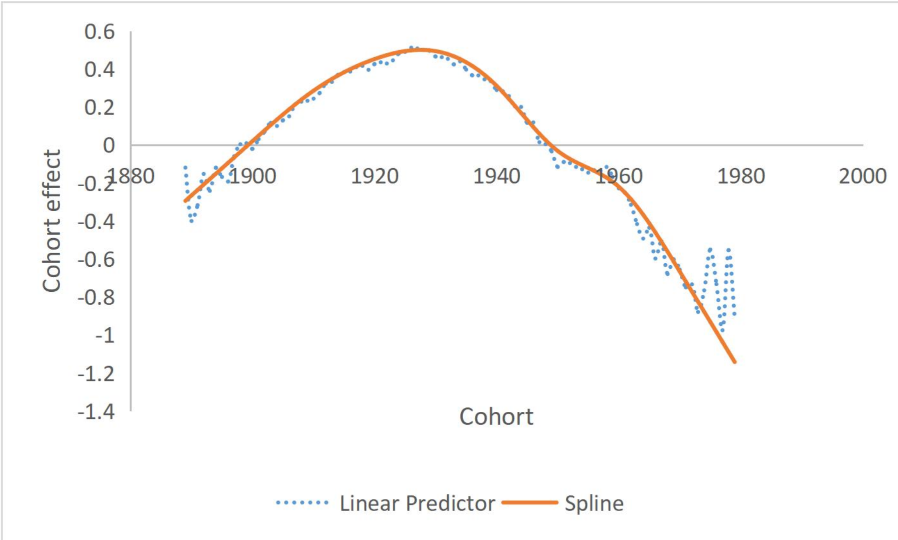

Figure 11. Cohort effects on lung cancer incidence in SEER registries

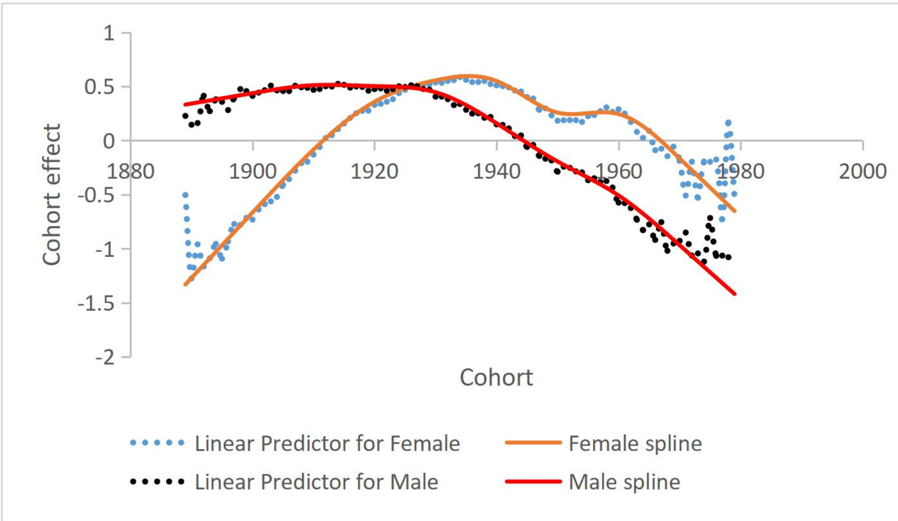

Figure 12. The cohort effects on lung cancer incidence in SEER lung cancer registries

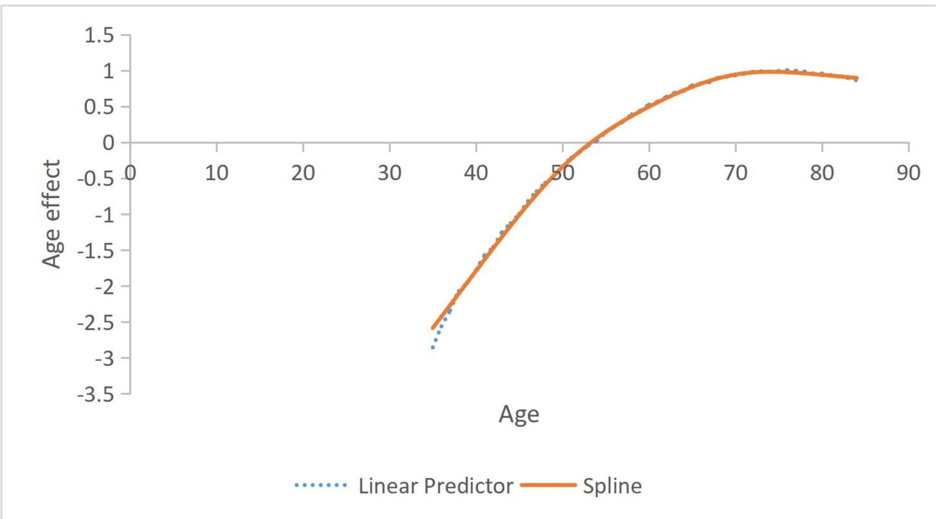

Figure 13. Age effects on lung cancer mortality in SEER registries.

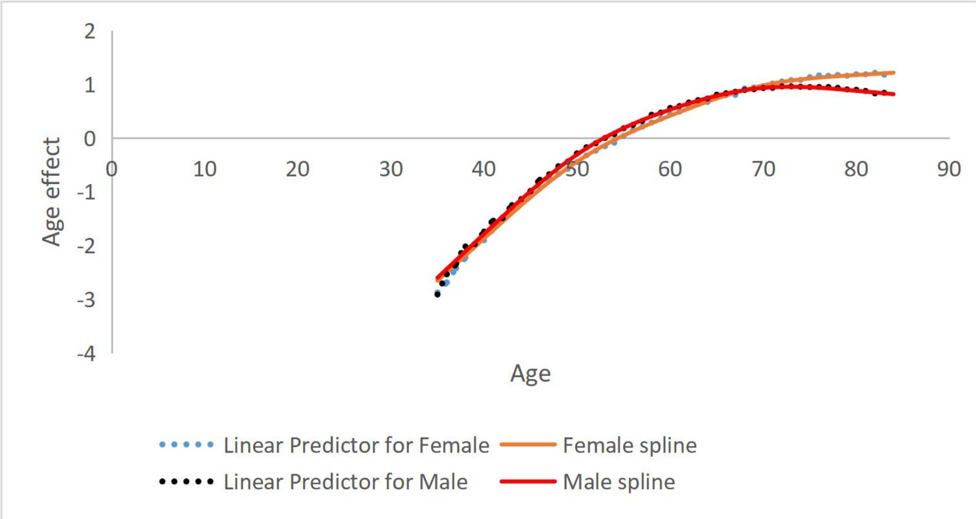

Figure 14. The age effects on lung cancer mortality in SEER lung cancer registries.

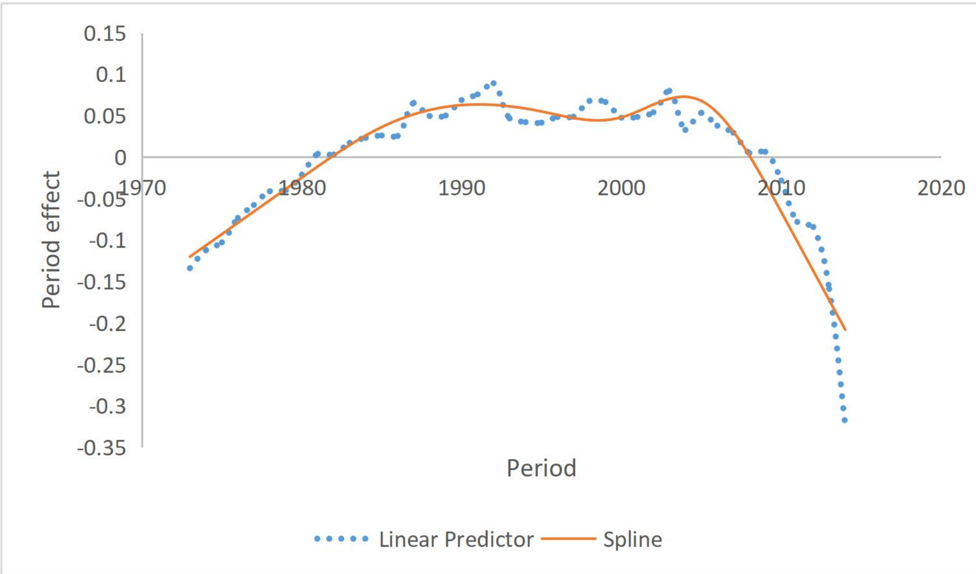

Figure 15. The period effects on the lung cancer mortality in SEER lung cancer registries.

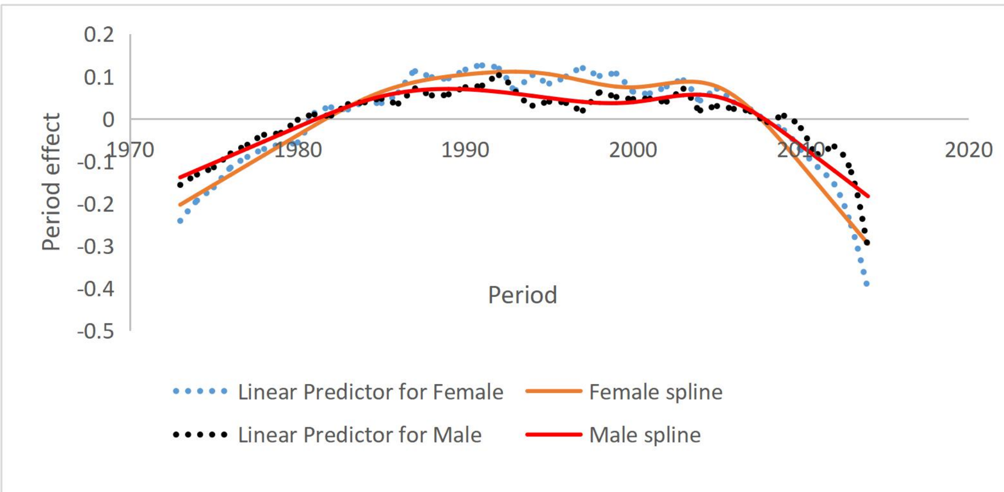

Figure 16. The period effects on lung cancer mortality in SEER cancer registries.

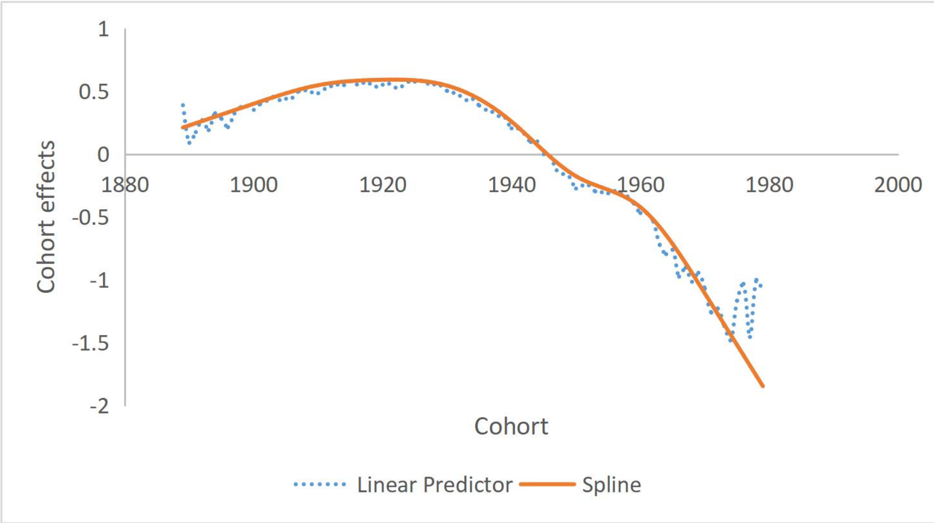

Figure 17. The crude cohort effects on the lung cancer mortality in SEER lung cancer registries.

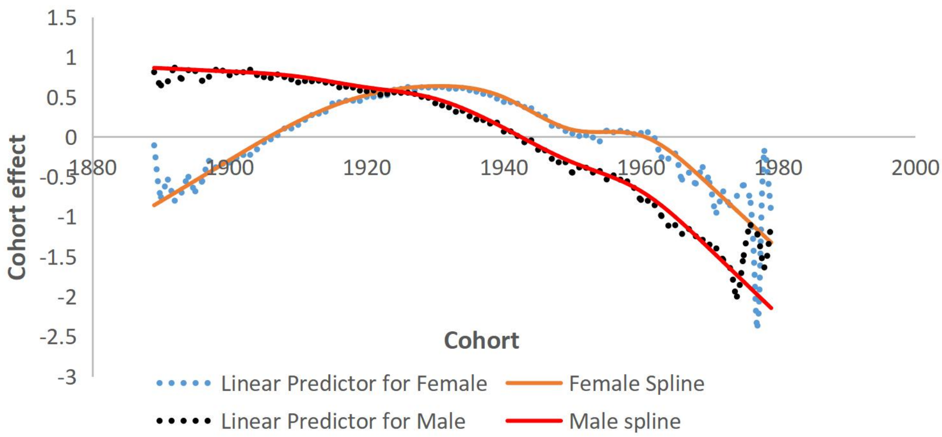

Figure 18. The cohort effects on the lung cancer mortality in SEER lung cancer registries.

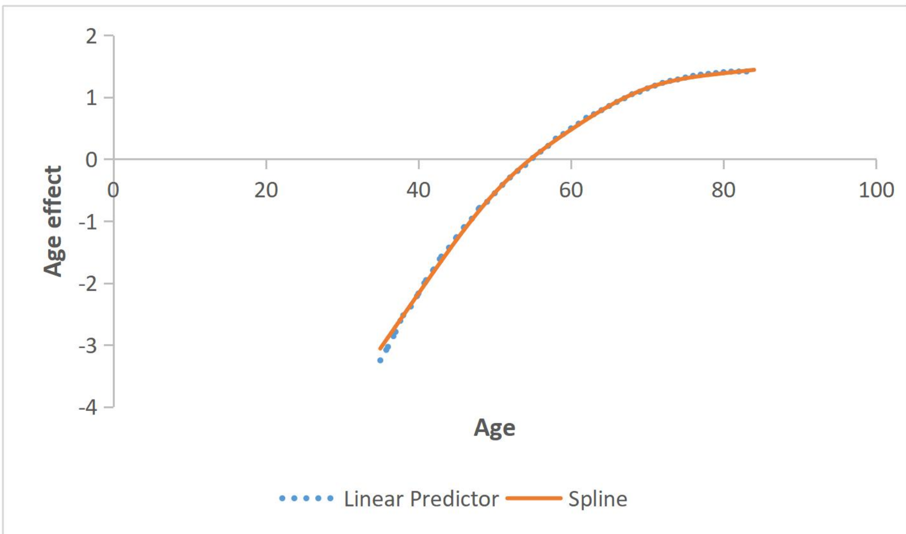

Figure 19. The crude age effects on lung cancer mortality in the U.S.

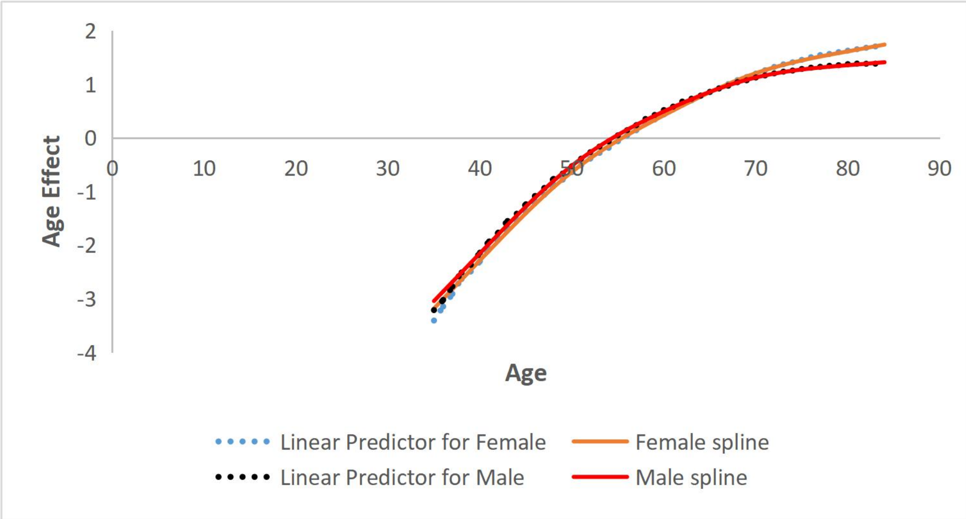

Figure 20. Age effects on lung cancer mortality in the U.S

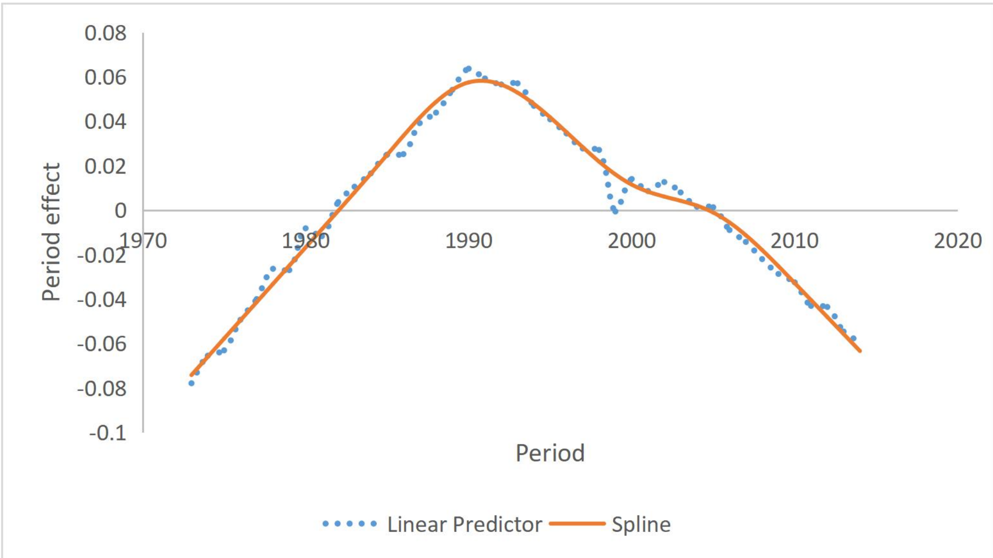

Figure 21. The crude period effects on lung cancer mortality in the U.S

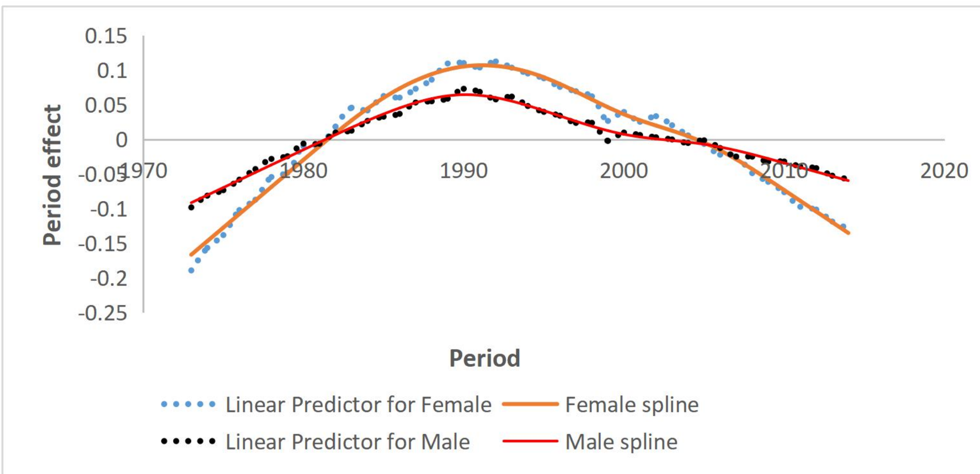

Figure 22. The period effects on the lung cancer mortality in the U.S

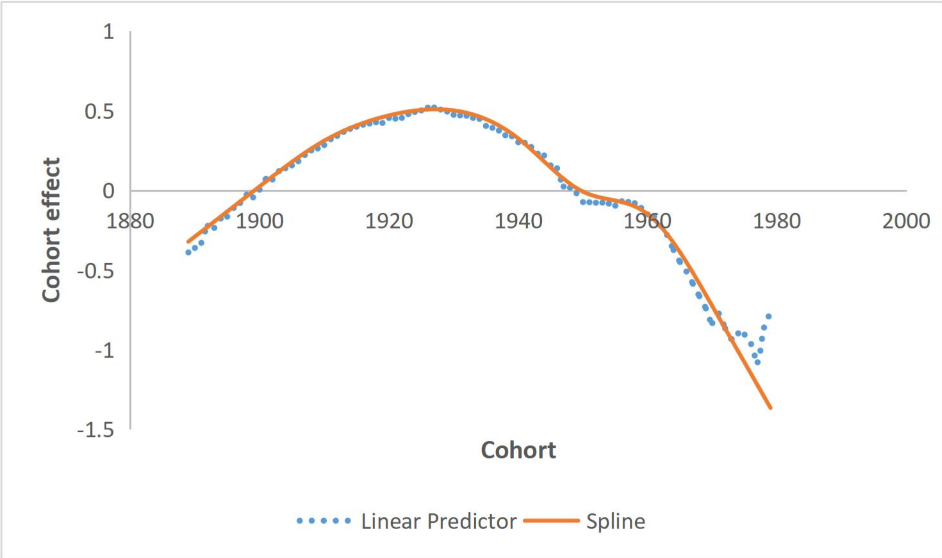

Figure 23. The crude cohort effects on the lung cancer mortality in the U.S.

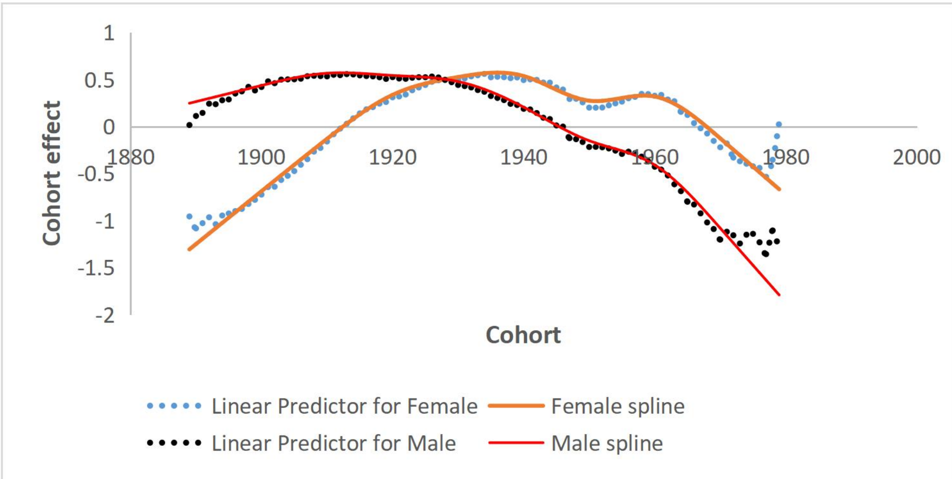

Figure 24. The cohort effects on the lung cancer mortality in the U.S

3. Model comparison.

The F test is used in the analysis to analyze age, period and cohort effects by model comparison. According to the outputs, all three temporal effects are significant in lung cancer incidence and mortality (Table.1, Table.2 and Table.3).

Table.1 Model comparison for SEER lung cancer incidence

Model	Deviance	Scaled Deviance	Df	A	P	C	F-test	P
All sex								
Full model	2144.6638	1918.9191	1920	Yes	Yes	Yes	N/A	N/A
Model 1	46035.7341	2207.5862	1968	No	Yes	Yes	914.4	<0.0001
Model 2	2430.4462	1961.0141	1960	Yes	No	Yes	7.1	<0.0001
Model 3	19247.9222	1977.0033	2009	Yes	Yes	No	192.2	<0.0001
Male								
Full model	2145.828	1926.2518	1920	Yes	Yes	Yes	N/A	N/A
Model 1	15976.3404	2187.3958	1968	No	Yes	Yes	288.1	<0.0001
Model 2	2575.2981	1976.0183	1960	Yes	No	Yes	10.7	<0.0001
Model 3	13039.7561	1945.9164	2009	Yes	Yes	No	122.4	<0.0001
Female								
Full model	2100.9995	1920.4648	1920	Yes	Yes	Yes	N/A	N/A
Model 1	28462.9274	2213.8054	1968	No	Yes	Yes	549.2	<0.0001
Model 2	2410.76	1960.9015	1960	Yes	No	Yes	7.7	<0.0001
Model 3	8539.2543	1985.2316	2009	Yes	Yes	No	72.3	<0.0001

Note: A, P and C in the table above represents the presence of age, period and cohort effects.

Table.2 Model comparison for SEER lung cancer mortality

Model	Deviance	Scaled Deviance	Df	A	P	C	F-test	P
All sex								
Full model	2088.8285	1920.4152	1920	Yes	Yes	Yes	N/A	N/A
Model 1	32456.8256	2209.6821	1968	No	Yes	Yes	632.7	<0.0001
Model 2	3906.3292	1999.3743	1960	Yes	No	Yes	45.4	<0.0001
Model 3	11789.0553	1978.7592	2009	Yes	Yes	No	109.0	<0.0001
Female								
Full model	2023.049	1931.806	1920	Yes	Yes	Yes	N/A	N/A
Model 1	10179.1812	2180.9569	1968	No	Yes	Yes	170.0	<0.0001
Model 2	3592.6792	1998.5743	1960	Yes	No	Yes	39.2	<0.0001
Model 3	9038.3692	1952.9466	2009	Yes	Yes	No	78.8	<0.0001
Male								
Full model	2011.8698	1920.1052	1920	Yes	Yes	Yes	N/A	N/A
Model 1	22171.9082	2218.4874	1968	No	Yes	Yes	420.0	<0.0001
Model 2	3070.1139	1979.7888	1960	Yes	No	Yes	26.5	<0.0001
Model 3	5143.5159	1996.9795	2009	Yes	Yes	No	35.2	<0.0001

Note: A, P and C in the table above represents the presence of age, period and cohort effects.

Table.3 Model comparison for U.S lung cancer mortality

Model	Deviance	Scaled Deviance	Df	A	P	C	F-test	P
All sex								
Full model	2079.7235	1921.4562	1920	Yes	Yes	Yes	N/A	N/A
Model 1	29664.994	2217.19	1968	No	Yes	Yes	574.7	<0.0001
Model 2	4433.1915	2018.2971	1960	Yes	No	Yes	58.8	<0.0001
Model 3	11789.0553	1982.4251	2009	Yes	Yes	No	109.3	<0.0001
Female								
Full model	3003.1299	1907.6287	1920	Yes	Yes	Yes	N/A	N/A
Model 1	94916.3879	2213.8336	1968	No	Yes	Yes	1914.9	<0.0001
Model 2	11347.5737	1989.6678	1960	Yes	No	Yes	208.6	<0.0001
Model 3	80130.9023	1931.6032	2009	Yes	Yes	No	866.6	<0.0001
Male								
Full model	2772.4528	1915.1487	1920	Yes	Yes	Yes	N/A	N/A
Model 1	202647.1553	2226.6305	1968	No	Yes	Yes	4164.1	<0.0001
Model 2	7532.8773	1965.9661	1960	Yes	No	Yes	119.0	<0.0001
Model 3	56445.0405	1990.7468	2009	Yes	Yes	No	603.1	<0.0001

Note: A, P and C in the table above represents the presence of age, period and cohort effects.

Discussion:

For the overall lung cancer mortality trend, it is noticeable that mortality increased with higher age. Meanwhile, there is slight increase for overall and female lung cancer mortality by period. For cohort, we observe that the lung cancer mortality peaks around 1920-1930, and the overall trend is decreasing by cohort.

The age effects on lung cancer incidence and mortality are consistent regardless the target population and sex, which is biologically plausible because there is age-dependent decline in the immunity for cancer in the aged. People with higher age becomes more susceptible to cancer, which results in higher risk of lung cancer compare to young people[3]. In addition, the median age of patients who have lung cancer recurrence after treatment is around 69 years [4]. Another issue is that there might be a potential gap in knowledge translation because aged patients were shown less likely to refer and accept lung cancer treatment, which are frequently reported in Canada. All these factors potentially contribute to the association between age and lung cancer incidence and mortality[5].

For period and cohort effects on lung cancer incidence and mortality, the mechanisms are more related to the cigarette distribution, smoking policy and relevant intervention in the American history.

By looking at the period effects, the overall lung cancer mortality trends are relatively constant, but females show increasing lung cancer mortality from 1973 to 2014. The smoking data in the U.S suggest that the smoking rates in males dropped by 23.6% from 1970 to 2013, while the dropping 16.2% in females, which might explain the reason why we observed obvious decreasing tendency in male lung cancer mortality but not female[6]. In detail, there is common concave down in period effects between 1980 and 1995, suggesting improvements in lung cancer mortality and incidence after 1995.

The period effects could be related to the smoking ban in the U.S, while the difference in period effects between SEER and U.S may come from the different time point regarding to the smoking ban. For example, California enacted a statewide smoking ban in 1995[7] while the Alaska banned the statewide smoking in 2018[8]. On the other hand, lung cancer screening was introduced and became widely processed in the United States. In the late 1990s, the first trial of low dose computed Tomography on lung cancer screening was completed in the United States by the Early Lung cancer, which more malignant and benign nodule were detected. Later, positron emission tomography (PET) and fluorodeoxyglucose (FDG) were introduced in 2003 and generated more promising results in lung cancer screening[9]. These screening technologies help people detect the lung cancer earlier and drive the negative departure in lung cancer mortality trends by period.

For cohort effects, there are also common concave down observed for lung cancer incidence and mortality in SEER and the U.S except those effects in female. This overall concave shape occurs between 1900 and 1940, suggesting an overall improvement in lung cancer incidence and mortality after 1940. For the cohort effects in female, the cohort effect reaches peaks around 1940 and 1960, then they declined after 1960. In the smoking history in the U.S, cigarette smoking grew dramatically in the early parts of the 20th century. The aggressive advertisement, automatic cigarette rolling machine invention and promotion contributed the wide cigarette distribution [10]. On the other hand, cigarette smoking increased rapidly in the U.S military during the World War I in 1918, when cigarette could help soldiers psychologically escape from the circumstances of war and boost the troop morale, according to the tobacco companies at that time. Then, tobacco companies stimulated the wartime smoking culture continuously during World War II [11][12][13]. The dynamics of cohort curvature effects on female is a little bit different from these effects on males and the overall population. In 1920s, the suffrage movement in the U.S made many women learn a sense of entitlement and freedom. During that period, tobacco companies took advantage of the suffrage movement and targeted women by aggressive advertisement, which convinced them that smoking cigarette was an effective way for showing their freedom and entitlement. These tobacco companies even encouraged women smoke instead of eating candies and exaggerated the benefits of cigarette[14]. Then in 1950s and 1960s, the smoking rate in women increased rapidly under the impact of TV show and advertisement, which was much more than the previous cigarette marketing strategy for women in the U.S. It was reported that around 33.9% women smoked in 1965. The history of women smoking between 1920s and 1960s explains the two peaks around 1940 and 1960. In 1970s and health warnings about the dangers of smoking began to be print on the advertisement and annual reports of health consequence of smoking was reported. In 1980s, the first Surgeon General's Report on the Health Consequences of Smoking for Women was carried out, and the smoking rate in women dropped to 29.3%[15].The smoking history event in 1970s and 1980s explains the cohort effects change into negative departure in the lung cancer mortality trend by cohort.

Conclusion:

The age, period and cohort effects are significant on the lung cancer mortality and incidence. Historic events of interest including lung cancer screening and tobacco selling are strongly associated with these curvature changes in the lung cancer incidence trend and mortality trend. The study of age, period and cohort effects is helpful for evaluating public health interventions on cancer and predicting the outcomes the future lung cancer trend of those interventions. Because our research belongs to the field of cancer surveillance in the U.S, the lung cancer modeling in this paper provides an overview of the lung cancer patterns under the temporal effects in U.S. This pattern analysis will be helpful for evaluating the impacts of health policy, healthcare innovation, technology improvement and historic events on the lung cancer incidence and mortality at population level. Besides, the identifiability problems in the APC model due to the collinearity and unequal intervals are solved by analyzing the curvature effects and the application of smoothing spline function, which provides better estimate of these temporal effects. One limitation is that we didn’t analyze the potential interaction between age, period and cohort, which should be the future research direction.

Reference:

1. Holford, T, H. (1983). The Estimation of Age, Period and Cohort Effects for Vital Rates. Source: *Biometrics, Vol. 39, No. 2 (Jun., 1983), pp. 311-324*.

2. Holford, T. H. (2006). Approaches to ftting age-period-cohort models with unequal intervals. *Statist. Med. 2006; 25:977–993.*

3. Nagaratnam, N. & Nagaratnam, S. A. (2018). Immune System, Immunosenescence and Immunisation in the Elderly. *Advanced Age Geriatric Care pp 45-51.*

4. Sugimura, H., Nichols, F. C., Yang, P., Allen, M. S., Cassivi, S. D., Deschamps, C., Williams, B. A. & Pairolero, P. C. (2007). Survival After Recurrent Nonsmall-Cell Lung Cancer After Complete Pulmonary Resection. *The Annals of Thoracic Surgery Volume 83, Issue 2, February 2007, Pages 409-418.*

5. Doherty, J., Dawe, D.E., Pond, G. R.& Ellis, P. M. (2018). The effect of age on referral to an oncologist and receipt of chemotherapy among small cell lung cancer patients in Ontario, Canada. *Journal of Geriatric Oncology.*

6. Smoking Prevalence Among U.S. Adults, 1955-2013. https://www.infoplease.com/science-health/health/smoking-prevalence-among-us-adults-1955a2013.

7. Overview List – How many Smokefree Laws? Americans for Nonsmokers' Rights, January 2, 2014. Retrieved January 12, 2014.

8. Laws of Alaska. (2018). Retrieved from https://legiscan.com/AK/text/SB63/2017.

9. Sharma, D., Newman, T. G.& Aronow, W. S. (2015). Lung cancer screening: history, current perspectives, and future directions. *Arch Med Sci 2015 11 5:* 1033–1043.

10. Cummings, K. M., & Proctor, R. N. (2014). The changing public image of smoking in the United States: 1964-2014. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*, *23*(1), 32–36. doi:10.1158/1055-9965.EPI-13-0798.

11. Brandt, A. M. (2007). The Cigarette Century: The Rise, Fall, and Deadly Persistence of the Product that Defined America. *New York: Basic Books, pp. 50–53*.

12. Goodman, J. (Ed.). (2005). Tobacco history and culture: An encyclopedia. *Detroit: Scribner's.*

13. Smith, E. Z. & Malone, R. E. (2009). Everywhere the Soldier Will Be': Wartime Tobacco Promotion in the US Military. *American Journal of Public Health. 99:*

1595–1602. doi:10.2105/ajph.2008.152983. PMC 2724442.

14. Brandt, A. M. (2007). The Cigarette Century: The Rise, Fall, and Deadly Persistence of the Product that Defined America. *New York: Basic Books, pp. 70–73.*

15. Women and smoking. (n.d.). *In Wikipedia, Retrieved April 6, 2019, from https://en.wikipedia.org/wiki/Women_and_smoking#cite_note-tobacco.org-8*