

# **The Holford Puzzle: The Cohort Effects in Death Rates from Lung Cancer**

**Gustav N. Kristensen<sup>1</sup>**

## **Abstract**

The increasing death rate from lung cancer for women and the small hope of a cure attract attention. The declining death rate at old ages causes surprise and is here called the Holford puzzle.

The present model shows protective and detrimental cohort effects in relation to the incidence of and death rate from lung cancer, and shows how diagonally calculated cohort effects can be used as susceptibility variables in age-specific models.

The applied method solves the Holford puzzle about why the risk of death from lung cancer seemingly does not continue to increase from the age of 70-74. The method can thus turn the conclusions on the development in health upside down.

This study gives an optimistic picture of the future development in women's death rate from lung cancer. A turnaround is on its way and must be expected from 2018 for all age groups.

**Keywords:** Cohort modeling, lung cancer, age, period, identification, death rate.

## **1 Introduction**

Lung cancer for women is an important disease seemingly without any significant progress in outlook. This article compares the results of Holford [1] for incidence rates of lung cancer for women with results for death rate from lung cancer for women (and men) based on Danish data.

In Holford's data, in simple or plain figures, the number of lung cancer (diagnostic) cases for women in Connecticut was 1,439 for the period 1970-74, and 3,199 for the period 1980-84.

In simple or plain figures, the total number of deaths from cancer for Danish women grew from 1,354 in 1995 to 1,649 in 2005.

---

<sup>1</sup>University of Southern Denmark.

In 2009-2011 the survival rate in Denmark five years after the diagnosis for lung cancer was 11% for men and 14% for women, which is the lowest survival rate for the 15 biggest cancer categories.

There is a high degree of similarity between the development in lung cancer in Connecticut and Denmark. This similarity in developed countries is further underlined in the study of Bosetti et al. [2], which shows an (almost) parallel development in 33 European countries. See also Bray and Møller [3].

The purpose of this article is to develop a model which comprehends different time periods and different national cultures by including a cohort effect as an explanatory variable.

The method is based on Kristensen [4] on secular cohort effects. For a discussion of the age-period-cohort models, see also Clayton and Schifflers [5], [6], Holford [1], Osmond and Gardner [7], Rostgaard et al. [8], and Kristensen [9], [10].

### 1.1 The Holford Puzzle

Holford's data give a highly pessimistic picture of the rate of lung cancer incidence for women. However, more specifically he mentions a certain characteristic in his data, which in this article will be discussed as the Holford puzzle. With the words of Holford ([1], pp 426-427), the Holford puzzle can be defined as:

"... rates tend to reach a plateau or even decline in the oldest age groups.

The pattern in the age distribution for lung cancer might seem inconsistent with the expectation that lung cancer risk, like the risk of epithelial tumors in general, would continue to increase with age."

The Holford data shown will for pedagogical reasons start from the age group 35-39. The age group 35-39 is in Figure 1 indicated by 35. Similarly, 40 indicates the age group 40-44. The peak in incidence is reached for the age group 70-74.

Holford's data for the rate of lung cancer incidence for women can now be compared to the Danish data for the death rate from lung cancer for women, shown in Figure 2.

The Danish data are available for 1977-2012. To underline the Holford puzzle, Figure 2 only shows the empirical data from 1977 to 2005. For practical purposes, the patterns in the Figures 1 and 2 are identical. Both peak for the age group 70-74.

As the periods cover five-years in Holford's data versus one year in the Danish data, Holford's curves are smoothed out compared to the curves for Danish data

Holford's article is about "incidence", while this article is about "death rates" from lung cancer. Nevertheless, the similarity between the two data sets is striking. The "Holford puzzle" that "rates tend to decline in the oldest age" is the same in the two datasets. The peak is reached in the age group 70-74 in Holford's data but in the age group 75-79 in the Danish data.

However, what is peculiar about the Holford puzzle is that if we for the Danish data include the observations from 2006 to 2011, we get a slightly different picture as shown in Figure 3.

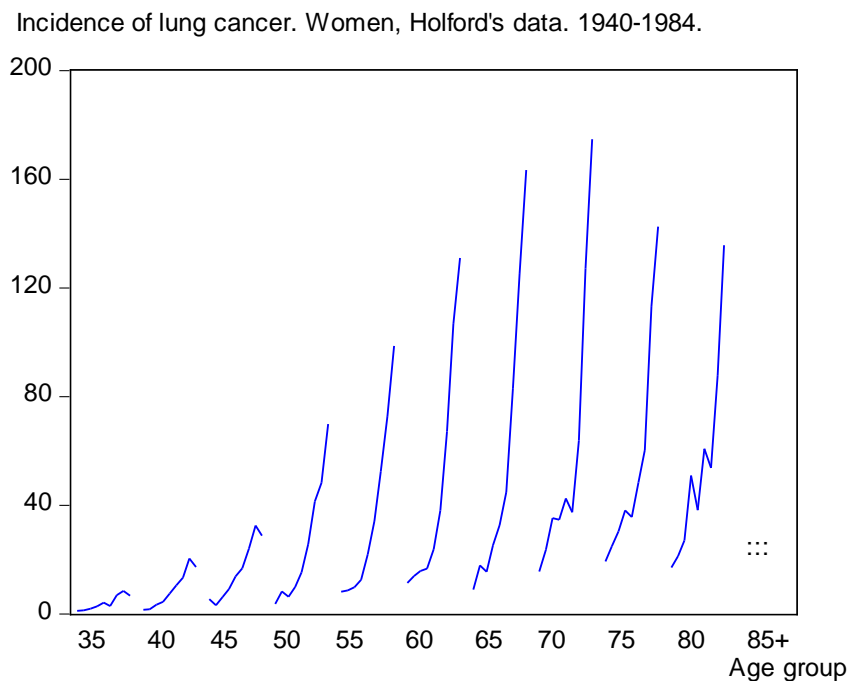


Figure 1: The incidence of lung cancer. Shown by Holford's data for women in Connecticut for each age group over the period 1940-1984.

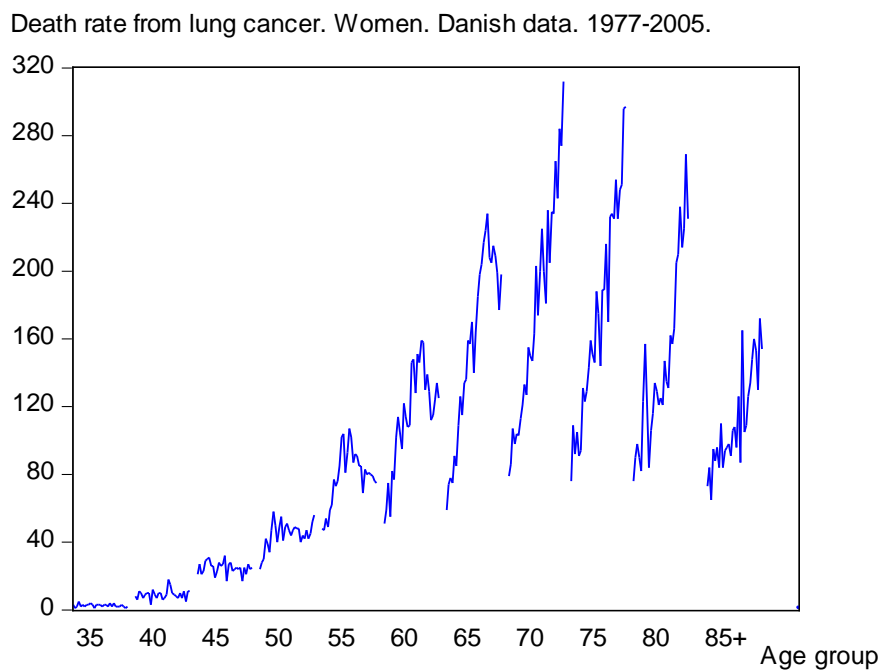


Figure 2: The death rate from lung cancer shown by data for Danish women for each age group over the period 1977-2005.

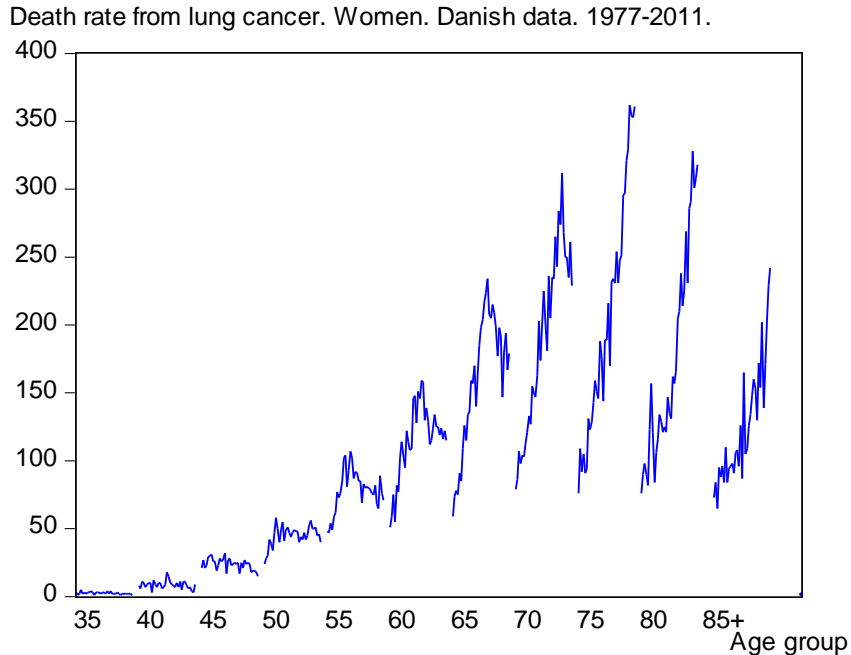


Figure 3: The death rate from lung cancer shown by data for Danish women for each age group over the period 1977-2011.

We see that the Holford puzzle is maintained. In Figure 3, however, the decline in death rates starts after the age of 75-79, not after the age of 70-74. Including the data from 2006-2011, we see that the top has now moved forward to the age group 75-79. What will happen if we move the data forward to 2022?

This opens for a discussion of what creates the Holford puzzle. We are here in line with Holford's use of the Age-Period-Cohort model.

## 2 Method

In line with Robinson and Jackson [11] the age-period-cohort effects are defined as follows: *Cohort effects* indicate that each new birth cohort enters (adult) life with a distinctive value of the dependent variable – in this case a detrimental cohort effect change with protective cohort effects over age in relation to lung cancer (see also Ryder [12]).

Cohort effects are not linearly related to time, and the cause of changing protective and detrimental effects is in general unknown.

### *The identification problem*

The basic assumption in most age-period-cohort studies is that cohort effects develop over age and period.

The identification problem caused by linearity between age, period, and cohort is well described elsewhere (Glenn [13]; Osmond and Gardner [7]; Breslow et al. [14], Clayton

and Schifflers [5], [6]; Holford [1]; Robertson and Boyle [15]; Rostgaard et al. [8]; Kristensen [4]).

Clayton and Schifflers discuss and exemplify the identification problem and also mention the “spurious cohort effects”, which can result from a sudden change in birth rates. This effect is not included in this paper, but can be shown for age groups from the age of 75 (Kristensen, [9]).

The numbers of deaths from a certain disease are count data. Estimations on count data are often based on Poisson regression (Clayton and Schifflers [5], [6]; Robertson and Boyle [15]; Rostgaard et al. [8]) and theoretically well founded (Brillinger [16]). Clayton and Schifflers argue that Weighted Least Squares and Poisson maximum likelihood might be equally efficient.

In empirical work, the Poisson regression seems less obvious to apply. Death rates (e.g. per 100,000 persons) have rounding errors, especially when rounded down to zero. Besides, there can be omitted explanatory variables as well as errors connected to the explanatory variables.

Likewise, it is difficult to test whether the assumptions for the Poisson regression are fulfilled; see for example Wooldridge ([17], p 646): “The variance-mean equality has been rejected in numerous applications, and later we show that assumption [19.2  $\text{Var}(y|\mathbf{x}) = E(y|\mathbf{x})$ ] is violated for fairly simple departures from the Poisson model.”

Consequently, this study applies Weighted Least Squares regression.

### 3 Data

Holford’s dataset with: Period “five years”, Age “five years” is held up against a Danish dataset with: Period “one year”, Age “five years”. The “death rate” is here applied instead of “mortality” to underline that the data are age specific.

Holford’s data are on the *incidence* of lung cancer for women in Connecticut. The Danish data on the *death rate* from lung cancer (women and men) are obtained from: The Danish Health and Medicines Authority (Statens Serum Institut [18]): Causes of death from cancer in trachea, bronchi, lung B-016 - here referred to as lung cancer. In principle, the present article is based on the total dataset for deaths from lung cancer in Denmark 1977-2012.

The explanatory variables: age (Age), period (T), and cohort (CohBorn).

T period (or year), 1970 = 1

Age age at death

DLCw actual death rate from lung cancer for women (Denmark)

DLCm calculated death rate from lung cancer for men (Denmark)

CohBorn cohort indicated by a dummy (CohBorn = 1) following diagonal a cohort over period and age. “Born” is the year of birth of the youngest person(s) in an age group. Applied age groups are 35-39 to 80-84 for the Holford data, and from 35-39 to 85+ for the Danish data. As the Danish empirical data runs 1977-2012, we see that 1977+35=2012. Accidentally the last included cohort is born in 1977.

Cohort coefficients express protective and detrimental effects according to year of birth that are supposed to influence the death rate over the entire life.

## 4 The Model

The Gompertz-Makeham equation is generally known and recognized as being very effective in describing death rates. Simplified and in the present notation the Gompertz-Makeham equation for death rates from apoplexy would be Gompertz (from 1825), and Gavrilova and Gavrilov [19]:

$$\text{DLCw} = \alpha e^{\beta_1 \text{Age}} \quad (1)$$

$$\text{Log(DLCw)} = \alpha_0 + \alpha_1 \text{Age} \quad (2)$$

However, no simple exponential function could match the death rate from lung cancer. The “new mortality trend”, which lets the death rate curve at all ages decline with almost the same percentage, was added to the Gompertz-Makeham equation:

$$\text{Log(DLCw)} = \alpha_0 + \alpha_1 \text{Age} - \alpha_2 T \quad (3)$$

To this almost classical model we now add what Manton and Stallard [20] call a “susceptibility parameter  $s$  [here called  $B$ ] as systematically vary with birth cohorts”.

$$\text{Log(DLCw)} = \alpha_0 + \alpha_1 \text{Age} - \alpha_2 T + \alpha_3 B \quad (4)$$

This formula was the basis for developing equation (5) into an Age-Period-Cohort model.

### 4.1 Modeling the Danish Death Rate from Lung Cancer

The unequal groupings are of Periods (one year) and Age (five years). For example, the earliest groups of two “different” cohorts start in 1892 and 1893.

In total 1892-1977 = 85 cohorts are represented by 85 diagonal dummy variables. Each dummy for a five-year age group in principle covers a diagonal across 12 age groups.

In the empirical estimations the youngest included cohort (where the youngest member was 35 years old) started in 1977.

The equation including the cohort effects is:

$$\text{Log(DLC)} = \alpha_1 / \text{Age} + \alpha_2 \text{Age} + \alpha_3 \text{Age}^2 + \alpha_4 / T + \alpha_5 \text{Age} / T^2 + \alpha_6 \text{Age}^2 / T^3 + \beta_1 \text{Coh1892} + \beta_2 \text{Coh1893} + \dots + \beta_{85} \text{Coh1977} \quad (5)$$

The creation of  $B$  will be explained in details below.

There is no constant element (origo regression), and therefore we can use dummies for the entire period 1892-1977. The equation was estimated by WLS using Age as weight.

$$\begin{aligned} \text{Log(DLC)} * \text{Age} = & \alpha_1 + \alpha_2 \text{Age}^2 + \alpha_3 \text{Age}^3 \\ & + \alpha_4 \text{Age} / T + \alpha_5 \text{Age}^2 / T^2 + \alpha_6 \text{Age}^3 / T^3 \\ & + \beta_1 \text{Coh1892} * \text{Age} + \beta_2 \text{Coh1893} * \text{Age} + \dots + \beta_{85} \text{Coh1977} * \text{Age} \end{aligned} \quad (6)$$

The time series formed by the beta coefficients ( $\beta_1 - \beta_{85}$ ) are shown for women in Figure 4 and for men in Figure 5.

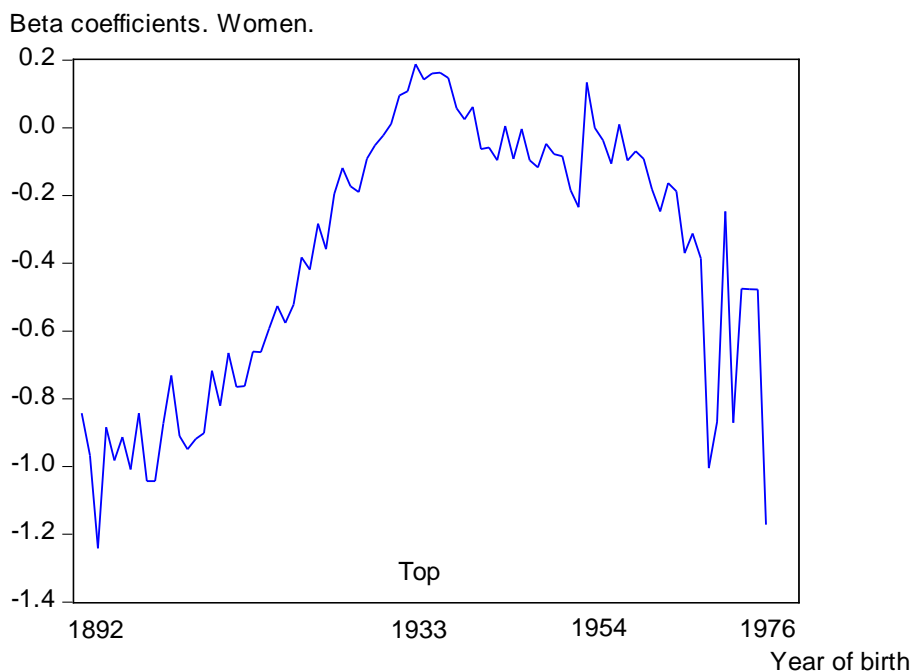


Figure 4: The beta coefficients 1892-1977 from the estimation of equation (5) for women.



Figure 5: The beta coefficients 1892-1977 from the estimation of equation (5) for men.

In themselves, the beta coefficients form a *time series* so that the discussion involves *two* time series: The time series for death rates and the time series for the cohort coefficients.

The beta coefficients show that women become weaker when born from 1907 to 1933 in relation to lung cancer. Born after 1933 they grow stronger. The top for men (the worst year) is in 1908. The top for women is 25 years later in 1933.

There is no solid biological explanation for the period of deterioration. This study takes it as a historical fact and looks at the consequences. An educated guess, however, is that women born in the period 1907 to 1933 will about 18 years later enter a period in their life where cigarette smoking becomes more and more popular in society among teenage girls.

## 4.2 Age-specific Estimations

Reorganizing the beta coefficients to explanatory variables in age-specific models improves the discussion on age-specific development in incidence and death rate. The  $\beta$  coefficients can be seen as variables when estimating incidence or death rate for the individual age groups and can be made in the following way:

*Step 1.* In order to get the information in the data diagonals the model must be estimated on the form given in equation (5) for the Danish data.

$$+ \beta_1 \text{Coh1892} + \beta_2 \text{Coh1893} + \dots + \beta_{85} \text{Coh1977} \quad (7)$$

The  $\beta$  coefficients can for the respective age groups be presented as shown in Table 1.

*Step 2.* For a given age group we have the model:

$$\begin{aligned} \text{Log(DLC)} = & [\alpha_1/\text{Age} + \alpha_2 \text{Age} + \alpha_3 \text{Age}^2] \\ & + \alpha_4 /T + [\alpha_5 * \text{Age}]/T^2 + [\alpha_6 * \text{Age}^2]/T^3 + B_{\text{Age}} \end{aligned} \quad (8)$$

Insertion of Age gives:

$$\text{Log(DLCwAge)} = \gamma_{0,\text{Age}} + \gamma_{1,\text{Age}}/T + \gamma_{2,\text{Age}}/T^2 + \gamma_{3,\text{Age}}/T^3 + B_{\text{Age}} \quad (9)$$



Table 1: The  $\beta$  coefficients seen as time series variables

Age	35	40	45	⋮	65	70	75	80	85+
Year\B <sub>Age</sub>	B <sub>35</sub>	B <sub>40</sub>	B <sub>45</sub>	⋮	B <sub>65</sub>	B <sub>70</sub>	B <sub>75</sub>	B <sub>80</sub>	B <sub>85</sub>
1977	$\beta_{51}$	$\beta_{46}$	$\beta_{41}$	⋮	$\beta_{21}$	$\beta_{16}$	$\beta_{11}$	$\beta_6$	$\beta_1$
1978	$\beta_{52}$	$\beta_{47}$	$\beta_{42}$	⋮	$\beta_{22}$	$\beta_{17}$	$\beta_{12}$	$\beta_7$	$\beta_2$
1979	$\beta_{53}$	$\beta_{48}$	$\beta_{43}$	⋮	$\beta_{23}$	$\beta_{18}$	$\beta_{13}$	$\beta_8$	$\beta_3$
1980	$\beta_{54}$	$\beta_{49}$	$\beta_{44}$	⋮	$\beta_{24}$	$\beta_{19}$	$\beta_{14}$	$\beta_9$	$\beta_4$
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
2011	$\beta_{85}$	$\beta_{80}$	$\beta_{75}$	⋮	$\beta_{55}$	$\beta_{50}$	$\beta_{45}$	$\beta_{40}$	$\beta_{35}$
2012	$\beta_{86}$	$\beta_{81}$	$\beta_{76}$	⋮	$\beta_{56}$	$\beta_{51}$	$\beta_{46}$	$\beta_{41}$	$\beta_{36}$
<i>Forecast</i>									
2013	$\beta_{87}$	$\beta_{82}$	$\beta_{77}$	⋮	$\beta_{57}$	$\beta_{52}$	$\beta_{47}$	$\beta_{42}$	$\beta_{37}$
2014	$\beta_{88}$	$\beta_{83}$	$\beta_{78}$	⋮	$\beta_{58}$	$\beta_{53}$	$\beta_{48}$	$\beta_{43}$	$\beta_{38}$
2015	$\beta_{89}$	$\beta_{84}$	$\beta_{79}$	⋮	$\beta_{59}$	$\beta_{54}$	$\beta_{49}$	$\beta_{44}$	$\beta_{39}$
2016	$\beta_{90}$	$\beta_{85}$	$\beta_{80}$	⋮	$\beta_{60}$	$\beta_{55}$	$\beta_{50}$	$\beta_{45}$	$\beta_{40}$
⋮									
2018	$\beta_{92}$	$\beta_{87}$	$\beta_{82}$	⋮	$\beta_{62}$	$\beta_{57}$	$\beta_{52}$	$\beta_{47}$	$\beta_{42}$
⋮									
2022	$\beta_{96}$	$\beta_{91}$	$\beta_{86}$	⋮	$\beta_{66}$	$\beta_{61}$	$\beta_{56}$	$\beta_{51}$	$\beta_{46}$

Step 3. As CohBorn is a dummy equal to one, the form of the models in practical estimation (or forecast) for women in the age group 80-84 becomes (remember that T=1 for 1970):

$$\begin{aligned}
 \text{Log(DLCw80}_{1977}) &= \gamma_{0,80} + \gamma_{1,80}/7 + \gamma_{2,80}/7^2 + \gamma_{3,80}/7^3 + \beta_6 \\
 \text{Log(DLCw80}_{1978}) &= \gamma_{0,80} + \gamma_{1,80}/8 + \gamma_{2,80}/8^2 + \gamma_{3,80}/8^3 + \beta_7 \\
 \text{Log(DLCw80}_{1979}) &= \gamma_{0,80} + \gamma_{1,80}/9 + \gamma_{2,80}/9^2 + \gamma_{3,80}/9^3 + \beta_8 \\
 &\vdots \\
 \text{Log(DLCw80}_{2011}) &= \gamma_{0,80} + \gamma_{1,80}/41 + \gamma_{2,80}/41^2 + \gamma_{3,80}/41^3 + \beta_{40} \\
 \text{Log(DLCw80}_{2012}) &= \gamma_{0,80} + \gamma_{1,80}/42 + \gamma_{2,80}/42^2 + \gamma_{3,80}/42^3 + \beta_{41}
 \end{aligned}
 \tag{9}$$

### Forecast

$$\text{Log(DLCw80}_{2013}) = \gamma_{0,80} + \gamma_{1,80}/43 + \gamma_{2,80}/43^2 + \gamma_{3,80}/43^3 + \beta_{42}$$

$$\text{Log(DLCw80}_{2014}) = \gamma_{0,80} + \gamma_{1,80}/44 + \gamma_{2,80}/44^2 + \gamma_{3,80}/44^3 + \beta_{43}$$

...

The  $\beta_i$  is thus (in this form) an element in an extra explanatory variable B with an expected coefficient of one. Having estimated  $\beta_i$  with equation (5), we can apply  $B_{Age}$  to estimate

the *age-specific* death rate for the period 1977-2012. The age-specific cohort effects are calculated on the *entire* dataset by equation (5).

For all age groups there are two methods to form a model for forecast:

a. Re-estimate the coefficients with the model used in Table 1.

$$\text{Log(DLC)} = \alpha_1/\text{Age} + \alpha_2 \text{Age} + \alpha_3 \text{Age}^2 + \alpha_4/\text{T} + \alpha_5 \text{Age}/\text{T}^2 + \alpha_6 \text{Age}^2/\text{T}^3 + \alpha_7 B_{Age} \quad (10)$$

b. Or apply the estimated coefficients from equation (5) together with  $B_{Age}$  setting  $\alpha_7 = 1$ .

## 5 The model forecast

The model forecast calculated by method b is shown in Figure 6.

The calculated death rates for the individual age groups are reported from 1977 to 2022. By following the 1977 death rates you will see the Holford puzzle, and likewise if you follow the tops. When you follow the 2022 calculated values of death rates, the Holford puzzle has disappeared. Figure 7 shows the same pattern for men.

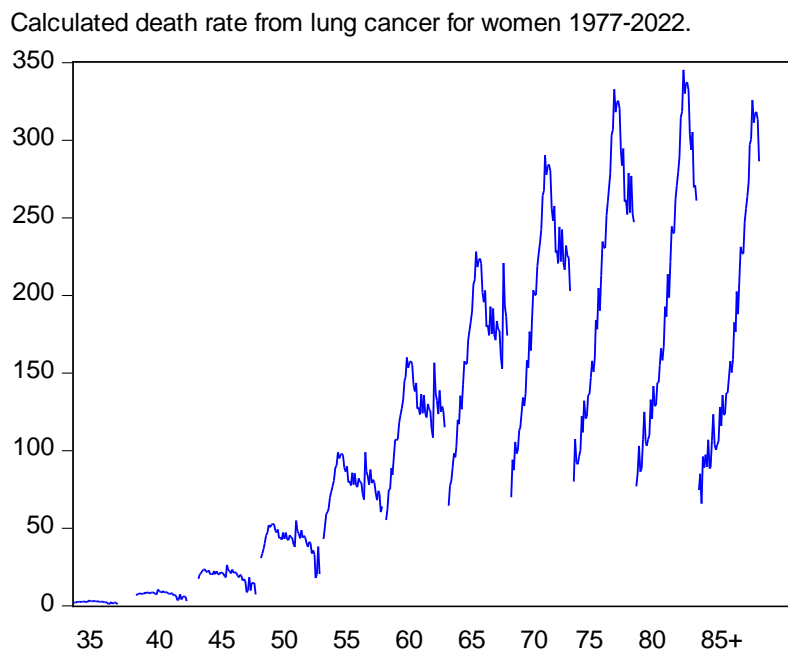


Figure 6: Death rates for women 1977-2022 calculated by method b.

### 5.1 The Death Rate from Lung Cancer for Men and Women

The focus will now be on the turning points in the death rates for men and women. Only the age groups from 55-59 to 85+ will be included.

Figure 7 shows how the tops of the detrimental cohort effect shown in Figures 4 and 5 are mirrored in the tops of the death rates for men and women, which is the very reason for the origin of the Holford puzzle. After 2018 the present model predicts a decline in the death rate from lung cancer for all age groups (even) without medical progress.

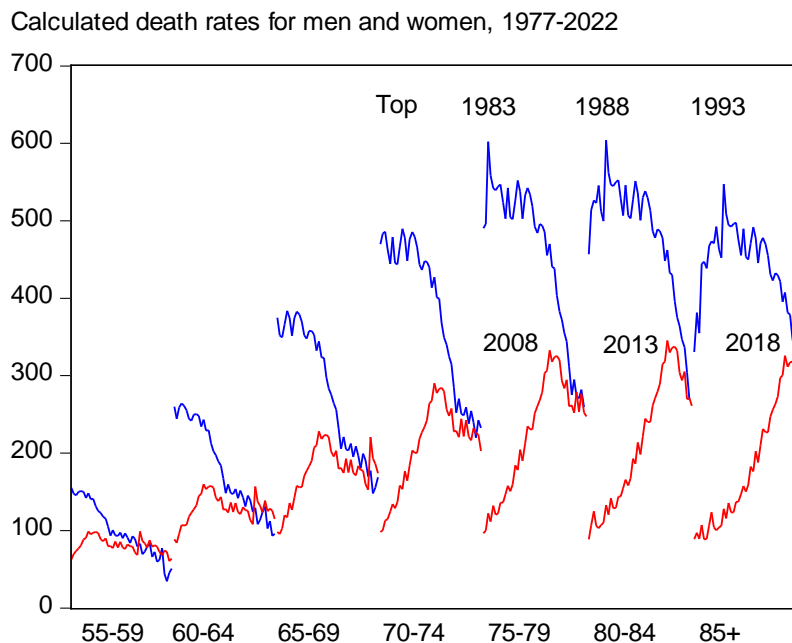


Figure 7: Calculated death rates for women and men 1977-2022 for the age groups 55-59 to 85+.

## 6 Discussion

The year of birth is here applied as the “starting points”, but other starting points could also be relevant. Cigarette smoking is associated with birth cohorts even if a cohort does not start smoking before the age of 15-19. Similarly, lung cancer is usually reported by year of diagnosis and age.

A weakness in the above estimations is that the results are quite sensitive to the specification of the models before inclusion of the cohort effect, especially of course when the data set is of limited size. Different specifications were tried for the Danish data. The differences in the results, however, were small, and in all cases the general picture could be maintained. Comparing Holford’s data with the Danish, we find a surprisingly high similarity between the incidences of lung cancer in Connecticut and the death rate from lung cancer in Denmark.

The increasing death rate from lung cancer for women was created in 1907-1933, and for men in 1892-1908.

Due to the vintage effect (Kristensen [9]), which involves that the old age groups are growing and their average age thereby declining, the model gives a too optimistic picture of the development of the death rate in those age groups. The death rates for age groups 80-84 and 85+ are therefore slightly underestimated.

Similar to lung cancer the basis for the death rate from COLD was laid down in the human body 30-40 years ago, see Lykkegaard et al. [21]. Using the cohort effects in the here described way the future development in the death rates for COLD can therefore, similar, be predicted.

## 7 Conclusion

This study shows that period, age, and cohort effects are dominating in a regression model for the death rate from lung cancer. Each cohort is traced by dummies following five-year age groups for each year of birth of the youngest group member.

The model shows protective and detrimental cohort effects in relation to the incidence of and death rate from lung cancer, and shows how diagonally calculated cohort effects can be used as variables in age-specific models.

The cohort effect is a powerful confounder which should be taken into account in describing health situations for a given age group.

The difference between using data with groupings into Periods (five years) and Age (five years), and data with groupings into Periods (one year) and Age (five years), is important but not destructive.

This study shows that more comparative cross-country studies on the same subject could be useful due to the striking parallel development between Connecticut and Denmark.

The applied method solves the Holford puzzle, about why the risk of death from lung cancer seemingly does not continue to increase from the age of 70-74.

This study gives an optimistic picture of the future development in death rates from lung cancer; a turnaround to the better for all age groups must be expected from about 2018.

## References

- [1] T.R. Holford. Understanding the effects of age, period, and cohort on incidence and mortality. *Annu. Rev. Publ. Health* **12**: (1991), 425-457.
- [2] C. Bosetti, F. Levi, F. Lucchini, E. Negri, C. la Vecchia. Lung cancer mortality in European women: recent trends and perspectives. *Annals of Oncology* **16**: (2005), 1597-1604.
- [3] F. Bray, B. Møller. Predicting the future burden of cancer. *Nat Rev cancer*. **6**: (2006), 63-74.
- [4] G.N. Kristensen. Cohort Coefficients. Describing the secular development in protective and detrimental cohort effects associated with apoplexy. *Journal of Statistical and Econometric Methods*. **2**, (4): (2013), 119-127.
- [5] D. Clayton, E. Schifflers. Models for temporal variation in cancer rates. I. Age period and age-cohort models. *Statistics in Medicine*, **6**: (1987), 449-467.
- [6] D. Clayton, E. Schifflers. Models for temporal variation in cancer rates. II. The age-period-cohort model. *Statistics in Medicine*, **6**: (1987), 469-481.
- [7] C. Osmond, M.J. Gardner. Age, Period and Cohort Models applied to Cancer Mortality Rates. *Statistics in Medicine*, **1**: (1982), 245-259.
- [8] K. Rostgaard, M. Vath, H. Holst, M. Madsen, E. Lynge. Age-period-cohort modeling of breast cancer incidence in Nordic countries. *Statistics in Medicine*, **20**: (2001), 47-61.
- [9] G.N. Kristensen. The Vintage Waves in the Death Rate Data for Apoplexy. (Paper presented at the *Symposium in Applied Statistics*; pp 209-219, (2013) University of Aarhus).
- [10] G.N. Kristensen. Testing ‘Clemmensen’s hook’ in the death rate from breast cancer. *Journal of Statistical and Econometric Methods*. **3**, (2): (2014), 15-30.

- [11] R.V. Robinson, E.F. Jackson. Is trust in others declining in America? An age-period-cohort analysis. *Social Science Research* **30**: (2001), 117-145.
- [12] N.B. Ryder. The Cohort as a Concept in the Study of Social-Change. *American Sociological Review*, **30**: (1965), 843-861.
- [13] N.D. Glenn. Cohort Analysts' Futile Quest: Statistical Attempts to Separate Age, Period and Cohort Effects. *American Sociological Review*, **41** (5): (1976), 900-904.
- [14] N.E. Breslow, J.H. Lubin, P. Marek, and B. Langholz. Multiplicative Models and Cohort Analysis. *Journal of the American Statistical Association*, **78** (381): (1983), 1-12.
- [15] C. Robertson, P. Boyle. Age-period-cohort analysis of chronic disease rates. I: Modeling approach. *Statistics in Medicine*, **17**: (1998), 1305-1323.
- [16] D.R. Brillinger. The Natural Variability of Vital Rates and Associated Statistics. *Biometrics*, **42**, (4): (1986), 693-734.
- [17] J.M. Wooldridge. *Econometric Analysis of Cross Section and Panel Data*. The MIT Press, Cambridge, Massachusetts, London, England, (2002).
- [18] Statens Serums Institut. *Kræftoverlevelse i Danmark fra 1997 til 2011*. (2014).
- [19] N.S. Gavrilova and L.A.Gavrilov. Aging and Longevity: Mortality laws and mortality forecasts for aging populations. *Demografie*, **53** (2): (2011), 109-128.
- [20] K.G. Manton, and E. Stallard. A Two-Disease Model of Female Breast Cancer: Mortality in 1969 Among White Females in the United States. *Journal of the National Cancer Institute* **64**(1): (1980), 9-16.
- [21] J. Lykkegaard, J.R. Davidsen, M.S. Paulsen, M. Andersen, J. Søndergaard. On the crest of a wave: Danish prevalence of hospitalization-required COPD 2002-2009. *Respiratory Medicine* **106**, (2012), 1396-1403.