

Frailty modelling of testicular cancer incidence using Scandinavian data

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SUMMARY

The incidence of testicular cancer is highest among young men, and then decreases sharply with age. This points towards a frailty effect, where some men have a much greater risk of testicular cancer than the majority of the male population. Those with the highest risk get cancer, drain the group of individuals at risk, and leave a healthy male population which has approximately zero risk of testicular cancer. This leads to the observed decrease in incidence. We discuss a frailty model, where the frailty is compound-Poisson-distributed. This allows for a non-susceptible group (of zero frailty). The model is successfully applied to incidence data from the Danish and Norwegian registries. It is indicated that there was a decrease in incidence for males born during World War II in both countries. Bootstrap analysis is used to find the degree of variation in the estimates. In the Armitage–Doll multistage model, the estimated number of transitions needed for a cell to become malignant is close to 3 for non-seminomas and 4 for seminomas in both the Danish and Norwegian data. This paper demonstrates that a model including a frailty effect fits the incidence data well and gives interesting results and interpretations, although this is no proof of the effect's truth.

Keywords: Carcinogenesis; Compound Poisson; Frailty; Susceptibility; Testicular cancer.

1. INTRODUCTION

Modelling of cancer incidence rates has a long tradition. Fisher and Hollomon (1951) and Nordling (1953) found that the logarithm of the death rate for cancer increased six times as rapidly as the logarithm of the age. The suggestion made by Nordling to explain this relationship was that a cancer cell could be the end result of seven successive mutations. This was the inspiration for the multistage model of Armitage and Doll (1954). However, the Armitage–Doll model and the other standard models of carcinogenesis refer to the development in single individuals. If the models are applied to populations of individuals, there are good reasons why one has to allow the parameters in the models to vary between individuals. The risk of

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the occurrence of the various stages leading to malignancy may differ substantially. There are a number of known factors that may increase the risk of various cancers. Undoubtedly, there will also be a large number of still unknown factors that could influence carcinogenesis. Among these, genetic factors will be prominent and increasingly in focus, but certainly also many environmental and lifestyle factors remain to be discovered. The variation in risk factors could lead to incidence curves which decline at a certain age, even though the hazard at individual level is increasing for the bulk of the population. This paper shows how the presence of frailty in an Armitage–Doll model can explain the observed incidence curves.

Incidence rates of cancer usually have to be inferred from data collected by cancer registries. These data do not commonly contain detailed information about individuals' risk factors. One is then faced with the fact that the individual risk factors are generally unknown in studies used to explain incidence patterns. To account for their influence, one has to allow for some random quantity to model individual heterogeneity. This is precisely what is done in frailty theory, where the hazard is multiplied by some random factor which represents the varying level of risk of different individuals (see e.g. Manton *et al.* (1997)).

The incidence of testicular cancer reaches a peak at 30–35 years of age, and then decreases sharply. This points towards a frailty effect, with some men having a much greater risk of testicular cancer than the majority of men. When those with the highest risk get cancer, the remaining population consists mainly of individuals who are virtually non-susceptible to cancer. This paper is a follow-up of a previous paper presented in an epidemiological setting (Aalen and Tretli, 1999), where a frailty model threw light on this selection. They used a compound Poisson frailty distribution, which naturally allows for a non-susceptible group (of zero frailty). The most important parameter is the proportion of susceptibles. The model corresponds well to biological theories concerning the etiology of testicular cancer (Henderson *et al.*, 1988). There has been a strong increase of testicular cancer in recent birth cohorts, suggesting an environmental effect. Because of this, the proportion of susceptibles was modelled as a function of birth cohorts.

This paper uses the same model as Aalen and Tretli (1999) on incidence data from both the Norwegian and Danish cancer registries, we shall compare the characteristics in cancer incidence over calendar time and age for the two countries. Important issues are the parameter estimates, the increase in incidence over calendar time and the decrease in incidence observed during World War II (see e.g. Bergström *et al.* (1996) and Aalen and Tretli (1999)). Bootstrap estimation is used to get information on the uncertainty of the estimates.

For reviews of frailty theory, see for example the introductions by Aalen (1994) or Hougaard (2000). As usual in frailty theory we will assume that the hazard rate (i.e. incidence rate) of cancer for an individual equals the product of an individual-specific quantity Z and a basic rate $\lambda(t)$, hence the individual hazard rate is $Z\lambda(t)$, where t denotes age. The basic rate is common to all individuals and specifies how the hazard changes with age. The frailty variable, Z , specifies the level of the hazard for the given individual, a high value of Z giving a large risk for this individual, and a low value giving a small risk.

Obviously, this frailty model is a simplification. However, as pointed out above, there are biological reasons to believe that a considerable part of the frailty variation is determined by events happening very early in life (Aakre *et al.*, 1996; Wanderaas *et al.*, 1998), and it is therefore reasonable to assume a fixed frailty variable independent of t . Furthermore, the concept of frailty here may also include hereditary differences, which are of course determined at conception.

In order to apply the model one has to assume a reasonable distribution for the frailty Z , and a reasonable shape for the basic hazard rate $\lambda(t)$. When applying frailty models in a univariate setting, the analysis is often quite speculative since one has little knowledge about both the frailty distribution and the basic hazard. However, in testicular cancer there is a good biological basis for making these assumptions, and the frailty modelling in this setting is not particularly speculative. This is not to deny that a good fit of the model is no proof of its truth, and other models can give equally good results.

2. FRAILTY AND MULTISTAGE MODELS

The basic hazard rate is influenced by the process of carcinogenesis, i.e. development of cancer, for which a number of well established statistical models exist. These models of carcinogenesis operate at the level of the individual, so they disregard the frailty effect. The classical multistage model of cancer development (the Armitage–Doll model, Armitage and Doll (1954)) leads to the assumption that $\lambda(t)$ is the hazard rate of a Weibull distribution. This may also be inferred from extreme value theory. One may imagine that cancer arises by one cell turning malignant (or giving rise to a daughter cell that turns malignant). There are innumerable cells for which this could happen, and the probability distribution of the time required for the first malignant cell would therefore be expected to follow an extreme value distribution. This argument was put forward by Pike (1966). The Weibull distribution is one of the most frequently applied extreme value distributions. In many cases empirically obtained incidence curves have an approximate Weibull shape. The similarity between empirically obtained curves and the hazard rate of an Armitage–Doll model is one of its strengths, and the primary reason why the model is used.

There are also a number of other more complex models of carcinogenesis, see for example Kopp-Schneider (1997) for an excellent review. However, the resulting expressions for the distribution of time to tumour are far more complex and not suitable for the statistical analysis carried out here. It appears, though, that under quite wide assumptions the Weibull distribution is a good approximation as the time to tumour in carcinogenesis (Kaldor and Day, 1987; Kopp-Schneider and Portier, 1991).

The Weibull model has the form $\lambda(t) = at^k$. In multistage models the number $k + 1$ is biologically interpreted as the number of transitions necessary to reach malignancy. So, one might think that the variation between individuals is mainly in the factor a , which is what the frailty model assumes.

By adding a frail proportion of individuals to a population in an Armitage–Doll model, we will show the effect this has on the hazard curve of the total cohort. The model is illustrated above left in Figure 1. It is a discrete-time Markov chain with seven states of malignancy development, where all states are transient except for state seven, which is an absorbing state. This corresponds to a phase type distribution. The cell starts as a normal cell in state one and reaches full malignancy in state seven. After having reached state seven, the cell subsequently gives rise to a clone, thus starting the neoplasia. If p_1, \dots, p_6 denote one-step transition probabilities, the transition probability matrix is given by

$$\mathbf{P} = \begin{pmatrix} 1 - p_1 & p_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 - p_2 & p_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 - p_3 & p_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 - p_4 & p_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 - p_5 & p_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 - p_6 & p_6 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

The model illustrated here is irreversible, which may not be expected in biological systems with repair and tumour suppressor mechanisms. A model with non-zero elements on the sub-diagonal can yield different shaped hazard curves, see Aalen (1995). Of course, the transition probability p_1 is most important in determining the shape of the hazard curve. A large value of p_1 gives a steeper curve. The time index set for the Markov chain is $T = (0, \dots, 80)$, which can be viewed as the age of an individual in years. To be comparable to the clinical incidence curves, one has to assume that the time from malignant cell to clinically detectable tumour is relatively constant between individuals. The frailty effect is produced by adding a small proportion of individuals (e.g. 1%) who are at great risk of obtaining malignant cells, parallel to the testicular carcinoma situation. The rest of the population (99%) is regulated to have a very low risk, and a Weibull-shaped hazard for the malignancy. All individuals start in state one. Let $\mathbf{S}(t)$ be the

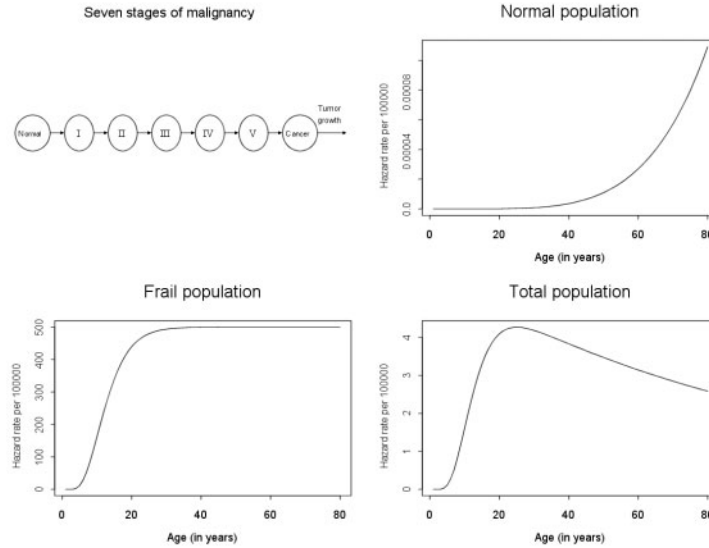


Fig. 1. The effect of mixing a frail population with a normal population in an Armitage–Doll model. Illustration of the model and hazard curves of the normal, frail and mixed populations based on artificial data.

vector showing the distribution of the seven states at time t . The seventh element of $\mathbf{S}(t) = \mathbf{S}(t-1)^T \times \mathbf{P}$ is the number of individuals who have reached malignancy at t .

Let N be the total number of individuals, and let $n(t)$ and $f(t)$ be the number of malignancies at time t in the normal and frail population, respectively. In this example, we assume that there are a total of 1000 individuals in the population. However, the size of the population does not affect the shape of the curves. The hazard curve for the normal population can be produced by calculating the number of new malignancies divided by the number at risk for each time index:

$$\frac{n(t) - n(t-1)}{N - n(t-1)}. \quad (2.1)$$

This is shown above right in Figure 1, and roughly follows a Weibull distribution. The transition probabilities are $p_1 = 0.00350$, $p_2 = 0.00035$, $p_3 = 0.00035$, $p_4 = 0.00035$, $p_5 = 0.00350$, $p_6 = 0.00350$. The hazard curve of the frail population is calculated correspondingly to equation (2.1), and is shown below left in Figure 1. The parameters are fitted to account for a much greater probability for malignancy, which is reflected in the hazard curve. The frail population has larger transition probabilities relative to the normal population. The values are $p_1 = 0.005$, $p_2 = 0.350$, $p_3 = 0.350$, $p_4 = 0.150$, $p_5 = 0.150$, $p_6 = 0.150$. The hazard curve for the total population can be produced by calculating the weighted hazard

$$\frac{0.99 \times \{n(t) - n(t-1)\} + 0.01 \times \{f(t) - f(t-1)\}}{N - 0.99 \times n(t-1) - 0.01 \times f(t-1)},$$

for each time index. The result is shown below right in Figure 1. We see that the hazard curve starts to fall at a certain age, as if the probability for malignancy, given that one has not reached it at this point, goes down. This is the frailty effect.

3. APPLICATION TO TESTICULAR CANCER DATA

3.1 The compound Poisson frailty model

As in Aalen and Tretli (1999), Z is assumed to be compound-Poisson-distributed. The distribution has a discrete part at 0 for men with zero frailty, and a continuous part corresponding to positive frailties. This deals with the fact that most men are virtually non-susceptible to cancer, as well as giving a simple formula for the population survival function when integrating out the frailty. Furthermore, it is rather easy to include further hierarchical levels, like family membership, in the model. The distribution belongs to the three-parameter family of power variance function (PVF) distributions which are much used in frailty theory (Hougaard, 2000). The PVF distributions also include the gamma, inverse Gaussian and stable distributions.

The distribution is defined as a sum of N independent gamma-distributed variables X_i with scale and shape parameter ν and η , where N is a Poisson-distributed random variable with expectation ρ . The probability of zero frailty is given by

$$p = P(Z = 0) = \exp(-\rho).$$

In a way, the distribution can be seen as a sum of a random number of impulses, from different unknown factors, where each impulse contributes to the total frailty of an individual.

The survival function of an individual with a given frailty is $\exp\{-Z \Lambda(t)\}$, where $\Lambda(t) = \int_0^t \lambda(s) ds$. Integrating out the unknown frailty variable, produces the population survival function $S(t) = L_Z(\Lambda(t))$, where $L_Z(a)$ denotes the Laplace transform of Z . The Laplace transform of the compound Poisson distribution (Aalen, 1992) are

$$L_Z(s) = \exp[-\rho\{1 - L_X(s)\}],$$

where $L_X(a)$ denotes the Laplace transform of X_i . Hence the population survival function and hazard rate are

$$S(t) = \exp\{-\rho + \rho L_X(\Lambda(t))\} \quad \gamma(t) = -\rho L'_X(\Lambda(t)) \lambda(t). \quad (3.2)$$

In the gamma case, $L_X(s)$ is given by $(1 + \nu^{-1}s)^{-\eta}$. By using this, and inserting the Weibull basic rate with $a = 1$ to avoid over-parametrization, we get the following population survival function and hazard rate (Aalen, 1992):

$$S(t) = \exp\left\{\rho \left(1 + \frac{1}{\nu} \frac{1}{k+1} t^{k+1}\right)^{-\eta} - \rho\right\} \quad \gamma(t) = \frac{\left(\frac{\rho\eta}{\nu}\right)t^k}{[1 + \{\nu(k+1)\}^{-1}t^{k+1}]^{\eta+1}}. \quad (3.3)$$

The individual hazard rate increases indefinitely for $k > 0$. The equation $\gamma'(t) = 0$ has three solutions: $t = 0$, $t = \left\{\frac{1+k(\eta+1)}{k(k+1)\nu}\right\}^{k+1}$, and $t = \infty$. Since the curve starts at zero at $t = 0$, the population hazard rate is unimodal, and has a maximum at $t = \left\{\frac{1+k(\eta+1)}{k(k+1)\nu}\right\}^{k+1}$.

An important feature of the hazard rate in equations (3.2) and (3.3) is that the Poisson parameter ρ is a proportionality factor. Hence, if covariates are introduced only into this parameter, we have a proportional hazards model. An interesting issue is that the frailty model in this case actually leads to proportional hazards, whereas most models of frailty type would lead to non-proportional hazards. Since proportional hazards play such a fundamental role in survival analysis, it is nice to see that proportionality can occur naturally, instead of being an assumption introduced just for convenience.

The result here is a special case of a more general result for proportional hazards and Lévy processes (Aalen and Hjort, 2002). As another example, let the frailty be gamma-distributed. Then, if covariates are included only in the shape parameter of the gamma distribution, the resulting marginal model will have proportional hazards. The connection between this and the compound Poisson example is the fact that covariates are introduced via the time parameter of a Lévy process.

3.2 Data and statistical analysis

Norwegian incidence data have been collected by the Cancer Registry of Norway, which has received information on all cancer patients in the country since 1953. The reporting of cancer cases is compulsory for physicians. The reporting system is based on pathology and cytology reports, clinical records and death certificates. Ninety-eight per cent of testicular tumours are histologically verified. The Danish Cancer Society established one of the world's first cancer registries, which includes cancers diagnosed since 1943. In the statistical analysis all testicular cancers reported between 1943 and 1997 in Denmark and between 1953 and 1997 in Norway are included. The data are separated into seminomas or non-seminomas, and the same model is used for both.

We use the same model as in Aalen and Tretli (1999). The data are divided into 18 five year birth cohort intervals, starting with 1885–89 and going up to 1970–74, and 13 age intervals, 0–14 years, 15–19 years, 20–24 years, . . . , 65–69 years, 70 years and above. As in Aalen and Tretli (1999), let R_{ij} be the number of observed testicular cancer cases of a specified type in birth cohort i and age group j , and let T_{ij} be the number of person years at risk. The partition points of the age intervals, starting with 15 years and going up to 70 years, are denoted by t_1, \dots, t_{12} . We exclude the age interval 0–14 years. There are very few cancers in early childhood, and they are presumably of a different kind than those occurring after the start of sexual maturity (Jørgensen *et al.*, 1993). We assume that time $t = 0$ in the frailty model is the 13th birthday of the individual.

Define the expected number of cases, μ_{ij} , as the average hazard rate per year for birth cohort i and age interval j multiplied by the number of person years:

$$\mu_{ij} = T_{ij} [\ln \{S(t_{j-1} - 13)\} - \ln \{S(t_j - 13)\}] / 5. \quad (3.4)$$

The likelihood function, based on a Poisson model, is given as follows:

$$L = \prod_{i=1}^{18} \prod_{j=2}^{13} \mu_{ij}^{R_{ij}} \exp(-\mu_{ij}).$$

Parameters to be estimated by the method of maximum likelihood are the Weibull shape parameter k , the Poisson parameter ρ and the scale and shape parameters ν and η of the underlying gamma distributions. A penalized likelihood term is added to account for changes in the parameter ρ over calendar time. Each birth cohort is then assumed to have its own specific value, ρ_i for cohort i , so only the probability p of susceptibility is assumed to change with time. Since the damage leading to testicular cancer is supposed to take place during the foetal development (Henderson *et al.*, 1988), a change in risk of damage over time would give a birth cohort effect, but no period effect (Wanderaas *et al.*, 1998). This leads to a pure cohort model. The seminomas and non-seminomas are analysed separately.

The following penalization term is subtracted from the log likelihood (we define $\rho_0 = 0$):

$$\frac{1}{2} \delta \sum_{i=1}^{18} (\rho_i - \rho_{i-1})^2.$$

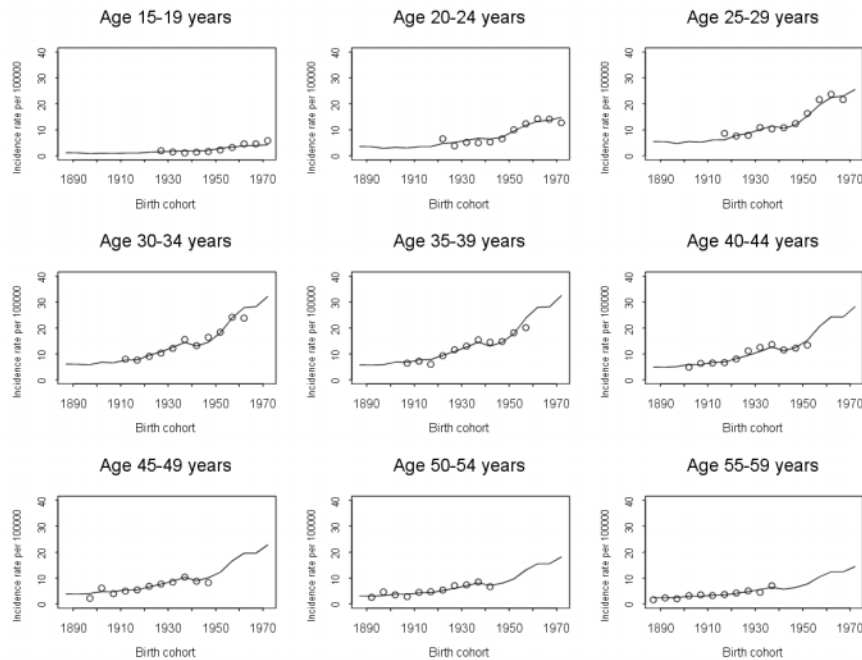


Fig. 2. Observed (discrete points) and expected (continuous curve) incidence rates for testicular cancer by cohort for some age groups. The curves include both seminomas and non-seminomas from Denmark and Norway.

The parameter δ determines the extent of smoothing to be applied. In our analysis we put $\delta = 4$, as in Aalen and Tretli (1999).

We are especially interested in how the proportion of susceptible individuals develops over time, that is, in plotting the values $p_i = 1 - \exp(-\rho_i)$. A plot was given in Aalen and Tretli (1999), but with no indications of uncertainty. Since the penalization term will give strong correlations between the estimates for cohorts close to each other, simply drawing pointwise confidence intervals on a plot of p_i versus cohort is not very informative. The degree of smoothness of the curves will not be indicated in such a plot. Instead we will show the results of the bootstrap estimation. The advantage of the bootstrap is that features of the curves can be judged for their significance in a far more flexible way than with more traditional methods.

3.3 Results

The estimates from the penalized likelihood are shown in Table 1. Compared to the previous publication (Aalen and Tretli, 1999), the birth cohort intervals are shifted one year to match the intervals of the acquired Danish data. Hence, the parameter estimates from the Norwegian data in Table 1 are not exactly equal to the estimates given there. The higher incidence of testicular cancer in Denmark is probably the reason why most of the Danish parameters have somewhat smaller standard errors than the Norwegian parameters. One may test if ν , η and k are equal for the two countries, which yields proportional hazards. Since the Danish and Norwegian data are independent, the pooled standard error of each parameter is $\sqrt{se_{\text{Denmark}}^2 + se_{\text{Norway}}^2}$. We assume that the difference between the parameters divided by the pooled standard error follows an approximately standard Normal distribution. The tests for equal parameters for

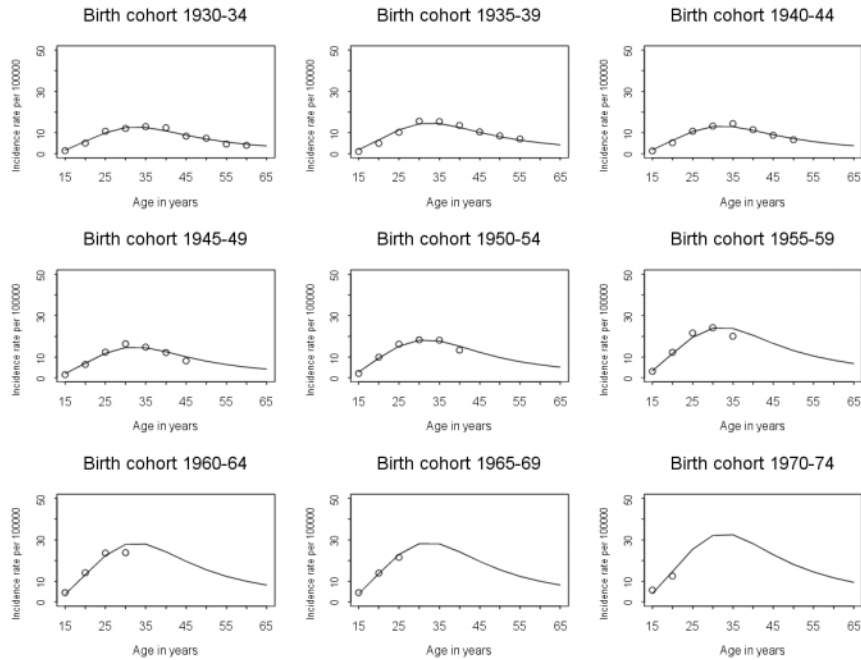


Fig. 3. Observed (discrete points) and expected (continuous curve) incidence rates for testicular cancer by age group for some of the most recent cohorts. The curves include both seminomas and non-seminomas from Denmark and Norway.

Table 1. Maximum likelihood estimates of the parameters

Parameters	Seminomas		Non-seminomas			
	ν	η	k	ν	η	k
Danish						
Estimates	1.76×10^5	0.25	3.37	1.21×10^3	0.23	2.13
se	0.51×10^5	0.06	0.14	0.23×10^3	0.07	0.15
Norwegian						
Estimates	8.98×10^4	0.33	3.09	1.18×10^3	0.32	2.08
se	3.10×10^4	0.10	0.18	0.30×10^3	0.11	0.19
Joint analysis						
Estimates	1.34×10^5	0.30	3.26	0.98×10^3	0.35	2.00
se	0.30×10^5	0.06	0.12	0.12×10^3	0.06	0.10

seminoma cancer give two-sided p -values of 0.17, 0.73 and 0.22 for ν , η and k , respectively. For non-seminomas, the corresponding p -values are 1, 0.49 and 0.83. Hence, we assume that the hazards are proportional, and carry out a joint analysis. The resulting estimates are shown at the bottom of Table 1. Figures 2 and 3 demonstrate the good fit of the model to the Danish data. Since examples of good fit to the Norwegian data were given in Aalen and Tretli (1999), we will not repeat those figures here.

Figures 4 and 5 show the estimated proportions of susceptibles, p , in the two countries for seminomas

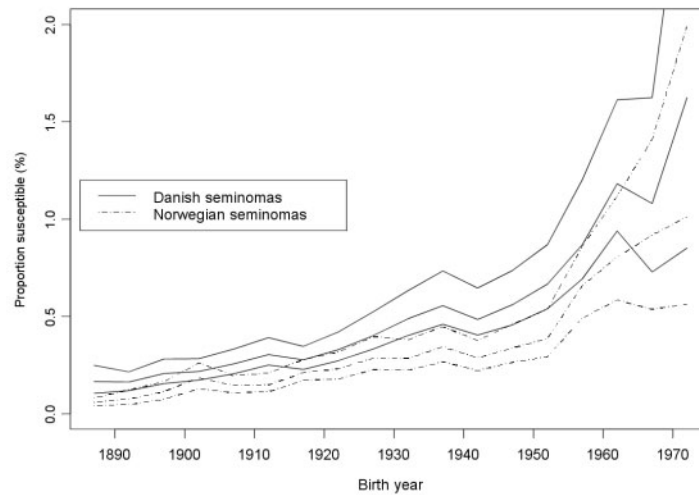


Fig. 4. Estimated proportion (middle curve) of men susceptible to seminoma cancer in Denmark and Norway with pointwise 95% confidence bands based on 200 bootstrap samples.

and non-seminomas, respectively. They also include 95% pointwise confidence bands based on the percentile method (Efron and Tibshirani, 1993, chapter 13) from 200 bootstrap samples. The increase in the proportion of susceptible men in recent birth cohorts is obvious in all four curves, but particularly for Danish seminomas. The confidence bands are wider for the most recent birth cohorts, since these are incomplete. One may perform an overall test for the difference in proportion of susceptibles in Denmark and Norway by adding the 200 seminoma and non-seminoma bootstrap samples, and accumulating over all 18 birth cohorts. This yields 3526 out of 3600 samples with positive differences, giving a two-sided p -value of 0.04. All birth cohorts show a significant difference at the 5% level, except the 1900–04 cohort and the two most recent cohorts.

In Aalen and Tretli (1999), it was indicated that there was a slight decrease in risk during World War II in Norway. This also seems to be the case in Denmark, at least for seminoma cancer. Both Denmark and Norway were under German occupation in World War II between 1940 and 1945. This is evident in Figure 6, which shows the estimated proportion of men susceptible to seminoma cancer in the birth cohorts around World War II. Since the plotting of more samples in the same figure yields a dense plot of curves which cannot be distinguished individually, we have chosen to show just 20 samples. A sample of 200 bootstraps from the Danish seminoma data shows that 197 of the estimated curves drop during World War II, giving a two-sided p -value of 0.03. A 95% confidence interval for the difference in proportion of susceptibles between the 1940–44 cohort and the 1935–39 cohort is $(-0.134\%, -0.007\%)$. A similar bootstrap from the Norwegian seminoma data produces 194 incidence curves that drop during the war, corresponding to a p -value of 0.06. The confidence interval for the difference is $(-0.116\%, 0.003\%)$. For non-seminoma cancer, the bootstrap sample of 200 shows at best a levelling off in the proportion of susceptibles during the war. The confidence intervals for the difference are $(-0.058\%, 0.039\%)$ and $(-0.023\%, 0.061\%)$, for Denmark and Norway respectively.

As an illustration, we can use the model to predict the development in the number of testicular cancer cases over calendar time. If we assume that the age and population distributions do not change, and that

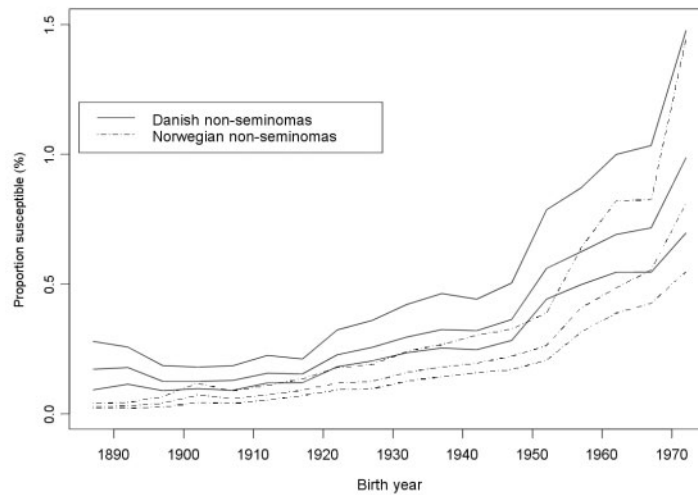


Fig. 5. Estimated proportion (middle curve) of men susceptible to non-seminoma cancer in Denmark and Norway with pointwise 95% confidence bands based on 200 bootstrap samples.

the proportion of susceptibles (decided by the parameter ρ) is constant since the most recent birth cohorts, the expected number of new cases per year can be calculated from equation (3.4). For instance, to get the total number of cancer cases in the calendar period from 1985–89, we add the expected number of cancers in the age groups 15–19 year-olds born in 1970–74, 20–24 year-olds born in 1965–69, and so on. For future calendar periods, we use the expected number of cancers in the different age groups from the 1970–74 cohort. The population sizes are 1.9 million for Denmark and 1.5 million for Norway. These correspond to the mean numbers of males over 14 years of age in 1985–89. The population increases slowly in both countries. For the Norwegian data, this gives a prediction curve with a starting point near the most recent observed value of 246 cases in 1999, shown in Figure 7. As all data are organized in five-year intervals, the figure shows the mean number of cases per year in future five-year periods from 1995–99 up to 2030–34. For the Danish data, however, using the 1970–74 cohort as a basis for the curve gives a starting point which is far too high. The resulting estimate for the period 1995–99 is 379 cases per year, while the observed number of testicular cancer cases in Denmark today is around 300. This indicates that the ρ for the 1970–74 cohort is overestimated, as it is based on only two observed values. Instead, we have used the ρ from the 1965–69 cohort as the most recent estimate from the Danish data. This gives a curve which starts at 310 cases per year, shown in Figure 7. As more and more cohorts are dominated by the ρ from the most recent birth cohort, the curves flatten out. The figure clearly illustrates the dynamics of the population, since the number of cases continues to increase for several years, even though the proportion of men susceptible to testicular cancer is assumed constant after the 1970–74 and 1965–69 birth cohorts.

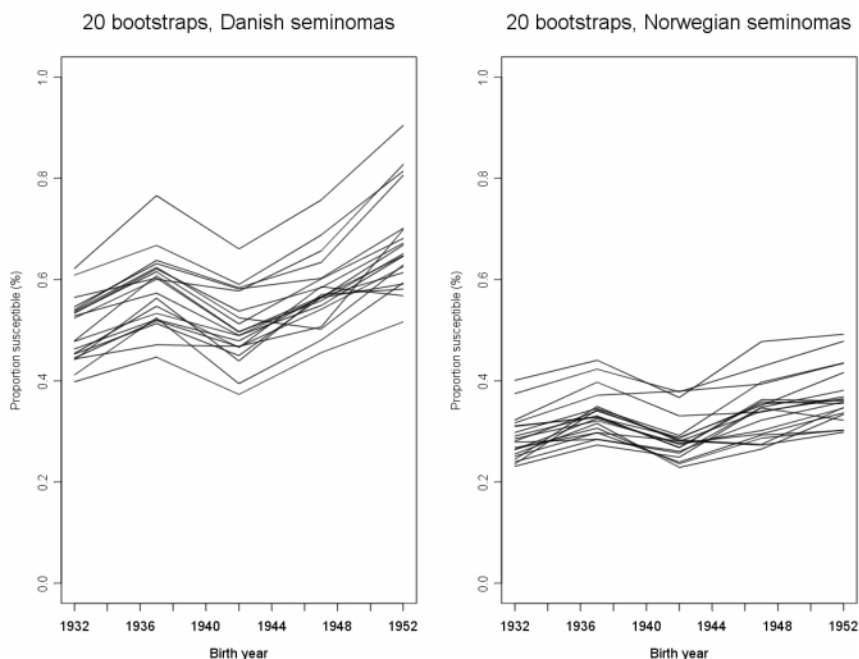


Fig. 6. 20 bootstrap estimates for the proportion of Danish and Norwegian men susceptible to seminoma cancer in the birth cohorts around WWII.

4. DISCUSSION

An important question is whether the incidence in susceptibility is still rising today, or is levelling off. The overestimated ρ for the 1970–74 cohort from the Danish data clearly illustrates that this question is difficult to assess. Figures 4 and 5 indicate that the incidence continues to increase, except perhaps for Norwegian seminomas. For this group the estimated proportion could be levelling off for individuals born after 1964. Of the 200 bootstrap samples, 77 even yield a decrease in the estimated proportion of susceptibles from birth cohort 1965–69 to 1970–74. However, the estimates are based on few observations for these cohorts, and Figure 4 shows that the observation is consistent both with a decline in susceptibility, and with a continued strong increase.

Prediction of testicular cancer development in the Nordic countries up to 2022 has been done by Møller *et al.* (2002, pp. 50–1). They applied a Poisson regression-based age-period-cohort model, and projected trends in incidence from recent to future periods. To avoid the problem with rates that grow exponentially over time, they used a power link instead of a log link. They also projected only half the linear trends for the periods 2013–17 and 2018–22, based on the belief that the curves would eventually tend to flatten. This resulted in a significantly lower number of cases per year than the compound Poisson frailty model. In addition, the predicted incidence curves for Denmark and Norway seem to cross after 2020, which is not possible in the simple prediction model used here. Still, the curves presented here correspond to a conservative prediction from the compound Poisson frailty model, since the proportion of susceptibles is assumed to be constant for future birth cohorts.

An interesting feature is the drop or levelling off in estimates both for Norwegian and Danish men born during World War II. This was observed in the original estimates (Aalen and Tretli, 1999) and are

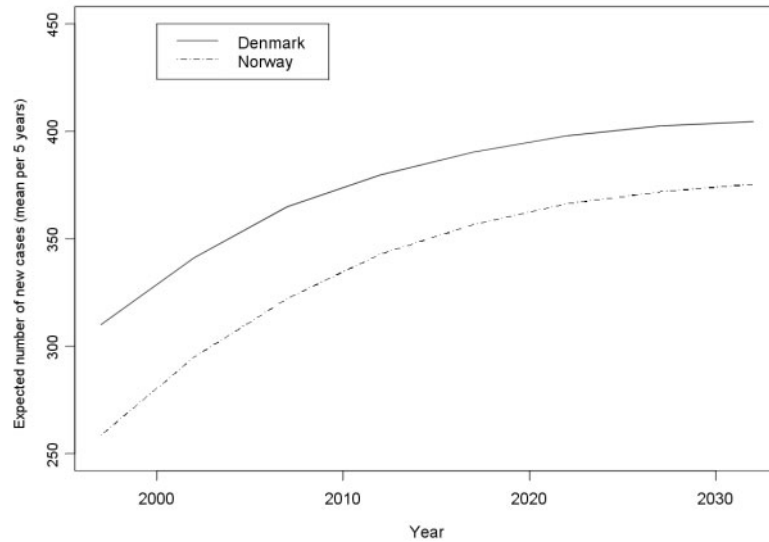


Fig. 7. Prediction lines for the number of testicular cancer cases per year in future five-year periods in Denmark and Norway.

also in accordance with Bergström *et al.* (1996). It is a consistent feature in the bootstrap estimates, so it might be a real phenomenon. Beneficial health effects of the change in diet and lifestyle in Norway during World War II have also been seen in other contexts (Knapp, 1997; Toverud, 1956; Tretli and Gaard, 1996).

For non-seminoma cancer, the estimated values of the Weibull parameter k are close to 2 in both the Danish and the Norwegian data. According to the Armitage–Doll interpretation of k , these values would mean that a cell has to go through three transitions in order to become malignant. For seminoma cancer, the estimated values of k indicate that four transitions are necessary in order to reach malignancy. However, for the Danish seminomas the 95% confidence interval for k is (3.10, 3.64), so it does not include the value 3. There is also no biological support that we are aware of for these estimates. For retinoblastoma cancer, which occurs in early childhood, Knudson (1971) estimated that two events are required to reach malignancy. For colorectal cancer, which occurs late in life, Fearon and Vogelstein (1990) proposed that five or more events are required. Hence, the estimates for testicular cancer, which occurs in early adulthood, lie within that range.

The proportion of susceptible individuals is increasing in the birth period 1890–1970, but the increase is somewhat larger for the seminomas. This indicates that one or several exposure factors may influence the susceptibility for seminomas and non-seminomas differently. The different k -values may also indicate that the genetic pathway differs between the two types of testicular cancer.

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REFERENCES

- AAKRE, O., EKBOM, A., HSIEH, C. C., TRICHOPOULOS, D. AND ADAMI, H. O. (1996). Testicular nonseminoma and seminoma in relation to perinatal characteristics. *Journal of the National Cancer Institute* **88**, 883–889.
- AALEN, O. O. (1992). Modelling heterogeneity in survival analysis by the compound Poisson distribution. *Annals of Applied Prob.* **2**, 951–972.
- AALEN, O. O. (1994). Effects of frailty in survival analysis. *Statistical Methods in Medical Research* **3**, 227–243.
- AALEN, O. O. (1995). Phase type distributions in survival analysis. *Scandinavian Journal of Statistics* **22**, 447–463.
- AALEN, O. O. AND HJORT, N. L. (2002). Frailty models that yield proportional hazards. *Statistics and Probability Letters* **58**, 335–342.
- AALEN, O. O. AND TRETTLI, S. (1999). Analyzing incidence of testis cancer by means of a frailty model. *Cancer Causes and Control* **10**, 285–292.
- ARMITAGE, P. AND DOLL, R. (1954). The age distribution of cancer and a multi-stage theory of carcinogenesis. *British Journal of Cancer* **8**, 1–12.
- BERGSTRÖM, R., ADAMI, H. O., MÖHNER, M., ZATONSKI, W., STORM, H. H., EKBOM, A., TRETTLI, S., TEPPONEN, L., AAKRE, O. AND HAKULINEN, T. (1996). Increase in testicular cancer incidence in six European countries: A birth cohort phenomenon. *Journal of the National Cancer Institute* **88**, 727–733.
- EFRON, B. AND TIBSHIRANI, R. J. (1993). *An Introduction to the Bootstrap*. New York: Chapman and Hall.
- FEARON, E. R. AND VOGELSTEIN, B. (1990). A genetic model for colorectal tumorigenesis. *Cell* **61**, 759–767.
- FISHER, J. C. AND HOLLIMON, J. H. (1951). A hypothesis for the origin of cancer foci. *Cancer* **4**, 916–918.
- HENDERSON, B. E., ROSS, R. AND BERNSTEIN, L. (1988). Estrogens as a cause of human cancer: the Richard and Hinda Rosenthal Foundation Award Lecture. *Cancer Research* **48**, 246–253.
- HOUGAARD, P. (2000). *Analysis of Multivariate Survival Data*. New York: Springer.
- HOUGAARD, P., MYGLEGAARD, P. AND BORCH-JOHNSEN, K. (1994). Heterogeneity models of disease susceptibility, with application to diabetic nephropathy. *Biometrics* **71**, 1178–1188.
- JØRGENSEN, N., GIWERCMAN, A., MÜLLER, J. AND SKAKKEBAEK, N. E. (1993). Immunohistochemical markers of carcinoma in situ of the testis also expressed in normal infantile germ cells. *Histopathology* **22**, 373–378.
- KALDOR, J. M. AND DAY, N. E. (1987). Interpretation of epidemiological studies in the context of the multistage model of carcinogenesis. In Barrett, J. C. (ed.), *Mechanisms of Environmental Carcinogenesis*, USA: CRC Press, **II**, p. 24.
- KNAPP, H. R. (1997). Dietary fatty acids in human thrombosis and hemostasis. *American Journal of Clinical Nutrition* **65**, 1687–1698.
- KNUDSON, A. G. JR. (1971). Mutation and cancer: Statistical study of retinoblastoma. *Proceedings of the National Academy of Sciences, USA* **68**, 820–823.
- KOPP-SCHNEIDER, A. (1997). Carcinogenesis models for risk assessment. *Statistical Methods in Medical Research* **6**, 317–340.
- KOPP-SCHNEIDER, A. AND PORTIER, C. J. (1991). Distinguishing between models of carcinogenesis: The role of clonal expansion. *Fundamental and Applied Toxicology* **17**, 601–613.
- MANTON, K. G., LOWRIMORE, G., YASHIN, A. AND TOLLEY, H. D. (1997). Analyses of cohort mortality incorporating observed and unobserved risk factors. *Math. and Comput. Model.* **25**, 89–107.
- MØLLER, B., FEKJÆ, R. H., HAKULINEN, T., TRYGGVADÓTTIR, L., STORM, H. H., TALBÄCK, M. AND HALDORSEN, T. (2002). Prediction of cancer incidence in the Nordic countries up to the year 2020. *European Journal of Cancer Prevention* **11** (suppl 1), 50–51.

- NORDLING, C.O. (1953). A new theory on the cancer-inducing mechanism. *British Journal of Cancer* **7**, 68–72.
- PIKE, M. C. (1966). A method of analysis of a certain class of experiments in carcinogenesis. *Biometrics* **22**, 142–161.
- TOVERUD, G. (1956). The influence of war and post-war conditions on the teeth of Norwegian school-children. *Milbank Memorial Fund Quarterly* **34**, 354–430.
- TRETLI, S. AND GAARD, M. (1996). Lifestyle changes during adolescence and risk of breast cancer: An ecologic study of World War II in Norway. *Cancer Causes and Control* **7**, 507–512.
- WANDERAAS, E. H., GROTMOL, T., FOSSÅ, S. AND TRETLI, S. (1998). Maternal health and pre- and perinatal characteristics in the etiology of testicular cancer: a prospective register-based study on Norwegian males born between 1967 and 1995. *Cancer Causes and Control* **9**, 475–486.
- WANDERAAS, E. H., TRETLI, S. AND FOSSÅ, S. (1995). Trends in incidence of testicular cancer in Norway 1955–1992. *European Journal of Cancer* **31A**, 2044–2048.

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