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Estimating the loss in expectation of life due to cancer using flexible parametric survival models

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A useful summary measure for survival data is the expectation of life, which is calculated by obtaining the area under a survival curve. The loss in expectation of life due to a certain type of cancer is the difference between the expectation of life in the general population and the expectation of life among the cancer patients. This measure is used little in practice as its estimation generally requires extrapolation of both the expected and observed survival. A parametric distribution can be used for extrapolation of the observed survival, but it is difficult to find a distribution that captures the underlying shape of the survival function after the end of follow-up. In this paper, we base our extrapolation on relative survival, because it is more stable and reliable. Relative survival is defined as the observed survival divided by the expected survival, and the mortality analogue is excess mortality. Approaches have been suggested for extrapolation of relative survival within life-table data, by assuming that the excess mortality has reached zero (statistical cure) or has stabilized to a constant. We propose the use of flexible parametric survival models for relative survival, which enables estimating the loss in expectation of life on individual level data by making these assumptions or by extrapolating the estimated linear trend at the end of follow-up. We have evaluated the extrapolation from this model using data on four types of cancer, and the results agree well with observed data. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: cancer; mean survival; expectation of life; flexible parametric survival model; population-based; relative survival

1. Introduction

A useful summary measure for survival data is the expectation of life, or mean survival time, which can be obtained by calculating the area under a survival curve. The expectation of life from the date of cancer diagnosis until death (irrespective of cause of death), obtained by the area under the all-cause survival curve, gives an estimate of the number of years cancer patients are expected to live after they are diagnosed with cancer [1]. The loss in expectation of life due to cancer is the difference between the expectation of life the patients would have had if they had not been diagnosed with cancer, estimated using mortality data for the general population, and the observed expectation of life among the cancer patients. This can be expressed as a proportion of expected life lost by dividing the difference by the expectation of life. The loss in expectation of life, or the proportion of expected life lost, is a useful measure for quantifying the cancer burden in the society and differences in survival between groups [1, 2]. But it can also be quantified on an individual level and interpreted as the number of life years a cancer patient is expected to lose due to the cancer diagnosis. This measure, although theoretically easy to estimate, is used little in practice. The reason for this is mainly that its estimation, because of limited follow-up, generally requires extrapolation of both the expected (general-population) survival and the observed all-cause survival (of the cancer patients).

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The extrapolation of the expected survival is fairly straightforward, by making assumptions about the future mortality of the general population, but the assumptions made for the full all-cause survival curve of the cancer patients, that is, survival until everyone has died, are more difficult to define. One way is to assume a parametric distribution for the all-cause survival of the cancer patients, but it is difficult to find a statistical distribution that captures the underlying shape of the survival function. Even though a parametric distribution may fit well to the observed follow-up, it may extrapolate poorly. An alternative is to extrapolate the relative survival and use the interrelationship between observed, expected, and relative survival. Relative survival is defined as the observed survival among the cancer patients divided by the expected survival in a group similar to the patients but free of the disease under study [3]. The mortality analogue of relative survival is excess mortality and defines the cancer mortality as the mortality in excess to what would be expected if the patients did not have the cancer of interest. In the relative survival setting, the all-cause mortality among the cancer patients is assumed to be made up of two components: that associated with the cancer of interest and that associated with other causes, and the latter dominates for long-term follow-up. Even though the expected survival and mortality is obtained from general population mortality, where a proportion of the deaths are due to the disease of interest, it has been shown that this bias is negligible as long as the interest lies in one specific cancer type and not all cancers combined [4, 5]. Hakama and Hakulinen [6] suggested how extrapolations using relative survival could be performed for life tables (i.e., grouped data), by assuming that the excess mortality has reached zero (statistical cure) or has stabilized to a constant, and similar approaches have been suggested by others [1, 7–9]. Another approach has been to estimate the years of life lost as the difference between the age at death and the life expectancy of each patient or a pre-specified cut-off age [2, 10–12], but this approach relies on accurate cause of death information to identify individuals in the population that died because of cancer. Because this approach only includes patients that have died, and specifically only those who die of their cancer, irrespective of when they were diagnosed, it cannot be used for a specific cohort of patients. Also, if a cut-off is used, any differences between groups that occur after the cut-off age are ignored.

In this paper, we suggest how the approach by Hakama and Hakulinen can be extended for individual level data by the use of flexible parametric survival models. Flexible parametric survival models were first introduced by Royston and Parmar [13, 14] and extended to relative survival by Nelson *et al.* [15] and Lambert and Royston [16]. The models are fitted on the log cumulative hazard scale using restricted cubic splines [17] for the baseline. By the use of splines, these models can more easily capture the shape of the underlying hazard function. It is also possible to make a variety of assumptions about the future excess mortality within the modeling framework. We illustrate the method using data on patients diagnosed with colon cancer, breast cancer, bladder cancer or melanoma in year 1961–1970 in Sweden. Extrapolated survival functions are compared with the empirical all-cause survival experienced by these cancer patients, as a way of evaluating the extrapolation from the flexible parametric survival model.

The remainder of this paper is laid out as follows. Section 2.1 describes the flexible parametric survival model in a general framework. Section 2.2 describes relative survival and how the flexible parametric survival model is used within relative survival. Section 2.3 describes different approaches for extrapolating the survival function. Section 3 describes the data used, presents results of the loss in expectation of life, demonstrates the extrapolation, and compares extrapolation results with the empirical all-cause survival experience. Finally, Section 4 discusses the method proposed.

2. Methods

2.1. Flexible parametric survival model

The flexible parametric survival model [13, 14] is fitted on the log cumulative hazard scale, using restricted cubic splines [17] to estimate the baseline cumulative hazard. Restricted cubic splines are cubic splines that are forced to be linear beyond the boundary knots, which makes the estimated function less influenced by sparse data in the tail of the distribution. Before extending the flexible parametric survival model to a relative survival framework in the next section, the general model is explained here. The log cumulative hazard is modeled as a function of follow-up time, t:

$$\ln(H(t)) = \ln(-\ln S(t)) = s(x; \boldsymbol{\gamma_0}) \tag{1}$$

where $x = \ln(t)$ and $s(x; \boldsymbol{\gamma_0})$ is a restricted cubic spline function. The latter is defined as

$$s(x;\boldsymbol{\gamma_0}) = \gamma_{00} + \gamma_{01}v_1(x) + \gamma_{02}v_2(x) + \ldots + \gamma_{0K-1}v_{K-1}(x), \tag{2}$$

where K is the number of knots and the pth basis function is defined as

$$v_p(x) = \begin{cases} x, & \text{for } p = 1 \\ (x-k_p)_+^3 - \lambda_p\,(x-k_1)_+^3 - \left(1-\lambda_p\right)(x-k_K)_+^3, & \text{for } p = 2, \ldots, K-1 \end{cases} \tag{3}$$

where $u_+ = u$ if $u > 0$ and $u_+ = 0$ if $u \leqslant 0$, k_1 is the position of the first knot, k_K the position of the last knot, and $\lambda_p = \frac{k_K - k_p}{k_K - k_1}$.

Introducing covariates, $\mathbf{z}$, into Equation (1) gives

$$\ln(H(t;z)) = \ln(-\ln S(t;z)) = s(x;\boldsymbol{\gamma_0}) + z\boldsymbol{\beta}. \tag{4}$$

This is a proportional hazards model. Non-proportional hazards, that is, time-dependent covariate effects, can be modeled by including interactions between covariates and splines for log time. Because modeling of the departure from a time-fixed effect usually does not require as many knots as modeling the baseline cumulative hazard, a new set of spline parameters are introduced for each time-dependent effect, and separate knot positions can be chosen for each new covariate with a time-dependent effect, z_i. This gives the model:

$$\ln(H(t;z)) = s(x;\boldsymbol{\gamma_0}) + z\boldsymbol{\beta} + \sum_{i=1}^{D} s(x;\boldsymbol{\gamma_i})z_i, \tag{5}$$

where D is the number of time-dependent covariate effects and $s(x;\boldsymbol{\gamma_i})$ is the spline function for the i^{th} time-dependent effect.

2.2. *Relative survival*

The most common method used for studying cancer patient survival in a population-based setting is relative survival [3]. Relative survival, $R(t)$, is the observed (all-cause) survival, $S(t)$, among the cancer patients divided by the expected survival, $S^*(t)$, obtained from population mortality rates. In the relative survival model, the all-cause survival is written as

$$S(t) = S^*(t)R(t) \tag{6}$$

where t is the time since diagnosis. The hazard analogue of relative survival is the excess hazard rate. The all-cause hazard, $h(t)$, among the patients is the sum of two components, the expected hazard, $h^*(t)$, and the excess hazard, $\lambda(t)$, associated with a diagnosis of the cancer,

$$h(t) = h^*(t) + \lambda(t). \tag{7}$$

By integrating Equation (7), we obtain

$$H(t) = H^*(t) + \Lambda(t), \tag{8}$$

where $H(t)$ is the cumulative all-cause hazard, $H^*(t)$ the cumulative expected hazard, and $\Lambda(t)$ is the cumulative excess hazard. $S^*(t)$, $h^*(t)$, and $H^*(t)$ are assumed known and are usually obtained from population mortality rates (e.g., national or regional life tables), stratified on age, sex, calendar year, and possibly other covariates such as ethnicity or socio-economic factors. Equation (8) can be extended to include covariates

$$H(t;z) = H^*(t;z') + \Lambda(t;z), \tag{9}$$

where $\mathbf{z}$ includes patient characteristics such as sex, age, and calendar year of diagnosis, as well as tumor characteristics such as stage or grade. The expected mortality is allowed to vary by the stratification factors given in the population mortality rates, denoted with z', which is a subset of z. The flexible parametric survival model adapted for relative survival [15, 16] models the cumulative excess hazard, $\Lambda(t;z)$, on a log scale using restricted cubic splines as described in the previous section.

2.3. *Approaches for extrapolating survival*

To calculate the expectation of life for a cohort of cancer patients, the full all-cause survival curve of the cancer patients has to be either known or estimated. In cancer survival studies, the full all-cause survival curve of the patients is seldom known, because the studies are not conducted for a sufficiently long period to observe all deaths, or inclusion of old data is undesirable. It can be difficult to estimate the full all-cause survival curve because it requires assumptions about the survival function beyond the available data. Parametric distributions can be used for extrapolating the observed survival, but the available parametric distributions do not always provide a good estimate of the full all-cause survival curve, even if they fit well to the data to the end of the available follow-up.

A flexible parametric survival model for the cumulative all-cause mortality, $H(t)$, as described in Equations (1)–(5), can be used for extrapolating beyond the available follow-up, but the fit is not always good. Instead, by breaking down the (cumulative) all-cause mortality into two component parts, the (cumulative) expected mortality, $H^*(t)$, and the (cumulative) excess mortality, $\Lambda(t)$, we only have to model the excess mortality part using a flexible parametric survival model. The expected mortality can be obtained from population life tables, and extrapolation can be carried out on the basis of assumptions about the future population mortality rate. For most types of cancer, the excess mortality is low after some years from diagnosis, so the expected mortality dominates for long-term follow-up. Three possible approaches for the extrapolation from a flexible parametric survival model for relative survival are as follows:

1. assuming that the log cumulative excess hazard beyond the last boundary knot follows the linear trend given by the estimated model parameters;
2. assuming statistical cure beyond the last boundary knot, by imposing constraints on spline parameters; and
3. assuming a constant excess hazard beyond the last boundary knot, by imposing constraints on spline parameters.

The different approaches are described in more detail in the following text. On the basis of the model, the extrapolated relative survival can be estimated. When the full (extrapolated) relative survival function has been estimated, the full all-cause survival function can be estimated by multiplying the relative survival by the expected survival function.

2.3.1. Linear trend. On the basis of the parameters from a flexible parametric survival model for relative survival, the full relative survival function can be estimated for any covariate pattern of interest. The relative survival for an individual j, with covariate vector $\mathbf{z}$, is estimated from the model parameters as

$$R_j(t;\mathbf{z}_j) = \exp(-\exp(\ln(\Lambda_j(t;\mathbf{z}_j)))) = \exp\left(-\exp\left(s(x;\boldsymbol{\gamma_0}) + \mathbf{z}_j\boldsymbol{\beta} + \sum_{i=1}^{D} s(x;\boldsymbol{\gamma_i})\,\mathbf{z}_{\boldsymbol{i}_j}\right)\right) \quad (10)$$

where x, $s(x;\boldsymbol{\gamma_0})$, and $s(x;\boldsymbol{\gamma_i})$ are defined as in Equations (1)–(5) and t is the time since diagnosis. Because restricted cubic splines are linear beyond the boundary knots, the flexible parametric survival model gives a linear log cumulative excess hazard beyond the last knot, or equivalently behaves like a Weibull distributed excess hazard in the tail. The linear trend is mainly based on the observed trend towards the end of follow-up.

2.3.2. Cure. For many cancer types, the mortality rate in the patient group will, after some years from diagnosis, return to the same level as in the general population, that is, $\lambda(t)$ in Equation (7) is equal to zero after some time point. This point is called the cure point, and the patients still alive are considered 'statistically cured'; thus, after the cure point, we can use the expected survival alone when extrapolating. The assumption of cure can easily be incorporated by fitting a flexible parametric cure model [18], a special case of a flexible parametric survival model, where the log cumulative excess hazard is forced to be constant after a certain point. This is carried out by calculating the spline variables 'backwards', treating the knots in reversed order as described by Andersson *et al.* [18] and then restricting the parameter for the linear spline variable, γ_{01}, to be zero. When the splines are calculated backwards, all spline variables except the linear variable ($v_1(x) = x = \ln(t)$) are zero from the last knot onwards, so by restricting the parameter for the linear spline variable, γ_{01}, to be zero, the log cumulative excess hazard (and also the cumulative excess hazard) is forced to be constant (given by γ_{00}), that is, a cure point is

imposed at the location of the last knot. The full relative survival function is then estimated from the model parameters in a similar way as in Equation (10), but with the backwards splines and imposing the constraint described.

2.3.3. Constant excess hazard. For some cancers without a cure point, the excess mortality is more or less constant after some years from diagnosis. To incorporate an assumption of constant excess hazard, a similar approach as for the flexible parametric cure model is used. The spline variables are again calculated backwards, and the parameter for the linear spline variable, γ_{01}, is set to 1; this gives an excess hazard that behaves like an exponential distribution in the tail. The full relative survival function is then estimated from the model parameters in a similar way as in Equation (10) but with the backwards splines and imposing the constraint described.

Because splines are forced to have continuous first and second derivatives at the knots, they are smooth. This can lead to problems when one wants to change the slope of the log cumulative excess hazard after the last knot, as carried out, for example, when incorporating a constant excess hazard. The log cumulative excess hazard function is often concave towards the end of follow-up, which artificially imposes an inflection point towards the end of follow-up when the slope is set to 1 after the last knot, as described earlier. An inflection point for the log cumulative excess hazard gives an excess hazard that is first decreasing and then increasing, something not often observed for cancer mortality at late follow-up times. In an effort to overcome this problem, we relaxed the constraints of continuous first and second derivatives at the last knot when assuming a constant excess hazard. The constraints remain for all the other knots. These, more flexible splines, are described in Appendix A.

2.4. Estimating the loss in expectation of life

The loss in expectation of life, LL, for an individual, j, is estimated as the difference between the mean expected survival and the mean observed survival from the time of diagnosis,

$$LL_j = \int_0^\infty S_j^*\left(u; z_j'\right) \mathrm{d}u - \int_0^\infty S_j^*\left(u; z_j'\right) R_j(u; z_j)\mathrm{d}u, \tag{11}$$

where $S_j^*(t; z_j')$ is obtained using population life tables, stratified by age, sex, year, and possibly other covariates such as ethnicity or socio-economic factors. $R_j(t; z_j)$ is obtained from a flexible parametric survival model and can vary by covariates, as shown in Equation (10), with or without imposing the restrictions of cure or a constant excess hazard. The integrals are obtained numerically using the Gaussian quadrature rule [19]. The integration is carried out up to a point where both $S^*(t)$ and $S^*(t)R(t)$ are effectively zero. In our example, we integrated up to 40 years, to compare the extrapolation with the 40 years of available follow-up that we had.

The variance of the loss in expectation of life is obtained using the Delta method. $S_j^*(t)$, and therefore also $\int_0^\infty S_j^*(u)\mathrm{d}u$, are assumed to be known, so all that is needed is the variance for $\int_0^\infty S_j^*\left(u; z_j'\right) R_j\left(u; z_j\right) \mathrm{d}u$. This only takes the uncertainty about the parameters into account and assumes the model is of the correct form when extrapolating.

3. Results

3.1. Data

To evaluate and illustrate the method, we used data from the Swedish Cancer Registry. The Swedish Cancer Registry started in 1958, and the completeness for solid tumors is high [20]. We studied patients diagnosed at 50 years and older with colon cancer ($n = 17,000$), breast cancer ($n = 22,847$), malignant melanoma ($n = 2308$), or bladder cancer ($n = 8839$) in Sweden 1961–1970, with follow-up until 2010. Cases diagnosed at autopsy were excluded, and patients that emigrated were censored at the date of emigration. The reason for including four different cancer sites was to evaluate how well the flexible parametric survival model can predict survival for time points beyond the available data in different scenarios. Colon cancer is a typical example of a cancer with a statistical cure point, bladder cancer often shows a constant excess hazard after some point, melanoma is a cancer type with relatively high survival, and breast cancer is known to occur among both young and old women. Patients younger than 50 years

at diagnosis were excluded because the available follow-up was not enough to capture their full survival function.

When evaluating the extrapolation, we restricted the follow-up to 10 years and compared the estimated extrapolated survival to the true all-cause survival with 40 years of follow-up, separately for each of the four cancer sites. Age at diagnosis was treated categorically, with the four categories 50–59, 60–69, 70–79, and 80 years and older. The expected survival function was obtained from population mortality data stratified by sex, age, and year, using the method commonly referred to as Ederer I [21]. The Ederer I method calculates the expected survival for each member of the cohort from the time of diagnosis until the end of follow-up, by applying the population mortality rates applicable to the individual in each given follow-up year. The method therefore takes aging and changing rates over calendar time into account. For grouped data, the average survival within each follow-up year is calculated on the basis of all cohort members belonging to the specific group. For extrapolation of the population mortality data beyond the 10 years of follow-up, we used the mortality rates in 1980.

3.2. Evaluating the extrapolation

To evaluate the extrapolation of the observed survival, we compared the predicted extrapolated survival curves, using 10 years of follow-up, with Kaplan–Meier (K–M) estimates of all-cause survival using 40 years of follow-up together with 95% confidence intervals (CI) for the K–M estimates. This was carried out by fitting separate models for each age group and cancer site. We compared the four different approaches for extrapolation described in Section 2.3, extrapolating the all-cause survival (i.e., not using a relative survival approach), extrapolating relative survival using a linear trend, extrapolating relative survival assuming cure, and extrapolating relative survival assuming a constant excess hazard after the last knot. For the last approach, we used the more flexible splines described in Appendix A. All flexible parametric survival models were modeled with six knots, at default locations, using the Stata command `stpm2` [16]. The default knot locations are based on centiles of the event times, with the boundary knots placed at the first and last event times. For the flexible parametric cure model, one knot is located at the 95th centile, and the last knot placed at the last observed event time gives a cure point at that point. To investigate the importance of the flexible parametric model, and not only the use of a relative survival approach, to the performance of the extrapolation, we also fitted a model where the excess hazard followed a Weibull distribution. This was carried out by fitting a flexible parametric model with only one degree of freedom.

The observed mean survival time, based on the estimated K–M function, for each age group and cancer site is found in Table I. Table I also presents the difference in the predicted mean survival time from the five different extrapolation approaches and the observed mean survival time (estimated from the K–M function). The extrapolated all-cause survival seems to differ the most from the observed mean survival time for all cancer sites, with a difference as high as 4.7 years for bladder cancer age group 50–59. The extrapolated all-cause survival does not reach zero for all age groups during the 40 years of follow-up, for example, for age group 60–69, colon cancer patients have a survival proportion of 0.10, breast cancer 0.06, melanoma 0.22, and bladder cancer 0.06 at 40 years post diagnosis. A time point when the youngest person in the age group would be 100 years. The estimated mean survival times in Table I are therefore restricted mean survival times for these groups, suggesting that the differences between the observed mean survival times and the estimated mean survival times are often even larger than shown in table I. The extrapolated relative survival with a linear trend gives a good estimate of the mean survival time in most age groups and for most cancer sites, with the largest difference being −0.95 for melanoma age group 50–59. For colon cancer and melanoma, cancer sites often seen to reach statistical cure, the extrapolation assuming cure seem to give the best estimates of the mean survival time, but the models extrapolating the linear trend also perform well. Assuming constant excess hazard after the last knot or that the excess hazard follows a Weibull distribution does not give as good predictions of the mean observed survival times.

Even though our interest lies in predicting the mean survival time, we also wanted to evaluate how well the extrapolation predicts the full all-cause survival function. A good estimate of the mean survival time does not necessarily mean that the full all-cause survival function is well extrapolated, because a good estimate of the mean survival time could be obtained with poor extrapolation if biases cancel out. Figures 1–4 show the K–M survival function with 95% CI along with extrapolated survival functions, for the different cancer sites and each age group separately. Figure 1 shows results for colon cancer, where the extrapolated survival function using a relative survival approach with a linear trend and a relative

Table I. Mean observed survival time (in years) along with the difference between the observed and predicted mean survival times from five different extrapolation approaches, by cancer site and age group, diagnosis in Sweden 1961–1970.

	Age group			
	50–59	60–69	70–79	80+
Colon cancer				
Mean observed survival (years)	10.4	6.32	3.54	1.79
Difference:				
All-cause extrapolated	2.96	2.13	0.71	0.004
Relative survival extrapolated	−0.43	−0.23	−0.20	−0.24
Relative survival, cure	0.10	0.07	−0.13	−0.24
Relative survival, constant excess	−3.03	−1.12	−0.40	−0.26
Relative survival, Weibull distribution	−2.17	−0.95	−0.56	−0.43
Breast cancer				
Mean observed survival (years)	14.0	10.0	6.23	3.05
Difference:				
All-cause extrapolated	1.87	1.50	0.34	0.26
Relative survival extrapolated	−0.63	−0.26	−0.05	0.18
Relative survival, cure	1.54	0.88	0.30	0.25
Relative survival, constant excess	−2.66	−0.86	−0.16	0.17
Relative survival, Weibull distribution	−1.97	−0.63	−0.10	−0.15
Melanoma				
Mean observed survival (years)	15.9	10.4	5.50	3.22
Difference:				
All-cause extrapolated	3.52	4.60	0.43	0.17
Relative survival extrapolated	−0.95	−0.14	−0.04	−0.05
Relative survival, cure	−0.12	−0.12	0.21	−0.04
Relative survival, constant excess	−3.52	−1.34	−0.24	−0.06
Relative survival, Weibull distribution	−2.61	−1.13	−0.23	−0.04
Bladder cancer				
Mean observed survival (years)	13.8	7.94	4.54	2.28
Difference:				
All-cause extrapolated	4.71	1.86	0.39	−0.12
Relative survival extrapolated	0.35	0.05	−0.10	−0.24
Relative survival, cure	1.26	0.58	0.06	−0.20
Relative survival, constant excess	−1.62	−0.63	−0.26	−0.26
Relative survival, Weibull distribution	−0.67	−0.43	−0.30	−0.34

survival approach assuming cure is displayed. Even though the extrapolation assuming cure seems best, the models without the restriction also give a good fit. Figure 2 shows results for breast cancer, where the extrapolated survival function using a relative survival approach with a linear trend and a relative survival approach assuming a constant excess hazard is displayed. A constant excess hazard is not reasonable for the youngest age group, and although it seems better for the other age groups, the approach without the restriction is best for all age groups. Figure 3 shows results for melanoma, where the extrapolated survival function using a relative survival approach with a linear trend and a relative survival approach assuming cure is displayed. The two approaches give similar survival functions, but for the youngest age group, assuming cure gives a survival function more similar to the observed survival. Figure 4 shows results for bladder cancer, where the extrapolated survival function using a relative survival approach with a linear trend and a relative survival approach assuming a constant excess hazard is displayed. As for breast cancer, a constant excess hazard is not reasonable for the youngest age group, and although it seems better for the older age groups, the approach without the restriction is generally better.

3.3. Estimates of the loss in expectation of life

Table II shows the estimated observed and expected mean survival times, loss in expectation of life, and proportion of expected life lost, by cancer site and age group. These estimates are obtained as described in Equation (11) after fitting flexible parametric survival models, one for each cancer site, where age

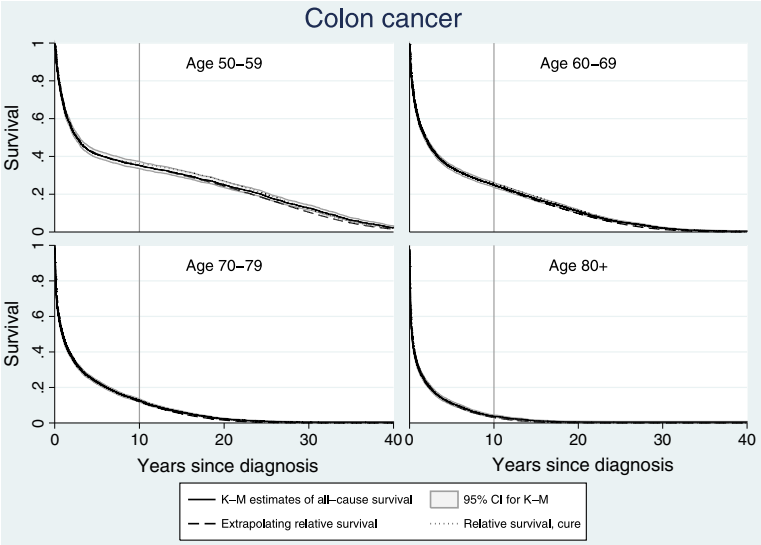

Figure 1. Kaplan–Meier (K–M) all-cause survival function with 95% confidence interval (CI) using 40 years of follow-up, along with extrapolated all-cause survival functions using a relative survival approach with and without assuming cure after 10 years, for colon cancer diagnosed in Sweden 1961–1970.

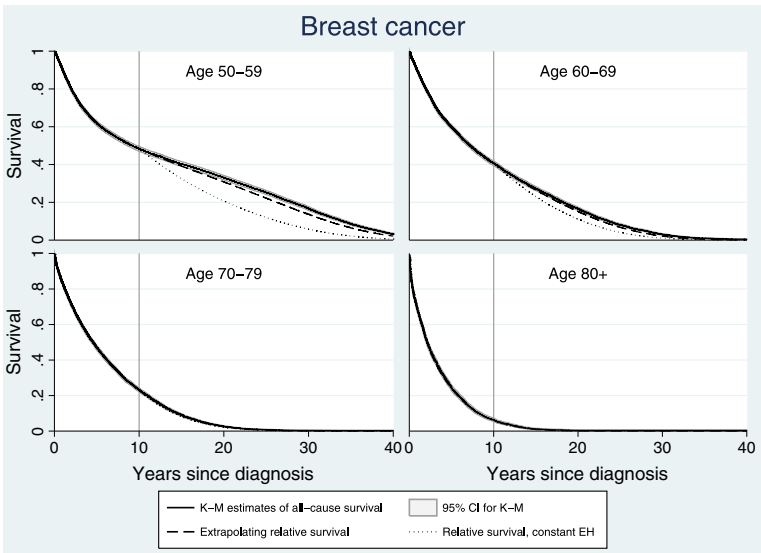

Figure 2. Kaplan–Meier (K–M) all-cause survival function with 95% confidence interval (CI) using 40 years of follow-up, along with extrapolated all-cause survival functions using a relative survival approach with and without assuming a constant excess hazard after 10 years, for breast cancer diagnosed in Sweden 1961–1970.

was included as a categorical variable including time-varying effects. All models had six knots for the baseline and three knots for the time-varying effects. On the basis of the extrapolation results in the previous section, we chose to not impose a restriction of cure or a constant excess hazard. As in the previous analysis, we restricted the follow-up to 10 years and extrapolated up until 40 years post diagnosis. We also calculated Ederer II [22] life table estimates of 5-year relative survival ratios (RSR), a commonly reported measure on cancer patient survival, for each cancer site and age group, and included this in Table II. The Ederer II method is the preferred approach for life table estimates of relative survival because it adjusts for the fact that the follow-up times of the patients are potentially of unequal length [23].

Generally, the survival, expressed as 5-year RSRs, decreases with increasing age. Although younger patients have a better prognosis, their loss in expectation of life is greater than for older patients, because

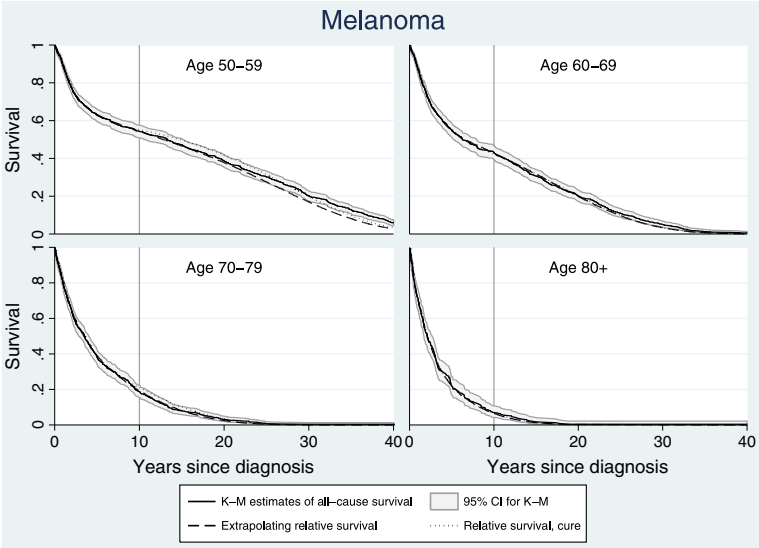

Figure 3. Kaplan–Meier (K–M) all-cause survival function with 95% confidence interval (CI) using 40 years of follow-up, along with extrapolated all-cause survival functions using a relative survival approach with and without assuming cure after 10 years, for melanoma diagnosed in Sweden 1961–1970.

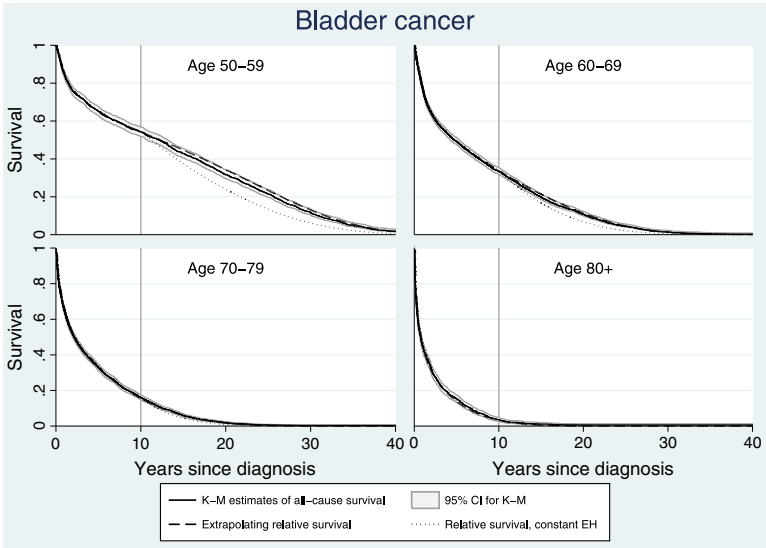

Figure 4. Kaplan–Meier (K-M) all-cause survival function with 95% confidence interval (CI) using 40 years of follow-up, along with extrapolated all-cause survival functions using a relative survival approach with and without assuming a constant excess hazard after 10 years, for bladder cancer diagnosed in Sweden 1961–1970.

they have a longer expected mean survival time. For breast cancer, the 5-year RSR is similar for the three youngest age group, but there are clear differences in the loss in expectation of life. For all age groups, colon cancer patients have the shortest observed mean survival time and the largest loss in expectation of life (ranging from 13.9 to 3.62 years for the youngest and oldest age groups, respectively).

3.4. Sensitivity analysis

To evaluate how sensitive the extrapolation from the flexible parametric (relative) survival model is to the number of knots, we refitted the models described in Section 3.2 using five and seven knots in addition to the models with six knots used in the main analysis, and the estimated loss in expectation life did not vary greatly between the models. The largest difference for the observed mean survival from the model extrapolating relative survival with linear trend was seen for bladder cancer age group 50–59, where the difference in the estimate between a model with five knots and a model with seven knots was 0.24 years.

Table II. Estimated observed and expected mean survival times (in years), loss in expectation of life, proportion expected life lost and 5-year relative survival ratios (RSR), by cancer site and age group, diagnosis in Sweden 1961–1970.

	Age group			
	50–59	60–69	70–79	80+
Colon cancer				
Expected mean survival	23.8	15.9	9.48	5.23
Observed mean survival	9.92	6.13	3.38	1.61
	(9.43;10.4)	(5.90;6.36)	(3.26;3.51)	(1.52;1.71)
Loss in expectation of life	13.9	9.79	6.09	3.62
	(13.4;14.4)	(9.55;10.00)	(5.97;6.22)	(3.52;3.72)
Proportion of expected life lost	0.58	0.61	0.64	0.69
	(0.56;0.60)	(0.60;0.63)	(0.63;0.66)	(0.67;0.71)
5-year RSR	0.43	0.38	0.32	0.25
	(0.41;0.45)	(0.37;0.40)	(0.31;0.33)	(0.22;0.27)
Breast cancer				
Expected mean survival	26.4	17.9	10.5	5.53
Observed mean survival	13.4	9.83	6.24	3.33
	(13.0;13.8)	(9.59;10.1)	(6.09;6.40)	(3.20;3.46)
Loss in expectation of life	13.0	8.04	4.26	2.20
	(12.6;13.4)	(7.80;8.28)	(4.11;4.41)	(2.07;2.33)
Proportion of expected life lost	0.49	0.45	0.41	0.40
	(0.48;0.51)	(0.44;0.46)	(0.39;0.42)	(0.37;0.42)
5-year RSR	0.64	0.65	0.62	0.53
	(0.63;0.65)	(0.64;0.67)	(0.60;0.63)	(0.49;0.56)
Melanoma				
Expected mean survival	24.3	16.5	9.83	5.20
Observed mean survival	15.2	10.3	5.51	3.36
	(14.2;16.1)	(9.55;11.0)	(5.01;6.00)	(2.93;3.80)
Loss in expectation of life	9.13	6.22	4.32	1.84
	(8.19;10.1)	(5.51;6.94)	(3.83;4.82)	(1.40;2.27)
Proportion of expected life lost	0.38	0.38	0.44	0.35
	(0.34;0.41)	(0.33;0.42)	(0.39;0.49)	(0.27;0.44)
5-year RSR	0.66	0.62	0.53	0.50
	(0.62;0.69)	(0.57;0.66)	(0.47;0.58)	(0.39;0.63)
Bladder cancer				
Expected mean survival	22.6	15.1	9.28	5.17
Observed mean survival	14.0	8.08	4.50	2.12
	(13.3;14.7)	(7.75;8.42)	(4.30;4.70)	(1.95;2.30)
Loss in expectation of life	8.65	7.05	4.78	3.04
	(7.97;9.33)	(6.71;7.38)	(4.58;4.98)	(2.87;3.22)
Proportion of expected life lost	0.38	0.47	0.51	0.59
	(0.35;0.41)	(0.44;0.49)	(0.49;0.54)	(0.56;0.62)
5-year RSR	0.69	0.57	0.47	0.34
	(0.66;0.71)	(0.55;0.59)	(0.44;0.49)	(0.30;0.39)

For all other age groups and cancer types, the differences were smaller than 0.17 years. The differences were even smaller for the models assuming cure or a constant excess hazard, with the largest difference less than 0.10 years.

Another sensitivity analysis was carried out to investigate how much follow-up is needed for the extrapolation to perform well. The extrapolation based on the linear trend using a relative survival approach was repeated with follow-up restricted to 3, 5, 7, and 10 years past diagnosis. The results can be seen in Table III. For older age groups, the extrapolation performs reasonably well in all four scenarios, but for younger ages, 10 years of follow-up is recommended.

Table III. Mean observed survival time (in years) along with the difference between the observed and predicted mean survival times from four different extrapolation points, by cancer site and age group, diagnosis in Sweden 1961–1970.

	Age group			
	50–59	60–69	70–79	80+
Colon cancer				
Mean observed survival (years)	10.4	6.32	3.54	1.79
Extrapolating from 3 years	−3.84	−1.34	−0.49	−0.32
Extrapolating from 5 years	−1.80	−0.82	−0.34	−0.28
Extrapolating from 7 years	−0.82	−0.48	−0.27	−0.25
Extrapolating from 10 years	−0.43	−0.23	−0.20	−0.24
Breast cancer				
Mean observed survival (years)	14.0	10.0	6.23	3.05
Extrapolating from 3 years	−4.65	−2.55	−0.22	0.19
Extrapolating from 5 years	−2.11	−0.20	−0.12	0.16
Extrapolating from 7 years	−1.00	−0.52	−0.04	0.16
Extrapolating from 10 years	−0.63	−0.26	−0.05	0.18
Melanoma				
Mean observed survival (years)	15.9	10.4	5.50	3.22
Extrapolating from 3 years	−4.43	−2.60	−0.27	−0.02
Extrapolating from 5 years	−2.51	−1.31	−0.56	−0.19
Extrapolating from 7 years	−1.51	−0.94	0.002	−0.07
Extrapolating from 10 years	−0.95	−0.14	−0.04	−0.05
Bladder cancer				
Mean observed survival (years)	13.8	7.94	4.54	2.28
Extrapolating from 3 years	0.99	−0.32	−0.20	−0.32
Extrapolating from 5 years	−0.46	0.16	−0.10	−0.23
Extrapolating from 7 years	−0.05	0.02	−0.08	−0.24
Extrapolating from 10 years	0.35	0.05	−0.10	−0.24

4. Discussion

The loss in expectation of life provides a measure of the impact a cancer has on society or on a patient's life expectancy, is useful for measuring cancer control progress, and for resource allocation in cancer prevention and control [1, 2, 12]. It can answer questions such as 'How many life years are lost in the population due to cancer?', 'How much does the life expectancy of an individual change if diagnosed with cancer?', 'How many life years are lost due to differences in cancer patient survival between socio-economic groups?', or 'How many life years would be gained if England had the same cancer patient survival as Sweden?'. The loss in expectation of life can be quantified either on an individual level or on a population level. Patients diagnosed with cancer at a young age usually have a better prognosis than patients diagnosed at an old age, but the long life expectancy for younger individuals compared with older ones means that they have more years to lose. In this way, the loss in expectation of life gives more weight to younger patients and can give a better understanding of the impact the cancer has on survival of the patients. Loss in expectation of life is also a more easily interpretable alternative to 'avoidable deaths', a measure that has been used to quantify differences in cancer patient survival between countries [24, 25], because this measure is highly time dependent. However, the loss in expectation of life is rarely reported because it is not available in software commonly used for relative survival analysis. The estimation requires extrapolation of the observed survival curve beyond the available follow-up, which can be problematic. In this paper, we have shown that this can be carried out using flexible parametric survival models within a relative survival framework. Even though this paper focuses on how to estimate the loss in expectation of life due to cancer, the application of the method is not limited to cancer.

We have shown that, although the interest lies in extrapolating the all-cause survival, using a relative survival approach gives better estimates of the full all-cause survival function. Many authors [1, 6–9]

have suggested approaches for estimating the loss in expectation of life for grouped data, by assuming statistical cure or that the excess mortality has reached a constant some time after diagnosis. Similar assumptions can be made using the flexible parametric survival model, but an advantage is that the extrapolation can also be carried out by extrapolating the linear trend given by the estimated model parameters. This is equivalent to an excess hazard that behaves like a Weibull distribution in the tail. Even though the extrapolation of the all-cause survival was sometimes better when cure was assumed, the all-cause survival can be extrapolated satisfactorily by the model parameters without imposing the cure restriction. Another advantage of the flexible parametric survival model is that estimation can be carried out on individual level data and not only on grouped data. With the use of individual level data, modeling can be carried out with any combination of covariates, and continuous covariates do not have to be categorized. For the evaluation purposes of this study, we have chosen to categorize age to simplify the presentation of the results.

Extrapolation is potentially sensitive to the model specification, and with the use of splines, a potential problem is sensitivity to the number of knots used. Our results suggest that the extrapolation is not very sensitive to the number of knots for the flexible parametric survival model. Another issue could be the amount of follow-up needed for the extrapolation to perform well. On the basis of our sensitivity analysis, we would recommend 10 years of follow-up for at least parts of the cohort. Even though this might seem like a long follow-up, it is not uncommon in population-based cancer studies to have at least 10 years of potential follow-up for a large part of the cohort. A period analysis [26, 27] can be used if the interest lies in predictions for recently diagnosed patients, by using information on long-term survival from patients diagnosed in earlier years. In a period analysis, recently diagnosed patients contribute to the estimation of short-term survival, and patients diagnosed earlier only contribute to the estimation of long-term survival; therefore, a longer follow-up than available for the recently diagnosed patients can be included for the extrapolation. Not only the relative survival of the cancer patients but also the expected survival has to be extrapolated in order to obtain an estimate for the full all-cause survival of the patients. Extrapolation of general population mortality rates is a research field of its own, and the use of population mortality forecasts should be considered. We have used the rather naive assumption that the population mortality rates stay the same from 1980 onwards. Even so, our extrapolations perform very well, but this might not be true in populations where there are larger changes in mortality over calendar time.

Extrapolation of survival functions is also carried out within cost-effectiveness studies, often by the use of parametric distributions [28–31]. Because of the problem with extrapolation, restricted mean survival, the area beneath the survival curve up to a certain point in time, is sometimes estimated [29]. Royston and Parmar [32] showed how the restricted mean survival time can be estimated using flexible parametric survival models and presented as an outcome measure in clinical trials. However, a restricted mean survival can never quantify the total cancer burden in the society, or the average loss in expectation of life for cancer patients. In a review of methodological issues in the economic analysis of cancer treatments, Tappenden *et al.* [33] state that alternative extrapolation methods are needed. Nelson *et al.* [34] have suggested an approach where extrapolation beyond a certain point is based on mortality as a function of age, predicted from the available data or an external data source. The drawback of this method is the assumption that after a certain point, the hazard only depends on age and no longer on time since diagnosis. Demiris and Sharples [35] and later Demiris *et al.* [36] have suggested Bayesian evidence synthesis and poly-Weibull models for extrapolating survival functions, but evaluation of the methods are not carried out on data with complete follow-up. Even though our approach has not been evaluated on small datasets or data from clinical trials or cost-effectiveness studies, we believe that our approach could be useful in these kind of studies, but further evaluation is needed.

To enable estimation of the loss in expectation of life, we have updated the Stata command for flexible parametric survival models [16] and added a post estimation option that will estimate the mean expected survival, the mean observed survival, and the loss in expectation of life, after fitting a relative survival model.

Appendix A

A cubic spline (with K knots) without constraint of continuous first or second derivative at the first knot is written as follows [37]:

$$s(x;\boldsymbol{\gamma}) = \gamma_{01}x + \gamma_{02}x^2 + \gamma_{03}x^3 + \sum_{j=2}^{K-1}\gamma_j(x-k_j)_+^3 + \gamma_1(x-k_1)_+^3 + \gamma_K(x-k_K)_+^3 + \gamma_{extra1}(x-k_1)_+^2 + \gamma_{extra2}(x-k_1)_+,$$

where k_j refers to the jth knot.

So, compared with general cubic splines, we now have two extra parameters γ_{extra1} and γ_{extra2} and the extra spline variables corresponding to these parameters $(x-k_1)_+^2$ and $(x-k_1)_+$.

Restricted cubic splines are forced to be linear before the first knot and after the last knot. To impose linearity before the first knot, we need to set $\gamma_{02} = \gamma_{03} = 0$. To impose linearity after the last knot, we use the fact that $s''(x) = s'''(x) = 0$ for linear functions [14].

So, for $x > k_K$

$$s'(x;\boldsymbol{\gamma}) = \gamma_{01} + 3\sum_{j=2}^{K-1}\gamma_j(x-k_j)^2 + 3\gamma_1(x-k_1)^2 + 3\gamma_K(x-k_K)^2 + 2\gamma_{extra1}(x-k_1) + \gamma_{extra2}$$

$$s''(x;\boldsymbol{\gamma}) = 6\sum_{j=2}^{K-1}\gamma_j(x-k_j) + 6\gamma_1(x-k_1) + 6\gamma_K(x-k_K) + 2\gamma_{extra1}$$

$$s'''(x;\boldsymbol{\gamma}) = 6\sum_{j=2}^{K-1}\gamma_j + 6\gamma_1 + 6\gamma_K$$

Setting $s''(x) = s'''(x) = 0$ gives

$$s'''(x;\boldsymbol{\gamma}) = 0 \implies \gamma_K = -\sum_{j=2}^{K-1}\gamma_j - \gamma_1$$

$$s''(x;\boldsymbol{\gamma}) = 0 \implies \gamma_1(x-k_1) = -\sum_{j=2}^{K-1}\gamma_j(x-k_j) - \gamma_K(x-k_K) - \gamma_{extra1}/3$$

substituting $\gamma_K \implies$

$$\gamma_1(x-k_1) = -\sum_{j=2}^{K-1}\gamma_j(x-k_j) + \sum_{j=2}^{K-1}\gamma_j(x-k_K) + \gamma_1(x-k_K) - \gamma_{extra1}/3$$

$$\implies \gamma_1 = -\sum_{j=2}^{K-1}\gamma_j\lambda_j - c\gamma_{extra1}$$

$$\implies \gamma_K = -\sum_{j=2}^{K-1}\gamma_j(1-\lambda_j) + c\gamma_{extra1}$$

where $\lambda_j = (k_K - k_j)/(k_K - k_1)$ and $c = 1/(3(k_K - k_1))$.

Therefore, a restricted cubic spline (with K knots) without constraint of continuous first or second derivative at the first knot is written as follows:

$$s(x;\boldsymbol{\gamma}) = \gamma_{01}x + \sum_{j=2}^{K-1}\gamma_j\left((x-k_j)_+^3 - \lambda_j(x-k_1)_+^3 - (1-\lambda_j)(x-k_K)_+^3\right) + \gamma_{extra1}\left((x-k_1)_+^2 - c(x-k_1)_+^3 + c(x-k_K)_+^3\right) + \gamma_{extra2}(x-k_1)_+,$$

where $\lambda_j = (k_K - k_j)/(k_K - k_1)$, $c = 1/(3(k_K - k_1))$ and k_j refers to the jth knot.

Following the approach by Andersson *et. al.* [18] for backwards restricted cubic splines, where knots are treated in reversed order, a restricted cubic spline (with K knots) without constraint of continuous first or second derivative at the LAST knot is written as follows:

$$s(x;\boldsymbol{\gamma}) = \gamma_{01}x + \sum_{j=2}^{K-1} \gamma_j \left(\left(k_{K-j+1} - x\right)_+^3 - \lambda_j \left(k_K - x\right)_+^3 - \left(1-\lambda_j\right)\left(k_1 - x\right)_+^3 \right) + \gamma_{extra1}\left(\left(k_K - x\right)_+^2 - c\left(k_K - x\right)_+^3 + c\left(k_1 - x\right)_+^3 \right) + \gamma_{extra2}\left(k_K - x\right)_+,$$

where $\lambda_j = \left(k_{K-j+1} - k_1\right) / \left(k_K - k_1\right)$, $c = 1/\left(3\left(k_K - k_1\right)\right)$ and k_j refers to the jth knot.

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