RESEARCH ARTICLE

On the choice of timescale for other cause mortality in a competing risk setting using flexible parametric survival models 📊

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Abstract

In competing risks settings where the events are death due to cancer and death due to other causes, it is common practice to use time since diagnosis as the timescale for all competing events. However, attained age has been proposed as a more natural choice of timescale for modeling other cause mortality. We examine the choice of using time since diagnosis versus attained age as the timescale when modeling other cause mortality, assuming that the hazard rate is a function of attained age, and how this choice can influence the cumulative incidence functions (CIFs) derived using flexible parametric survival models. An initial analysis on the colon cancer data from the population-based Swedish Cancer Register indicates such an influence. A simulation study is conducted in order to assess the impact of the choice of timescale for other cause mortality on the bias of the estimated CIFs and how different factors may influence the bias. We also use regression standardization methods in order to obtain marginal CIF estimates. Using time since diagnosis as the timescale for all competing events leads to a low degree of bias in CIF for cancer mortality (CIF_1) under all approaches. It also leads to a low degree of bias in CIF for other cause mortality (CIF_2), provided that the effect of age at diagnosis is included in the model with sufficient flexibility, with higher bias under scenarios where a covariate has a time-varying effect on the hazard rate for other cause mortality on the attained age scale.

KEYWORDS
attained age, choice of timescale, competing risks, flexible parametric models, simulation study

1 | INTRODUCTION

In a competing risk setting ($K \geq 2$ events), the cause-specific cumulative incidence function (*CIF*), that is, the risk of having event k by time T, can be derived nonparametrically (Aalen & Johansen, 1978), semiparametrically, either via cause-specific hazard (CSH) Cox models (Kalbfleisch & Prentice, 2011) models or subdistribution hazard models (Fine & Gray, 1999) and parametrically via CSH models (Lambert et al., 2017). We choose to focus on parametric CSH models in this study.

In competing risks analyses using CSH models, usually one common timescale is used for modeling all competing events. For example, for individuals diagnosed with a type of cancer, the main event of interest is death due to cancer with a competing event being death due to other causes. Time since diagnosis is generally accepted to be the natural choice of timescale for death due to cancer, with the models including age at diagnosis as a covariate, and is used as the timescale for all competing events in most cases. However, attained age, is argued to be a more natural choice of timescale for other cause mortality (Korn et al., 1997; Lee et al., 2017; Thiébaut & Bénichou, 2004) as the hazard rate can be perceived more as a function of attained age rather than a function of time since diagnosis. When using attained age as the timescale for death due to other causes we need to account for left truncation, that is, for the fact that individuals start being at risk at the age they are diagnosed with cancer. In this case, age at diagnosis is part of the data structure set-up, with individuals entering at their age at diagnosis (Canchola et al., 2003). As left truncation changes the structure of the risk sets for other cause mortality, it is expected that the hazard model under time since diagnosis timescale and the model under attained age will not yield the same results. Thus, the choice of timescale can influence the *CIF* estimates due to the different estimated hazard rates for other cause mortality. This choice is likely to have greater influence on the estimation of the *CIF* for other cause mortality.

When the hazard rate is a function of attained age rather than a function of time since diagnosis, choosing time since diagnosis as the timescale may lead to biased estimates, both due to modeling the effect of age at diagnosis with just a linear term in the model and due to the influence of other factors in single-event survival analyses (Chalise et al., 2015; Korn et al., 1997; Thiébaut & Bénichou, 2004). For competing risks analyses, Lee et al. (2017) compare the choice of timescale for modeling death due to other causes within a semiparametric framework. They show that, when the hazard rate for other cause mortality is a function of attained age, using time since diagnosis as the timescale may lead to biased estimation of the *CIF* for other cause mortality, unless the hazard rate has a Gompertz distribution.

It is unclear how the bias when estimating the *CIF*s may be influenced if a covariate of interest presents nonproportional hazards for other cause mortality on the attained age scale. It is also unclear to what degree the variance of the distribution of age at diagnosis and the complexity of how the effect of age at diagnosis is included in the model, influences the *CIF*s estimates. Chalise et al. (2012) discussed such an influence on the bias of parameter estimates derived from Cox models in single-event survival settings. The exploration of different shapes of hazard rates for other cause mortality (Lee et al., 2017) and different sample sizes is also of interest.

The aim of this paper is to extend previous work in a competing risk setting where cancer patients are followed from diagnosis and the events of interest are death due to cancer and death due to other causes, using flexible parametric survival models where different timescales can be used for other cause mortality and study the potential influence of various factors on the bias of the *CIF* estimates.

In the remainder of this paper, Section 2 describes the competing risk setting and defines cause-specific *CIF*s under the common timescale approaches (time since diagnosis as timescale for all competing events) and the different timescale approach (attained age as timescale for other cause mortality), using flexible parametric survival models. In Section 3, we present an example using colon cancer data from the population-based Swedish Cancer Register. In Section 4, a simulation study is performed to assess bias, coverage, and relative precision in the estimation of the *CIF* of each event by the "common" and "different" timescale approaches under a variety of scenarios. In Section 5, we define and apply standardized *CIF*s as a useful summary measure. Finally we discuss key issues in Section 6 and conclusions in Section 7.

2 | METHODS

2.1 | Definition of hazard, survival, and *CIF* functions under the alternative timescales

In a competing risks setting, K competing events ($k = 1, 2, .., K$) are considered. The CSH for event k is the instantaneous rate of experiencing event k, conditional on surviving up to time t. The timescale could be time since diagnosis or attained

age. If time T since diagnosis up to event k is used for the CSH model, then age at diagnosis is usually included as a covariate, that is, if a_{0_i} is the age at diagnosis of the i-th individual and $\boldsymbol{X_i}$ are other covariates of interest, then the CSH for event k on the time since diagnosis timescale is defined as:

$$h_k^{time}(t|\boldsymbol{X_i}, a_{0_i}) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t, K = k|T \geq t, \boldsymbol{X_i}, a_{0_i})}{\Delta t}. \tag{1}$$

When attained age A is used as the timescale of a CSH model, age at diagnosis is a component of the timescale ($A = a_0 + T$) and the CSH function can be defined either as a function of attained age or a function of time since diagnosis:

$$\begin{aligned} h_k^{age}(a|\boldsymbol{X_i}, a_{0_i})) &= \lim_{\Delta a \to 0} \frac{P(a \leq A < a + \Delta a, K = k|A \geq a, A \geq a_{0_i}, \boldsymbol{X_i})}{\Delta a} \\ &= \lim_{\Delta(a_{0_i}+t) \to 0} \frac{P((a_{0_i} + t) \leq A < (a_{0_i} + t) + \Delta(a_{0_i} + t), K = k|T \geq t, A \geq a_{0_i}, \boldsymbol{X_i})}{\Delta(a_{0_i} + t)} \\ &= h_k^{age}(a_{0_i} + t|\boldsymbol{X_i}, a_{0_i}). \end{aligned} \tag{2}$$

The cause-specific survival functions of an individual i for event k can be expressed in terms of hazards as a function of time since diagnosis both under the time since diagnosis timescale and the attained age timescale:

$$S_k^{time}(t|\boldsymbol{X_i}, a_{0_i}) = \exp\left(-\int_0^t h_k^{time}(u|\boldsymbol{X_i}, a_{0_i}) \ du\right) \tag{3}$$

under time since diagnosis timescale and

$$\begin{aligned} S_k^{age}(a|\boldsymbol{X_i}, a_{0_i}) &= \frac{S_k^{age}(a|\boldsymbol{X_i}, a_{0_i})}{S_k^{age}(a_{0i}|\boldsymbol{X_i}, a_{0_i})} = \frac{\exp\left(-\int_0^a h_k^{age}(u|\boldsymbol{X_i}, a_{0_i})du\right)}{\exp\left(-\int_0^{a_{0_i}} h_k^{age}(u|\boldsymbol{X_i}, a_{0_i})du\right)} = \exp\left(-\int_{a_{0_i}}^a h_k^{age}(u|\boldsymbol{X_i}, a_{0_i})du\right) \\ &= \exp\left(-\int_0^t h_k^{age}(a_{0_i} + w|\boldsymbol{X_i}, a_{0_i})dw\right) = S_k^{age}(a_{0_i} + t|\boldsymbol{X_i}, a_{0_i}) \end{aligned} \tag{4}$$

under the attained age timescale, conditional on the individual surviving at least until age at diagnosis.

The cause-specific CIF for event k as a function of time since diagnosis t, $CIF_k(t)$, is defined as $CIF_k(t) = P(T \leq t, K = k)$. For survival following a cancer diagnosis, we consider two competing events, death due to cancer ($k = 1$) and death due to other causes ($k = 2$). Death due to other causes can be modeled either with time since diagnosis, T, or attained age, A, as the timescale. Thus, the hazard for death due to cancer ($k = 1$) can be defined as $h_1^{time}(t|\boldsymbol{X_i}, a_{0_i})$. The hazard for death due to other causes ($k = 2$) under the attained age timescale can be defined as $h_2^{age}(a|\boldsymbol{X_i}, a_{0_i}) = h_2^{age}(a_{0_i} + t|\boldsymbol{X_i}, a_{0_i})$.

The cause-specific $CIFs$ can be expressed in terms of CSH and survival functions on the time since diagnosis timescale based on the definitions of Equations (1) through (4).

For the common timescale approach (indexed by $\boldsymbol{S}$), the CIF for cause k ($k = 1, 2$) can be defined as:

$$CIF_k^S(t|\boldsymbol{X_i}, a_{0_i}) = \int_0^t S_1^{time}(u|\boldsymbol{X_i}, a_{0_i}) S_2^{time}(u|\boldsymbol{X_i}, a_{0_i}) h_k^{time}(u|\boldsymbol{X_i}, a_{0_i}) \ du. \tag{5}$$

Following Lee et al. (2017) who defined the $CIFs$ allowing different time scales for two failure types, under attained age as the timescale for other cause mortality, that is, using different timescales (indexed by D), the CIF for death due to cancer ($k = 1$) can be defined for time since diagnosis timescale as:

$$CIF_1^D(t|\boldsymbol{X_i}, a_{0_i}) = \int_0^t S_1^{time}(u|\boldsymbol{X_i}, a_{0_i}) S_2^{age}(a_{0_i} + u|\boldsymbol{X_i}, a_{0_i}) h_1^{time}(u|\boldsymbol{X_i}, a_{0_i}) \ du, \tag{6}$$

while the *CIF* for other cause mortality ($k = 2$) can be expressed for the time since diagnosis or attained age timescale:

$$CIF_2^D(a_{0_i} + t|\boldsymbol{X_i}, a_{0_i}) = \int_0^t S_1^{time}(u|\boldsymbol{X_i}, a_{0_i}) \, S_2^{age}(a_{0_i} + u|\boldsymbol{X_i}, a_{0_i}) \, h_2^{age}(a_{0_i} + u|\boldsymbol{X_i}, a_{0_i}) \, du. \tag{7}$$

The CSHs can be modeled semiparametrically or parametrically. We focus on the application of flexible parametric survival models when modeling the CSH functions.

2.2 | Flexible parametric survival models

Royston and Parmar (2002) developed a class of flexible parametric models later extended by Lambert and Royston (2009) that allow both for right censoring and left truncation. This approach uses restricted cubic spline functions s to flexibly model the effect of the logarithm of time since diagnosis, $s(\ln t|\boldsymbol{\gamma}, \boldsymbol{m_0})$ or attained age, $s(\ln a|\boldsymbol{\gamma}, \boldsymbol{m_0})$ for the log baseline cumulative hazard, with $\boldsymbol{m_0}$ knots and parameters $\boldsymbol{\gamma}$.

A flexible parametric proportional hazards model on log cumulative hazard scale $\ln(H^{time})$ with time since diagnosis as the timescale, t, including age at diagnosis, a_0, as a linear covariate is:

$$\ln[H^{time}(t|\boldsymbol{X_i}, a_{0_i})] = s^{time}(\ln t|\boldsymbol{\gamma}, \boldsymbol{m_0}) + \boldsymbol{\beta}^T \boldsymbol{X_i} + \beta_{a_0} a_{0_i} \tag{8}$$

with $\boldsymbol{\beta}$ the coefficients for the covariates $\boldsymbol{X}$, and age at diagnosis a_0 a covariate with coefficient β_{a_0}.

The effect of age at diagnosis can be included more flexibly as a restricted cubic spline, \boldmath g()\unboldmath , with knots, $\boldsymbol{m_{a_0}}$, and spline term coefficients, $\boldsymbol{\gamma_{a_0}}$.

$$\ln[H^{time}(t|\boldsymbol{X_i}, a_{0_i})] = s^{time}(\ln t|\boldsymbol{\gamma}, \boldsymbol{m_0}) + \boldsymbol{\beta}^T \boldsymbol{X_i} + g(a_{0_i}|\boldsymbol{m_{a_0}}, \boldsymbol{\gamma_{a_0}}). \tag{9}$$

The model can incorporate covariate–timescale interactions to relax the proportional hazards assumption. The interaction between age at diagnosis and time since diagnosis as well as interactions between covariates $\boldsymbol{X}$ and time since diagnosis is modeled via splines:

$$\ln[H^{time}(t|\boldsymbol{X_i}, a_{0_i})] = s^{time}(\ln t|\boldsymbol{\gamma}, \boldsymbol{m_0}) + \boldsymbol{\beta}^T \boldsymbol{X_i} + g(a_{0_i}|\boldsymbol{m_{a_0}}, \boldsymbol{\gamma_{a_0}}) + \sum_{j=1}^{D} s^{time}(\ln t|\boldsymbol{\delta_m}, \boldsymbol{m_j}) \, \boldsymbol{Z_i} \tag{10}$$

with D the number of time dependent effects, $\boldsymbol{m_j}$, the knots for the jth time-dependent effect with parameters, $\boldsymbol{\delta_m}$, and the covariates vector $\boldsymbol{Z} = (\boldsymbol{X_i}, a_0)$.

The above approaches all use time since diagnosis as the timescale. When using attained age as the timescale, the model will be:

$$\ln[H^{age}(a|\boldsymbol{X_i}, a_{0_i})] = s^{age}(\ln a|\boldsymbol{\gamma}, \boldsymbol{m_0}) + \boldsymbol{\beta}^T \boldsymbol{X_i}, \tag{11}$$

with each beta coefficient interpreted as the log hazard ratio for other cause mortality across attained age under the assumption of proportional hazards.

Similarly with Equation (10), covariate–timescale interactions can be incorporated when using attained age as the timescale:

$$\ln[H^{age}(a|\boldsymbol{X_i}, a_{0_i})] = s^{age}(\ln a|\boldsymbol{\gamma}, \boldsymbol{m_0}) + \boldsymbol{\beta}^T \boldsymbol{X_i} + \sum_{j=1}^{D} s^{age}(\ln a|\boldsymbol{\delta_m}, \boldsymbol{m_j}) \, \boldsymbol{X_i}. \tag{12}$$

During the estimation process of the model parameters under the attained age timescale and accounting for left truncation, each individual contributes information to the likelihood from the age at diagnosis a_{0_i} up until the attained age of the event or the censoring a_i (see the Supporting Information). After fitting the models, the cumulative hazard functions

can be predicted for the whole range of the attained age timescale. Age at diagnosis is included in the prediction process by subtracting the cumulative hazard predicted for an attained age value equal to age at diagnosis $H^{age}(a_0)$ from $H^{age}(a)$ with $a \geq a_0$. From the $H^{age}(a) - H^{age}(a_0)$ difference the predictions for $S_k^{age}(a|a_0)$ and $h_k^{age}(a|a_0)$ can be derived.

2.3 | Estimation of CIFs

After fitting cause-specific parametric hazard models, we have analytical expressions for the CSH and survival functions. These can be incorporated into Equations (5) − (7) to derive the estimates of the *CIF*s via Stata command *standsurv*. Gaussian quadrature is used to numerically approximate the integral of Equations (5) − (7). The delta method is used to derive the standard errors and confidence intervals of the *CIF*s (Hinchliffe & Lambert, 2013).

3 | MOTIVATIONAL EXAMPLE

We illustrate how the choice of timescale for other cause mortality, and the level of complexity for age at diagnosis for other cause mortality, can influence the estimated *CIF*s for cancer and other cause mortality. This serves as motivation for the simulation study.

3.1 | Data

The nationwide population-based Swedish Cancer Register was established in 1958 (National Board of Health and Welfare, 2019). From 2005 until 2017 there were 53,630 adult individuals diagnosed with colon cancer. Information on date of death was retrieved from the Causes of Death Register maintained by the Swedish National Board of Health and Welfare. Record linkage was facilitated by the unique civic registration number assigned to all Swedish citizens. For patients that presented multiple colon cancers ($n = 4180$ individuals) only the first primary cancer was included. Patients whose cancer was detected during autopsy ($n = 507$) were excluded. Individuals are classified as dying from colon cancer, from other causes or still being alive at the end of the follow-up period, on December 31, 2017, being censored at that date (50.5% censoring). The median age at diagnosis was 71.4 years (range 18–106) with an average follow-up time of 4.6 years. The research was approved by the Karolinska Institutet Ethical Review Board.

3.2 | Common versus different timescales approach when estimating the *CIF*s

We use four different modeling approaches. The first approach uses time since diagnosis as the timescale for cancer mortality and attained age as the timescale for other cause mortality (different timescales approach). The three other approaches use time since diagnosis as timescale both when modeling cancer and other cause mortality (common timescale approaches), with an increasing level of complexity in modeling the effect of the age at diagnosis for other cause mortality. All approaches use the same CSH model for cancer mortality. The covariate of interest X is gender.

(1) For death due to cancer ($k = 1$), in all approaches, time since diagnosis is the timescale used, with 5 degrees of freedom (df) for the baseline hazard. The main effect of age at diagnosis was included in the model using restricted cubic splines with 5 knots (4 df) while its time-dependent effects were included with restricted cubic splines with 3 df (total of 4× 3 = 12 terms).
(2) For other cause mortality ($k = 2$) four different approaches were used,
   - Approach a—Attained age: Attained age as the timescale, with 5 df for the baseline hazard, without any inclusion of age at diagnosis in model.
   - Approach b—Linear: Time since diagnosis as the timescale, with 5 df for the baseline hazard, and age at diagnosis included in model as a linear term.
   - Approach c—Splines: Time since diagnosis as the timescale, with 5 df for the baseline hazard, and age at diagnosis included as a restricted cubic spline function with $df = 4$.
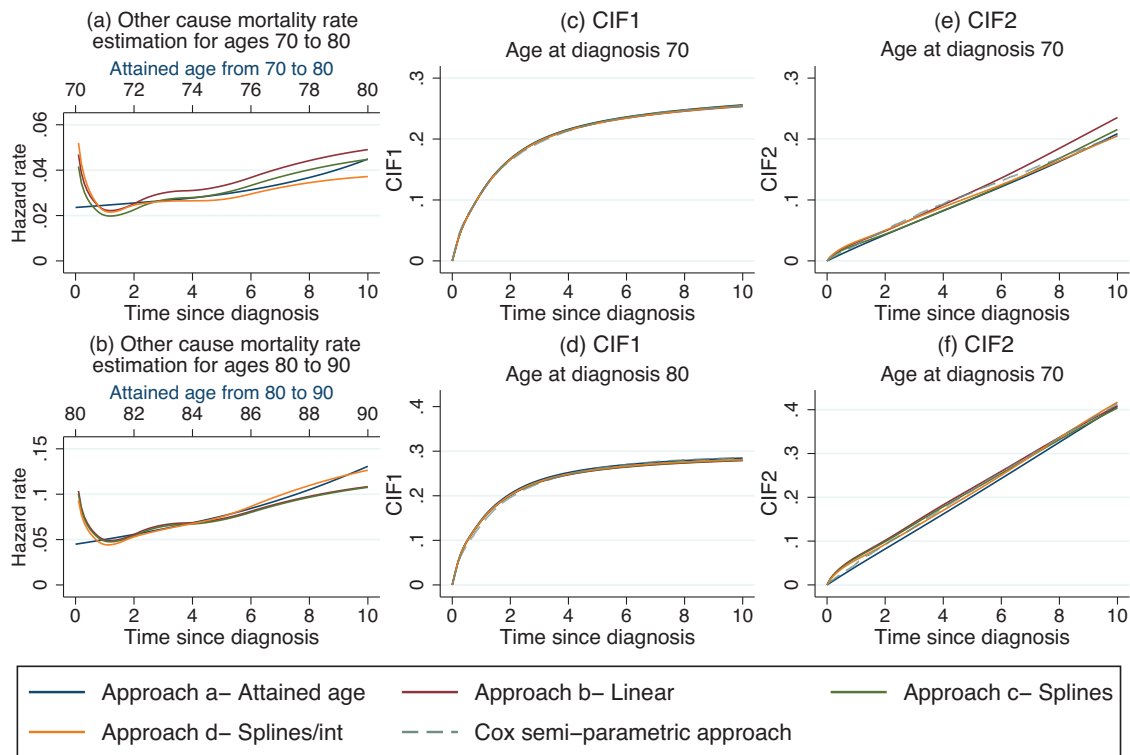
Subfigures a and b have two x axes, one for each timescale. Approach a–Attained age uses attained age as timescale while Approaches b, c and d use time since diagnosis as timescale.

FIGURE 1 Estimated other cause mortality rate, CIF_1 for death due to cancer and CIF_2 for other cause mortality for females *Note*: The estimated other cause mortality rate is given on the time since diagnosis scale (a) and attained age scale (b) for Approaches a—Attained age and d—Splines/Int. a_0 stands for the age at diagnosis, CIF_1 for death due to cancer (c,d) and CIF_2 for other cause mortality (e,f) up to 10 years after diagnosis for ages at diagnosis 70 and 80 for females as estimated by the alternative parametric approaches (Approaches a—Attained age, b—Linear, c—Splines, and d—Splines/Int and the semiparametric different timescales approach)

- Approach d—Splines/Int: Time since diagnosis as the timescale, with 5 df for the baseline hazard, and age at diagnosis included as a restricted cubic spline function with $df = 4$ plus a restricted cubic spline function for the interaction between age and time since diagnosis with $df = 3$ (total of $4 \times 3 = 12$ terms).
  - In all models, gender is included as a main effect together with restricted cubic splines with 3 df for the time-dependent effect on the timescale.

A different timescales approach using Cox proportional hazard models is also provided in order to serve as a comparison of reference based on previous work done by Lee et al. (2017). Age at diagnosis is included in both cancer mortality and other cause mortality models with restricted cubic splines.

Figure 1a,b shows the estimated other cause mortality rate as a function of time since diagnosis for the single timescale approaches and as a function of attained age (blue color) for the different timescale approach (Approach a—Attained age) for ages at diagnosis 70 (Figure 1a) and 80 (Figure 1b) for females. The single timescale approaches give different other cause mortality rate estimates compared to Approach a—Attained age, detecting a higher initial rate, with the estimates from Approach d—Splines/Int being the ones closest to those of Approach a—Attained age. This higher initial other cause mortality rate on the time since diagnosis timescale could be potentially attributed to cause of death misclassification in the death certificates (dying early on after cancer diagnosis but mistakenly classified as having died from other causes) or to incidental cancer diagnosis (being hospitalized for another reason, getting diagnosed with cancer and die soon afterwards due to the initial cause for hospitalization). For the attained age timescale, a risk set is comprised of people with different combinations of age at diagnosis and time since diagnosis. Thus, the hazard shape on the attained age timescale does not estimate an early peak. Figure 1c–f depicts the estimated $CIFs$ from the different parametric approaches plus the semiparametric approach (dashed blue line) for selected ages at diagnosis (70, 80) for females. Figure 1c,d shows

estimated *CIFs* for death due to cancer, with all the approaches giving similar estimates. Figure 1e,f shows the estimated *CIFs* for other cause mortality. It can be observed that the choice of the timescale for other cause mortality has influence on the estimates of CIF_2, due to the different estimates for other cause mortality rates (Figure 1a,b). When the level of complexity in modeling the effect of age at diagnosis increases, the CIF_2 estimates of the common timescale approaches get closer to the CIF_2 estimate of Approach a—Attained age, still presenting differences for the first 2 years after diagnosis. The semiparametric different timescales approach yields results very close to those of Approach a—Attained age, as expected. Table A1 of the Supporting Information shows the *CIF* point estimates and 95% confidence intervals from the flexible parametric approaches for selected ages at diagnosis and times since diagnosis for females. Figure A1 of the Supporting Information shows the aforementioned estimated measures for males while Figure A2 shows the estimated *CIF* differences between females and males for the different approaches. Figure A3 of the Supporting Information shows the estimated cumulative hazard rates in females.

4 | SIMULATION STUDY

4.1 | Aims

The simulation study aims to assess the performance of the approaches that use time since diagnosis as the timescale for other cause mortality in the estimation of cause-specific *CIFs* when the hazard for other cause mortality is a function of attained age, in a setting of survival following a cancer diagnosis, with death due to cancer and death due to other causes being the competing events. The common timescale approaches include Approach b—Linear, Approach c—Splines, Approach d—Splines/Int). The different scenarios assess the impact of the proportional/nonproportional hazards assumption (on the attained age scale), the variance of age at diagnosis, the sample size, and the shape of baseline hazard for other cause mortality on the bias of the common timescale approaches. The different timescale approach (Approach a—Attained age) serves as a comparison of reference.

4.2 | Estimands and performance measures

The estimands of interest in this study are $CIF_1(t)$ and $CIF_2(t)$. The performance measures used to evaluate the methods are the bias, coverage, and the relative precision. The true *CIFs* were obtained using numerical integration with the integrand evaluated at 3001 timepoints using the integ command in Stata (StataCorp, 2005). The bias is estimated as the difference between the true *CIF* value and the mean of the *CIF* estimates from the simulated samples. The relative precision compares each common timescale approach with the different timescale approach. The relative precision compares the precision of each common timescale approach to that of the different timescale approach. When comparing two estimation approaches (A and B), the relative precision of Approach B compared to Approach A is estimated by $100 \times (\frac{V(\hat{\theta}_A)}{V(\hat{\theta}_B)} - 1)$. Monte Carlo standard errors and convergence from each approach are also presented.

4.3 | Data generating mechanism

We generated age at diagnosis A_0 and gender X ($X = 0$ males, $X = 1$ females). Age at diagnosis was generated from a normal distribution $N(70, sd_{a_0})$. The standard deviation was either $sd_{a_0} = 10$ or $sd_{a_0} = 15$. The covariate X was generated from a Bernoulli distribution with probability $p = 0.5$ of assigning $X = 1$ to each simulated individual (female gender). All scenarios consist of $m = 1000$ simulations with a sample size of either $n = 2000$ or $n = 500$, with administrative censoring at 10 years. For simulating the survival times for death due to cancer ($k = 1$), a mixture of Weibull distributions was used for the baseline hazard ($\lambda_1 = 0.713$, $\gamma_1 = 0.766$, $\lambda_2 = 0.007$, $\gamma_2 = 0.791$, $p_{mix} = 0.281$) (Figure 2a), with a quadratic effect of age at diagnosis ($\beta_{1_{age}} (a_{0_i} - 65) + \beta_{2_{age}} (a_{0_i} - 65)^2$, $\beta_{1_{age}} = -0.00307$, $\beta_{2_{age}} = 0.00013$) and a null effect of the gender covariate X ($\beta = 0$, $HR = 1$). For other cause mortality ($k = 2$), there are scenarios under different shapes of baseline hazards: (a) an adapted form of Weibull distribution incorporating a small initial hazard ($h(a) = c + \lambda \gamma a^{\gamma-1}$ with $c = 0.01$, $\lambda = 1.002e - 24$, $\gamma = 12.274$), (b) a Gompertz Makeham distribution ($h(a) = c + \lambda \exp(\gamma a)$ with $c = 0.01$, $\lambda = 7 \times 10^{-4}$, $\gamma = 0.087$), and (c) a hazard form which we refer to as "Polynomial" ($\log H(a) = (z_1 a^2 + z_2 a - z_3)$ with
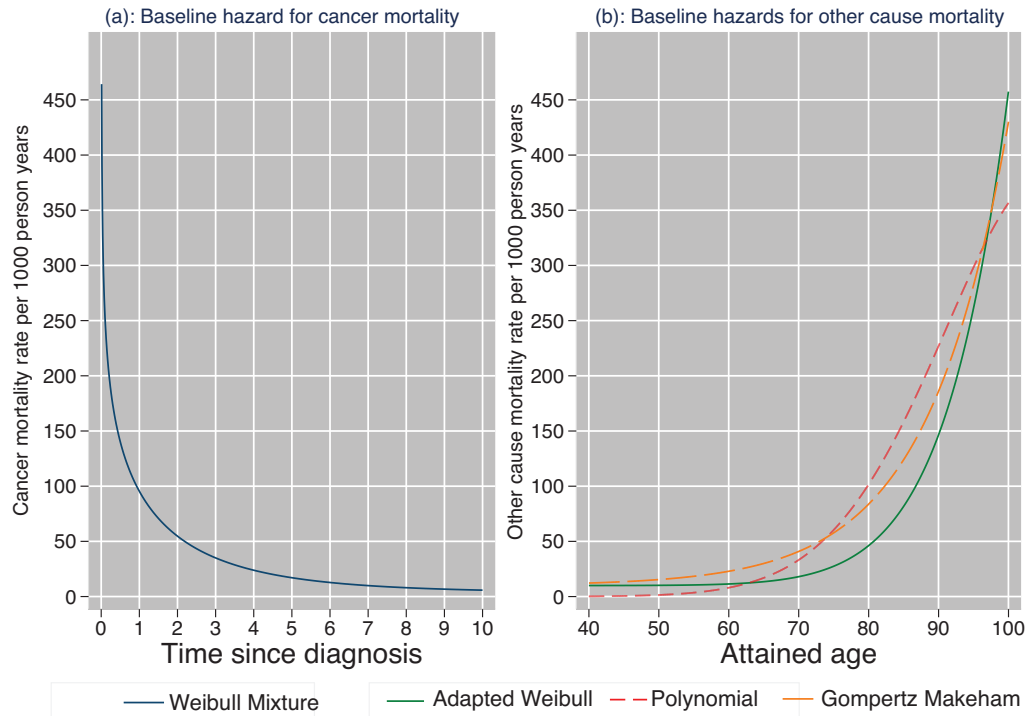
FIGURE 2   Scenarios of baseline hazards for cancer and other cause mortality

Note: (a) Baseline hazard for cancer mortality as a mixture of Weibull distributions and (b) different baseline hazard distributions for other cause mortality

$z_1 = -13.26 \times 10^{-4}, z_2 = 0.331, z_3 = -18.15)$ (Figure 2b), representing higher other cause mortality in ages over 70. The other cause mortality hazard functions were chosen to be broadly similar to that of individuals diagnosed with colon cancer in Sweden. The simulated sample size ensures there are sufficient events at low ages at diagnosis. The effects of gender on other cause mortality on the attained age timescale included proportional ($\beta = -0.356$, $HR = 0.7$) or non-proportional hazards. In the latter case a quadratic form that gives $HR = 0.4$ at 20 years of age, $HR = 0.5$ at 50 years of age, and $HR = 1$ at 100 years of attained age was chosen ($HR(a)_X = \exp(\beta_{1_X} + \beta_{2_X} a + \beta_{3_X} a^2$ with $\beta_{1_X} = -0.997, \beta_{2_X} = 0.0023, \beta_{3_X} = 7.667 \times 10^{-5}$). Based on the parameters set above, censoring varies from 44% to 48% for scenarios under the adapted form of Weibull distribution and from 37% to 39% for the rest of the scenarios.

4.4 | Scenarios structure

Figure 3 presents the simulation scenarios, with four hierarchical levels in the simulation structure of the scenarios. The top level is the sample size $n = 2000$ (Scenarios 1–12) or $n = 500$ (Scenarios 13–24). Then, proportional or nonproportional effects of gender on the hazard for other cause mortality for attained age (second level). The third level is the standard deviation of age at diagnosis ($sd_{a_0} = 10$ or $sd_{a_0} = 15$). The bottom level is the shape of the baseline hazard for other cause mortality (adapted Weibull, Polynomial, Gompertz Makeham).

4.5 | Modeling approaches

There are four modeling approaches to estimate the cause-specific *CIF*s. Approach a—Attained age, the different timescale approach, serves as the comparison reference. Approach b—Linear, Approach c—Splines, and Approach d—Splines/Int will be the common timescale approaches with different levels of flexibility when modeling the effects of age at diagnosis for other cause mortality.
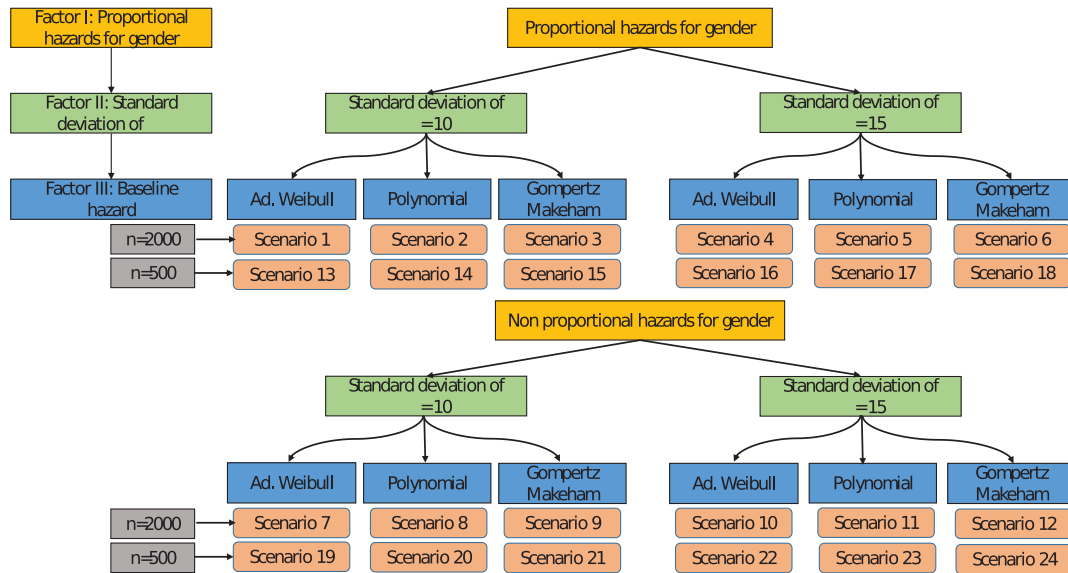
FIGURE 3 Diagram of scenario structure in the simulation

Note: PH stands for proportional hazards for gender (non-PH for non-proportional hazards). a_0 stands for the age at diagnosis. The scenarios are numbered from 1 to 24

Approaches

Cause I ($k = 1$): All modeling approaches are the same for death due to cancer ($k = 1$), using time since diagnosis as timescale, with 5 df for the baseline hazard, with age at diagnosis included in the model using restricted cubic splines with 5 knots ($4\ df$). Proportional hazards are assumed for gender, as, based on the DGM, the effect of gender is constant over time since diagnosis.

Cause II ($k = 2$): Approach a—Attained age, Approach b—Linear, Approach c—Splines, Approach d—Splines/Int are the same as in Section 3.2. Under scenarios where the effect of gender is proportional for the other cause mortality rate on the attained age timescale, we fit cause-specific proportional hazard models, so the estimated hazard ratio of gender is constant on the timescale used. Under scenarios where the effect of gender is nonproportional on other cause mortality rate on the attained age scale, the CSH models allow for nonproportional hazards on the timescale used by the model. Hence, the estimated hazard ratio for other cause mortality is a function of time since diagnosis for the common timescale approaches and a function of attained age for Approach a—Attained age.

4.6 | Results

For brevity, we focus on CIFs at ages 70 and 80 years at diagnosis under scenarios with sample size $n = 2000$ for females. In Table 1 and Table 2, the bias, coverage (%), and relative precision (relative to Approach a—Attained age) are shown for time since diagnosis $t = 5$ for CIF_1 and CIF_2. Tables with performance measures for $t = 10$ are shown in the Supporting Information, in Tables A2 and A3. The Supporting Information also includes performance measures for $t = 5$ under scenarios with sample size $n = 500$ (Tables A4 and A5, Figure A6). Performance measures for males are given in the Supporting Information (Tables A6, A7). The choice of timescale and the factors under study influence the estimated other cause mortality and through it the estimation of the CIFs. The other cause mortality estimates influence the CIF_2 estimates to a greater magnitude than the CIF_1 estimates. Thus, more focus is given in presenting the performance results for CIF_2.

4.6.1 | CIF for death due to cancer—CIF_1

Table 1 shows that, for CIF_1, all approaches have negligible biases and good coverage. This is expected, as CIF_1 is predominantly influenced by the cancer mortality rate, which is appropriately modeled by all approaches. In addition, the

TABLE 1 Simulation results for estimation of CIF_1 over scenarios for the different approaches. The results are depicted for $t = 5$ years after diagnosis and for ages at diagnosis 70 and 80: True values, Bias, Coverage (Cov%), Relative Precision (RP%), Convergence[a], and Monte Carlo error[b]

CIF1, Age at diagnosis = 70

Scenario	Proportional hazards gender	Standard deviation of age at diagnosis	Baseline hazard	True value	Approach a — Attained age		Approach b — Linear			Approach c — Splines			Approach d — Splines/Int		
					Bias	Cov (%)	Bias	Cov (%)	RP (%)	Bias	Cov (%)	RP (%)	Bias	Cov (%)	RP (%)
1			Adapted Weibull	0.26620	0.00256	94.70	0.00221	94.70	0.13	0.00275	94.40	−0.26	0.00248	94.46	−0.88
2		10	Polynomial	0.26166	0.00263	94.90	0.00275	94.80	0.01	0.00199	94.80	0.59	0.00237	94.67	0.75
3	PH		Gompertz Makeham	0.26037	0.00267	94.50	0.00222	94.80	0.26	0.00255	94.60	0.08	0.00238	95.50	0.82
4			Adapted Weibull	0.26620	0.00251	94.60	0.00203	94.90	0.23	0.00317	94.10	−0.69	0.00301	94.64	1.58
5		15	Polynomial	0.26166	0.00328	94.20	0.00301	94.10	0.23	0.00224	94.20	0.68	0.00334	95.17	3.38
6			Gompertz Makeham	0.26037	0.00307	94.30	0.00224	94.30	0.29	0.00305	94.10	−0.23	0.00287	94.41	0.22
7			Adapted Weibull	0.26904	0.00001	95.54	−0.00054	95.70	0.53	−0.00004	95.40	0.11	−0.00025	95.11	−1.62
8		10	Polynomial	0.26484	0.00014	94.58	−0.00045	94.70	0.98	−0.00117	94.90	1.49	−0.00054	94.93	−0.28
9	Non-PH		Gompertz Makeham	0.26366	0.00016	94.98	−0.00085	95.00	1.40	−0.00050	94.80	1.27	−0.00095	95.51	2.66
10			Adapted Weibull	0.26904	0.00002	94.94	−0.00110	94.80	2.18	0.00001	95.10	1.29	0.00025	95.72	2.24
11		15	Polynomial	0.26484	0.00078	94.68	−0.00077	95.00	1.93	−0.00146	94.90	2.34	−0.00047	96.15	9.46
12			Gompertz Makeham	0.26366	0.00044	94.73	−0.00137	94.90	1.97	−0.00052	94.70	1.31	−0.00089	95.64	4.35

CIF1, Age at diagnosis = 80

Scenario	Proportional hazards gender	Standard deviation of age at diagnosis	Baseline hazard	True value	Approach a — Attained age		Approach b — Linear			Approach c — Splines			Approach d — Splines/Int		
					Bias	Cov (%)	Bias	Cov (%)	RP (%)	Bias	Cov (%)	RP (%)	Bias	Cov (%)	RP (%)
1			Adapted Weibull	0.25758	0.00206	94.50	0.00036	95.00	1.59	0.00162	94.20	0.56	0.00238	94.34	1.12
2		10	Polynomial	0.24444	0.00200	94.40	0.00391	94.20	−1.38	0.00276	94.20	−0.60	0.00169	95.08	1.90
3	PH		Gompertz Makeham	0.24901	0.00217	94.40	0.00087	94.50	1.27	0.00185	94.20	0.27	0.00228	94.14	0.49
4			Adapted Weibull	0.25758	0.00319	94.40	−0.00064	94.40	2.50	0.00177	94.60	0.89	0.00215	95.14	5.06
5		15	Polynomial	0.24444	0.00204	94.90	0.00630	93.50	−2.93	0.00127	94.90	0.72	0.00147	95.35	2.73
6			Gompertz Makeham	0.24901	0.00192	94.50	0.00003	94.60	1.60	0.00196	94.50	0.24	0.00235	94.30	0.83
7			Adapted Weibull	0.25933	−0.00033	94.83	−0.00212	95.00	1.27	−0.00073	94.70	0.28	0.00038	94.98	1.80
8		10	Polynomial	0.24560	−0.00049	94.18	0.00138	94.50	−1.65	0.00036	94.50	−1.11	−0.00021	95.07	1.25
9	Non-PH		Gompertz Makeham	0.25036	−0.00063	94.58	−0.00135	94.30	0.25	−0.00022	94.20	−0.78	0.00065	94.22	0.49
10			Adapted Weibull	0.25933	0.00097	94.84	−0.00406	94.50	1.42	−0.00136	94.50	−0.35	−0.00046	95.03	5.76
11		15	Polynomial	0.24560	−0.00034	94.78	0.00264	94.40	−1.88	−0.00240	94.90	1.72	−0.00279	94.81	5.10
12			Gompertz Makeham	0.25036	−0.00053	94.93	−0.00344	94.30	1.83	−0.00120	94.60	0.24	−0.00045	94.94	2.10

a Minimum and maximum convergence over the scenarios: (98.60- 100.00) of Approach A—Attained age, (100.00- 100.00) for Approach b—Linear, (100.00- 100.00) for Approach C—Splines, and (71.00- 95.50) for Approach D—Splines/Int.

b Minimum and maximum Monte Carlo error over the scenarios for CIFi: (0.00042- 0.00139) of Approach A—Attained age, (0.00042- 0.00142) for Approach b—Linear, (0.00042- 0.00137) for Approach C—Splines, and (0.00044- 0.00159) for Approach d—Splines/Int.

TABLE 2 Simulation results for estimation of CIF_2 over scenarios for the different approaches. The results are depicted for $t = 5$ years after diagnosis and for ages at diagnosis 70 and 80: True values, Bias, Coverage (Cov%), Relative Precision (RP%), Convergence[a] and Monte Carlo error[b]

CIF2, Age at diagnosis = 70

Scenario	Proportional hazards gender	Standard deviation of age at diagnosis	Baseline hazard	True value	Approach a — Attained age Bias	Cov (%)	Approach b — Linear Bias	Cov (%)	RP (%)	Approach c — Splines Bias	Cov (%)	RP (%)	Approach d — Splines/Int Bias	Cov (%)	RP (%)
1			Adapted Weibull	0.05913	0.00097	96.10	0.00682	78.70	1.92	0.00087	95.10	−27.45	0.00192	94.58	−53.26
2		10	Polynomial	0.11679	0.00065	94.90	−0.00383	92.60	37.45	0.00454	93.70	−24.73	0.00072	95.49	−42.28
3	PH		Gompertz Makeham	0.12459	−0.00120	95.70	0.00465	91.50	35.07	0.00117	94.90	−16.75	0.00249	94.97	−36.02
4			Adapted Weibull	0.05913	0.00518	87.10	0.01224	49.40	−31.39	0.00028	94.40	−37.72	0.00109	95.39	−56.40
5		15	Polynomial	0.11679	0.00013	94.80	−0.00176	94.60	48.21	0.00562	91.70	−15.61	−0.00231	94.81	−24.27
6			Gompertz Makeham	0.12459	−0.00118	95.40	0.00879	82.40	19.31	0.00106	94.50	−18.96	0.00189	95.97	−36.46
7			Adapted Weibull	0.05532	0.00154	95.33	0.01018	62.20	17.30	0.00465	90.40	−13.86	0.00628	87.05	−47.39
8		10	Polynomial	0.10965	0.00062	94.88	0.00417	92.70	48.75	0.01199	81.80	−14.88	0.00777	90.85	−36.89
9	Non-PH		Gompertz Makeham	0.11684	−0.00128	95.29	0.01064	79.30	45.33	0.00718	90.20	−5.96	0.00903	90.27	−29.50
10			Adapted Weibull	0.05532	0.00654	83.25	0.01824	17.70	−16.46	0.00700	83.70	−26.05	0.00826	82.48	−51.59
11		15	Polynomial	0.10965	0.00017	94.48	0.01217	71.80	59.50	0.01792	65.20	−6.84	0.00981	88.27	−15.42
12			Gompertz Makeham	0.11684	−0.00027	95.54	0.01960	45.70	25.45	0.01189	82.50	−14.84	0.01381	81.86	−34.13

CIF2, Age at diagnosis = 80

Scenario	Proportional hazards gender	Standard deviation of age at diagnosis	Baseline hazard	True value	Approach a — Attained age Bias	Cov (%)	Approach b — Linear Bias	Cov (%)	RP (%)	Approach c — Splines Bias	Cov (%)	RP (%)	Approach d — Splines/Int Bias	Cov (%)	RP (%)
1			Adapted Weibull	0.15457	0.00129	95.10	0.01592	76.30	36.68	0.00281	95.00	−0.65	−0.00365	95.43	−14.83
2		10	Polynomial	0.28959	−0.00005	95.70	−0.01827	80.30	33.05	−0.00758	93.40	−12.95	−0.00084	94.81	−29.63
3	PH		Gompertz Makeham	0.24031	−0.00280	94.80	0.01014	88.30	22.68	0.00061	95.50	−16.93	−0.00370	95.08	−31.49
4			Adapted Weibull	0.15457	−0.00768	89.60	0.02572	43.10	6.22	0.00280	95.40	−6.60	−0.00207	95.39	−15.01
5		15	Polynomial	0.28959	−0.00198	95.70	−0.04669	14.70	75.96	0.00163	95.00	5.35	0.00330	94.63	−1.12
6			Gompertz Makeham	0.24031	0.00151	95.10	0.01655	79.30	81.54	−0.00083	95.80	37.91	−0.00401	94.41	22.52
7			Adapted Weibull	0.16514	0.00270	95.74	0.01563	81.40	16.39	0.00122	95.10	−7.60	−0.00573	94.06	−18.70
8		10	Polynomial	0.30679	0.00038	94.78	−0.01929	82.20	27.31	−0.01020	93.90	−12.40	−0.00529	95.21	−23.55
9	non PH		Gompertz Makeham	0.25528	0.00001	94.88	0.00608	93.80	13.37	−0.00474	95.40	−16.31	−0.00930	94.22	−27.49
10			Adapted Weibull	0.16514	−0.00780	92.10	0.03301	29.50	−7.30	0.00855	91.30	−18.10	0.00342	94.34	−24.81
11		15	Polynomial	0.30679	−0.00150	94.68	−0.03641	41.50	79.52	0.00947	92.50	14.23	0.00986	92.50	5.48
12			Gompertz Makeham	0.25528	0.00280	95.64	0.02203	70.80	49.37	0.00292	95.40	19.07	−0.00042	95.76	8.60

aMinimum and maximum convergence over the scenarios: (98.60-100.00) of Approach a—Attained age, (100.00-100.00) for Approach b—Linear, (100.00-100.00) for Approach c—Splines and (71.00-95.50) for Approach d—Splines/Int.

bMinimum and maximum Monte Carlo error over the scenarios for CIF2:(0.00003- 0.00154) of Approach a—Attained age, (0.00003- 0.00143) for Approach b—Linear, (0.00004- 0.00159) for Approach c—Splines, and (0.00010- 0.00199) for Approach d—Splines/Int.
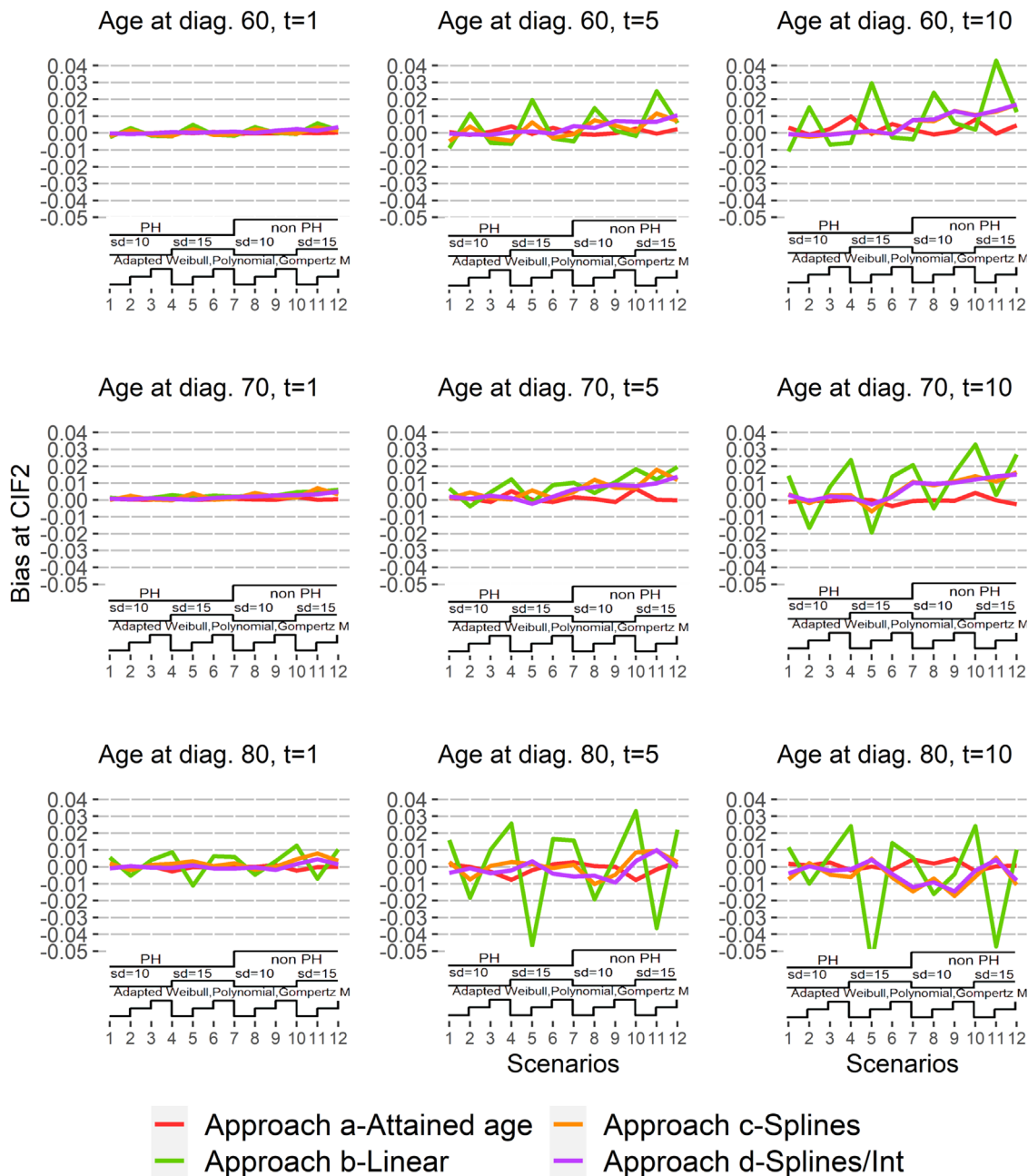
FIGURE 4 Nested loop line plot of bias in $CIF_2(t)$ from each approach over the scenarios

Note: The bias of the different approaches is given for ages at diagnosis (60,70,80) and times since diagnosis (1,5,10). Order from outer to inner loops: proportional/nonproportional hazards of gender on attained age (2 levels); standard deviation of age at diagnosis (2 levels, increasing); shape of baseline hazard for other cause mortality (3 levels). The periodic turn of the loops is illustrated by the black lines at the bottom of each plot

relative precision of the common timescale approaches (Approach b—Linear, Approach c—Splines, and Approach d—Splines/Int) versus the different timescale approach (Approach a—Attained age) is close to 0, indicating a similar level of precision.

4.6.2 | CIF for death due to other causes—CIF_2

In order to get a better overview of the bias in $CIF_2(t)$, a nested loop plot (Rücker & Schwarzer, 2014) of bias of the approaches over scenarios with sample size $n = 2000$ and different ages at diagnosis and times since diagnosis was

generated. Each row specifies the age at diagnosis (60, 70, or 80) and each column specifies the time since diagnosis t (1, 5, or 10) (Figure 4). The Supporting Information includes a nested loop plot of bias that was generated over scenarios with sample size $n = 500$ (Figure A6) with results very close to those of Figure 4. An alternative way of depicting the bias of each approach via dot plots is presented in the Supporting Information via Figures A4 and A5.

Proportional/nonproportional effects of the covariate of interest on attained age.
The first six scenarios have proportional hazards and the second six scenarios nonproportional hazards for gender on attained age. It can be observed that for ages at diagnosis 60 and 70 and times since diagnosis 5 and 10 the common timescale approaches using splines for the effect of age and allowing for nonproportional hazards of gender on the time since diagnosis timescale, are having difficulties in fully capturing the time-varying effects of gender on the attained age scale, resulting in a small increase in bias under the nonproportional hazards cluster of scenarios (scenarios 6–12). The same observation seems to hold for ages at diagnosis 80 and time since diagnosis 10 but only for the subcluster of scenarios with small variance of age at diagnosis.

Variance of age at diagnosis.
Scenarios 1 to 3 and 7 to 9 have low variance ($sd_{age} = 10$) and scenarios 4 to 6 and 10 to 12 have high variance of age at diagnosis ($sd_{age} = 15$). For ages at diagnosis 60 and 70 and times since diagnosis 5 and 10, scenarios under nonproportional hazards for gender with high variance in age at diagnosis tend to have a slightly increased bias compared to their low variance counterparts. However, for age at diagnosis 80 and time since diagnosis 10 under nonproportional hazards for gender, the lower variance in age at diagnosis scenarios present higher bias. Low variance in age at diagnosis leads to small risk sets and fewer events for older ages at diagnosis, thus influencing the estimates.

Shape of baseline hazard for other cause mortality.
Scenarios 1, 4, 7, 10 have an adapted Weibull baseline hazard, scenarios 2, 5, 8, 11 have a polynomial baseline hazard, and scenarios 3, 6, 9, 12 have Gompertz Makeham baseline hazard. Scenarios with small "changes" translate to low sensitivity to the shape of the baseline hazard for other cause mortality, with big "changes" indicating the opposite. Approach b—Linear is highly sensitive to this factor for most ages at diagnosis and times since diagnosis for most scenarios, presenting increased bias. For age at diagnosis 80 and time since diagnosis 5 and 10, all approaches are sensitive to the shape of the baseline hazard, leading to higher bias. In older ages at diagnosis the risk sets are smaller with different baseline hazards lead to different number of other cause mortality events, influencing the (CIF_2 estimations.

Sample size.
Figure A6 of the Supporting Information contains scenarios under the small sample size ($n = 500$) with results similar with Figure 4, suggesting that sample size does not seem to significantly influence the bias in $CIF_2(t)$. Tables A4 and A6 of the Supporting Information correspond to Tables 1 and 2, with performance results under scenarios with sample size of 500.

Relative precision and coverage.
In Table 2 depicting scenarios under $n = 2000$, for CIF_2, Approach b—Linear, is more precise than Approach a—Attained age, an attribute that cannot support the use of Approach b—Linear due to its high bias in CIF_2. With increasing complexity when modeling the effect of age, the precision of Approach c—Splines and Approach d—Splines/Int tends to be lower than Approach a—Attained age in most scenarios, with the exception of scenarios 11 and 12 for age at diagnosis 80. The coverage of Approach a—Attained age is close to 95% for all scenarios. For scenarios where bias was small (< 0.01) under Approach c—Splines, the coverage was over 90.2% for age at diagnosis 70 and over 91.3% for age at diagnosis 80. For scenarios where bias was small (< 0.01) under Approach d—Splines/Int, the coverage was over 82.5% for age at diagnosis 70 and over 92.5% for age at diagnosis 80. Factors that affect the precision is the overall complexity of the model, adding to the variance of the estimations, as well as the risk set structure, which differs between the different timescale approach and the common timescale approaches. The relative precision of the single timescale Approaches b—Linear and c—Splines with Approach a—Attained age serving as comparison, tends to be higher under the smaller sample size scenarios showing that the precision of Approach a—Attained age is more sensitive to changes in sample size compared to the single timescale approaches. Moving to a smaller sample size, the convergence of Approach d—Splines/Int was substantially reduced to a range of 27% to 60%. If comparisons are drawn between Table 2 ($n = 2000$) and Table A5 ($n =$

500) regarding performance measures for CIF_2, the coverage tends to be higher for the smaller sample sizes, especially for scenarios under adapted Weibull shape for other cause mortality and for nonproportional hazard scenarios for gender.

5 | ESTIMATION OF MARGINAL *CIF*s USING REGRESSION STANDARDIZATION

Regression standardization is a useful technique for summarizing the marginal probability of each competing event through averaging over the same covariate distribution. If the *CIF* estimates are influenced by confounders in the model (e.g., age at diagnosis) but presenting the overall effect of a certain covariate on the *CIF*s is of interest (e.g., gender), then regression standardization over the confounders allows direct comparability between different groups (males vs. females) (Cole et al., 2015; Kipourou et al., 2019). We derive the marginal (standardized) *CIF*s for females and males as well as *CIF* differences, using the *CIF*s estimated from the alternative approaches in the motivational example (Approach a—Attained age, Approach b—Linear, Approach c—Splines, Approach d—Splines/Int).

The marginal *CIF*s are derived under two counterfactuals, one where everyone is female and one where everyone is male, forcing the same age distributions for both values of the gender covariate (standardization over the combined age distribution). In the unlikely situation that age at diagnosis is the only confounder, the difference between $CIF_k^{females}(t)$ and $CIF_k^{males}(t)$ would be the average causal effect (Young et al., 2020) but in practice more detailed potential confounders would be required. Even if that is not the case, the derived marginal *CIF*s would be the *CIF*s over a common age distribution.

After fitting a *CSH* model for death due to cancer and a *CSH* model for other cause mortality we can derive conditional *CIF* estimates for every individual in the study. In order to derive the marginal *CIF* for each competing event, the exposure of interest X (gender) is forced to take a specific value (e.g., female) for all individuals. Then, the average of all predicted individual *CIF*s for each event is derived over the distribution of covariates $\boldsymbol{Z}$, in this case age at diagnosis, and is defined as standardized or marginal *CIF*.

$$CIF_k^S(t|X=x,\boldsymbol{Z}) = \frac{1}{N}\sum_{i=1}^{N} CIF_k(t|X=x,\boldsymbol{Z}=\boldsymbol{z_i}). \tag{13}$$

Contrasts of the marginal *CIF*s can then be made between the different groups,

$$CIF_{k\ diff}^S(t|\boldsymbol{Z}) = \frac{1}{N}\sum_{i=1}^{N} CIF_k(t|X=1,\boldsymbol{Z}=\boldsymbol{z_i}) - \frac{1}{N}\sum_{i=1}^{N} CIF_k(t|X=0,\boldsymbol{Z}=\boldsymbol{z_i}). \tag{14}$$

The estimated marginal *CIF*s and *CIF* differences may differ depending on the modeling approach used. However, as the marginal *CIF* is an average over all predictions, one may expect the variation between the different approaches to be less than the estimates conditional on covariates. Figure 5 shows that the estimates of the marginal *CIF*s for cancer and other cause mortality between the common timescale approaches (Approach b—Linear, Approach c—Splines, Approach d—Splines/Int) are almost identical both for males and females. The marginal CIF_2 estimates of the different timescale approach (Approach a—Attained age), albeit similar, present differences compared to the estimates of the single timescale approaches, suggesting that the choice of timescale influences the marginal CIF_2 estimates. The marginal CIF_1 difference is close to zero under all the approaches. That means that the marginal probability of death when standardizing over age is similar for males and females. For other cause mortality the results in marginal CIF_2 difference show a higher probability of death for males versus females, with the difference increasing over time since diagnosis.

6 | DISCUSSION

We compared using attained age versus using time since diagnosis as the timescale when modeling other cause mortality in competing risk settings where cancer patients are followed from diagnosis and the events of interest are death due to cancer and death due to other causes, using flexible parametric survival models. The motivating example illustrated that the choice of timescale for other cause mortality can influence the *CIF* estimates for other cause mortality. The simulation showed how the choice of timescale and different modeling assumptions can lead to differences in bias and
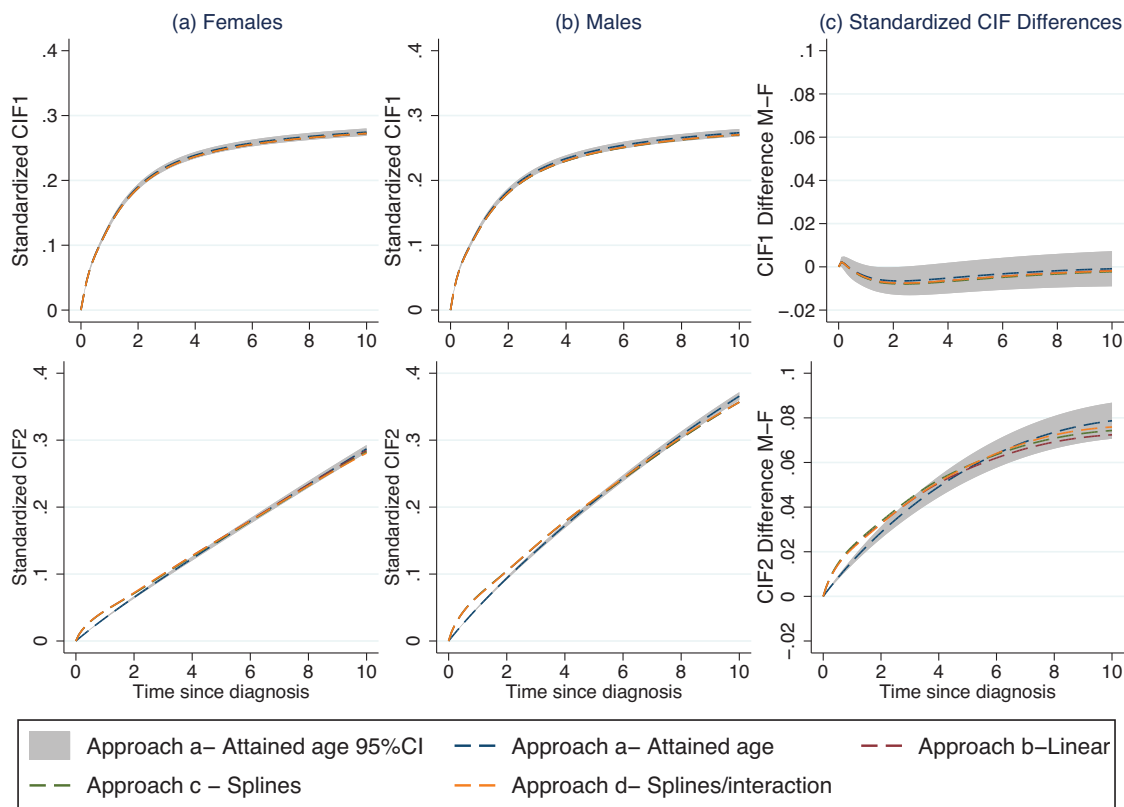
FIGURE 5 Standardized *CIF*s for cancer (CIF_1) and other causes (CIF_2)

Note: (a) Females, (b) males. Panel (c) shows the difference in standardized *CIF*s (Males – Females)

other performance measures. We studied how several factors (proportional/nonproportional hazards of a covariate on the attained age scale, variance in age at diagnosis, shape of the baseline hazard for other cause mortality and sample size) may influence the bias of the different approaches.

In all scenarios there was negligible bias for the *CIF* of death due to cancer for all approaches. This is expected as the *CIF* of death due to cancer is predominantly influenced by the cancer mortality rate, which is appropriately modeled by all approaches. Regarding other cause mortality, using time since diagnosis as a common timescale generally led to low bias for the CIF_2 provided that the effect of age at diagnosis is modeled with sufficient complexity. The assumption of a simple linear association between age at diagnosis and other cause mortality is likely to be unreasonable, leading to high bias for the *CIF* for other cause mortality. Additionally, greater modeling complexity can lead to lower precision and lower convergence under small sample sizes. This is the trade-off in using models specified on the time-on-study timescale for other cause mortality that includes the effect of age at diagnosis with a high degree of complexity. The time-varying effects of a covariate on the other cause mortality rate that is a function of attained age (as assumed in the DGM) are difficult to be fully captured by CSH models that assume the hazard is a function of time since diagnosis, resulting in a small but not negligible degree of bias in the *CIF* for other cause mortality. Even though the motivating context is a large epidemiological study, the choice of timescale also applies in smaller studies where the issue of a time-varying effect can also be of particular interest. Smaller sample sizes tend to lead to better relative precisions for the single timescale approaches compared to larger sample sizes, with Approach c—Splines being preferable as it is less biased compared to Approach b—Linear and does not suffer from convergence issues under small sample sizes as opposed to Approach d—Splines/Int. However, the different timescale approach still is the recommended approach, especially if there is an indication of nonproportional hazards on the attained age scale.

Previous work by Lee et al. (2017) compares the common timescale modeling approach (with age at diagnosis as linear function) with the different timescales approach when estimating the *CIF*s in competing risks with use of semiparametric models, comparing two scenarios of baseline hazards for other cause mortality. We used flexible parametric models and extended the exploration to scenarios with nonproportional effects of the covariate of interest on the hazard for other

cause mortality on the attained age timescale while studying different shapes of hazards for other cause mortality, different variances in age at diagnosis, and sample sizes.

The marginal estimates of *CIF*s are a useful summary tool. The models we have presented here are simple in that we have only incorporated age and gender. When modeling more covariates it becomes infeasible to present results for many combinations of covariates and it is particularly useful to present marginal estimates. As shown in the colon cancer example, the marginal estimate is likely to be more stable than conditional predictions, even when using different approaches when modeling the CSH. This is similar to the work of Syriopoulou et al. (2019) who showed that standardized relative survival estimates were insensitive to different modeling assumptions.

7 | CONCLUSIONS

In a competing risks setting where cancer patients are followed from diagnosis and the events of interest are death due to cancer and death due to other causes, it is possible to obtain estimates of *CIF*s with negligible bias using flexible parametric survival models. Even if the hazard rate for other cause mortality is a function of attained age, using time since diagnosis as a timescale should lead to *CIF* estimates for other cause mortality with small bias, as long as age at diagnosis is modeled with sufficient complexity. However, if a covariate has time-varying effects on the attained age scale, those effects are difficult to be fully captured by CSH models that assume the hazard is a function of time since diagnosis, resulting in small but not negligible bias in the *CIF* for other cause mortality. When attained age is the natural choice of timescale for other cause mortality, using attained age instead of time since diagnosis offers a simpler, unbiased model, less prone to misspecification.

CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest. Coauthor Michael J. Crowther is a paid consultant to StataCorp for work not associated with this study.

DATA AVAILABILITY STATEMENT
The data that support the findings of the motivational example of this study are available from the Swedish Cancer Register—National Board of Health and Welfare, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. We provide simulated data that mimics the features of the real data and produce similar results.

OPEN RESEARCH BADGES
This article has earned an Open Data badge for making publicly available the digitally-shareable data necessary to reproduce the reported results. The data is available in the Supporting Information section.

This article has earned an open data badge "**Reproducible Research**" for making publicly available the code necessary to reproduce the reported results. The results reported in this article could fully be reproduced.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.