COMPETING RISKS: MODELLING CRUDE CUMULATIV INCIDENCE FUNCTIONS

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Abstract

The clinical course of a disease is often characterized by the possible occurrence of several types of events, each one having a specific role for the evaluation of the therapeutical strategies. The event occurring as first is of particular interest, since it could be considered as ''treatment failure'' or ''response to treatment''. The measure of concern is the crude cumulative incidence, i.e. the probability of developing a specific event as first accounting for the competing action of the other events. A widespread approach to infer on this quantity, accounting for the effect of covariates, is the semi-parametric Cox regression model on the cause specific hazard. However, it has to be pointed out as the inference on the prognostic impact of a covariate on the cause specific hazard cannot be extended to the crude cumulative incidence. To face this issue, Fine and Gray (1999) observed as the crude cumulative incidence can be thought as the incidence associated to a quantity referred as subdistribution hazard. They proposed a semi-parametric regression model, accounting for the covariate effects. Despite the crude cumulative incidence is of interest in several clinical applications, Fine and Gray's model has not been routinely applied in the medical literature.

Aiming at promoting the application of this model, the present note emphasizes the differences between the Cox model on the cause specific hazard and Fine and Gray's model on the subdistribution hazard, resorting to a standard probabilistic formalism.

To enlighten the differences between the results of the two inferences, themodels are applied on two historical data sets; a carcinogenesis experiment on mice and a clinical trial on breast cancer patients.

Keywords: competing risks, crude cumulative incidence, subdistribution hazard, survival analysis

1. INTRODUCTION

The clinical course of a disease is often characterized by the possible occurrence of several events, with different incidences and specific roles for the evaluation of the therapeutical strategies. In several clinical studies, the events are recorded sequentially during the patient's follow-up. The event occurring as first is of particular interest, since it could be considered as "treatment failure" or "response to the treatment". The events can be thought as "competing" with each other to originate the failure.

In the phase of treatment planning, or when the efficacy of different treatments is compared, the measure of concern is the probability of developing a specific event as first. This is generally referred as "crude cumulative incidence" (CCI) of the event (Kay and Schumacher, 1983; Korn and Dorey, 1992; Pepe and Mori, 1993; Fine and Gray, 1999).

To infer on the treatment effect, as well as on other covariates effect, on the CCI of a given event, regression models suitable to account for the competing action of the other events have to be used. A widespread approach involves the semi-parametric Cox regression model on the cause specific hazard (CSH), i.e. the hazard of failure due to the event of interest considering at risk subjects free from any event. When the aim is to investigate disease dynamic to support biological hypotheses on the course of the disease, the CSH has a meaningful interpretation. For example, the shape of the hazard for local-regional and/or distant recurrence during the first 4 years after surgery provided information on the metastasis process in breast cancer patients undergoing primary tumour removal (Demicheli et al., 2004). However, it has to be pointed out as the prognostic impact of a covariate on CSH cannot be extended to CCI. This motivated the development of nonparametric tests to compare CCI functions regarding different levels of a discrete covariate (Gray, 1988; Pepe, 1991; Pepe and Mori, 1993; Aly et al., 1994; Lin, 1997; Carriere and Kochar, 2000; Mc Keague et al., 2001). To model the covariate effects on CCI, Fine and Gray (1999) observed as the CCI can be viewed as the incidence associated to a quantity referred as the subdistribution hazard (SDH). Unlike CSH, in SDH the subjects are considered at risk if they did not develop the event of interest, regardless of whether they developed any other event. A semi-parametric model based on the SDH, akin to the Cox model for univariate failure times, has been proposed (Fine and Gray, 1999).

As far as we are concerned, although CCI is the measure of interest in several clinical applications, SDH regression models are not routinely applied in the medical literature. A possible complication to the use of SDH based models might be that unlike CSH ratios, which are well-known to clinical/biological researchers, SDH ratios do not have a straightforward clinical interpretation. In addition, the

computing facilities, that for the Cox model are provided in standard statistical software, for the SDH based model are available only in the S environment.

Aiming at stimulating the adoption of appropriate inference procedures on CCI, the present note points out the differences between results of inferences based on CSH and on SDH. Some theoretical aspects of the time functions for competing risks, nonparametric estimation of incidence curves, and semi-parametric regression models are described using a standard probabilistic formalism. The theoretical properties of statistical tests for SDH regression models described in the Fine and Gray's (1999) paper, are not treated in detail, given their complexity. The relationships between SDH and CCI are discussed and the relative risk is proposed as a measure of the covariate prognostic impact on CCI.

The models based on CSH and SDH are applied on two historical data sets: a standard carcinogenesis experiment on animal models, and a randomized clinical trial on breast cancer patients. In the carcinogenesis experiment, 177 male mice exposed to X- radiation were placed in two different laboratory environments and followed till death (Hoel and Walburg, 1972). Complete information on time and cause of death was available (absence of censoring). Each cause of death is investigated accounting for the covariate laboratory environment and for the action of competing causes. In the clinical trial, the effect of the type of surgery and other 5 clinical covariates on the time to death was investigated on 716 breast cancer patients enrolled at the Istituto Nazionale per lo Studio e la Cura dei Tumori di Milano between 1964 and 1968 (Valagussa et al., 1978). For illustrative aims, here we consider breast cancer mortality and we treat mortality due to other causes as a competing event.

In section 2 (Methods), the time functions for competing risks and semi-parametric regression models on CSH and SDH are introduced. The role of censoring on the score functions of the SDH model is also described. In section 3 (Application examples) the data sets are described and the results achieved by CSH and SDH models are reported. The differences attained by the two approaches are discussed.

2. METHODS

2.1 TIME FUNCTIONS FOR COMPETING RISKS

Let us consider a generic population's subject who has been submitted to a therapeutic intervention. The treatment failure is defined as the occurrence of the first event among the $R\ 5\ 2$ possible competing events (causes of failure), enumerated by $r = 1, 2, ..., R$. Let T_f be the random variable (r.v.) "failure time",

defined as the time elapsed from the beginning of the period of observation and the occurrence of the failure. T_f can be thought as the minimum of the set of the potential times $\{T_1, ..., T_R\}$ of occurrence of the whole set of events. The couple of r.v. of concern is $(T_f, :_f)$, where $:_f$ represents the cause that originated the failure.

The CSH of the rth cause is defined as the instantaneous hazard of failure due to the rth cause

$$h_r(t) = \lim_{!t \to 0^+} \frac{1}{!t} \cdot \Pr\left(t < T_f \leq t + !t;\ :_f = r \mid T_f > t\right) \tag{1}$$

where ";" denotes the intersection operator. It has to be pointed out as $h_r(t)$ defined as (1), does not match the ordinary definition of hazard of a r.v. In fact it cannot be defined any r.v. Y such as $h_Y(t) = \lim_{!t \to 0^+} \frac{1}{!t} \cdot \Pr\{t < Y \leq t + !t \mid Y > t\} = h_r(t)$. Thus, the relationship linking the hazard function to the corresponding survival function (see Marubini and Valsecchi, 1995 p.145-146) cannot be used to derive a survival function starting from $h_r(u)$. As a consequence, the cause specific survival function (CSS) defined as

$$G_r(t) = \exp\left(-\int_0^t h_r(u)du\right) \tag{2}$$

does not represent a survival function.

Assuming that simultaneous causes of failures cannot occur, the relationship between the CSHs and the hazard of failure (due to any cause), defined as

$$h_{T_f}(t) = \lim_{!t \to 0^+} \frac{1}{!t} \cdot \Pr\{t < T_f \leq t + !t \mid T_f > t\} \tag{3}$$

is

$$h_{T_f}(t) = \lim_{!t \to 0^+} \frac{1}{!t} \cdot \sum_{r=1}^{R} \Pr\left(t < T_f \leq t + !t;\ :_f = r \mid T_f > t\right) = \sum_{r=1}^{R} h_r(t) \tag{4}$$

Thus, the hazard of failure due to any cause is the summation of the CSHs of each possible cause. The failure free survival

$$S_{T_f}(t) = \Pr\{T_f > t\} = \exp\left(-\int_0^t h_{T_f}(u)du\right) \tag{5}$$

is related to the CSSs $\{G_1(t), ..., G_r(t), ..., G_R(t)\}$ through

$$S_{T_f}(t) = \prod_{r=1}^{R} \exp\left\{-\int_0^t h_r(u)du\right\} = \prod_{r=1}^{R} G_r(t)$$

The CCI of the rth cause is the probability of failure due to the rth cause

$$F_r(t) = \Pr\left(T_f \leq t, \varepsilon_f = r\right)$$

that can be written as

$$F_r(t) = \int_0^t f_r(u)du \tag{6}$$

where

$$f_r(t) = \lim_{\Delta t \to 0^+} \frac{1}{\Delta t} \cdot \Pr\left(t < T_f \leq t + \Delta t, \varepsilon_f = r\right) \tag{7}$$

is commonly referred as subdistribution density function for the rth cause. Let us observe as $f_r(t)$ is an improper probability density function, being $\int_0^{+\infty} f_r(u)du = \lim_{t \to +\infty} F_r(t) = \Pr\left(\varepsilon_f = r\right) < 1$. From (7), (5) and (1), $f_r(t)$ can be written in terms of $S_{T_f}(t)$ and $h_r(t)$ as

$$f_r(t) = h_r(t) \cdot S_{T_f}(t) \tag{8}$$

Moreover, substituting (8) in (6), $F_r(t)$ can be related to $h_r(t)$ through

$$F_r(t) = \int_0^t h_r(u) \cdot S_{T_f}(u)du \tag{9}$$

Thus, to derive $F_r(t)$ from $h_r(t)$, the knowledge of $S_{T_f}(t)$ is needed, which, from (5) and (4) depends on the whole set of CSHs.

From (6) $F_r(t)$ can be written in terms of $f_r(t)$, which can be proved to be the continuous part of the distribution of a fictitious r.v. $\mathcal{T}_r$ defined on $R^+ \cup \{+\infty\}$

$$\mathcal{T}_r = T_f \cdot I\left(\varepsilon_f = r\right) + \infty \cdot I\left(\varepsilon_f \neq r\right) \tag{10}$$

In fact, for $t \in R^+$, $\lim_{\Delta t \to 0^+} \frac{1}{\Delta t} \cdot \Pr\{t < \mathcal{T}_r \leq t + \Delta t\} = f_r(t)$, and the discrete component (for $t = +\infty$) is $\Pr\{\mathcal{T}_r = +\infty\} = \Pr\left(\varepsilon_f \neq r\right)$. $\mathcal{T}_r$ can be thought as the failure r.v. in an artificial competing risks setting, where improvements care or maintenance lead to $+\infty$ the times for the causes different from the rth (Crowder, 2000).

The hazard function of $\mathcal{T}_r$ (subdistribution hazard) is

$$h_{\mathcal{T}_r}(t) = \lim_{\Delta t \to 0^+} \frac{1}{\Delta t} \cdot \Pr\{t < \mathcal{T}_r \leq t + \Delta t \mid \mathcal{T}_r > t\} \tag{11}$$

that can be written in terms of T_f, ε_f as

$$h_{\mathcal{T}_r}(t) = \lim_{\Delta t \to 0^+} \frac{1}{\Delta t} \cdot \frac{\Pr\left(t < T_f \leq t + \Delta t;\ \varepsilon_f = r\right)}{\Pr\left((T_f > t) \cap (T_f \leq t;\ \varepsilon_f \neq r)\right)} = \tag{12}$$

$$= \frac{f_r(t)}{1 - \Pr\left(T_f \leq t;\ \varepsilon_f = r\right)} = \frac{f_r(t)}{1 - F_r(t)} \tag{13}$$

From (13) and (8), the relationship between $h_{\mathcal{T}_r}(t)$ and $h_r(t)$ is

$$h_{\mathcal{T}_r}(t) = h_r(t) \cdot \frac{S_{T_f}(t)}{1 - F_r(t)}$$

and, being $S_{T_f}(t) = 1 - \Pr\{T_f \leq t\} = 1 - \sum_{j=1}^{R} F_j(t) \geq 1 - F_r(t)$, it follows (for any t)

$$h_{\mathcal{T}_r}(t) \geq h_r(t) \tag{14}$$

The cumulative incidence of $\mathcal{T}_r$, for $t \in R^+$, is

$$F_{\mathcal{T}_r}(t) = \Pr\{\mathcal{T}_r \leq t\} = \Pr\left(T_f \leq t;\ \varepsilon_f = r\right) = F_r(t) \tag{15}$$

and

$$\begin{aligned} F_{\mathcal{T}_r}(+\infty) &= \lim_{t \to +\infty} F_r(t) + \Pr\{\mathcal{T}_r = +\infty\} = \\ &= \Pr\left(\varepsilon_f = r\right) + \Pr\left(\varepsilon_f \neq r\right) = 1 \end{aligned}$$

Let us observe as $h_{\mathcal{T}_r}(t)$ does match the definition of hazard of a r.v. As a consequence the relationship that links the hazard of a r.v. to the corresponding survival (that for T_f is the (5)), can be used to derive $1 - F_{\mathcal{T}_r}(t)$ from $h_{\mathcal{T}_r}(t)$. This together with (15), implies that $F_r(t)$ can be directly obtained from $h_{\mathcal{T}_r}(t)$ through

$$F_r(t) = 1 - \exp\left\{-\int_0^t h_{\mathcal{T}_r}(u)\right\} = 1 - \exp\{-H_{\mathcal{T}_r}(t)\} \tag{16}$$

where $H_{\mathcal{T}_r}(t)$ is the cumulative subdistribution hazard.

Let us observe as from (16), (2) and (14) it follows (for any t)

$$F_r(t) \geq 1 - G_r(t) \tag{17}$$

2.2 SUBDISTRIBUTION HAZARD AND RIGHT CENSORING

Let us consider the case of right censoring, that is typical when dealing with survival data. Two r.v. are considered: the failure time T_f and the censoring time C (i.e. the time elapsed from the beginning and the end of the subject's period of observation). The data can be represented by the couple of r.v. $(T, :)$, where $T = \min\{T_f, C\}$, $: = 0$ if $T = C$, and $: = :_f$ if $T = T_f$. If $: \neq 0$ the subject is said to be uncensored, whereas if $: = 0$ the subject is said to be censored.

In several studies, a common length (M) of the period of observation is planned for any subject, and T_f may observed only if $T_f < M$. We can distinguish between two situations: i) all the subjects are recruited at the beginning of the study and a common ending date defines M, ii) the subjects may enter at different recruitment dates, however an ending date specific for each subject guarantees M. Other studies present the situation iii) where the subjects may enter at different dates but a common ending date is fixed (i.e. the length of the period of observation can vary). If accidental losses to follow-up do not occur within the planned period of observation, we say the data are submitted to administrative censoring. The cases i) and ii) are referred as type I censoring, whereas the case iii) is referred as generalized type I censoring (Klein and Moeschberger, 1997). Fine and Gray (1999) refer this kinds of censoring as "censoring complete", enlightening that regardless of whether a common length of the period of observation is planned or not, the censoring time C is known at the recruitment.

Accidental losses to follow-up may happen when the subject experiences an event other than the causes of failure considered, that stops the period of observation. In this case C is equal to the time elapsed between the recruitment date and the occurrence of such event. This kind of censoring is referred as random censoring (Klein and Moeschberger, 1997). When the events that originate the random censoring can be considered independent from the R causes of failure, censoring is said to be non informative. Let us observe that, differing from the case of censoring complete (where C is known for any subject) in the case of random censoring C is known only if the subject is actually censored, whereas if the failure occurs within the period of observation, the only information available is $C > T_f$ and less or equal than the subject's period of observation.

It is worth of note as these kinds of censoring are routinely dealt in classical survival analysis, provided the non informativeness. In the presence of competing risks, although some authors refer the occurrence of causes of failure different from that of interest as "censoring due to competing risks", in the rest of this note censoring will be intended as a non informative interruption of the patient's

follow-up.

In the presence of right censoring, $\mathcal{T}_r$ is no longer observable for the censored subjects. From (10) it follows that a censored time (i.e. $T = C$) cannot be attributed to any of the two conditions used to define $\mathcal{T}_r$. In this case, the definition (12) does not allow to express the SDH in terms of the observed r.v. $(T, :)$. However, if C is independent from $T_f, :_f$, and C is observed (i.e. type I/ generalized, or if the patient is lost to follow-up after the occurrence of a non fatal causes of failure $k \neq r$) it can be proved as the quantity

$$\lim_{\Delta t \to 0^+} \frac{1}{\Delta t} \cdot \Pr\{t < \mathcal{T}_r \leq t + \Delta t \mid \mathcal{T}_r > t\,;\, C > t\} \tag{18}$$

is equal to $h_{\mathcal{T}_r}(t)$.

Considering $T_f, :_f$ and C, (18) can be written as

$$\lim_{\Delta t \to 0^+} \frac{1}{\Delta t} \cdot \frac{\Pr\left(t < T_f \leq t + \Delta t\,;\, :_f = r\,;\, C > t\right)}{\Pr\left((T_f > t\,;\, C > t) \cup (T_f \leq t\,;\, :_f \neq r\,;\, C > t)\right)} \tag{19}$$

$$= \lim_{\Delta t \to 0^+} \frac{1}{\Delta t} \cdot \frac{\Pr\left(t < T_f \leq t + \Delta t\,;\, :_f = r\,;\, C > t\right)}{\Pr\left((T_f > t) \cup (T_f \leq t\,;\, :_f \neq r)\,;\, C > t\right)} \tag{20}$$

and using the assumption of non informative censoring, it follows

$$\lim_{\Delta t \to 0^+} \frac{1}{\Delta t} \cdot \frac{\Pr\left(t < T_f \leq t + \Delta t\,;\, :_f = r\right) \cdot \Pr\{C > t\}}{\Pr\left((T_f > t) \cup (T_f \leq t\,;\, :_f \neq r)\right) \cdot \Pr\{C > t\}} = h_{\mathcal{T}_r}(t)$$

It can be proved as (18) involves only the observed r.v. $(T, :)$ and C, in fact (19) can be written as

$$h_{\mathcal{T}_r}(t) = \lim_{\Delta t \to 0^+} \frac{1}{\Delta t} \cdot \frac{\Pr\{t < T \leq t + \Delta t\,;\, : = r\}}{\Pr\{T > t \cup (T \leq t\,;\, : \neq r; C > t)\}} \tag{21}$$

Finally, by considering (21) in (16), the $F_r(t)$ can be still expressed in terms of the observed r.v. $(T, :)$ and C.

2.3 ESTIMATION AND TEST

2.3.1 INFERENCE ON $(T_f, :_f)$

Given a sample of N subjects (indexed by $i = 1, ..., N$), let $(T_1, :_1), .., (T_N, :_N)$ be the r.v. $(T, :)$ on the sample with realizations $\{(t_1, :_1), .., (t_N, :_N)\}$. Let $t_{(1)}, ..., t_{(L)}$ be the ordered observed failure times (indexed by $l = 1, ..., L$) and $t_{(0)} = 0$. If T_f (regardless of the cause of failure) is of concern, the common approach to estimate the survival function (5) is the Kaplan-Meier. Moreover, under the proportional hazards assumption, in the light of the relationship (5), survival curves can be compared by the log-rank test on the equality of the hazards of failure. To measure the impact of a vector of covariates $\mathbf{X}$ on the hazard of failure, the Cox regression model on (3) is commonly used.

If the attention is focused on the time to occurrence of the rth cause of failure and the time function of interest is the CSH, the times to failure due to causes $k \neq r$ are considered as censored (in a coherent way to (1)). In this setting, the application of the Kaplan-Meier method provides an estimate of the CSS (2), which is not of practical interest. However, the corresponding log-rank test leads to the comparison of the CSHs. The impact of $\mathbf{X}$ on the CSH can be evaluated by the Cox regression model.

The classical approach to infer on the CCI curves resorts to relationship (9). The CCIs curve for discrete covariate levels are estimated by the nonparametric estimator (see Marubini and Valsecchi, 1995 p. 338)

$$\hat{F}_r(t) = \sum_{l|t_{(l)} \leq t} \hat{h}_r(t_{(l)}) \cdot \hat{S}_{T_f}(t_{(l-1)}) \tag{22}$$

where $\hat{h}_r(t_{(l)}) = d_r(t_{(l)})/n_{(l)}$, $d_r(t_{(l)})$ is the number of failures due to the rth cause occurred at $t_{(l)}$, and $n_{(l)}$ the number of subject at risk of failure at $t_{(l)}$; $\hat{S}_{T_f}(t_{(l-1)})$ is the Kaplan-Meier estimate of the failure free survival (5) and $\hat{S}_{T_f}(t_{(0)}) = 1$. To compare CCIs specific nonparametric tests (Gray, 1988; Pepe, 1991; Pepe and Mori, 1993; Aly et al., 1994; Lin, 1997; Carriere and Kochar, 2000) have to be used.

However, if the quantity of interest is CCI, the natural choice is to refer to the r.v. $\mathcal{T}_r$ and the SDH function. In the next sections we review this topic, with particular emphasis on the regression model proposed by Fine and Gray.

2.3.2 INFERENCE ON $\mathcal{T}_r$

We need to distinguish among three situations: i) complete data (i.e. absence of

censoring), ii) censoring-complete and iii) random censoring.

COMPLETE DATA In the case of complete data, the realizations of $\mathcal{T}_r$ on the sample, $\mathcal{T}_{r1}, ..., \mathcal{T}_{rN}$, are observed. The sampling data can be summarized as $(<_{r_1}, :_1, \mathbf{x}_1), ..., (<_{r_N}, :_N, \mathbf{x}_N)$. For discrete covariate levels an estimate of $F_r(t)$ equal to (22) is obtained through Kaplan-Meier method on these data. The risk set at the time t for $\mathcal{T}_r$ is $e_r(t) = \{j : <_{r_j} > t\}$, which is coherent with the conditioning event in SDH (11). Let us observe that being $<_{r_j} = t_j \cdot I(:_j = r) + \infty \cdot I(:_j \neq r)$, $e_r(t)$ includes: i) the subjects $\{j : t_j \geq t\}$ who are still at risk of failure at t, and ii) the subjects $\{j : (t_j \leq t) \mid (:_j \neq r)\}$ who had a first event different from the rth (i.e. $<_{r_j} = +\infty$) by the time t. Thus, $e_r(t)$, that we refer as "modified" risk set, can be written in terms of the realizations of $(T, :)$ as

$$e_r(t) = \{j : (t_j > t) \cup (t_j \leq t, :_j \neq r)\} \tag{23}$$

The log-rank test can be subsequently applied to compare CCIs.

In the light of the relationship (16), an appropriate model for the CCI, based on the SDH (Fine and Gray, 1999), has to be used. The basic model assumes proportional SDHs, with the relationship between SDH and $\mathbf{X}$ expressed as

$$h_{\mathcal{T}_r}(t, \mathbf{X}) = h_{\mathcal{T}_r o}(t) \cdot \exp(\beta_r \cdot \mathbf{X}) \tag{24}$$

where $h_{\mathcal{T}_r o}(t)$ is the baseline hazard and β_r is the vector of regression coefficients. The Partial likelihood approach (Cox, 1972) is applicable to infer on $h_{\mathcal{T}_r}(t, \mathbf{X})$. On the ground of the definition of $\mathcal{T}_r$, considering the risk set $e_r(t)$ (23), one can write

$$PL_r = \prod_{i=1}^{N} \left[\frac{\exp(\beta_r \cdot \mathbf{x}_i)}{\sum_{j \in e_r(t_i)} \exp(\beta_r \cdot \mathbf{x}_j)} \right]^{I(\Omega_i = r)} \tag{25}$$

obtaining a proper partial likelihood for the improper distribution function $F_r(t; \mathbf{x})$. The estimates of the regression coefficients can be obtained from the score function

$$U_r(\beta_r) = \sum_{i=1}^{N} I(:_i = r) \cdot \left[\mathbf{x}_i - \frac{\sum_{j \in e_r(t_i)} \mathbf{x}_j \cdot \exp(\beta_r \cdot \mathbf{x}_j)}{\sum_{j \in e_r(t_i)} \exp(\beta_r \cdot \mathbf{x}_j)} \right] \tag{26}$$

Likelihood ratio, Wald, or score statistics can be used for testing covariate effects (Fine and Gray, 1999). The (25) and (26) show as a regression model on SDH can

be estimated by a Cox regression model on $\{<_{r_1}, ..., <_{r_N}\}$.

If the proportional hazards assumption is tenable, the estimation of CCI for discrete covariate levels can be obtained by adapting the standard Breslow estimator for the baseline hazard (Breslow, 1974).

In the presence of time-dependent effects, a covariate vector $\mathbf{Z}(t) = \mathbf{X} * \mathbf{U}(t)$, where the components of $\mathbf{U}(t)$ depend only on t, is included in the model

$$h_{\mathcal{T}_r}(t, \mathbf{X}, \mathbf{Z}(t)) = h_{\mathcal{T}_r o}(t) \cdot \exp\left(\bar{}_r \cdot \mathbf{X} + \bar{}_{rt} \cdot \mathbf{Z}(t) \right) \tag{27}$$

where $\bar{}_{r_t}$ is the vector of the regression coefficients for the time-dependent effects. To address this case, Fine and Gray (1999) proposed an "ad hoc" strategy to estimate CCI as function of covariates.

For sake of simplicity, in the rest of this note we consider the case of proportional hazards (24).

CENSORED DATA In the case of censored data, the realization of $\mathcal{T}_r$ is unobserved for those subjects where $C = T$. The strategy previously described for complete data cannot be generally used to estimate CCI for discrete covariate levels and for the SDH based model (24). However, under the assumption of independence between $(T_f, \ :_f)$ and C, the risk set

$$e_r^c(t) = \left(j : \mathcal{T}_{r_j} > t \ ; \ C_j > t \right) = \left(j : \min(\mathcal{T}_{r_j}, \ C_j) > t \right)$$

which is coherent with the SDH (11), can be considered. Let us observe as $e_r^c(t)$ includes: i) the subjects $\{j : T_j \ 5 \ t\}$ who did not develop any event and were not censored by t (i.e. at risk of failure at t) and ii) the subjects $\left(j : T_j \ 4 \ t \ ; \ :_j \ \forall \ r \ ; \ C_j > t \right)$ who failed from a cause different from the rth and were not censored by t. Thus, $e_r(t)$ can be written in terms of the r.v. $(T, \ :)$ and C as

$$e_r^c(t) = \left(j : (T_j > t) \ \{ \ (T_j \ 4 \ t \ ; \ :_j \ \forall \ r; \ C_j > t) \right) \tag{28}$$

Let us observe as a subject j who fails at T_j for a cause different from the rth one, is included in $e_r^c(t)$ only at times $t \ 4 \ C_j$. Thus, the realization of C_j is needed to build $e_r^c(t)$.

CENSORING-COMPLETE In the case of type I censoring, C_i is observed for any subject, being $C_i = M$ (for $i = 1, ..., N$). The CCI for discrete covariate levels and the SDH based model (24) can be estimated by applying Kaplan-Meier method and Cox model, on the ground of the risk set (28) that for $t \ 4 \ M$, reduces

to $e_r(t)$, defined in (23). Thus, estimates of CCI and SDH for $t \leq M$ are equal to the corresponding ones in the case of complete data.

When generalized type I censoring is considered, C_i is still observed for any subject, but it is not necessarily constant. Fine and Gray (1999) showed as in case of censoring complete a proper partial likelihood for the improper distribution $F_r(t)$ can still be defined with the pertinent score function, which differs from (26). The Likelihood ratio, Wald, or score statistics are usable for testing covariate effect (Fine and Gray, 1999).

As this situation can be considered as a particular case of random censoring, the score function for the latter case is used in practice.

RANDOM CENSORING When the censoring time is unknown for some sample subjects, the partial likelihood approach is no longer usable, being the knowledge of the censoring times required for $e_r^c(t)$. Let us observe as the subjects $\{j : T_j > t\}$ surely belong to $e_r^c(t)$, whereas the subjects $(j : T_j \leq t ; \varepsilon_j = r)$ may belong to $e_r^c(t)$ depending on whether $C_j > t$ or $C_j \leq t$. The whole set of patients which either belong or are "candidate" to belong to $e_r^c(t)$ is

$$R_r(t) = \left(j : (T_j > t) \cup (T_j \leq t ; \varepsilon_j = r ; \varepsilon_j = 0) \right) \tag{29}$$

To address this case, Fine and Gray (1999) suggested a modification of the score function on the ground of the risk set (29), by an adaptation of the inverse probability of censoring weighting (IPCW). The IPCW was originally proposed to take into account the presence of dependent censoring and non-compliance in AIDS clinical trials (Robins and Rotnitzky, 1993; Robins and Finkelstein, 2000). A weight equal to the probability of belonging to $e_r^c(t)$

$$w_i(t) = \Pr\{C_i > t | C_i > T_i\} \tag{30}$$

is associated to each subject of $R_r(t)$ (29). Let us observe as $w_r(t) = 1$ for the subjects who surely belong to $R_r(t)$ (i.e. $T_i > t$), being $\Pr\{C_i > t ; C_i > T_i\} = \Pr\{C_i > T_i\}$.

Under the assumption of independence between (T, ε) and C, the weights (30) depend only on the distribution of the censoring times. Thus, $w_i(t)$ becomes $w_i(t) = S_C(t) / S_C(T_i)$, where $S_C(t)$ is the survival function of the r.v. C on the whole population.

Let us consider the sampling data $\left((t_1, \varepsilon_1, \mathbf{x}_1), ..., (t_N, \varepsilon_N, \mathbf{x}_N) \right)$. $w_i(t)$ can be estimated by $\hat{w}_i(t) = \hat{S}_C(t) / \hat{S}_C(t_i)$ where $\hat{S}_C(\cdot)$ is the Kaplan-Meier estimate of $S_C(\cdot)$. The score function (26) modified with the weighting system $\{\hat{w}_1(t), ..., \hat{w}_N(t)\}$ becomes

$$U_{rw}(\bar{}_r) = \sum_{i=1}^{N} I(:_i = r) \cdot \mathbf{x}_i \left(\frac{\sum_{j \in \Re_r(t_i)} \pounds_j(t_i) \cdot \mathbf{x}_j \cdot \exp(\bar{};_r \cdot \mathbf{x}_j)}{\sum_{j \in \Re_r(t_i)} \pounds_j(t_i) \cdot \exp(\bar{};_r \cdot \mathbf{x}_j)} \right)$$

It is worth of note that only the score function is modified by the weighting, being the corresponding partial likelihood function left undefined. The weighting system is extended to the variance matrix of the model, thus only the statistics based on score function or variance matrix are used for inference on $\bar{}_r$.

2.4 INTERPRETING AND USING MODEL RESULTS

2.4.1 GENERAL CONSIDERATION ON THE COMPARISON OF A COVARIATE EFFECT ON CSH AND CCI

Models on CSHs are widely used given their established clinical interpretation for disease dynamic. However, it has to be pointed out as when the focus is also on CCIs, the prognostic role of $\mathbf{X}$ on CSHs can be considerably different from the corresponding one on CCIs. In fact, from (9), there is not a direct relationship between $h_r(t)$ and $F_r(t)$. Let us consider for instance two covariate patterns ($\mathbf{x}_1$ and $\mathbf{x}_2$). If $h_r(t, \mathbf{x}_1) > h_r(t, \mathbf{x}_2)$ (for any t) this does not imply $F_r(t, \mathbf{x}_1) > F_r(t, \mathbf{x}_2)$ (for any t) as can be noticed from the following counter example. Let us consider the case of $R = 2$ with constant CSHs: $h_1(\mathbf{x}_1) = 3$, $h_2(\mathbf{x}_1) = 12$, $h_1(\mathbf{x}_2) = 2$, $h_2(\mathbf{x}_2) = 4$, and let $r = 1$ be the event of interest. Starting from (9) we can write for $k = 1, 2$

$$F_1(t, \mathbf{x}_k) = \frac{h_1(\mathbf{x}_k)}{h_1(\mathbf{x}_k) + h_2(\mathbf{x}_k)} \cdot \{1 \quad \exp[\quad (h_1(\mathbf{x}_k) + h_2(\mathbf{x}_k)) \cdot t]\}$$

obtaining the CCI functions plotted in Figure 1, which cross at $t = 0.1$. Thus, while the ratio $h_1(\mathbf{x}_1)/h_1(\mathbf{x}_2)$ is constant over time, $F_1(t, \mathbf{x}_1)$ is not always greater than $F_1(t, \mathbf{x}_2)$.

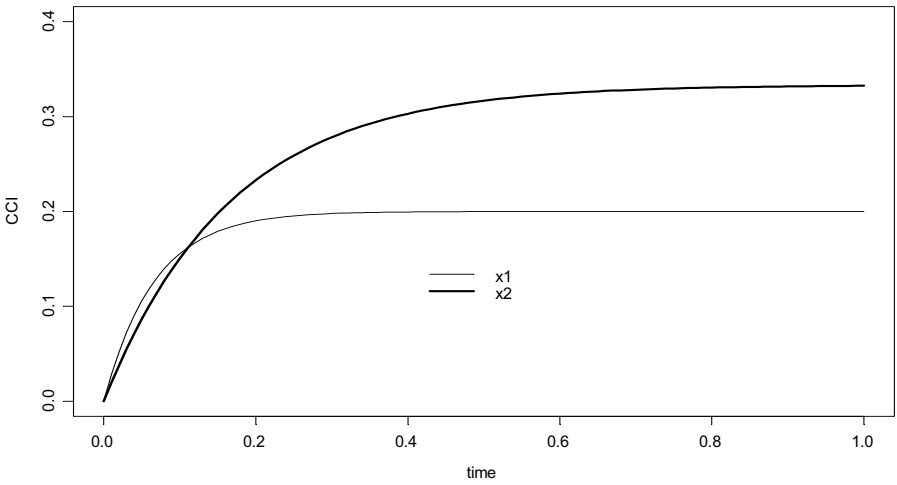

Figure 1: CCI of the event 1, corresponding to the covariate patterns $\mathbf{x}_1$ and $\mathbf{x}_2$.

2.4.2 RELATIONSHIP BETWEEN INFERENCE ON MODEL COEFFICIENTS AND CRUDE CUMULATIVE INCIDENCE

If T_f is of interest, the regression coefficients estimated from the Cox model enable to obtain an estimate of the hazard ratio of failure, which is a clinically interpretable measure usually reported.

When conducting inference on CCI curves through Fine and Gray's model, the SDH ratios can be estimated from the regression coefficients. However, unlike the hazard of failure, SDH does not have a "physical" interpretation. Thus, although the prognostic role of $\mathbf{X}$ on SDHs can be tested by Wald statistic on β_r, if the null hypothesis $\beta_r = \mathbf{0}$ is rejected, it is relevant to investigate how the information provided by the inference on β_r can be extended to CCIs.

Under model (24), for two covariate patterns $\mathbf{x}_1$ and $\mathbf{x}_2$ such as $\beta_r' \cdot \mathbf{x}_1 < \beta_r' \cdot \mathbf{x}_2$, the estimated SDH ratio (SDHR) $\widehat{SDHR}_r(t, \mathbf{x}_2/\mathbf{x}_1) = \hat{h}_{\mathcal{T}_r}(t, \mathbf{x}_2)/\hat{h}_{\mathcal{T}_r}(t, \mathbf{x}_1)$ is greater than 1. From (16) it follows that $\hat{F}_r(t, \mathbf{x}_1) < \hat{F}_r(t, \mathbf{x}_2)$ for any t. In such a case results of the inference on β_r can be directly extended to CCIs.

In the presence of time dependent effects (27), the results of the inference on β_r cannot be directly extended to CCIs and a careful examination of the shape of the logarithm of the SDHR (logSDHR), that now is a function of time, is needed. If $\log \widehat{SDHR}_r(t, \mathbf{x}_2/\mathbf{x}_1) > 0$ (for any t) it follows $\hat{F}_r(t, \mathbf{x}_1) < \hat{F}_r(t, \mathbf{x}_2)$ for any

t, while CCI curves may cross each other if $\log \; SDHR_r(t, \mathbf{x}_2/\mathbf{x}_1)$ changes its sign. This is shown by the following examples.

Starting from the SDH functions for the covariate patterns $\mathbf{x}_1, \mathbf{x}_2, \mathbf{x}_3$ (Figure 2, panel (a)), considering $\mathbf{x}_1$ as reference, $\log \; SDHR_r(t, \mathbf{x}_2/\mathbf{x}_1)$ is always greater than 0, and $\log \; SDHR_r(t, \mathbf{x}_3/\mathbf{x}_1)$ is not constant in sign (Figure 2, panel (b)).

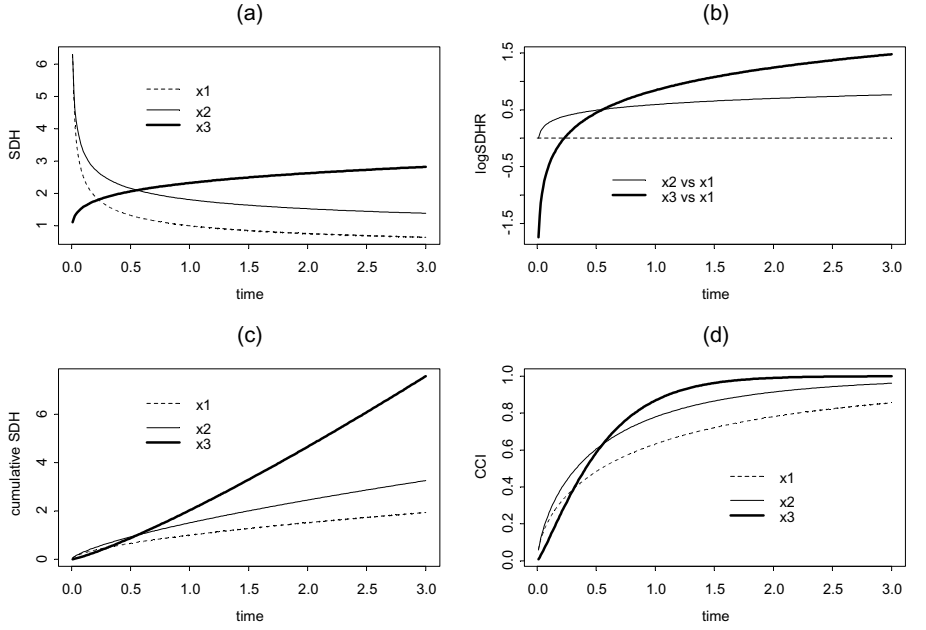

Figure 2: Relationship between logSDHR and CCI for covariate patterns $\mathbf{x}_1$ (reference), $\mathbf{x}_2$, $\mathbf{x}_3$. The SDH of $\mathbf{x}_1$ not crossing the SDH of $\mathbf{x}_2$ but crossing (once) the SDH of $\mathbf{x}_3$. (a): SDH functions. (b): LogSDHR functions. (c): Cumulative SDH functions. (d): CCI functions.

It can be noticed as being $\mathcal{h}_{\mathcal{T}_r}(t, \mathbf{x}_2) > \mathcal{h}_{\mathcal{T}_r}(t, \mathbf{x}_1)$ for any t, the same ordering is maintained also for the corresponding cumulative hazard (Figure 2, panel (c)) and for CCIs (Figure 2, panel (d)). By contrast, $\mathcal{h}_{\mathcal{T}_r}(t, \mathbf{x}_3) > \mathcal{h}_{\mathcal{T}_r}(t, \mathbf{x}_1)$ only for $t > 0.22$, this reflects in a crossing between the cumulative SDHs (Figure 2, panel (c)) and between CCIs (Figure 2, panel (d)) at $t = 0.30$.

Starting from the SDH functions for the covariate patterns $\mathbf{x}_4$ and $\mathbf{x}_5$, where $\mathcal{h}_{\mathcal{T}_r}(t, \mathbf{x}_4) > \mathcal{h}_{\mathcal{T}_r}(t, \mathbf{x}_5)$ for $0.68 \; 4 \; t \; 4 \; 2.16$ (Figure 3, panel (a)), the $\log \; SDHR_r(t, \mathbf{x}_5/\mathbf{x}_4)$ is not constant in sign (Figure 3, panel (b)). However,

the functions $\hat{H}_{\mathcal{T}_r}(t, \mathbf{x}_4)$ and $\hat{H}_{\mathcal{T}_r}(t, \mathbf{x}_5)$ (Figure 3, panel (c)), $\hat{F}_r(t, \mathbf{x}_4)$ and $\hat{F}_r(t, \mathbf{x}_5)$ (Figure 3, panel (d)) do not cross each other.

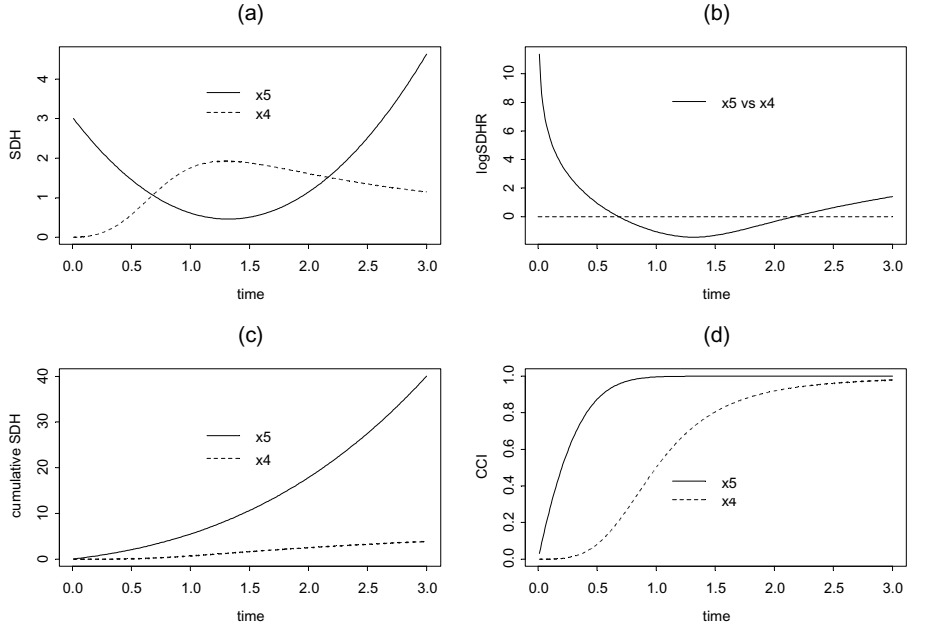

Figure 3: Relationship between logSDHR and CCI for covariate patterns $\mathbf{x}_4$, $\mathbf{x}_5$. The SDH of $\mathbf{x}_4$ (reference) crossing twice the SDH of $\mathbf{x}_5$. (a): SDH functions. (b): LogSDHR function. (c): Cumulative SDH functions. (d): CCI functions.

These examples showed as in the presence of time dependent effects, the patterns of CCI curves cannot be generally derived from the corresponding patterns of the logSDHR functions, and the estimation of CCI curves is needed.

2.4.3 REPRESENTATION OF MODEL RESULTS

To provide a measure of the impact of covariates on the CCI, we can resort to one of the well-known quantities used in epidemiological studies. The commonly used measures are: the risk ratio (or relative risk), the risk difference and the odds ratio (King and Zeng, 2002), which can be calculated (at any time point t) from the model estimated CCIs. Considering that the impact of covariates in the Cox model is commonly evaluated in terms of hazards ratio, a natural choice is resorting to the relative risk (RR).

The estimated RR of the CCI at the time point t, for two covariate patterns $\mathbf{x}_1$ and $\mathbf{x}_2$, is the probability ratio

$$RR_r(t, \mathbf{x}_2/\mathbf{x}_1) = \frac{F_r(t, \mathbf{x}_2)}{F_r(t, \mathbf{x}_1)}$$

Considering the relationship between CCI and cumulative SDH, $RR_r(t, \mathbf{x}_2/\mathbf{x}_1)$ can also be written starting from the SDHs as

$$RR_r(t, \mathbf{x}_2/\mathbf{x}_1) = \frac{1 - \exp\left(-H_{\mathcal{T}_r}(t, \mathbf{x}_2)\right)}{1 - \exp\left(-H_{\mathcal{T}_r}(t, \mathbf{x}_1)\right)}$$

For the sake of clarity it has to be pointed out as the $RR_r(t, \mathbf{x}_2/\mathbf{x}_1)$ in general differs from $SDHR_r(t, \mathbf{x}_2/\mathbf{x}_1) = h_{\mathcal{T}_r}(t, \mathbf{x}_2)/h_{\mathcal{T}_r}(t, \mathbf{x}_1)$. This can be argued considering that in the presence of proportional SDHs, RR varies over time. For instance, let us consider the SDH functions reported in Figure 4, panel (a), referring to covariate patterns $\mathbf{x}_1, \mathbf{x}_2$ and $\mathbf{x}_3$, where $\mathbf{x}_1$ is the reference. The corresponding RRs and the SDHRs are reported in Figure 4, panel (b). Since the SDHRs are greater than 1 (for any t), the RRs are greater than 1 as well. However the RRs, decrease over time and lie beyond the corresponding constant SDHRs. The difference between the SDHR and the RR is also illustrated in the case of non proportional SDH models. As an example, let us consider the SDH functions reported in Figure 4, panel (c) for the covariate patterns $\mathbf{x}_5, \mathbf{x}_6, \mathbf{x}_7$, where $\mathbf{x}_5$ is the reference. SDHRs with the corresponding RRs are reported in Figure 4, panel (d); RRs are lower than the corresponding SDHRs. At the beginning of the follow-up, both SDHR and RR are less than 1, both functions become greater than 1 but there is shift between the change times.

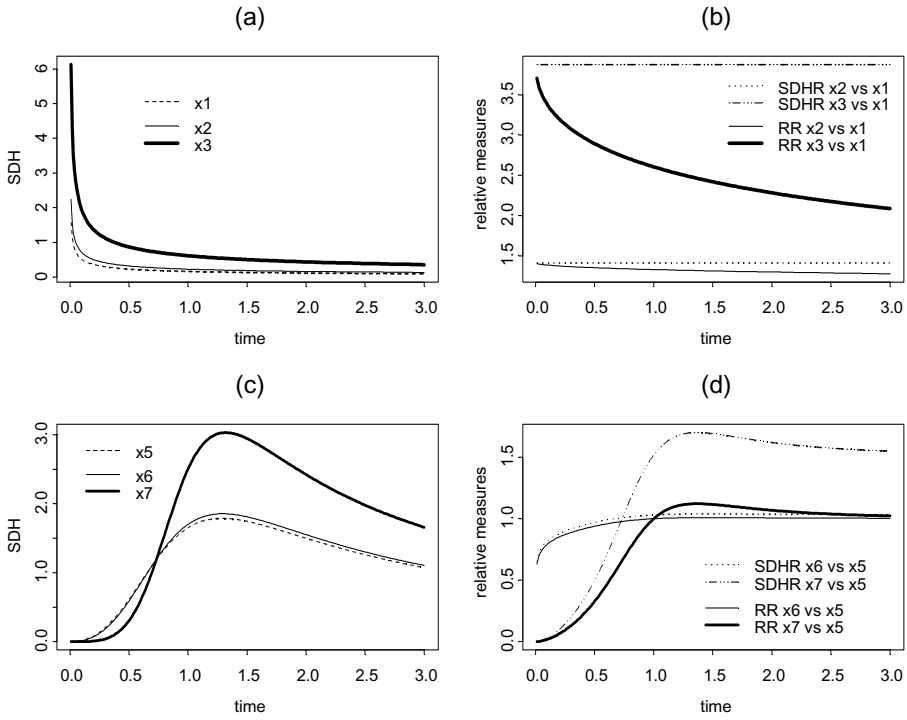

Figure 4: Relationship between SDHR and RR. Proportional hazards for covariate patterns $\mathbf{x}_1$(reference), $\mathbf{x}_2$, $\mathbf{x}_3$. (a): SDH functions. (b): SDHR functions and corresponding RR functions. Non proportional hazards for covariates patterns $\mathbf{x}_5$(reference), $\mathbf{x}_6$ and $\mathbf{x}_7$. (c): SDH functions. (d): SDHR functions and corresponding RR functions.

3. APPLICATION EXAMPLES

3.1 DATA DESCRIPTION

3.1.1 A CLASSICAL ANIMAL CARCINOGENESIS EXPERIMENT: CAUSES OF DEATH IN A RADIATION-EXPOSED MALE MICE

A group of 177 male mice were first submitted to a radiation dose of 300 rad at an age of 5-6 weeks, then they were placed in two laboratory environments: conventional (CE, 95 mice) and germ-free (GFE, 82 mice). The mice were followed until death, and necroscopy was performed to ascertain the cause of death. Complete data are available regarding the age to death (in days) and the cause: 51 mice died from thymic lymphoma (TL), 53 from reticulum cell sarcoma (RCS) and 73 from other causes (OC). Age to death is the time variable considered. The laboratory environment is the considered covariate (x_e: coded as 0= CE and 1= GFE). A detailed data description is given by Hoel and Walburg (1972). Analysis on SDHs was performed by Andersen et al. (2002) to compare the regression model they proposed with that of Fine and Gray (1999). Models on CSH were not discussed in the cited paper.

3.1.2 RANDOMIZED CLINICAL TRIAL ON BREAST CANCER PATIENTS SUBMITTED TO RADICAL AND EXTENDED RADICAL MASTECTOMY

A group of 716 patients with breast cancer, recruited at Istituto Nazionale per lo Studio e la Cura dei Tumori di Milano, from January 1964 to January 1968, were randomized for two surgical treatments: radical and extended radical mastectomy. Patients included in the study were those with disease classified as M_0 with T stage T_1, T_2, T_{3a}, and with nodal status N_0, N_1.

In the present analysis a 20-year follow-up (updated to June 1986) is considered. With such a follow-up, 462 patients died. 376 deaths were classified as due to breast cancer, 12 as due to primary tumor in other site and 74 as not related to neoplastic causes. Previous analyses on the same data set (Valagussa et al., 1978; Mezzanotte et al., 1987) were based on overall survival. Overlapping survival curves were obtained for the two kinds of surgeries (Valagussa et al., 1978).

Clinical variables were coded as follows. Treatment: 0= radical, 1= extended; metastatic involvement of axillary lymph-nodes (x_N): 0= N-, 1= N+; menopausal status (x_M): 0= pre-menopause 1= menopause; T stage by two indicator variables: x_{T_1} and x_{T_2}, where $0, 0$= T_1, $1, 0$= T_2, $1, 1$= T_{3a}, respectively.

3.2 MODELLING STRATEGY

In both examples we assumed to be interested in estimating the CCIs and to perform a consistent inference. In addition, models on CSH were also considered for the interpretation of the disease dynamics.

Fine and Gray's software (cmprsk library, version for S-PLUS 2000, available at http://bioww w.dfci.harvard.edu/~gray/), was used to obtain nonparametric estimates of CCI and 1 CSS curves (for discrete covariate levels) and to fit regression models on SDH and CSH.

Concerning SDH estimation, a status variable coded according to the different causes of death and censoring was defined. In the first example the coding was: 1= TL, 2= RCS, 3= OC, and in the second example the coding was: 0= censored, 1= breast cancer, 2= non neoplastic, 3= other tumors.

Concerning CSH estimation, for each cause of death, a status variable coded as 1 if the cause occurred, and 0 otherwise, was defined. CCI curves were estimated by (22) and 1 CSS curves were estimated by the Kaplan-Meier method. Differences between CCIs were tested by resorting to the regression models (24) or (27) on the SDH, while the Cox model based on CSH was used for inference on the 1 CSS curves.

To the above aim, the assumption of proportional hazards was evaluated by examining plots of Schoenfeld type residuals (Schoenfeld, 1982), adding a locally weighted regression smoothing to identify the shapes of possible time-dependent effects. When lack of proportionality was hypothesized, interaction terms between covariates and a function of time were included in the models. To account for possible non linear effects, 3-knot restricted cubic splines for time (Heinzl et al., 1996; Coradini et al., 2000) were adopted, resorting to the rcs function in S-PLUS 2000 Design library. When a time-dependent effect was modelled, the effect was tested by a "global" Wald statistic on the regression coefficients of the linear and nonlinear time components.

3.3 RESULTS

3.3.1 A CLASSICAL ANIMAL CARCINOGENESIS EXPERIMENT: CAUSES OF DEATH IN RADIATION-EXPOSED MALE MICE

The distributions of age to death for the three causes of death (TL, RCS, OC), are reported in Figure 5.

The nonparametric estimates of CCI and 1 CSS (according to the laboratory environment) for TL mortality, are reported in Figure 6, panels (a), (b).

The two estimates are similar for the two laboratory environments. This can be explained observing as RCS mortality (Figure 5, panels (c), (d)) acted at older

age than TL mortality (Figure 5, panels (a), (b)), and age to OC mortality (Figure 5, panels (e), (f)) was partly overlapped to that for TL. As a consequence the competing effect of RCS and OS on TL mortality was weak.

Regression models on SDH and CSH were used for inference on CCI and
1 CSS, respectively.

For the SDH, residual analysis suggested a non linear time-dependent effect of laboratory environment (x_e). Thus, the terms: $(x_e \cdot t)$ and $(x_e \cdot t^{\cdot})$ (i.e. the linear and non linear time-dependent effects) were included in the model. The laboratory environment is a significant prognostic factor for TL mortality having also a time-dependent effect (Table 1).

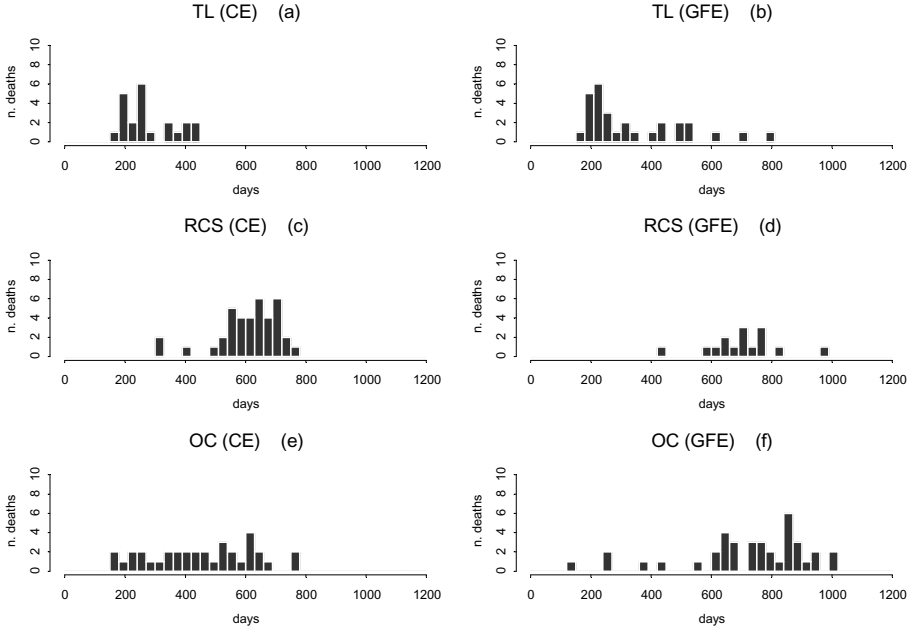

Figure 5: Distribution of age to death for the three causes, by laboratory environment.

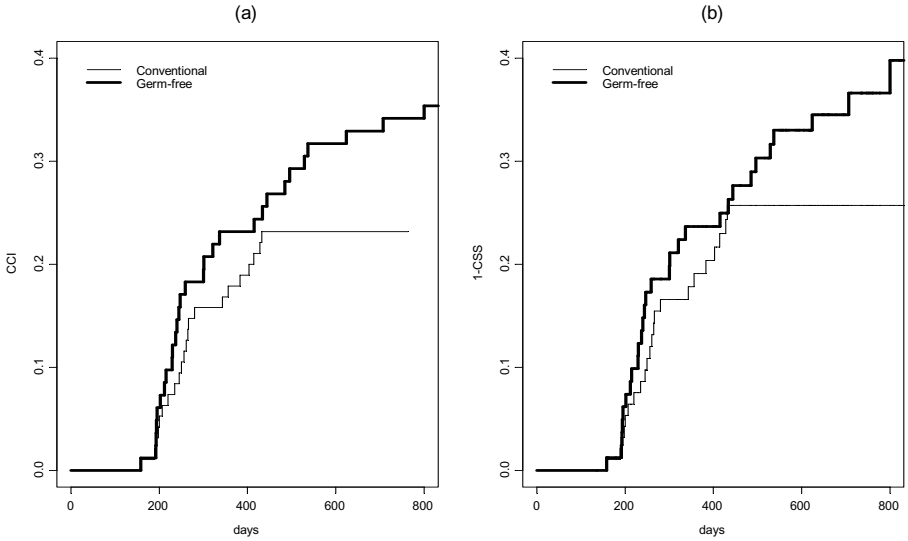

Figure 6: Nonparametric estimates of TL mortality incidences by the laboratory environment. (a): CCI. (b): 1-CSS.

Table 1: Effect of laboratory environment on the three causes of death: results of SDH regression models

Cause	model terms	$\frac{\xi}{,}^{t}$	s.e.$(\frac{\xi}{,})^{t}$	X^2	d.f.	p
TL	x_e	291.95	219.58	1.77	1	0.18
	$(x_e \cdot t)$	-1.22	0.93	1.73	1	0.19
	$(x_e \cdot t')$	4.71	2.54	3.46	1	0.06
	$(x_e \cdot t) + (x_e \cdot t')$	-	-	6.60	2	0.04
	$x_e + (x_e \cdot t) + (x_e \cdot t')$	-	-	9.08	3	0.03
RCS	x_e	-126.89	321.88	0.16	1	0.69
	$(x_e \cdot t)$	-0.12	0.57	0.05	1	0.83
	$(x_e \cdot t')$	1.13	0.64	3.15	1	0.08
	$(x_e \cdot t) + (x_e \cdot t')$	-	-	7.76	2	0.02
	$x_e + (x_e \cdot t) + (x_e \cdot t')$	-	-	14.85	3	<0.01
OC	x_e	14.47	128.40	0.01	1	0.91
	$(x_e \cdot t)$	0.45	0.34	2.12	1	0.15
	$(x_e \cdot t')$	1.77	0.61	8.48	1	<0.01
	$(x_e \cdot t) + (x_e \cdot t')$	-	-	13.23	2	<0.01
	$x_e + (x_e \cdot t + (x_e \cdot t')$	-	-	16.85	3	<0.01

Table 2: Effect of laboratory environment on the three causes of death: results of CSH regression models

Cause	model terms	$\frac{\xi}{,}^{t}$	s.e.$(\frac{\xi}{,})^{t}$	X^2	d.f.	p
TL	x_e	292.20	223.40	1.71	1	0.19
	$(x_e \cdot t)$	-1.23	0.95	1.68	1	0.20
	$(x_e \cdot t')$	4.44	2.66	2.78	1	0.10
	$(x_e \cdot t) + (x_e \cdot t')$	-	-	4.07	2	0.13
	$x_e + (x_e \cdot t) + (x_e \cdot t')$	-	-	5.59	3	0.15
RCS	x_e	-203.21	34.01	35.69	1	<0.001
OC	x_e	-110.20	28.70	17.75	1	<0.001

$^{t}\times 10^{P2}$

Legend of tables 1,2. estimates of the regression coefficient $\frac{\xi}{,}$; standard error s.e. $(\frac{\xi}{,})$; X^2: Wald statistic; d.f.: degrees of freedom; p: p-value; x_e: effect of laboratory environment; $(x_e \cdot t)$: linear time-dependent effect; $(x_e \cdot t')$: non linear time-dependent effect; $(x_e \cdot t) + (x_e \cdot t')$: global time dependent effect; $x_e + (x_e \cdot t) + (x_e \cdot t')$: global effect of laboratory environment.

The shape of the estimated logSDHR is non monotone and non constant in sign (Figure 7, panel (a)). A protective effect of the CE is observed only at ages to death from about 250 to 350 days. Afterward, the greater was the age to death the stronger is the prognostic effect of laboratory environment on the SDH. Inference on CCI curves cannot be directly derived from that on the regression coefficients since the presence of the non monotone SDH function.

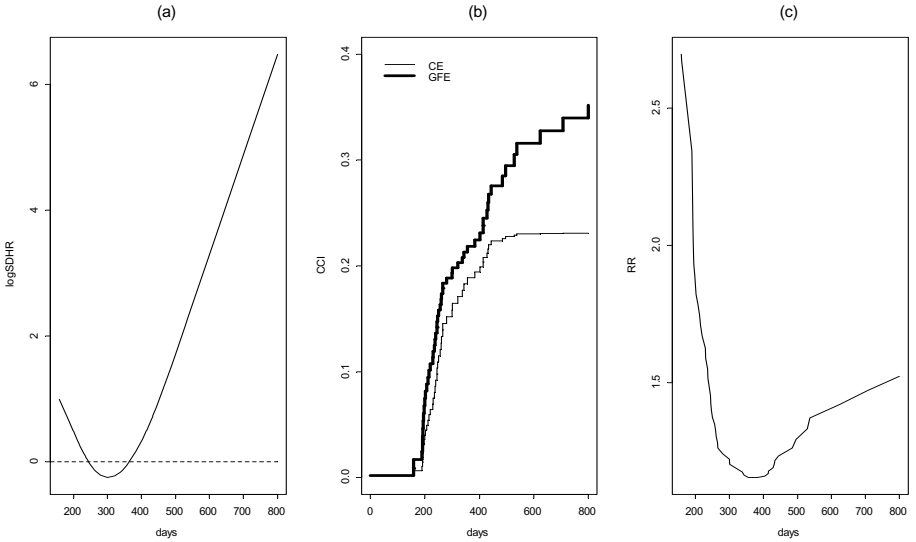

Figure 7: SDH regression model on TL mortality: estimated time functions. (a): LogSDHR of GFE versus CE. (b): CCI by laboratory environment.(c): CCI Relative risk (RR) of GFE versus CE.

The model estimated CCI curves (Figure 7, panel (b)) show as the mice in GFE had greater risk of TL death than the mice in CE at all ages. As a consequence the corresponding RR curve (Figure 7, panel (c)), is always greater than 1. The prognostic impact of the covariate on the RR decreases until about 400 days, (i.e. the point where the CCI curves are the closest), and afterward it increases reaching about 1.50 at 800 days. Since at the beginning of the period of observation the number of deaths was low in both groups (see Figure 5, panels (a), (b)), the CCIs are close to 0 thus the RR does not provide reliable information. Starting from about 500 days, the CCI curve of the CE reaches its maximum (i.e. SDH is about 0) whereas the CCI curve for the GFE kept on increasing (i.e. SDH is greater than 0). Let us observe as this behavior justifies the high values reached by the SDHR towards the end of the period of observation. In this period all the possible deaths has already occurred and the SDHR does not provide reliable information.

Concerning the CSH, residuals analysis again suggested a possible non linear time dependent effect of the laboratory environment, and the terms $(x_e \cdot t)$ and

$(x_e \cdot t)$ were included in the model. The time-dependent effect does not result statistically significant as well as the prognostic effect of laboratory environment (Table 2). It is worth of note that although the competing effect of other causes of death was expected to be weak (Figure 5), test results are quite different.

The nonparametric estimates of CCI and 1 CSS according to the laboratory environment for RCS mortality are reported in Figure 8, panels (a), (b).

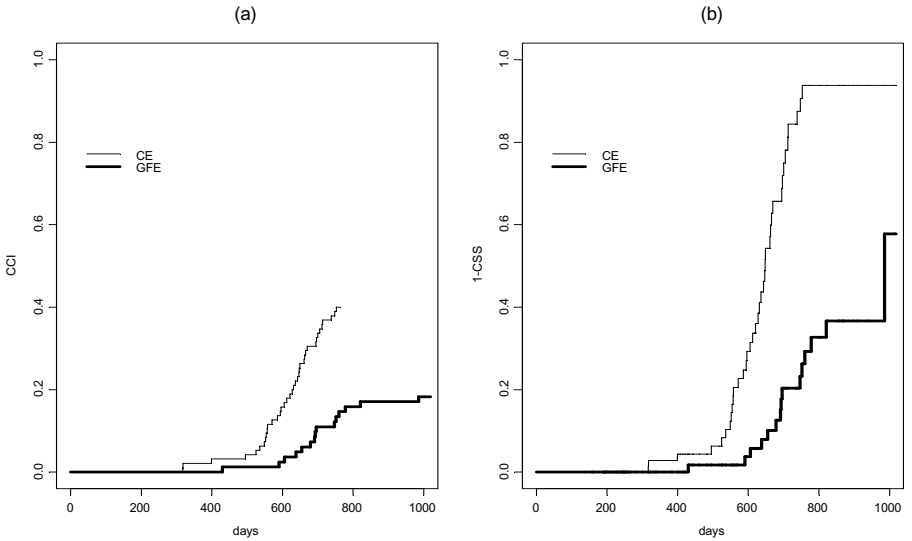

Figure 8: Nonparametric estimates of RCS mortality incidence curves by laboratory environment. (a): CCI. (b): 1-CSS.

A relevant difference is observed between CCI and 1 CSS curves. This can be explained as TL mortality (Figure 5, panels (a), (b)) and partly OC mortality (Figure 5, panels (e), (f)) acted at earlier ages than RCS mortality (Figure 5, panels (c), (d)), so the competing effect on RCS mortality was strong.

Concerning the SDH model for RCS mortality, the residual analysis suggested a possible non linear time dependent effect of the laboratory environment, and the terms $(x_e \cdot t)$ and $(x_e \cdot t)$ were included in the model. The laboratory environment is a significant prognostic factor having also a time dependent effect (Table 1).

The shape of the logSDHR is non monotone and non constant in sign (see Figure 9, panel (a)); a protective effect of the GFE is present only until about 700 days, and the prognostic effect of the laboratory environment is greater the older was the age to death.

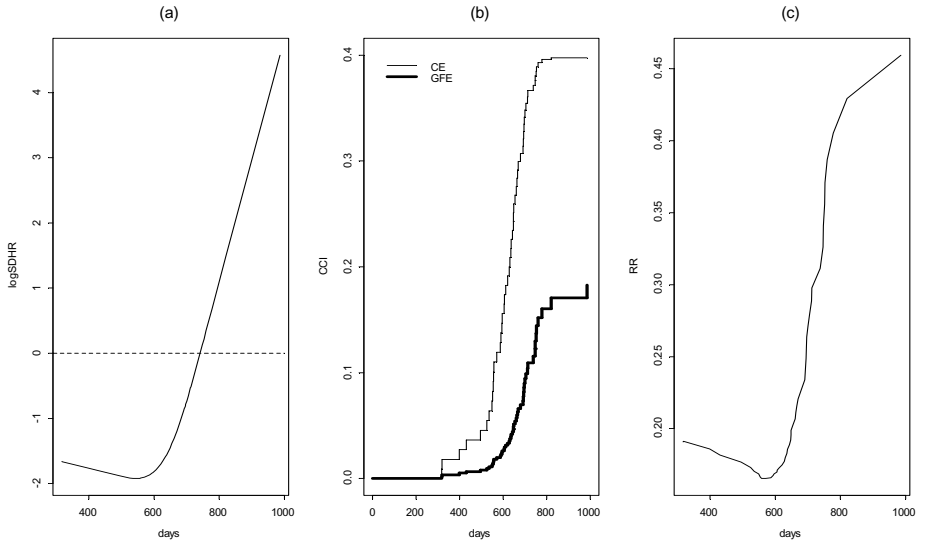

Figure 9: SDH regression model on RCS mortality: estimated time functions. (a): logSDHR of GFE versus CE. (b): CCI by laboratory environment. (c) CCI Relative risk (RR) of GFE versus CE.

The same considerations reported for TL on the behavior towards the end of the period of observation applies also for RCS, and inference on CCI curves cannot be directly derived from that on the regression coefficients.

The model estimated CCI curves are reported in Figure 9, panel (b). A protective effect of GFE is shown at all ages to death. The corresponding RR curve (Figure 9, panel (c)), is always less than 1 and the strongest prognostic impact of laboratory environment is at about 600 days.

Concerning the CSH model for RCS mortality, the residual analysis did not suggest a possible time-dependent effect of the laboratory environment. Thus, the proportional hazard model was used. The laboratory environment is a significant prognostic factor (see Table 2). The constant CSH ratio is 0.13, showing a protective effect of the GFE. This behavior is very different from that obtained for SDHR.

The analysis for OC mortality shows similar patterns of estimated CCIs and 1-CSSs and similar model results to those discussed for RCS mortality.

This example application shows as the nonparametric estimate of CCI is always less than the corresponding 1 CSS curve, as expected from the inequality (17) on the corresponding population functions. Such a difference is greater the stronger is the competing effect of the other causes of death. The results of regression models based on SDH and CSH are substantially different. In particular, the environment has a significant prognostic effect on SDH for TL mortality ($X^2 = 9.08$, $p =$

0.03), but not on CSH ($X^2 = 5.59$, $p = 0.15$). Concerning the other two causes of death, SDH shows a time dependent effect that is not evidenced for CSH. The pattern of the prognostic impact of the environment on the measure of interest (RR) is different from the corresponding one on SDH.

3.3.2 RANDOMIZED CLINICAL TRIAL ON BREAST CANCER PATIENTS SUBMITTED TO RADICAL AND EXTENDED RADICAL MASTECTOMY

The estimated CCI and 1 CSS curves for breast cancer mortality according to surgical treatment are very similar, and no relevant differences are observed between radical and extended radical mastectomy (Figure 10, panels (a), (b)).

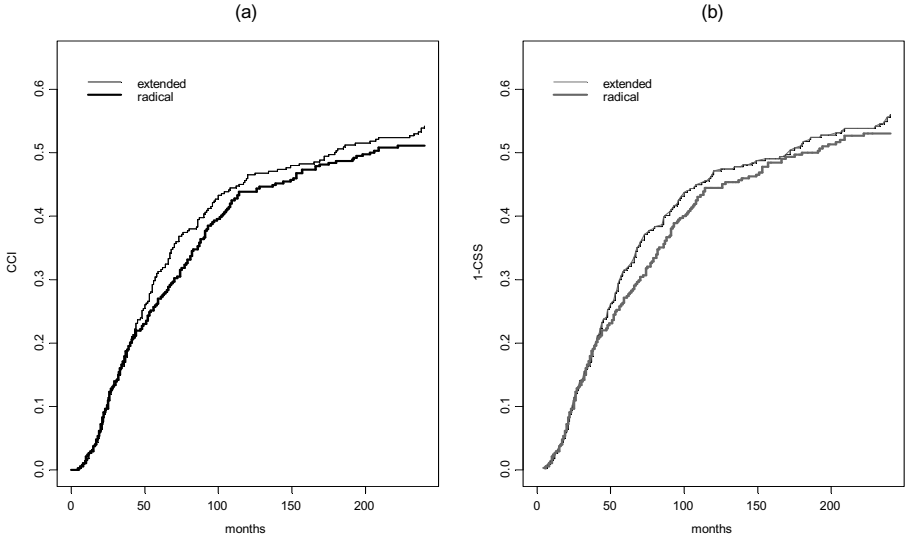

Figure 10: Nonparametric estimates of breast cancer mortality incidence curves by surgery. (a): CCI. (b): 1-CSS.

Residual analysis did not suggest the presence of time dependent effects, so proportional hazard models were used for SDH and CSH. The estimates of two models are very similar and the difference between surgical treatments are not statistically significant ($p = 0.40$ for SDH and $p = 0.44$ for CSH). This is coherent with previous analyses reported on the trial results (Valagussa et al., 1978; Mezzanotte et al., 1987). In the present analysis, further investigations on the effect of surgery were not carried out.

Concerning the other covariates, the estimated of CCI and 1 CSS curves for breast cancer mortality, according to the same covariate levels, are very similar

(Figure 11). This can be explained by the weak competing effect of mortality due to other causes than breast cancer, being breast cancer mortality the event with the highest incidence.

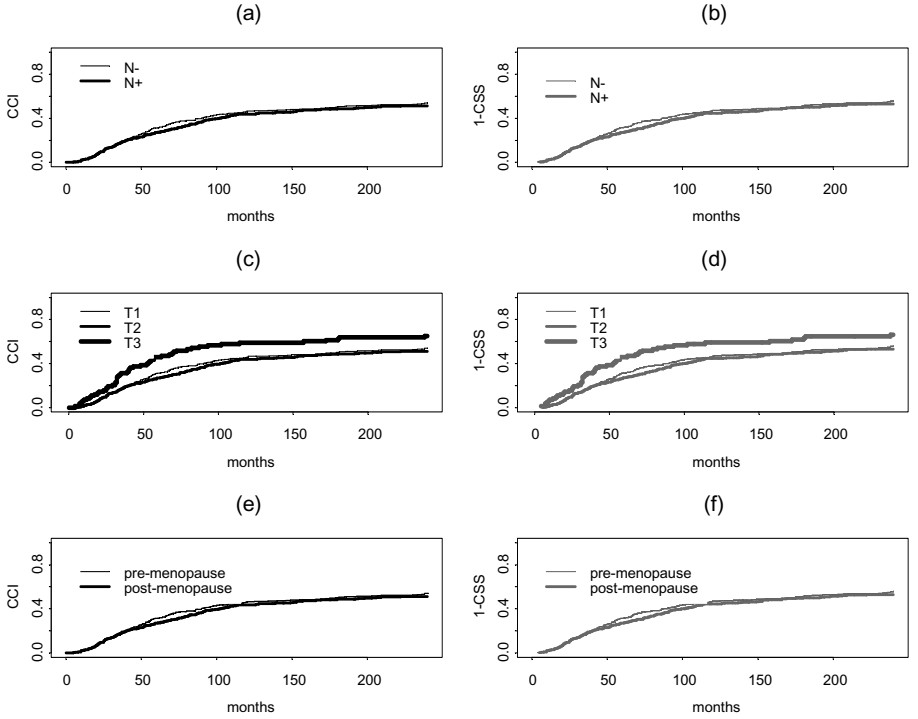

Figure 11: Nonparametric estimates of breast cancer mortality incidence curves by covariate levels. (a): CCI by metastatic involvement of axillary lymph-node (N). (b): 1-CSS by N. (c): CCI by T stage. (d): 1-CSS by T stage. (e): CCI by menopausal status. (f): 1-CSS by menopausal status.

Concerning the metastatic involvement of axillary lymph nodes, residual analysis did not suggest a time dependent effect both on SDH and CSH, thus proportional hazard models including the term x_N were used. This covariate is a significant prognostic factor and estimated regression coefficients for SDH and CSH models are very similar, (Tables 3, 4). Considering N- as reference level, the estimated SDHR is 4.03, the model estimated RR for CCI are 3.61, 3.31, 2.83, and 2.55 at 3, 5, 10 and 20 years, respectively.

Concerning the T stage, the residual analysis suggested a possible non linear time dependent effect on both SDH and CSH. Non proportional hazard models were used including the following terms: x_{T_1}, $(x_{T_1} \cdot t)$, $(x_{T_1} \cdot t')$, x_{T_2}, $(x_{T_2} \cdot t)$, $(x_{T_2} \cdot t')$, where $(x_{T_1} \cdot t)$,$(x_{T_1} \cdot t')$, $(x_{T_2} \cdot t)$,$(x_{T_2} \cdot t')$ are the variables for linear

and non linear time-dependent effects of x_{T_1} and x_{T_2}, respectively. The T stage is a significant prognostic factor having also a significant time dependent effect and the estimated regression coefficients for SDH and CSH models are very similar (Tables 3, 4). For x_{T_1}, the shape of the logSDHR is non monotone and constant in sign. It reaches its minimum at about 120 months. For x_{T_2}, the shape of the logSDHR is non monotone and not constant in sign. It is below zero from 98 and 166 months, and reaches its minimum at about 128 months.

The SDHRs for T_2 versus T_1 are 3.86, 2.00, 1.03 and 3.43; for T_{3a} versus T_2 are 1.65, 1.28, 0.95 and 1.23 at 3, 5, 10 and 20 years respectively. The greatest prognostic impact on SDH is at early follow-up. The same consideration applies for the RR. In fact, RR for T_2 versus T_1 are 5.18, 1.97, 1.53 and 1.23; for T_{3a} versus T_2 are 1.77, 1.06, 1.47 and 1.61 at 3, 5, 10 and 20 years respectively.

Concerning the menopausal status, the residual analysis suggested a possible non linear time dependent effect on both SDH and CSH. Non proportional hazard models were used including the following terms: x_M, $(x_M \cdot t)$, $(x_M \cdot t')$, where $(x_M \cdot t)$, $(x_M \cdot t')$ are the variables for linear and non linear time-dependent effects of x_M. Menopausal status is a significant prognostic factor having also a significant non linear time dependent effect; the estimated regression coefficients for SDH and CSH models are very similar (Tables 3, 4). Considering pre-menopause as reference category, the shape of the logSDHR is non monotone and not constant in sign. It is below zero from 46 and 206 months, and reaches its minimum at about 112 months. The SDHRs are 1.14, 0.84, 0.64 and 1.24, at 3, 5, 10 and 20 years respectively. The RRs for CCI are not greater than 1 for whole follow-up, in fact they are 1.33, 1.15, 0.95 and 0.94 at 3, 5, 10 and 20 years respectively.

The above results are substantially similar to those obtained by multiple regression models on SDH and CSH including all variables. This example shows as in presence of a weak competing effect of other causes of death on the breast cancer mortality, models based on SDH and CSH could provide similar results.

Table 3: Effect of covariates (X) on breast cancer mortality: results of SDH regression model on each covariate.

X	model terms	$\hat{\beta}$	s.e.($\hat{\beta}$)	X^2	d.f.	p
N	x_N	1.39	0.12	138.58	1	<0.0001
T	x_{T_1}	2.47	0.78	10.09	1	<0.01
	$x_{T_1} \cdot t$	-0.03	0.01	6.80	1	<0.01
	$(x_{T_1} \cdot t')$	0.04	0.02	6.28	1	0.01
	x_{T_2}	0.924	0.33	7.97	1	<0.01
	$(x_{T_2} \cdot t)$	-0.012	0.01	2.48	1	0.12
	$(x_{T_2} \cdot t')$	0.014	0.01	1.11	1	0.29
	$(x_{T_1} \cdot t) + (x_{T_1} \cdot t') + (x_{T_2} \cdot t) + (x_{T_2} \cdot t')$	-	-	11.11	4	0.03
	$(x_{T_1} \cdot t) + (x_{T_2} \cdot t)$	-	-	10.08	2	0.01
	$(x_{T_1} \cdot t') + (x_{T_2} \cdot t')$	-	-	8.03	2	0.02
M	x_M	0.64	0.27	5.85	1	0.02
	$(x_M \cdot t)$	-0.01	0.01	7.28	1	0.01
	$(x_M \cdot t')$	0.020	0.01	4.98	1	0.03
	$(x_M \cdot t) + (x_M \cdot t')$	-	-	7.91	2	0.02

Legend: N: metastatic axillary involvment; T: T stage; M: menopausal status; $\hat{\beta}$: estimate of the regression coefficient; s.e.($\hat{\beta}$) estimate of standard error; X^2: Wald statistic; d.f.: degrees of freedom; p: p-value; : $x_N, x_{T_1}, x_{T_2}, x_M$ covariate effects; $(x_\bullet \cdot t)$: linear time-dependent effect ; $(x_\bullet \cdot t')$: non linear time-dependent effect.; $(x_\bullet \cdot t) + (x_\bullet \cdot t')$ global time dependent effect.

Table 4: Effect of covariates (X) on breast cancer mortality: results of CSH regression model on each covariate.

X	model terms	β	s.e.(β)	X^2	d.f.	p
N	x_N	1.40	0.12	138.72	1	<0.0001
T	x_{T_1}	2.45	0.77	10.03	1	<0.01
	$(x_{T_1} \cdot t)$	-0.03	0.01	6.57	1	0.01
	$(x_{T_1} \cdot t')$	0.04	0.02	5.97	1	0.01
	x_{T_2}	0.93	0.33	8.15	1	<0.01
	$(x_{T_2} \cdot t)$	-0.01	0.01	2.73	1	0.10
	$(x_{T_2} \cdot t')$	0.01	0.01	1.25	1	0.26
	$(x_{T_1} \cdot t) + (x_{T_1} \cdot t') +$ $(x_{T_2} \cdot t) + (x_{T_2} \cdot t')$	-	-	11.17	4	0.02
	$(x_{T_1} \cdot t) + (x_{T_2} \cdot t) +$	-	-	10.10	2	<0.01
	$(x_{T_1} \cdot t') + (x_{T_2} \cdot t')$	-	-	7.88	2	0.02
M	x_M	0.65	0.27	5.98	1	0.01
	$(x_M \cdot t)$	-0.01	0.01	7.38	1	<0.01
	$(x_M \cdot t')$	0.02	0.01	5.96	1	0.01
	$(x_M \cdot t) + (x_M \cdot t')$			7.52	2	0.02

Legend: N: metastatic axillary involvment; T: T stage; M: menopausal status; β: estimate of the regression coefficient; s.e.(β) estimate of standard error; X^2: Wald statistic; d.f.: degrees of freedom; p: p-value; : $x_N, x_{T_1}, x_{T_2}, x_M$ covariate effects; $(x_\bullet \cdot t)$: linear time-dependent effect ; $(x_\bullet \cdot t')$: non linear time-dependent effect.; $(x_\bullet \cdot t) + (x_\bullet \cdot t')$ global time dependent effect.

4. DISCUSSION

The presence of multiple events is usual during the course of a disease. As events have a different clinical interpretations, a common approach is their investigation (separately or jointly) to estimate specific occurrence probabilities or to detect specific prognostic factors. Nowadays, the classical approach is the Cox model on CSH, regardless of the study aims and the clinical interest. CSH is the measure of concern in several explorative studies, being the interest focused on disease dynamics, but in other clinical situations, such as for supporting clinical decision making, CCI is more useful than CSH. Inference performed on CSH regression models is not consistent with the corresponding one on SDH (Fine and Gray, 1999). Therefore, suitable regression models for CCI have been developed (Fine and Gray, 1999; Fine, 1999; Fine, 2001; Andersen et al., 2002). Several clinical studies concerning competing risks have been published, but it is worth of note as finding applications of CCI models using a database such as PubMed is a difficult task since these statistical methods are generally not mentioned neither in abstracts

nor in Key-words. As far as we are concerned, the application of Fine and Gray's model is still limited (some papers have been available since 2002: Rocha et al., 2002; Wallgren et al., 2003 among others). Possible reasons could be that the authors in their original paper resorted to an efficient notation based on counting processes in order to show the properties of the proposed model. However, this notation is difficult to understand for most applied statisticians.

In clinical situations, where the competing action of the events which are not of interest is weak, CSH and SDH based models could provide similar results. This may have discouraged to mention SDH models preferring the well-known based on CSH. On the other hand, CSH models are more "attractive" than SDH models as CSH is a clinically interpretable measure which can be directly obtained from estimated regression coefficients. Nevertheless, consistent inference procedures on CCI are needed.

Aiming at stimulating potential users to adopt SDH regression models, the present note resorts to a standard notation for competing risks to emphasize the difference between CSH and SDH models. In order to provide insight on the prognostic effect of covariates on CCI, relationships between the pattern of logSDHRs and the corresponding CCI was discussed and the relative risk is proposed as a measure of prognostic impact. It had been shown as in presence of time-dependent effects the SDHR pattern provides information on CCI pattern only in the case of SDHR grater than 1 (less than 1) for the whole considered time. Otherwise the ordering of the estimated CCI curves cannot be inferred from the shape of the logSDHR functions since CCI curves might be crossed. In the case of complete data (absence of censoring), standard software for Kaplan-Meier, log-rank test and Cox model can be used to make inference on CCI and SDH simply by considering as exposed at risk for the whole follow-up also the patients who experienced events competing with the event of interest. This strategy cannot be generally adopted in the presence of censoring; a dedicated software for competing risk is needed. For the score function proposed by Fine and Gray (1999), censoring is assumed to be non informative. However, causes of loss to follow-up that might be related to the event of interest, can originate informative censoring. These causes should be considered and treated as competing events only if they can be considered as "treatment failure", since competing events have a role in the score function different from that of censoring. In this context, Fine and Gray (1999) stated that it is possible to modify weight functions to make allowance for informative censoring.

The application of the CSH and SDH models on literature data regarding carcinogenesis experiment on mice and clinical data regarding breast cancer, showed how results do not necessarily agree. In the mice data set, the proportional hazards assumption was tenable in CSH models on RCS and OC causes of

death, whereas for SDH models, time-dependent effects for the environment were present. These results showed that proportional effects on CSH do not necessarily imply proportionality on SDH. Moreover, in presence of time dependent effects, the pattern of the prognostic impact of environment on SDH is different to the corresponding one on relative risks, confirming a difficult interpretability of model results. This example was also analyzed by Andersen et al. (2002) to compare Fine and Gray's model with the "pseudo observation model" they have proposed. The authors found that Fine and Gray's model poorly fitted OC deaths, but issues on modelling techniques were not addressed and, in particular, time-dependent effects were not accounted for.

Breast cancer mortality is the typical end-point considered to evaluate prognostic factors. Metastatic axillary lymph-node involvement and T stage are well known clinical characteristics related to disease recurrence and, as a consequence, to breast cancer mortality. For these covariates, results of SDH and CSH models are very similar. It is expected that times to death from breast cancer of patients considered to be at high risk tend to be shorter than times to death for other causes, so the competing effect of these latter on deaths for breast cancer tend to be weak. This is a possible explanation for the similar estimates of CSHs and SDHs.

Models on CSH are indeed useful in a biological framework where the dynamics of competing events is of interest. However, in a clinical framework, CCI may be more interesting, thus justifying the need for suitable regression models with a consistent inference procedure.

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RISCHI COMPETITIVI: IL MODELLAMENTO DELLE FUNZIONI DI INCIDENZA CRUDA CUMULATIVA

Riassunto

Il decorso clinico di una malattia è usualmente caratterizzato dalla possibile occorrenza di diversi eventi ed ognuno di essi ha un ruolo specifico per la valutazione delle strategie terapeutiche. L'interesse è focalizzato sull'evento che si verifica per primo in quanto è tipicamente considerato come indicatore di "fallimento della terapia" o "risposta al trattamento". La probabilità dell'occorrenza di un evento specifico in presenza di altri eventi (incidenza cruda cumulativa) è la misura più indicata per la valutazione dei trattamenti. Il modello di regressione semiparamentrico di Cox sui rischi istantanei specifici per causa è l'approccio usulamente adottato per tenere conto della presenza di covariate clinico/biologiche. Dovrebbe tuttavia essere considerato che l'effetto di una covariata sul rischio istantaneo specifico per causa potrebbe essere sostanzialmente diverso da quello sull'incidenza cruda cumulativa. Per modellare l'effetto delle covariate su tale quantità, Fine e Gray (1999) hanno proposto un modello di regressione basato sui rischi istantanei di "sottodistribuzione". A nostra conoscenza, tali modelli di regressione non sono abitualmente applicati in letteratura medica. La presente nota ha come obiettivo di promuovere l'utilizzo della tecnica di modellamento sull'incidenza cruda cumulativa; si è quindi fatto ricorso ad una notazione "standard" per i rischi competitivi per sottolineare le differenze tra il modello di Cox e quello di Fine e Gray. Inoltre, l'applicazione dei due modelli su una casistica di letteratura riguardante un esperimento di carcinogenesi effettuato su topi e su una casistica storica riguardante 716 pazienti affette da tumore alla mammella ha permesso di evidenziare come i risultati su questi due modelli non sempre concordino.