

Statistical Models for Disease Processes: Markers and Skeletal Complications in Cancer Metastatic to Bone

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In many chronic diseases, the presence and concentration of molecular compounds circulating in the blood are associated with the stage of the disease and the risk of disease progression. In diabetes, for example, individuals with poor blood glucose control are at elevated risk of vascular complications involving the heart, eyes and kidneys. The level of glycosylated hemoglobin (HbA1c) in the blood reflects how well blood glucose levels are regulated, so measurements of HbA1c are used routinely in evaluating the effectiveness of medical or behavioral interventions in diabetes. In individuals with autoimmune diseases such as rheumatoid arthritis, levels of C-reactive protein (CRP) in the blood reflect the degree of inflammation which in turn predicts joint damage. In individuals with human immunodeficiency virus (HIV) infection, physicians monitor viral load, which is the concentration of the virus in the blood at any given time. In each of these settings, the measurements in the blood are termed markers which reflect disease activity or severity. They often play a useful role in predicting the course of disease and the occurrence of serious debilitating events. This chapter describes some ways to use marker data in patients with cancer metastatic to bone.

11.1 Skeletal Complications in Individuals Suffering from Cancer Metastatic to Bone

Bone resorption is the process by which osteoclast cells break down bone tissue and release minerals such as calcium into the bloodstream. In healthy individuals the process of bone resorption is usually well coordinated with that of bone formation, to ensure repair and maintenance of normal bone

tissue. In many cancers, however, metastatic lesions develop in the skeleton, disrupt this equilibrium, and thereby compromise the structural integrity of the bone. This weakens the skeleton and puts individuals at increased risk of complications such as fractures, spinal cord compression, hypercalcemia, and bone pain requiring intervention. These complications significantly reduce a person's ability to carry out normal daily activities and decrease their quality of life. With the increased effectiveness of anti-tumor therapy in recent decades, patients are living longer following cancer diagnosis, so management of the skeletal metastases is an important aspect of patient care.

N-telopeptide of type I collagen (Ntx) is a marker of bone resorption that has been found to be associated with the presence and volume of skeletal metastases in breast cancer patients (Lipton et al., 2001), as well as the occurrence of skeletal complications (Coleman et al., 1997). In addition, the bone formation marker, bone-specific alkaline phosphatase (BALP) is often elevated in prostate cancer patients (Smith et al., 2011). Scientists are interested in relating the levels of bone formation and resorption markers to the occurrence of skeletal complications to better understand the disease process (Demers et al., 1995).

Bisphosphonates are a class of drugs which combat abnormal bone resorption to help maintain the integrity of the skeleton. These drugs are used extensively in the treatment of osteoporosis and substantial evidence has emerged that suggests treatment with bisphosphonates can reduce the incidence of skeletal complications from malignant bone disease. Three large randomized, multi-center, double-blind, phase III clinical trials evaluated the safety and efficacy of a bisphosphonate called zoledronic acid in more than 3,000 patients with malignant bone disease from a broad range of primary cancers (Rosen et al., 2003, 2004; Saad et al., 2004). Upon recruitment to these studies patients were randomly assigned to receive an intravenous infusion of zoledronic acid or a placebo control every three to four weeks for up to 24 months. Measurements of Ntx and BALP were taken at randomization, after one month of treatment, and quarterly thereafter during the course of the study.

Figure 11.1 shows the measurements of Ntx and BALP for four prostate cancer patients in the study by Saad et al. (2004). Also indicated on the horizontal axes are the times of skeletal events (E), death (D), and end of followup (C). It is apparent that there can be considerable variation in the bone marker values within patients over time, and that the two markers are not necessarily elevated at the same time. Also apparent is the variation in the period over which markers are measured due to incomplete assessments, study withdrawal, or death.

Here we highlight work of an international multidisciplinary collaborative team of investigators studying the utility of bone marker measurements collected in these trials. One goal of this team was to study the prognostic value of the marker measurements taken at study entry for skeletal events and death. Insight into their prognostic role could help researchers select high-risk patients for inclusion in experimental studies, or for more intensive monitor-

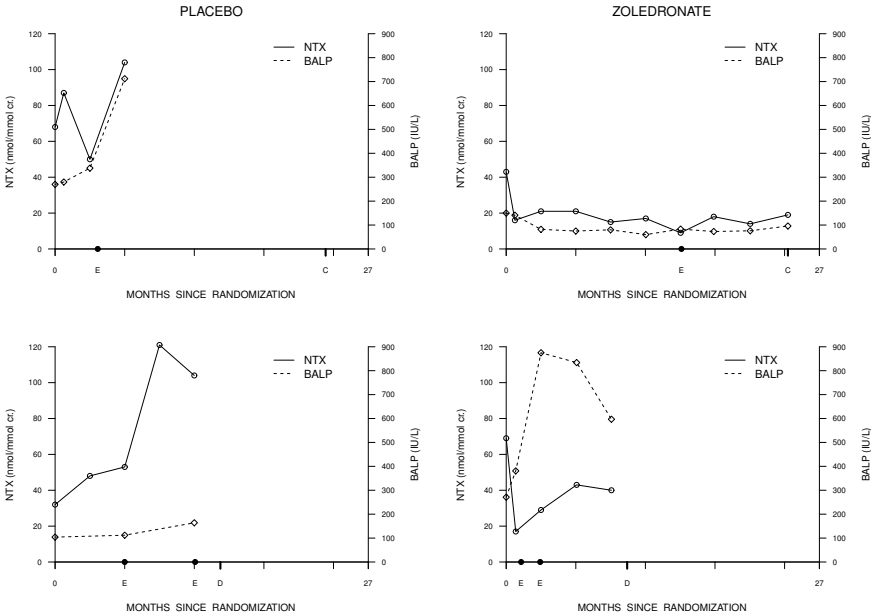


FIGURE 11.1: Sample profiles of an osteoclast (Ntx) and osteoblast (BALP) marker of bone disease along with indications of the times of skeletal events (E), death (D), and end of follow-up (C) for two prostate cancer patients receiving placebo (left panels) and two prostate cancer patients receiving zoledronate (right panels); data from Saad et al. (2004).

ing and treatment. Interest also lies in modeling how the markers vary over time and in exploration of the effect of treatment with zoledronic acid on the marker values. Several challenges arise when attempting to do this because (i) marker values are only available when blood samples are provided; (ii) measurement of markers ends upon withdrawal from the study; and (iii) the marker process naturally terminates upon death. Models which jointly examine marker values, skeletal events, and death are therefore needed to provide a complete description of the disease process and treatment effects. This research program addressed these challenges and led to considerable advances in the understanding of the pathophysiology and prognostic value of bone markers in patients with cancer metastatic to bone. Some statistical aspects of the works are described below in more detail.

11.2 Bone Markers and Prognosis for Adverse Events

Many studies examine the times to specific adverse events; such times are often termed lifetimes. In studies of lifetime data, events are often recorded as the time from study entry until their occurrence. For example, we may wish to study the times when skeletal events such as fractures occur. If T denotes the time of a disease-related event of interest, Kaplan–Meier estimates of $\Pr(T \leq t)$ reflect the cumulative risk of the event as a function of time (Kaplan and Meier, 1958). When interest lies in the effect of prognostic factors which change over time, however, it is more natural to model the risk of event occurrence at an instant in time. We describe next how this may be done.

Consider a set of factors measured at time t that may affect the risk of an event. These factors, denoted $x(t)$, are often called covariates (or covariables) since they arise along with (“co-”) the variable (here, an event time) of primary interest. If there are p covariates then $x(t) = (x_1(t), \dots, x_p(t))^T$ is a $p \times 1$ covariate vector; some elements in $x(t)$ may be fixed but others may vary over time. In the present setting we may think of $x(t)$ as containing values for markers of bone metabolism and possibly other factors.

In time to event analyses, the intensity function is a mathematical function that specifies the instantaneous risk of an event among individuals who are event-free at a given time. It is denoted by

$$\lambda\{t|x(t)\} = \lim_{\Delta t \downarrow 0} \frac{\Pr\{t \leq T < t + \Delta t | t \leq T, x(t)\}}{\Delta t},$$

where the vertical line “|” demarcates the event that is being modeled ($t \leq T < t + \Delta t$) and the information that is being conditioned upon ($t \leq T, x(t)$). In other words, here we are modeling the risk of the event occurring in the interval $[t, t + \Delta t)$ given that it did not happen before t , and given the covariate values at time t .

The effects of the time-varying bone markers discussed earlier are naturally and most commonly studied through what are termed intensity-based regression models (Kalbfleisch and Prentice, 2002; Lawless, 2003). Such models require specification of a particular mathematical form for the intensity function to reflect the trends in risk over time, as well as how covariates alter this risk. The most widely used intensity-based model in this setting is called the Cox model (Cox, 1972). This model takes the form

$$\lambda\{t|x(t)\} = \lambda_0(t)e^{x(t)^T \beta},$$

where $\lambda_0(t)$ is a reference intensity function characterizing risk for individuals with $x(t) = 0$, $\beta = (\beta_1, \dots, \beta_p)^T$ is a $p \times 1$ vector of unknown parameters called regression coefficients, and

$$x(t)^T \beta = \sum_{j=1}^p x_j(t)\beta_j.$$

There is routinely a trade-off between the desire for simplicity and the desire for flexible models which describe a process of interest well. The appeal of the Cox regression model is that the form of the reference intensity function $\lambda_0(t)$ is left unspecified, thereby enabling the model to accommodate a wide range of shapes. This formulation also has the appealing property that the exponential of the j th element of β , e^{β_j} , is a relative risk (Prentice and Farewell, 1986). To see why, note that when $p = 1$ and x_0 is a specific value of $x(t)$,

$$\frac{\lambda\{t|x(t) = x_0 + 1\}}{\lambda\{t|x(t) = x_0\}} = e^{\beta_1},$$

is a ratio of instantaneous risks reflecting the effect of a one unit increase in the covariate (e.g., marker) value.

Despite the complexity of the disease process and the many types of events that patients with bone metastases may experience, it is common in clinical trials for treatments to be assessed based on the time of the first adverse event. These outcomes are called composite endpoints and here we consider one based on the time of the first skeletal event or death for patients in the metastatic prostate cancer trial of Saad et al. (2004). Marker data prior to this composite event are used in the analyses that follow.

The first analysis we consider involves examining the relationship of the bone marker values (Ntx and BALP) measured at the time of randomization on the event intensity. For this purpose, the osteoclast marker Ntx and the osteoblast marker BALP were used in the models as categorical variables with four categories based on the quartiles of the baseline distributions; these were 54.5, 89.0 and 180.5 nmol/mmol cr. for Ntx and 150.25, 267.50 and 529.75 IU/L for BALP. Because of this categorization of the markers, the relative risks convey the effect of an individual having a value in the second quartile versus the first quartile, the third quartile versus the first quartile, and the fourth quartile versus the first quartile, for each of the two markers.

Each factor is examined in a separate model in univariate (i.e., single marker variable) analyses, where the results reflect the association between the baseline marker value and the risk of the event in the absence of other information. Covariates often reflect similar information (and hence are correlated) and so it is customary to also examine the effect of covariates simultaneously by fitting multivariate (i.e., several variable) regression models.

These models are used to identify factors which convey prognostic information in the presence of the other covariates in the model. In addition to examining the joint effect of Ntx and BALP, the multivariate models adjusted for several non-marker baseline variables (see the footnote of Table 11.1). Finally, the argument t in the covariate $x(t)$ reflects the fact that one can use the serial (time-dependent) marker values and we also do this for both univariate and multivariate models. In this case marker measurements were carried forward between assessments for up to six months, at which point if no updated values were available individuals were dropped from the analysis.

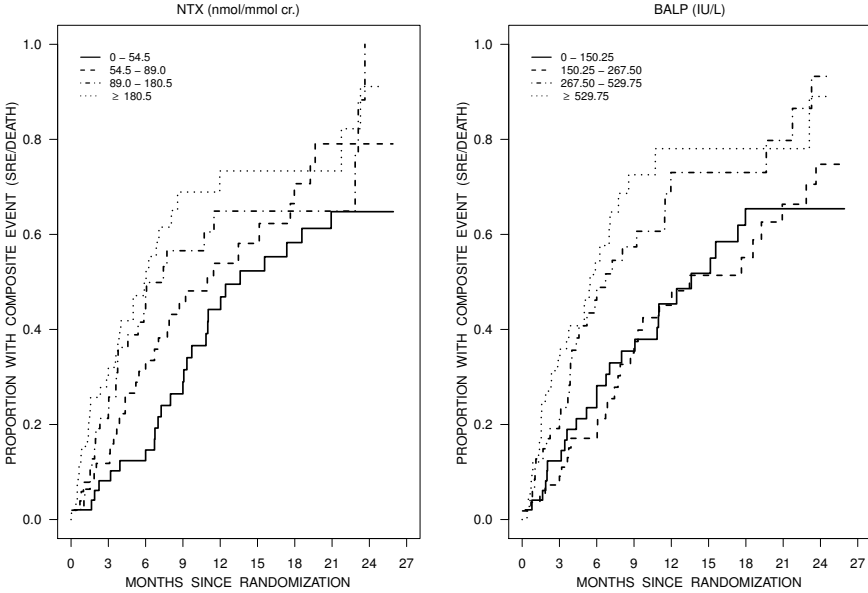


FIGURE 11.2: Kaplan–Meier estimates of the probability of an event by quartiles of urinary N-telopeptide (Ntx) (nmol/mmol cr.) and serum BALP (IU/L).

Further data from such individuals were used if subsequent measurements were made. The results of fitting univariate and multivariate models with baseline data are displayed in the top half of Table 11.1, with the corresponding results from time-dependent marker analyses in the bottom half of Table 11.1. These analyses are for simplicity restricted to placebo patients only. The table shows relative risks which are estimated by fitting Cox models to the data. It also shows 95% confidence intervals for each relative risk, which represent a standard margin of error for an estimate. Finally, p -values are shown for each relative risk; they are a measure of the evidence against the hypothesis that the relative risk is one, in which case the marker category is not associated with an increased risk of the event. Small p -values represent significant evidence against the hypothesis; values less than .05 are often considered to provide fairly strong evidence.

Table 11.1 indicates that when the baseline values are considered in univariate analyses, there is evidence of a strong relationship of both markers to event occurrence, with increasing risk associated with the higher marker quartiles. Figure 11.2 shows estimates of the probability that an event occurs as a function of time since entry to the study, estimated separately for the different

quartiles of Ntx and BALP. The probability that an event occurs by a given time increases with the level of each marker, and the effects are remarkably similar for the osteoblast marker BALP (left panel) and the osteoclast marker Ntx (right panel). In the multivariate analyses of baseline marker values (top right in Table 11.1), covariates included age (years), cancer duration (years), presence of metastases in the lymph nodes (yes/no), an indicator of advanced disease (ECOG score ≥ 1 vs. 0), bone pain (present/absent), prostate specific antigen (\log_{10} PSA, where PSA is measured in ng/mL), hemoglobin (g/dL), creatinine (≥ 1.4 mg/dL), albumin (g/L), lactate dehydrogenase (LDH > 454 units/L), an indicator of analgesic use (yes/no), and an indicator of whether they had experience a prior skeletal event (yes/no). After controlling for all of these factors, there is less evidence of an association between the markers and event occurrence. We can infer from this that the baseline markers do not convey prognostic information about event occurrence beyond that contained in other available covariates (see the footnote of Table 11.1).

A different picture arises when we consider the serial (time-dependent) values of the two bone markers (bottom half of Table 11.1). In univariate analyses of these marker values there is stronger evidence of an association with event occurrence and the relative risks are considerably larger than those seen using only baseline values. Moreover, even in the multivariate analyses, the level of BALP is significantly associated with event occurrence (p -value = .0144); risk of the event is more than double when BALP is the upper quartile compared to the lowest quartile.

There are two points to be noted from these analyses. First, as time goes by, the prognostic relevance of a marker value measured at baseline might be expected to decrease relative to a more recent measurement of a marker. A comparison of the top and bottom portions of Table 11.1 suggests this is the case. Second, the prognostic utility of a marker depends on whether other potentially important variables are considered. That is, when other variables are available and in a model, one is implicitly examining the incremental prognostic utility of the marker in the presence of the other variables. This tends to reduce the effect (as measured by the relative risk) compared to the univariate model.

11.3 Joint Models for Dynamic Bone Markers and Adverse Events

Outcomes such as skeletal events and death are of clear importance and offer a natural basis for the comparison of treatments. Not all individuals experience these events during a study, however, and there is interest in modeling changes in marker values over time and studying how they may be affected by treatment. This can give insight into the effect of bisphosphonate therapy on the

TABLE 11.1: Relative risks obtained from univariate and multivariate Cox regression analyses for intensity-based models of skeletal event-free survival in placebo patients of Saad et al. (2004); results based on baseline marker values are displayed in the top half of the table and serial marker values in the bottom half of the table.

Marker ¹	Univariate			Multivariate		
	RR	95% CI	<i>p</i> -value	RR	95% CI	<i>p</i> -value
Baseline Marker Values						
Ntx < 54.5	—	—	—	—	—	—
54.5 ≤ Ntx < 89.0	1.49	(.87, 2.55)	.151	1.52	(.81, 2.86)	.196
89.0 ≤ Ntx < 180.5	2.05	(1.15, 3.64)	.015	1.77	(.86, 3.63)	.120
180.5 ≤ Ntx	2.22	(1.28, 3.86)	.004	1.40	(.63, 3.13)	.411
Global Test, <i>p</i> -value			.021			.411
BALP < 150.25	—	—	—	—	—	—
150.25 ≤ BALP < 267.50	.91	(.53, 1.59)	.750	.67	(.36, 1.24)	.200
267.50 ≤ BALP < 529.75	1.60	(.91, 2.83)	.102	1.47	(.73, 2.96)	.284
529.75 ≤ BALP	2.24	(1.28, 3.94)	.005	1.39	(.67, 2.90)	.381
Global Test, <i>p</i> -value			.005			.102
Time-varying (Serial) Marker Values						
Ntx < 54.5	—	—	—	—	—	—
54.5 ≤ Ntx < 89.0	1.83	(.94, 3.56)	.075	1.64	(.80, 3.38)	.179
89.0 ≤ Ntx < 180.5	2.80	(1.53, 5.11)	.001	1.68	(.82, 3.46)	.158
180.5 ≤ Ntx	4.09	(2.23, 7.49)	< .001	1.77	(.78, 3.98)	.169
Global Test, <i>p</i> -value			< .001			.466
BALP < 150.25	—	—	—	—	—	—
150.25 ≤ BALP < 267.50	1.15	(.55, 2.40)	.703	.86	(.39, 1.90)	.711
267.50 ≤ BALP < 529.75	2.98	(1.59, 5.61)	.001	2.10	(1.02, 4.32)	.045
529.75 ≤ BALP	3.62	(2.00, 6.55)	< .001	2.33	(1.10, 4.91)	.027
Global Test, <i>p</i> -value			< .001			.014

¹ Ntx is measured in units of nmol/mmol cr. and the units for BALP are IU/L.

process of bone resorption and formation. The analyses in the previous section revealed that serial BALP measurements are significantly associated with the occurrence of skeletal events and death. Given the role of BALP in bone formation, it is natural to consider the effect of bisphosphonate treatment on this marker.

Levels of BALP change continuously over time but they are only measured when blood samples are taken at the periodic follow-up assessments. Serial marker values are often compared for different treatments by estimating average values at different times. When the assessment times are variable, due to random variation or possibly missed assessments, estimation and interpretation of mean values can be challenging since they correspond to individuals who survived to the respective time and who provided a blood sample. Often average values are computed at different assessment times and lines are drawn to connect these averages. There is a tendency to interpret these graphs as representing the average course of markers over time, but it is now well known that such profiles are not interpretable at the individual level (Wu, 2009). Another approach is to study the rate of change of marker values using individual-specific linear or non-linear models. When marker values, and trends in marker values, alter the risk of events such as death, models based on the rate of change are also problematic.

We address these challenges by considering joint models for the serial marker values and the event of interest by defining distinct marker states in terms of the quartiles of the marker values. Figure 11.3 contains a so-called multistate diagram with marker States 1 to 4 corresponding to ranges

$$\begin{aligned} 0 \leq \text{BALP} < 150.25, & \quad 150.25 \leq \text{BALP} < 267.50, \\ 267.50 \leq \text{BALP} < 529.75, & \quad 529.75 \leq \text{BALP}, \end{aligned}$$

and State 5 representing the clinical event of interest (death or a skeletal event). The idea behind this multi-state diagram is that at any given time, an individual's disease state can be represented by one of the states, and dynamic features of the marker and event process can be represented by stochastic

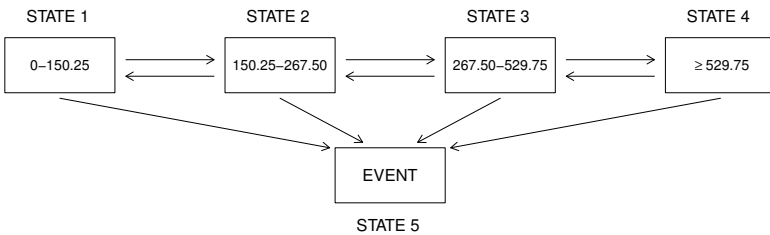


FIGURE 11.3: A multistate diagram for modeling changes in bone alkaline phosphatase prior to the occurrence of the clinical event of interest.

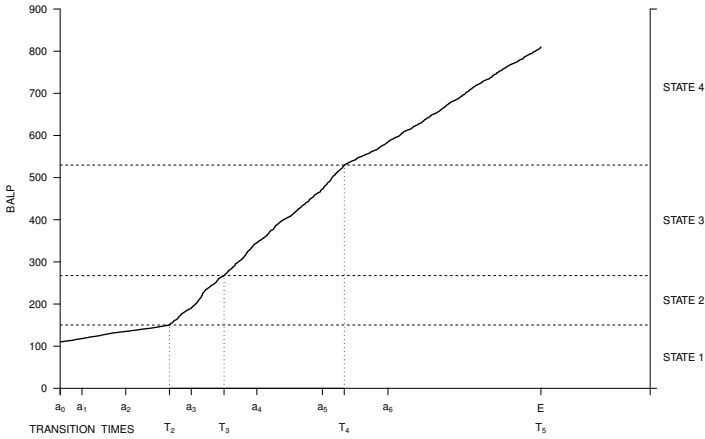


FIGURE 11.4: A plot of BALP values in continuous time for a hypothetical individual with the assessment times $(a_r, r \in \{0, \dots, 6\})$ and event time E indicated on the horizontal axis.

models for the transitions between the states. We consider a transition into State 5 the end of the process because one component of the composite event is death, and values will not be available after this. Moreover, the goal is to model marker dynamics before skeletal complications since the complications themselves may alter marker values.

We let $Z(t)$ represent the state occupied at time t so that $Z(t) = k$ if an individual is in state k at time t ; for example, $Z(t) = 3$ if at time t an individual has a BALP value in the interval $[267.50, 529.75)$. Starting with $t = 0$ at the study entry, the path of the marker as depicted in Figure 11.3 is traced, and $\{Z(s), s > 0\}$ denotes the corresponding multi-state process. When the path is considered only up to a particular time t , we denote the history of the process up to that time as $\mathcal{H}(t) = \{Z(s), 0 < s < t\}$, which captures the nature and timing of all transitions over the interval $(0, t)$. The transitions between states are again governed by intensity functions, which in this context reflect the instantaneous risk of movement from one state to another given the history of the process. The transition intensity from state k to ℓ is denoted as $\lambda_{k\ell}\{t|\mathcal{H}(t)\}$ and defined formally as

$$\lambda_{k\ell}\{t|\mathcal{H}(t)\} = \lim_{\Delta t \downarrow 0} \frac{\Pr\{Z(t + \Delta t^-) = \ell | Z(t^-) = k, \mathcal{H}(t)\}}{\Delta t}, \quad k \neq \ell. \quad (11.1)$$

Figure 11.4 contains a plot of the continuous time course of BALP values for a hypothetical individual. The times at which measurements of BALP are available are indicated by $a_r, r \in \{0, \dots, 6\}$, along with the event time (T_5) . The horizontal dashed lines in Figure 11.4 correspond to the quartiles of the

baseline distribution of BALP which in turn define the states of Figure 11.3. The time that the BALP curve crosses the lowest dashed line (T_2) is therefore the time of the transition from State 1 to State 2 and subsequent transition times (T_3 and T_4) are similarly defined. Because individuals are only seen periodically we do not observe the precise times of any of the transitions between the first four states; indeed, because an individual's BALP values can go either up or down over time, we do not even know the number of transitions between measurements. In contrast, if the event occurs during the course of followup, its time is known (see $T_5 = T$ in Figure 11.4), but in some cases all we know is that it did not happen while the individual was on study.

To formalize this, we let C denote the duration of time an individual was on study. If T denotes the time of the event, then we let $U = \min(T, C)$ and $\delta = \mathbf{1}(U = T)$ indicate whether U is the event time, or a lower bound for the event time (called a censoring time). Blood samples are drawn at times $a_0 < \dots < a_R$, and so the data consist of the sequence of assessment times and states occupied at those times, along with the information on the event time: this is equivalent to $\{(a_r, Z(a_r)), r = 0, \dots, R; (U, \delta)\}$. Under intermittent inspection we define the observed history as of the r th assessment as $H(a_r) = \{(a_s, Z(a_s)), s = 0, \dots, r-1, a_r, a_r < U\}$; since data are not available between assessments, for $a_r \leq t < a_{r+1}$, we assume that $H(t) = H(a_r)$.

Statistical inference concerning the process in Figure 11.3 can be based on a likelihood function which is obtained from the probability of observing the realized data (Sprott, 2000). In this setting this is

$$\left[\prod_{r=1}^R \Pr\{Z(a_r)|H(a_r)\} \right] \times \left[\sum_{k=1}^4 \Pr\{Z(s^-) = k|H(s)\} \lambda_{k5}^\delta \{s|Z(s^-) = k, H(s)\} \right].$$

For many processes the probabilities above may be difficult to express in terms of the intensity functions used to specify the models. Researchers often model such data using Markov assumptions (Cook and Lawless, 2013) for which the transition intensities are of the form

$$\lambda_{k\ell}\{t|\mathcal{H}(t)\} = \lambda_{k\ell}\{t|Z(t^-) = k\},$$

i.e., the instantaneous risk of the event given the entire history, is governed by simply the current marker state. Jackson (2011) has written useful software which facilitates the sort of multi-state analyses which we employ here.

Figure 11.5 shows nonparametric Kaplan–Meier estimates of the cumulative probability $\Pr(T \leq t)$ of the composite event according to the baseline quartile of BALP. These estimates, provided separately for each treatment group, use only raw data and are not based on the model in Figure 11.3. Also displayed are the same probabilities estimated based on the model depicted

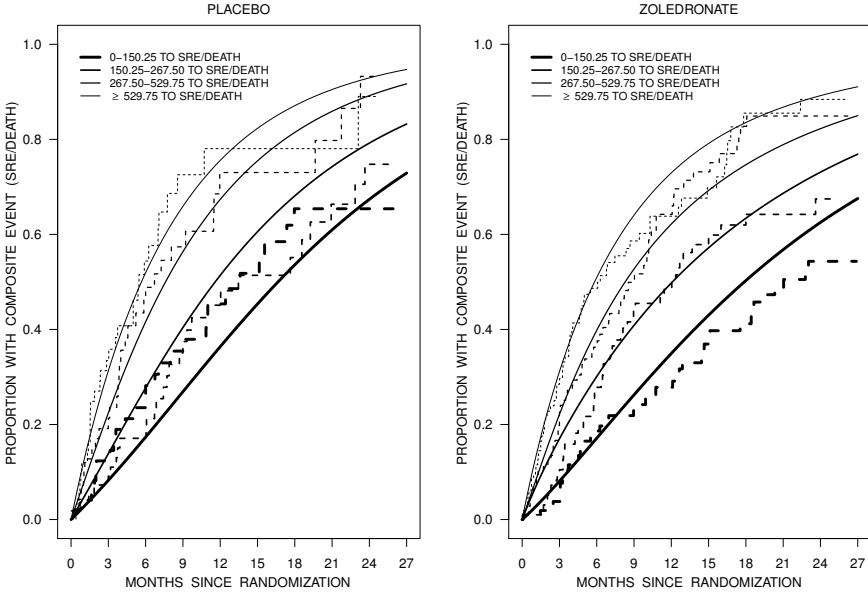


FIGURE 11.5: Kaplan–Meier estimates (dotted line) and $\hat{P}\{Z(t) = 5 | Z(0) = k\}$ for $k = 1, 2, 3, 4$ based on a multistate model (solid line) for the probability of having a skeletal event or died by quartiles of serum BALP (IU/L).

in Figure 11.3. The two methods of analysis give estimates of cumulative risk which are in fairly good agreement.

An appeal of the multi-state analysis is that it can also be used to examine treatment effects on the transition intensities between the marker states. For example, if we let $x = 1$ for individuals receiving zoledronate and $x = 0$ for those receiving the placebo, we may fit proportional intensity models of the form

$$\lambda_{k\ell}\{t|H(t), x\} = \lambda_{k\ell}\{t|Z(t^-) = k\}e^{\beta_{k\ell}x}$$

for which the instantaneous risk of a $k \rightarrow \ell$ transition differs by a multiplicative factor $e^{\beta_{k\ell}}$ in the zoledronate versus placebo groups. Table 11.2 shows the results of fitting such a model and it can be seen that zoledronate significantly increases the transition rate to states of lower marker values; the rate of transition from State 2 ($150.25 \leq \text{BALP} < 267.50$) to State 1 ($\text{BALP} < 150.25$) is 2.7 times higher in the treated group compared to the placebo control group, and similarly increased rates of transition are seen for the transitions from States 3 to 2 and 4 to 3. A key message is therefore that treatment with zoledronate can help reduce the value of BALP. Interestingly there appears to be

TABLE 11.2: Relative risks for the effect of zoledronate on the intensities of transitions between BALP marker states in the five-state Markov model depicted in Figure 11.3.

Transitions		RR	95% CI	p-value
From	To			
Reduction in BALP (IU/L)				
0 – 150.25	—	—	—	—
150.25–267.50	0 – 150.25	2.72	(1.66, 4.47)	< .001
267.50–529.75	150.25–267.50	3.38	(1.84, 6.21)	< .001
≥ 529.75	267.50–529.75	1.84	(.92, 3.69)	.085
Increase in BALP (IU/L)				
0 – 150.25	150.25–267.50	.96	(.63, 1.45)	.842
150.25–267.50	267.50–529.75	1.45	(.96, 2.18)	.076
267.50–529.75	≥ 529.75	1.14	(.76, 1.69)	.533
≥ 529.75	—	—	—	—

relatively little effect of zoledronate on the transition rates to higher BALP states based on this model.

11.4 Discussion

Marker data can play an important role in understanding disease processes, evaluating treatment effects and making predictions about the course of disease. We have focused here on the relationship between marker values and the primary response in the clinical trials, the time to the first skeletal event or death. We also considered the effect of treatment on the marker values through specification of a multi-state model. More elaborate multi-state models could of course be specified which may, for example, distinguish between the first skeletal event and death, accommodate the occurrence of multiple skeletal complications (Cook et al., 2009) or distinguish between the different types of skeletal complications. Such models would provide a better repre-

sentation of the disease process but require strong assumptions warranting critical assessment.

Analyses must deal with the fact that marker values change in continuous time but are usually only available at periodic assessment times. In the bone marker studies, the assessments were scheduled according to a trial protocol and so measurement times are unrelated to the disease process. In observational cohort studies, however, marker measurements are often only made when individuals attend a clinic at which they receive medical care. In such circumstances, measurements of markers may be made more often when their values correspond to severe disease activity. This can make standard analyses invalid and may require more challenging analysis based on joint models of the assessment process and marker values (Chen et al., 2010; Sweeting et al., 2010).

There has been increased interest in the design and conduct of clinical trials aiming to evaluate use of markers to guide therapy, an objective that falls within the framework of personalized medicine. In asthma, inflammatory markers can be measured in sputum samples obtained from patients experiencing exacerbations and the cellular analysis can be used to guide therapy (Jayaram et al., 2006). A recent trial in the United Kingdom was designed to assess the utility of serial bone marker values in guiding the dose and frequency of bisphosphonate therapy in patients with cancer metastatic to bone. In such settings markers need to be highly predictive of events of importance to patients since otherwise marker driven dose reduction or other treatment modifications may increase the risk of adverse events.

Acknowledgments

The author thanks the editor for constructive comments and suggestions during the preparation of this chapter, Novartis for permission to use the data from the prostate cancer trial, Robert E. Coleman, Allan Lipton, Pierre Major, and Matthew Smith for collaboration on the bone marker research program, and Ker-Ai Lee for assistance with the statistical programming. This research was supported by grants from the Natural Sciences and Engineering Research Council of Canada, the Canadian Institutes for Health Research, and the Canada Research Chairs Program.

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Bibliography

- Chen, B., Yi, G. Y., and Cook, R. J. (2010). Analysis of interval-censored disease progression data via multi-state models under a nonignorable inspection process. *Statistics in Medicine*, 29:1175–1189.
- Coleman, R. E., Purohit, O. P., Vinholes, J. J., and Zekri, J. (1997). High dose pamidronate: Clinical and biochemical effects in metastatic bone disease. *Cancer*, 80(Suppl):1686–1690.
- Cook, R. J. and Lawless, J. F. (2013). Statistical issues in modeling chronic disease in cohort studies. *Statistics in Biosciences*, in press.
- Cook, R. J., Lawless, J. F., Lakhal-Chaieb, L., and Lee, K.-A. (2009). Robust estimation of mean functions and treatment effects for recurrent events under event-dependent censoring and termination: Application to skeletal complications in cancer metastatic to bone. *Journal of the American Statistical Association*, 104:60–75.
- Cox, D. R. (1972). Regression models and life tables (with discussion). *Journal of the Royal Statistical Society, Series B*, 34:187–220.
- Demers, L. M., Costa, L., Chinchilli, V. M., Gaydos, L., Curley, E., and Lipton, A. (1995). Biochemical markers of bone turnover in patients with metastatic bone disease. *Clinical Chemistry*, 41:1489–1494.
- Jackson, C. H. (2011). Multi-state models for panel data: The MSM package for R. *Journal of Statistical Software*, 38:1–28.
- Jayaram, L., Pizzichini, M. M., Cook, R. J., Boulet, L.-P., Lemièrre, C., Pizzichini, E., Cartier, A., Hussack, P., Goldsmith, C. H., Laviolette, M., Parameswaran, K., and Hargreave, F. E. (2006). Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations. *European Respiratory Journal*, 27:483–494.

- Kalbfleisch, J. D. and Prentice, R. L. (2002). *The Statistical Analysis of Failure Time Data*, Second Edition. Wiley, New York.
- Kaplan, E. L. and Meier, P. (1958). Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association*, 53:457–481.
- Lawless, J. F. (2003). *Statistical Models and Methods for Lifetime Data*, Second Edition. Wiley, Hoboken, NJ.
- Lipton, A., Costa, L., Ali, S. M., and Demers, L. M. (2001). Bone markers in the management of metastatic bone disease. *Cancer Treatment Reviews*, 27:181–185.
- Prentice, R. L. and Farewell, V. T. (1986). Relative risk and odds ratio regression. *Annual Review of Public Health*, 7:35–58.
- Rosen, L. S., Gordon, D., Kaminski, M., Howell, A., Belch, A., Mackey, J., Apfelstaedt, J., Hussein, M. A., Coleman, R. E., Reitsma, D. J., Chen, B.-L., and Seaman, J. J. (2003). Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: A randomized, double-blind, multicenter, comparative trial. *Cancer*, 98:1735–1744.
- Rosen, L. S., Gordon, D., Tchekmedyian, N. S., Yanagihara, R., Hirsh, V., Krzakowski, M., Pawlicki, M., de Souza, P., Zheng, M., Urbanowitz, G., Reitsma, D., and Seaman, J. (2004). Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: A randomized, phase III, double-blind, placebo-controlled trial. *Cancer*, 100:2613–2621.
- Saad, F., Gleason, D. M., Murray, R., Tchekmedyian, S., Venner, P., Lacombe, L., Chin, J. L., Vinholes, J. J., Goas, J. A., and Zheng, M., for the Zoledronic Acid Prostate Cancer Study Group (2004). Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *Journal of the National Cancer Institute*, 96:879–882.
- Smith, M. R., Cook, R. J., Lee, K.-A., and Nelson, J. B. (2011). Disease and host characteristics as predictors of time to first bone metastasis and death in men with progressive castration-resistant nonmetastatic prostate cancer. *Cancer*, 117:2077–2085.
- Sprott, D. A. (2000). *Statistical Inference in Science*. Springer, New York.
- Sweeting, M. J., Farewell, V. T., and De Angelis, D. (2010). Multi-state Markov models for disease progression in the presence of informative examination times: An application to hepatitis C. *Statistics in Medicine*, 29:1161–1174.
- Wu, L. (2009). *Mixed Effects Models for Complex Data*. Chapman & Hall, London.