RESEARCH COMMUNICATION

Comparison of Aalen's Additive and Cox Proportional Hazards Models for Breast Cancer Survival: Analysis of Population-Based Data from British Columbia, Canada

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Abstract

Background: Regression models for survival data have traditionally been based on the Cox regression model. However, its validity relies heavily on assumption of proportional hazards. Another restriction of the Cox model is insufficiency in dealing with time-varying covariate effects, since the regression coefficients are assumed constant. These weaknesses have generated interest in alternative approaches and with Aalen's additive model, the effect of the covariates acts on an absolute rather than a relative scale. We here fit the Cox and Aalen's additive models to breast cancer data for comparison through practical application. Methods: The data related to 14,826 women diagnosed with breast cancer in BC during 1990-1999 and followed to 2010. Plots of the Martingale Residual Process and Arja's Plot was used to assess the fit of the additive model. The Cox-Snell residuals, Martingale residuals and scaled Schoenfeld residuals were used to check the Cox model. Results: In the category of patients younger than 65 years the proportional hazard assumption was satisfied. In this category, by the Cox model, the variables "stage", "surgery", "radiotherapy", "chemotherapy", "hormone therapy" and interaction between "stage" and "surgery" proved significant. In the same category, by the Aalen's additive model, similar significant variables are selected except for "hormone therapy". The sign of estimated coefficients from survival functions based on the both Cox and Aalen's additive models were alike although estimated coefficients in the two models differed from the viewpoint of magnitude. In the category of patients older than 65 years, the proportional hazard assumption was not satisfied, and the Stratified Cox model and Aalen's additive model gave similar results. Conclusions: Based on our findings, if the proportional hazard assumption is not satisfied, the Aalen's additive model is an appropriate alternative for the Cox model. If the proportional hazard assumption is satisfied, both models are appropriate. Generally, the two models give different pieces of information.

Keywords: Aalen's additive model - standard Cox model - stratified Cox model - breast cancer - survival analysis

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Introduction

Cancer is the second leading cause of death in developed countries and a public health problem worldwide (Fisch et al., 2005). Breast cancer is the most common malignant disease for females in northern Europe and North America, corresponding to an age-corrected annual incidence of 100 to 120 per 100000 females. The median age for new breast cancer diagnosis is 60 to 64 years (Törner, 2004). In Canada during 2011, breast cancer is estimated to be the most common cancer in women, with more than 23,000 new diagnoses. Breast cancer is expected to have killed more than 5,000 Canadian women in 2011, more than any other type of cancer except lung (Canadian Cancer Society, 2011). Breast cancer accounted for an estimated 95,300 potential years of life lost in Canada during 2009 (Yavari et al., 2010). Therefore, the identification of factors associated with survival from this disease is very important.

Survival analysis is a class of statistical methods for studying and modeling the relationship between risk factors and a patient's time to death. Survival data have some features that are difficult to analyze using traditional statistical methods: censoring and time-dependent covariates. Survival analysis has traditionally been based on the Cox model. This model is popular because it is intuitive, simple to fit and the results are easy to explain. The Cox model is called a proportional hazards model because the hazard ratio for each explanatory variable is assumed to be constant over time. The validity of analyses using the Cox model relies heavily on the proportional hazards assumption. Another limitation of this model is that it cannot include time-varying covariate effects since the regression coefficients are assumed constant.

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However, many real applications do need such flexibility (Martinussen and Scheike, 2006). These weaknesses in the Cox model have generated interest in alternatives. In Aalen's additive model, the effect of a covariate acts on an absolute scale rather than a relative one. The coefficients in Aalen's model are functions of time without any particular form or dependence on the other parameter functions. Thus, it is truly non-parametric, as opposed to the semi-parametric nature of Cox's proportional hazards model, and therefore well suited to study possible changes over time in the effects of the covariates.

In this paper, we fit the Cox and Aalen's additive models to breast cancer data and compare these models through application.

Materials and Methods

Study population

Data for 14826 women diagnosed with breast cancer in BC during 1990-1999 and followed to 2010 has been used in this research. Variables used in this analysis are: survival time (period between diagnosis and death or end of study), status (status=0 if the survival time for a patient is censored, status=1 if the patient died of breast cancer), age (age of the subject when breast cancer was diagnosed), stage (this takes values 1 to 4. We changed this variable to four nominal variables of stage1 stage4 for use in the model), and treatment (treatment(s) assigned to patient. They include hormontherapy, chemotherapy, surgery, and radiotherapy). A patient can have more than one kind of treatment.

Analysis

Two models for analyzing breast cancer survival data were considered: (1) the standard and stratified Cox model and (2) Aalen's additive model.

All models used the covariates included in data set.

The Cox model is specified as:

$$h(z) = h_0 \exp(b_1 age + b_2 stage + b_3 surgery + b_4 radiotherapy + b_5 chemotherapy + b_6 hormontherapy + b_7 stage * surgery + b_8 stage * radiotherapy + b_9 stage * chemotherapy + b_{10} stage * hormontherapy)$$

and Aalen's additive model is specified as:

$$h(z) = h_0 \exp(b_1 age + b_2 stage + b_3 surgery + b_4 radiotherapy + b_5 chemotherapy + b_6 hormontherapy + b_7 stage * surgery + b_8 stage * radiotherapy + b_9 stage * chemotherapy + b_{10} stage * hormontherapy)$$

To compare these models, there are several statistical challenges. Firstly, the models are not nested except in special cases. This excludes using statistical tests such as the likelihood ratio test, score test and Wald test. Secondly, the likelihood function is difficult to specify for additive hazards models containing nonparametric terms. This implies that likelihood based model selection criteria, such as Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC) and Schwarz's Bayesian criterion (SBC) can not be used in this situation (Huffer and McKeague, 1991). A plot of the Martingale Residual Process and Arja's Plot can used to check the fit of Aalen's model (Törner, 2004). Both types of plots were used to assess the fit of this model. The Arjas plot gives a clearer indication of lack of model fit than the Martingale residual plot, but the Martingale residual plot, which explicitly involves time, gives a clearer indication where problems exist in the model. In the Cox model, we used Cox-Snell residuals for assessing the overall fit of the model, Martingale residuals for identifying the best functional form of continuous covariates and, finally, examined scaled Schoenfeld residuals (Klein and Moeschberger, 2003) to assess the proportional hazards assumption.

Table 1. Results of Preliminary Fitting of Standard Cox Model (for Quantitative and Categorical Age Variables)

Variable	Coefficient	Hazard ratio	CI (95%)	P-value
Age (quantitative)	-0.0033	0.997	(0.99, 1.00)	0.37
Stage	1.109	3.03	(2.927, 3.140)	<0.001
Radiotherapy	-0.125	0.882	(0.812, 0.96)	0.038
Chemotherapy	0.1765	1.193	(1.08, 1.32)	0.0034
Hormone therapy	0.18	1.198	(1.01, 1.42)	<0.001
Age (categorical)	0.229	1.258	(1.167, 1.356)	<0.001
Stage	1.26	3.527	(3.022, 4.116)	<0.001
Surgery	0.465	1.593	(1.049, 2.418)	0.029
Radiotherapy	-0.218	0.804	(0.746, 0.867)	<0.001
Chemotherapy	0.119	1.126	(1.045, 1.214)	0.0019
Stage*surgery	-0.159	0.853	(0.729, 0.999)	0.049

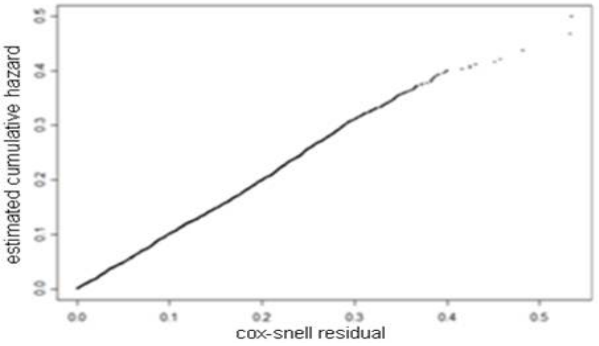

Figure 1. Cox-snell Residual Plot

Results

Results of fitting the Cox model are summarized in Table 1. Despite being non-significant, "age" was kept in the model because it is important in epidemiological research. The preliminary model was fitted, not withstanding the functional form of continuous "age" and consideration of the proportional hazard assumption. Figure 1 shows a plot of the Cox-Snell residuals versus the estimated cumulative hazards of residuals. If a model fits well, the graph will be approximately a 450 line. Figure 1 suggests that the model can be accepted. Our study shows that the cut-point for age variable must fall in the interval 45-70. To determine the best choice, for each value of "stage", profile likelihood was calculated and we determined that the log-partial likelihood was maximized for λ=65, corresponding to the optimal cut-point for "age". A Cox model using the binary variable "age" was fitted and results are shown in Table 1. According to a plot of Cox-Snell residuals (not shown), using the Cox model seems reasonable. Results of testing the proportional hazard assumption shows that only the variable "stage" doesn't satisfy the proportional hazard assumption(p=0.0076).

Table 2. Cox regression Model and Aalen's Additive Model Coefficient for Age

Age	Model	stage & total stage	surgery	radio therapy	chemo therapy	hormone therapy	stage*surgery	P-value
>65	SC	stage1	-	0.888	0.283	-	-	0.005
	Aa		-	0.00034	0.00014	-	-	<0.001
	SC	stage2	0.589	-	0.392	-	-	<0.001
	Aa		0.00035	-	0.0003	-	-	<0.001
	SC	stage3	-	0.675+	-	-	-	0.045
	Aa		-	0.0021	-	-	-	0.014
	SC	stage4	-	0.557	-	-	-	0.05
	Aa		-	0.0028	-	-	-	0.015
<65	SC	total stage 1.665	1.367	-0.354	0.132	-0.113	-0.55	<0.001
	Aa	0.00042	0.00024	-0.00005	0.00003	-	-0.00021	<0.001

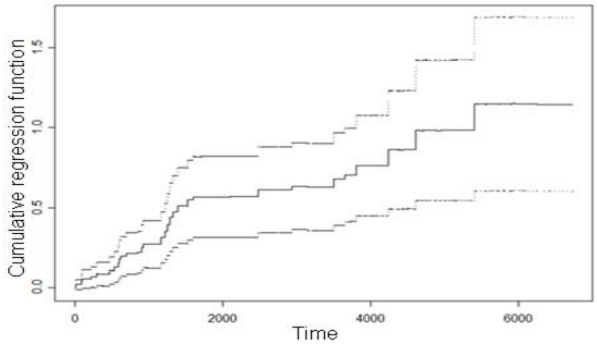

Figure 2. Cumulative Regression Function for "Stage"

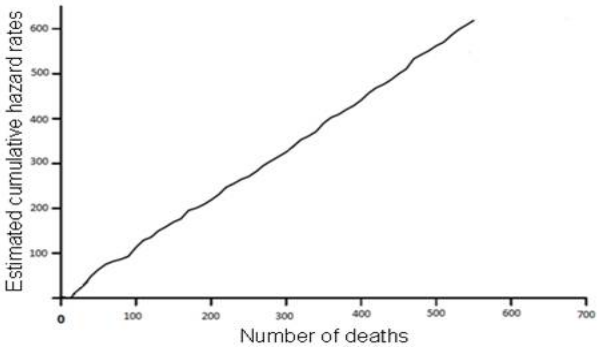

Figure 3. Arjas Plot for "Age<65"

Table 3. Comparison of P-values for Covariates Under the Cox Model and the Additive Model for Age<65 (Total Stages)

covariate	Cox P-value	Additive p-value
stage	<0.001	<0.001
surgery	0.011	0.007
radio therapy	<0.001	<0.001
chemo therapy	0.012	<0.001
hormone therapy	0.027	-
stage*surgery	0.00077	0.0082

The models were fitted in each category of age separately. In the category of patients younger than 65 years, all selected variables satisfied the proportional hazard assumption, but in the category of patients older than 65 years, the variable "stage" didn't satisfy the proportional hazard assumption. In the second category, separate Cox models were fitted for each value of the variable "stage". Results of fitting are shown in Table 2. For variables in all of these models, the proportional hazard assumption was checked.

Aalen's additive model was fitted to all data for which the Cox model had been used. To illustrate the results, we plotted cumulative regression functions versus time in which dots show 95% confidence intervals. For instance, results of the analysis restricted to patients younger than 65 years are shown in Figure 2. This shows a positive slope that is much steeper during the first 1800 days. The risk increases as the time goes on.

The results of fitting Aalen's additive model are summarized in Table 2. The preliminary additive model was checked by focusing on plots of the Martingale residuals and Arjas plot. For the variable "age", we evaluated the same subgroups that were considered in the Cox model. Figure 3 shows the Arjas plot for subgroup of "age" less than 65. The residuals in the graph are near to the 450 line, so it is acceptable to categorize the variable "age". A plot of the Martingale residuals for the same age subgroup (that not shown here) imply that there is no evidence against categorizing.

Discussion

The Cox proportional hazard model and Aalen's additive model consider different relationships between the hazard and covariates. For a specific application, it is not clear in advance which model is preferred. Sometimes, these two models give substantially different results. For example, in a study of cancer mortality among Japanese atomic bomb survivors, Muirhead and Darby (1987) note that the models give substantially different estimates of the age-specific probability that an individual will develop radiation-induced cancer (Zhang, 2007).

In this paper, our interest was to compare the Cox proportional hazard model and Aalen's additive models for survival data related to 14826 women diagnosed with breast cancer in BC. The Cox model and Aalen's additive model gave almost similar results regarding covariates selected to remain in the final model. The sign of estimated coefficients from both of the models are alike, but coefficients from the two models are different in magnitude. This is not surprising because coefficients of the Aalen's model are related to risk differences but coefficients of the Cox model are related to risk ratios. A crude way of comparing the models would be comparing p-values for selected covariates (Törner, 2004). Some believe that the greatness of p-value shows power of reject null hypothesis. For example, Table 3 shows p-values of two models for the category of "age" that is under 65. In general, nonparametric models have less power to detect significant effects in comparison to other models. Table 3 shows that p-values related to Aalen's model are always

lower than those in Cox model except for an interaction variable, suggesting Aalen's model might be better than the Cox model. This is untrue however because alternative hypotheses are different in the two models. The result of the studies agrees with those found by Anna Törner, Lim and Klein (Klein and Moeschberger, 2003; Törner, 2004; Lim and Zhang, 2009). Klein's study shows that p-values for significant variables (and non-significant variables) in both models are close to each other. However, Törner's and Lim's show that p-values related to variables in Aalen's Model are a bit smaller than those in the Cox Model.

Finally, both the Cox Model and Aalen's Model do relatively well in many applications, but are difficult to distinguish from each other. Despite this, Aalen's Additive Model is not yet widely used. One reason for this is that the model is not available in commonly used statistical softwares such as SAS, SPSS and Stata, whereas statistical software is available and easy to use for fitting the Cox model (Schaubel and Wei, 2007). The Cox model and Aalen's model both give similar results with regard to the covariates selected as important, but the two models give different pieces of information. They should not be viewed as alternatives, but as complementary methods that together give a more comprehensive understanding of the data.

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