Solutions, Biostat III exam, Nov 18, 2011

1 Section 1

1. Question 1

   (a) No, to do so we would need to fit another model that is not adjusted for age. If the parameter estimates representing the effect of period are different in the two models we might suspect confounding by age. However, there is no formal test for confounding so our conclusion should be based also on subject matter knowledge.

   (b) No, in order to do so we would need to fit another model that also includes interaction effects between age and period. To assess if the interaction parameters are statistically significant (i.e. that the effect of period is modified by age) we could use for example a likelihood ratio test and compare the two nested models.

   (c) Since Model A is a main effects model the hazard ratio that compares patients in the oldest age group to patients in the youngest age group is the same within each level of calendar period, i.e. 4.20.

2. Question 2

   (a) No, to do so we would need to fit another model that is not adjusted for age. If the parameter estimates representing the effect of period are different in the two models we might suspect confounding by age. However, there is no formal test for confounding so our conclusion should be based also on subject matter knowledge.

   (b) Yes we can as model B now includes the interaction effect that was required according to our answer in Question 1b. The formal approach to test whether there is need to include an interaction term between age at diagnosis and calendar period in the model is to conduct a likelihood ratio test.

   The null hypothesis to be tested is:

   $$H_0 : \text{The interaction effect is 0.}$$

   against

   $$H_A : \text{The interaction effect is not 0.}$$

   The test statistic is defined as

   $$-2 \times (\text{log likelihood (model A)} - \text{log likelihood (model B)})$$

   and has a χ^2 distribution under H_0. Note that the degrees of freedom is determined by how many 'extra' parameters we need to estimate in the model containing the interaction compared to the main effects model.

   We thus calculate the difference in log likelihoods between model A (log likelihood:-48263.538) and model B (log likelihood: -48249.869) and get -13.669. This is multiplied by -2 to get 27.338 which is our test statistic.

   The critical value of a χ^2 with 8 degrees of freedom is 15.507 at the 95 % significance level. Since our test statistic of 27.338> 15.507 the LR test is statistically significant and we may reject the null hypothesis that the interaction effect is 0. In other words there is evidence that the effect of calendar period is modified by age at diagnosis.

   (c) The hazard ratio in the three periods are: 5.73, 3.50 (i.e. 5.725×0.612) and 2.67 (i.e. 5.725×0.467) respectively.

3. Question 3

   (a) -0.4961731 is an estimate of the log hazard ratio comparing patients with clear cell tumours to patients with serous tumours. The hazard ratio is adjusted for age at diagnosis and period of diagnosis.

   (b) The confidence interval is calculated on the log scale and then transformed to the hazard ratio scale as follows:

$$exp^{-0.557437 \pm 1.96 \times 0.0381453} = (0.5314, 0.6171)$$

   (c) The hazard ratio is given by:

$$\frac{exp^{1.306-0.55}}{exp^{0.705-0.424}} = 1.61$$

2 Section 2

1. Question 1 Since it was not possible to say which curve corresponded to serous tumours and which were endometrioid tumours there are two possible sets of solutions to this question (depending on your choice for labelling the two curves).
   If you labelled the top curve serous tumours the answers to this question are:

   (a) Serous tumours have the best survival

   (b) Around 0.55

   (c) About 4 years

   (d) It is hard to tell if this is ever the case. If anything the slope of the curve for serous tumours is slightly steeper than the curve for endometrioid tumours after 10 years.

   If you labelled the top curve endometrioid tumours the answers to this question are:

   (a) Endometrioid tumours have the best survival

   (b) Around 0.35

   (c) About 10 years

   (d) This seems to be the case for the first 5 years after diagnosis

2. Question 2

   (a) Proportional hazard means that the effect of the covariates are assumed to remain constant throughout the entire time scale. In other words, the hazard ratio does not depend on time.

   (b) The proportional hazards assumption seem to be violated for the period effect as well as for the histology effect (although the p-value for 3.histology is only borderline significant).

(c) The null hypothesis to be tested is:

H_0 : A straight line through the residuals (for the covariate calcium) as a function of time has slope 0.

against

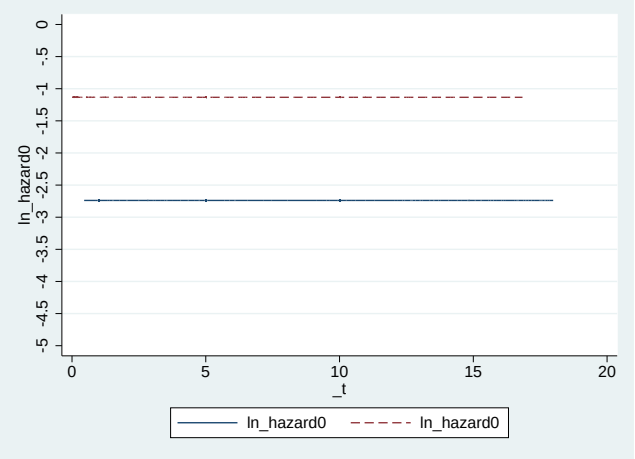
H_A : A straight line through the residuals (for the covariate calcium) as a function of time has not slope 0.

The assumption of proportional hazards is rejected since the p-value is 0.0006.

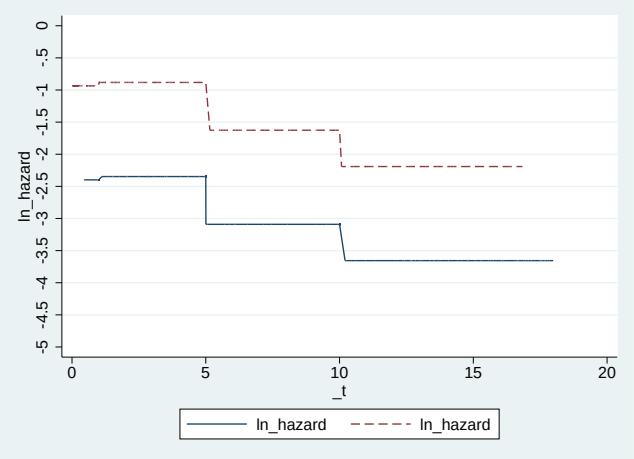
(d) If we were not interested in the effect of, say, calendar period *per se* we could stratify the Cox model on the levels of calendar period. This would allow separate baseline hazard rates for the different periods and therefore account for the non-proportionality, however, we would not get out any estimates of the effect of calendar period. Alternatively we could split the data across the time scale, for example at 1, 2, and 5 years after diagnosis and include interaction terms between the time bands that are generated from the split and the covariates that represent the effect of calendar period.

3. Question 3

(a) Marks are allocated for constant hazards throughout the time scale (1 mark) and for getting the values of the rates in the two groups correct (1 mark)



(b) Marks are allocated for getting the splits right (0.5 mark), constant rates within each time band (0.5 mark), parallellism (0.5 marks), correct values (0.5 marks)



(c) Marks are allocated if two continuous functions are drawn (1 mark), parallellism (1 mark) and if the lines are drawn roughly through the mid points of the timebands drawn in figure 3b (1 mark).