**Biost 536: Categorical Data Analysis in Epidemiology**

Emerson, Fall 2013

**Homework #3**

November 21, 2013

**Written problems:** To be submitted as an email attachment in by 5pm on Wednesday, November 27, 2013. See the instructions for peer grading of the homework that are posted on the web pages.

All questions relate to the question of whether the nadir PSA level following hormonal treatment for prostate cancer is prognostic of time in remission independently of any information from other commonly used covariates.

Note that all patients were followed for a minimum of 24 months. In all problems we will be considering the probability (or odds) of a patient surviving relapse-free for 24 months following therapy.

1. Provide suitable descriptive statistics for this dataset as might be presented in Table 1 of a manuscript appearing in the medical literature. (Because the primary question is comparing 24 month relapse free survival across groups defined by nadir PSA, you might consider presenting descriptive statistics in groups according to some dichotomization of nadir PSA levels. Alternatively, you could provide descriptive statistics within groups defined by whether the subjects relapse within 24 months or not.)

**I chose to dichotomize nadir PSA according to levels considered “healthy” (<=4.0 ng/ml) vs. “unhealthy” (>4.0 ng/ml) based on the information given in the study description file. Descriptive statistics for the cohort are:**

Table I: Descriptive Statistics for PSA Study Cohort

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **Missing** | **High Nadir PSA (> 4.0 ng/ml)****N=17** | **Low Nadir PSA** **(≤ 4.0 ng/ml)****N=33** | **Total****N=50** |
|  |  | Mean (SD) |
| Nadir PSA (ng/ml)  | 0 | 46.78 (56.8) | 0.69 (0.68) | 16.36 (39.25) |
| Age (years) | 0 | 68.71 (6.19) | 66.79 (5.53) | 67.44 (5.77) |
| Pretreatment PSA (ng/ml) | 7 | 938.4 (1597.99) | 527.37 (1092.68) | 670.75 (1287.64) |
| Performance Score | 2 | 77.5 (9.31) | 82.5 (11.64) | 80.83 (11.08) |
|  |  | N (%) |
| Bone Scan Score:  | 2 |  |  |  |
| 1 |  | 0 (0) | 5 (15.2) | 5 (10.0) |
| 2 |  | 3 (17.7) | 10 (30.3) | 13 (36.0) |
| 3 |  | 13 (76.5) | 17 (51.5) | 30 (60.0) |
| Tumor Grade: | 9 |   |   |   |
| 1 |  | 3 (17.7) | 7 (21.2) | 10 (20.0) |
| 2 |  | 5 (29.4) | 10 (30.3) | 15 (30.0) |
| 3 |  | 4 (23.53) | 12 (36.4) | 16 (32.0) |
| Relapsed within 24 months | 0 | 15 (88.2) | 7 (21.1) | 22 (40.0) |

1. Perform logistic regression analyses to determine whether the distribution of relapse within 24 months differs across groups defined by nadir PSA level after adjustment for bone scan score and performance status. For each of the following models, provide full statistical inference for your measure of association.
	1. Perform an adjusted logistic regression comparing the odds of relapse within 24 months across groups defined by the nadir PSA level when modeled as a continuous, untransformed variable.

|  |  |  |  |
| --- | --- | --- | --- |
| Predictor | OR | 95% CI  | p |
| Nadir PSA | 1.03 | (0.94 - 1.13) | 0.476 |
| Bone Scan Score | 2.62 | (0.94 - 7.3) | 0.064 |
| Performance Score | 0.95 | (0.88 - 1.03) | 0.211 |

**Note: For this model and all models below, I chose to model bone scan score (BSS) and performance score (PS) as having a linear association with relapse in 24 months (e.g. the probability of relapse increases with increasing bone scan score and decreasing performance score). This is only an assumption but allows me to proceed without “mining” the data before my main analysis.**

**From logistic regression of nadir PSA on relapse within 24 months, with robust standard errors, comparing men with the same bone scan score and performance score and a 1 ng/ml difference in nadir PSA, we estimate that the odds of relapse in 24 months are 1.03 times higher in the men with higher nadir PSA. This odds ratio is not statistically significant from 1.0 (p=0.476), with a 95% CI suggesting that the observed results would not be unusual if the true BSS-and PS-adjusted odds of relapse in 24 months were anywhere between 0.94 times as high and 1.13 times higher in men with 1 unit higher nadir PSA. Therefore we cannot reject the null hypothesis that after controlling for BSS and PS, the odds of relapse in 24 months does not differ by nadir PSA score.**

* 1. Perform an adjusted logistic regression comparing the odds of relapse within 24 months across groups defined by the nadir PSA level when modeled as a continuous, log transformed variable.

|  |  |  |  |
| --- | --- | --- | --- |
| Predictor | OR | 95% CI  | p |
| Log Nadir PSA | 2.36 | (1.27 - 4.40) | 0.007 |
| Bone Scan Score | 2.35 | (0.60 - 9.24) | 0.223 |
| Performance Score | 0.95 | (0.88 - 1.02) | 0.174 |

**From logistic regression of log nadir PSA on relapse within 24 months, with robust standard errors, comparing men with the same bone scan score and performance score and a 1 unit difference in log nadir PSA, we estimate that the odds of relapse in 24 months are 2.36 times higher in the men with 1 unit hhigher log nadir PSA. This result is highly statistically significant (p=0.007), with a 95% CI suggesting that the observed results would not be unusual if the true BSS-and PS-adjusted odds of relapse in 24 months were anywhere between 1.27 times higher and 4.40 times higher in men with 1 unit higher log nadir PSA. Therefore we reject the null hypothesis that after controlling for BSS and PS, the odds of relapse in 24 months does not differ by log nadir PSA score.**

* 1. Perform an adjusted logistic regression comparing the odds of relapse within 24 months across groups defined by the nadir PSA level when modeled as linear splines with knots at 1, 4, and 16 ng/ml.

|  |  |  |  |
| --- | --- | --- | --- |
| Predictor | OR | 95% CI  | p |
| Nadir PSA 0-1 | 29.62 | (1.36 - 645.63) | 0.0143 |
| Nadir PSA 1-4 | 0.90 | (0.33 - 2.5) |
| Nadir PSA 4-16 | 1.38 | (0.94 - 2.02) |
| Nadir PSA >16 | 0.98 | (0.96 - 1) |
| Bone Scan Score | 2.52 | (0.6 - 10.58) | 0.206 |
| Performance Score | 0.94 | (0.86 - 1.02) | 0.154 |

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**We performed logistic regression of nadir PSA on relapse within 24 months, with robust standard errors, comparing men with the same bone scan score and performance score and a 1 ng/ml difference in nadir PSA within 4 different groups of nadir PSA level. A global Wald test indicates that the overall effect of nadir PSA is statistically significant (p=0.0143), suggesting that we can reject the null hypothesis that after controlling for BSS and PS, the odds of relapse in 24 months does not differ by nadir PSA score.**

**The scatterplot above shows that the relationship between odds (or probability) of relapse in 24 months and nadir PSA is non-linear, with the odds increasing steeply for the increase in nadir PSA between 0 and 1 ng/ml, and between 4 and 16 ng/ml, and the odds decreasing with an increase in nadir PSA from 1-4 ng/ml and above 16 ng/ml.**

* 1. For each of the above regression models, provide an interpretation of the intercept.

**In the model in part (a), the intercept indicates that the log odds of relapse in 24 months when BSS, PS, and nadir PSA are all 0 is 0.729. This value is meaningless because BSS only ranges from 1-3 and cannot equal 0. In addition, performance scores were all above 50 so this is extrapolating well outside of our data.**

**In the model in part (b), the intercept tells us that the log odds of relapse in 24 months when BSS, PS, and log nadir PSA are all 0 is 1.12. Again, this value is meaningless because BSS only ranges from 1-3 and cannot equal 0. In addition, performance scores were all above 50 so this is extrapolating well outside of our data.**

**In the model in part (c), the intercept tells us that the log odds of relapse in 24 months when BSS, PS, and nadir PSA are all 0 is -0.679. Again, this value is meaningless because BSS only ranges from 1-3 and cannot equal 0. In addition, performance scores were all above 50 so this is extrapolating well outside of our data.**

1. In this longitudinal study, we could instead have considered the “reverse” analyses in which nadir PSA is used as the response and the predictor is the indicator of relapse within 24 months.
	1. Perform linear regression analyses to determine whether there is an association between mean nadir PSA level and relapse within 24 months after adjustment for bone scan score and performance status. Make clear the statistical analysis you perform. Provide full statistical inference for your measure of association.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Difference in nadir PSA | 95% CI  | p |
| Relapse in 24 months | 23.52 | (0.48 - 46.56) | 0.046 |
| Bone scan score | 6.85 | (-2.6 - 16.3) | 0.151 |
| Performance score | -0.51 | (-1.76 - 0.74) | 0.414 |
| Constant | 31.03 | (-76.03 - 138.09) | 0.562 |

**Note: For this model and all models below, I chose to model bone scan score (BSS) and performance score (PS) as having a linear association with nadir PSA (e.g. nadir PSA increases with increasing bone scan score and decreasing performance score). This is only an assumption but allows me to proceed without “mining” the data before my main analysis.**

**In linear regression with robust standard errors, comparing men with the same performance scores (PS) and bone scan scores (BSS), the mean nadir PSA in men who relapsed within 24 months is 23.52 ng/ml higher (on average) than the mean nadir PSA in men who did not relapse. This result is significantly different from 0 (P = 0.046), with a 95% CI suggesting that such observed results would not be unusual if the true mean nadir PSA was anywhere between 0.48 and 46.56 ng/ml higher in men who relapsed in 24 months, compared to those who did not relapse. We thus reject the null hypothesis that after controlling for PS and BSS, the mean nadir PSA does not differ in men who relapse and men who do not relapse.**

* 1. Perform linear regression analyses to determine whether there is an association between geometric mean nadir PSA level and relapse within 24 months after adjustment for bone scan score and performance status. Make clear the statistical analysis you perform. Provide full statistical inference for your measure of association. (Recall that inference on the geometric mean is obtained by performing linear regression on log transformed response variables.)

|  |  |  |  |
| --- | --- | --- | --- |
|  | Difference in log nadir PSA | 95% CI  | p |
| Relapse in 24 months | 2.61 | (1.42 - 3.81) | <0.001 |
| Bone scan score | 0.48 | (-0.12 - 1.08) | 0.113 |
| Performance score | -0.01 | (-0.06 - 0.05) | 0.795 |
| Constant | -1.17 | (-6.2 - 3.87) | 0.643 |

**In linear regression with robust standard errors, comparing men with the same performance scores (PS) and bone scan scores (BSS), the geometric mean of nadir PSA in men who relapsed within 24 months is e2.61 = 13.66 ng/ml higher (on average) than the geometric mean of nadir PSA in men who did not relapse. This result is significantly different from 0 (P <0.001), with a 95% CI suggesting that such observed results would not be unusual if the true geometric mean of nadir PSA was anywhere between e1.42 = 4.13 and e3.81 =45.16 ng/ml higher in men who relapsed in 24 months, compared to those who did not relapse. We thus reject the null hypothesis that after controlling for PS and BSS, the geometric mean of nadir PSA does not differ in men who relapse and men who do not relapse.**

1. Consider the analyses performed in problems 2 and 3 above.
	1. What are the relative merits of the five analyses. Which might you prefer *a priori*? Why?

**The outcome of relapse within 24 months seems more relevant or clinically meaningful than the outcome of nadir PSA level, making the analyses in problem 2 preferable to those in problem 3.**

**In problem 2, using (untransformed) nadir PSA makes the results easier to interpret but does not capture the true association with the odds of relapse since a 1 unit change in PSA does not have a big effect but a 1 log change does – PSA increases multiplicatively rather than linearly. The log transformed PSA is harder to interpret but better captures the association of nadir PSA and relapse. The splines allow us to capture flexibility in PSA without assuming that we know the shape of the distribution, but we have to know clinically meaningful cutoff points to choose the knots, and the results are very hard to interpret because the slope of the line is different for each category of PSA. Furthermore, here it appears the splines over-fit our data, with alternating positive and negative associations with relapse in 24 months.**

**As in problem 2, the use of log-transformed PSA in problem 3 makes more sense than the untransformed PSA, due to the non-linear distribution of nadir PSA among men in the study, but the results (geometric mean) are harder to interpret than the results of the untransformed analysis (traditional mean).**

**A priori I would prefer the logistic regression of relapse in 24 months on log-transformed PSA since I consider relapse in 24 months the more important outcome and log-transformed PSA a more appropriate predictor than untransformed PSA.**

* 1. All of these analyses suffer from a serious definitional problem inherent in this study. Can you deduce this problem? (Hint: There is no analysis that you can do to address this problem. It is a problem with the study design.)

**In those who relapsed within the 24 months, we don’t know whether nadir PSA levels occurred before or after the relapse, so we cannot determine whether high nadir PSA would be a cause/predictor, or consequence of the relapse.**