Homework 3

#3074

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| Table 1: Descriptive statistics of subjects followed for 24 months after hormonal treatment for prostate cancer by post-treatment relapse state (n=50) |
| **Relapse within 24 months** | N | mean or % | standard deviation | minimum | 25th percentile | median | 75th percentile | maximum |
| Age (years) | 22 | 68.36 | 5.68 | 61 | 64 | 68 | 71 | 86 |
| Nadir post-therapy PSA value (ng/ml) | 22 | 31.94 | 52.50 | 0.50 | 1.20 | 10.50 | 38 | 183 |
| Nadir post-therapy PSA value (log10 ng/ml) | 22 | 0.92 | 0.81 | -0.30 | 0.079 | 1.02 | 1.58 | 2.26 |
| Pre-therapy PSA value (ng/ml) | 20 | 732.40 | 1357.34 | 25 | 69.5 | 174 | 530 | 4797 |
| Performance status(score 0–100)\* | 22 | 76.50 | 11.82 | 50 | 70 | 80 | 80 | 100 |
| Bone scan score | 20 |  |  |  |  |  |  |  |
| most disease | 16 | 80.00 |  |  |  |  |  |  |
| moderate disease | 4 | 20.00 |  |  |  |  |  |  |
| least disease | 0 | 0 |  |  |  |  |  |  |
| Tumor grade | 17 |  |  |  |  |  |  |  |
| most aggressive | 7 | 41.18 |  |  |  |  |  |  |
| moderately aggressive | 7 | 41.18 |  |  |  |  |  |  |
| least aggressive | 3 | 17.65 |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
| **No relapse within 24 months** |  |  |  |  |  |  |
| Age (years) | 28 | 66.71 | 5.84 | 58 | 63 | 65.5 | 69.5 | 81 |
| Nadir post-therapy PSA value (ng/ml) | 28 | 4.12 | 17.28 | 0.10 | 0.20 | 0.20 | 0.95 | 92 |
| Nadir post-therapy PSA value (log10 ng/ml) | 28 | -0.28 | 0.64 | -1 | -0.70 | -0.70 | -0.023 | 1.96 |
| Pre-therapy PSA value (ng/ml) | 23 | 617.19 | 1252.08 | 4.80 | 45 | 100 | 387 | 4377 |
| Performance status(score 0–100)\* | 28 | 83.93 | 9.56 | 50 | 80 | 80 | 90 | 100 |
| Bone scan score | 28 |  |  |  |  |  |  |  |
| most disease | 14 | 50.00 |  |  |  |  |  |  |
| moderate disease | 9 | 32.14 |  |  |  |  |  |  |
| least disease | 5 | 17.86 |  |  |  |  |  |  |
| Tumor grade | 24 |  |  |  |  |  |  |  |
| most aggressive | 9 | 37.50 |  |  |  |  |  |  |
| moderately aggressive | 8 | 33.33 |  |  |  |  |  |  |
| least aggressive | 7 | 29.17 |  |  |  |  |  |  |

2. Association of relapse within 24 months by nadir post-hormonal treatment PSA level adjusting for bone scan score and performance status, n=48

|  |  |  |
| --- | --- | --- |
| a.  | Adjusted OR\*(95% confidence interval) | p value |
| Nadir post-therapy PSA value (ng/ml) | 1.03 (0.987, 1.083) | 0.156 |
| Intercept | 2.072 |  |
| \* Adjusted for bone scan score and performance status |

On average, the log odds of prostate cancer relapse within 24 months of hormonal treatment is estimated to increase by 1.03 for every ng/ml increase in nadir post-therapy PSA value, with higher PSA scores having more relapse, while holding bone scan score and performance status constant (95% CI 0.987 to 1.083). This association is not statistically significant on the alpha=0.05 level. This result would be typical when there is no true difference in nadir post-therapy PSA levels between men who relapsed within 24 months and men who did not relapse within 24 months of receiving hormonal treatment while holding bone scan score and performance status constant (p=0.156).

|  |  |  |
| --- | --- | --- |
| b.  | Adjusted OR\*(95% confidence interval) | p value |
| Nadir post-therapy PSA value (log10 ng/ml) | 7.24 (2.239, 23.407) | 0.001 |
| Intercept | 3.061 |  |
| \* Adjusted for bone scan score and performance status |

On average, the log odds of prostate cancer relapse within 24 months of hormonal treatment is estimated to increase by 7.23 for every one ng/ml increase in log10 nadir post-therapy PSA value, with higher PSA scores having more relapse, when holding bone scan score and performance status constant (95% CI 2.239 to 23.407). This association is statistically significant on the alpha=0.05 level. This result would not be typical when there is no true difference in log10 nadir post-therapy PSA levels between men who relapsed within 24 months and men who did not relapse within 24 months of receiving hormonal treatment while holding bone scan score and performance status constant (p=0.001).

|  |  |  |
| --- | --- | --- |
| c.  | Adjusted OR\*(95% confidence interval) | p value,overall relationship between nadir PSA and prostate cancer relapse |
| Nadir post-therapy PSA value (ng/ml) |  | 0.026 |
|  0–0.99 | 29.62 (0.721, 1217.343) |  |
|  1.00–3.99 | 0.90 (0.287, 2.846) |  |
|  4.00–15.99 | 1.38 (0.891, 2.138) |  |
|  16.00 and over | 0.98 (0.948, 1.017) |  |
| Intercept | 0.507 |  |
| \* Adjusted for bone scan score and performance status |

For interpretation of the linear spline results and changes that occur at the knots, see the graph on Figure 1.

On average, for nadir post-therapy PSA values from 0 ng/ml to 0.99 ng/ml, the log odds of prostate cancer relapse within 24 months of hormonal treatment is estimated to increase by 29.62 for one ng/ml increase in nadir post-therapy PSA value, with higher PSA scores having more relapse, when holding bone scan score and performance status constant (95% CI 0.721 to 1217.343).

For nadir post-therapy PSA values from 1.00 ng/ml to 3.99 ng/ml, the log odds of prostate cancer relapse within 24 months of hormonal treatment is estimated to increase by 0.90 for each ng/ml increase in nadir post-therapy PSA value, with higher PSA scores having more relapse, when holding bone scan score and performance status constant (95% CI 0.287 to 2.846).

For nadir post-therapy PSA values from 4.00 ng/ml to 15.99 ng/ml, the log odds of prostate cancer relapse within 24 months of hormonal treatment is estimated to increase by 1.38 for each ng/ml increase in nadir post-therapy PSA value, with higher PSA scores having more relapse, when holding bone scan score and performance status constant (95% CI 0.891 to 2.138).

For nadir post-therapy PSA values of 16.00 ng/ml and over, the log odds of prostate cancer relapse within 24 months of hormonal treatment is estimated to increase by 0.98 for each ng/ml increase in nadir post-therapy PSA value, with higher PSA scores having more relapse, when holding bone scan score and performance status constant (95% CI 0.948 to 1.017).

The overall association between nadir post-therapy PSA value and prostate cancer relapse within 24 months of hormonal treatment is statistically significant on the alpha=0.05 level. This result would not be typical when there is no true difference in nadir post-therapy PSA levels between men who relapsed within 24 months and men who did not relapse within 24 months of hormonal treatment while holding bone scan score and performance status constant (p=0.026).

Figure 1. Graph of relapse within 24 months after hormonal treatment for prostate cancer by nadir post-hormonal treatment PSA level holding bone scan score=3 and performance status=80 showing knots at

1 ng/ml, 4 ng/ml, and 16 ng/ml.



d. Interpretation of the intercept.

q2a. On average, the log odds of prostate cancer relapse within 24 months post-hormonal treatment is 2.072 when post-treatment nadir PSA is zero, bone scan score is zero, and performance score is zero. The intercept is not meaningful since PSA level in men does not go to zero and bone scan score does not go to zero.

q2b. On average, the log odds of prostate cancer relapse within 24 months post-hormonal treatment is 3.061 when the log10 nadir post-treatment PSA is zero, bone scan score is zero, and performance score is zero. A log10 nadir post-treatment PSA of 0 is equivalent to a nadir post-treatment PSA of 1.

q2c. On average, the log odds of prostate cancer relapse within 24 months post-hormonal treatment is 0.507 when post-treatment nadir PSA is zero, bone scan score is zero, and performance score is zero. The intercept is not meaningful since PSA level in men does not go to zero and bone scan score does not go to zero.

3. Association of nadir post-hormonal treatment PSA level by relapse within 24 months adjusting for bone scan score and performance status using linear regression with robust standard errors, n=48

|  |  |  |
| --- | --- | --- |
| a.  | Adjusted RR\*(95% confidence interval) | p value |
| Relapse within 24 months post-hormonal therapy | 23.52 (0.476, 46.559) | 0.046 |
| \* Adjusted for bone scan score and performance status |

Using linear regression with robust standard errors, on average, the mean of post-hormonal therapy nadir PSA score is expected to be 23.52 ng/ml higher among men who relapsed within 24 months compared to men who did not relapse within 24 months while holding bone scan score and performance status constant (95% CI 0.476 to 46.559). This difference is statistically significant on the alpha=0.05 level. This result would not be typical when there is no true difference in mean nadir post-therapy PSA levels between men who relapsed and men who did not while holding bone scan score and performance status constant (p=0.046).

|  |  |  |
| --- | --- | --- |
| b.  | Adjusted RR\*(95% confidence interval) | p value |
| Relapse within 24 months post-hormonal therapy | 1.14 (0.616, 1.655) | <0.001 |
| \* Adjusted for bone scan score and performance status |

Using linear regression with robust standard errors, on average, the mean log10 post-hormonal therapy nadir PSA score is expected to be 1.14 ng/ml higher among men who relapsed within 24 months compared to men who did not relapse within 24 months while holding bone scan score and performance status constant (95% CI 0.616 to 1.655). This association is statistically significant on the alpha=0.05 level. This result would not be typical when there is no true difference mean log10 nadir post-therapy PSA levels between men who relapsed within 24 months of receiving hormonal treatment and men who did not while holding bone scan score and performance status constant (p=<0.001).

4.

a. Relative merits of the five analyses

Keeping nadir PSA as a non-transformed, continuous variable is the most straightforward way to analyze this data. The interpretation of the results may be more easily understood by non-statistical audiences. The skewed nature of this variable is maintained with most values clustering around 1 ng/ml and a few very large values >100 ng/ml. The variable may not accurately follow the assumed linear association of nadir PSA to log odds of relapse with 24 months when performing logistic regression.

Performing a log10 transformation on nadir PSA reduces the range of this variable. The transformation minimizes the influence of the relatively few extremely large values. The transformed variable may more accurately follow the assumed linear association of nadir PSA to log odds of relapse within 24 months when performing logistic regression.

Adding splines to the model allows the data to deviate from the assumed linear assumption between nadir PSA and log odds of relapse within 24 months when performing logistic regression. In this way, the very large nadir PSA levels (>100 ng/ml) only influence the last spline and do not affect the earlier parts of the model. However, having multiple knots may allow overfitting of the data, especially in a data set with such a small sample size. The splines also reduce the parsimony of the model, adding a predictor to the model for each additional knot.

A priori, I would choose to perform analysis 2b and use nadir PSA level as a continuous log transformed variable. Log transformation is often appropriate for biological values which may be produced exponentially as, for example, a cancer grows. The untransformed nadir PSA value is highly skewed, and the transformation de-emphasizes the largest values. The transformed variable would be expected to have a more linear association with the log odds of relapse within 24 months. I would not choose to use splines because there are so few observations in the data set and adding 4 splines into the model increases the number of predictors by 3.

b. Although the data was collected prospectively, the way it has been provided to us is similar to cross-sectional data. No information is given on the timing of PSA score determination or on the timing of relapse determination. While both PSA levels and relapse were collected during the observation period, it is unknown if the nadir PSA level used in analysis occurred before or after relapse. Because of this, it is possible to analyze the data with either relapse by 24 months or nadir PSA as the outcome. However, no inference can be made on the direction of the association. The lowest values of PSA may have occurred before or after going into remission.