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| Table 1. Nadir PSA in groups defined by relapse at 24 months |
|  | No Relapse within 24 mo. | Relapse within 24 mo. | Total |
| N | 28 | 22 | 50 |
| Mean | 4.12 | 31.94 | 16.36 |
| SD | 17.28 | 52.50 | 39.25 |
| Min | 0.1 | 0.5 | 0.1 |
| p25 | 0.2 | 1.2 | 0.2 |
| Median | 0.2 | 10.5 | 0.95 |
| p50 | 0.95 | 38 | 10 |
| Max | 92 | 183 | 183 |
| IQR | 0.75 | 36.8 | 9.8 |
| Range | 91.9 | 182.5 | 182.9 |

1. Among men of the same age, bone scan score, and performance status, groups differing by one unit in nadir PSA have, on average, a 3.4% increase in odds of relapse within 24 months. This difference is not statistically significant from 0 (p=0.448). The estimated odds ratio of 1.034 would be typical of an actual odds ratio between 0.949 and 1.13.
2. Among men of the same age, bone scan score, and performance status, groups differing by one unit in log nadir PSA have, on average, a 137% increase in odds of relapse within 24 months. This difference is statistically significant (p=0.010). The estimated odds ratio of 2.37 would be typical of an actual average odds ratio between 1.23 and 4.56.
3. Among men of the same age, bone scan score, and performance status, individuals with nadir PSA have increasing odds of relapse within 24 months as nadir PSA increases up to a nadir PSA around 60. As illustrated in the following graph, the trend is not consistently linear across all levels of nadir PSA. After nadir PSA of approximately 60, groups differing in one unit of nadir PSA have lower odds of relapse. On average after approximately nadir PSA 130, odds of relapse increase as nadir PSA increases again. The number of observations in our data with nadir PSA over 60 is relatively small (4/50). The dramatic fluctuations of slope at higher levels of PSA may be due to over fitting of the data to our dataset. Differences in odds of relapse across all levels of PSA are statistically significant (p=0.0057).



1. In all three cases, the intercept is necessary to the model but is not scientifically meaningful. The intercept is the estimated average odds of relapse within 24 months for individuals with bone scan score, performance score, age and nadir PSA =0. This value is far outside the range of our data.
2. **A.** Among individuals with matching bone scan scores, performance scores, and age, those who relapsed within 24 months had, on average, a nadir PSA 24.39 ng/ml higher than those who did not relapse. This observed difference would be typical of a real average difference between 0.52 and 48.25 ng/ml. However, the association is not statistically significant at p=0.045. These point estimates and significance tests were performed through an ordinary least-squares regression, allowing for heteroskedasticity.

**B.** Adjusting for bone scan score, performance score, and age, individuals who relapsed within 24 months had a geometric mean nadir PSA 2.61 ng/ml higher than the geometric mean among individuals who did not relapse within 24 months. The estimated increase in geometric mean would be typical of an actual difference between 1.37 and 3.85 ng/ml. The difference in geometric means is significantly different from 0 (p<0.0005).

1. **A.** A priori, I would have investigated the association of nadir PSA and relapse within 24 months using relapse as the outcome variable and nadir PSA as a predictor. This approach more closely follows the scientific question of interest; we are more interested in predicting likelihood of relapse than estimating nadir PSA given relapse. I would also have transformed the PSA measurement using a log transformation because we have medical reason to believe that differences in PSA are more biologically meaningful on a multiplicative scale. I would have chosen analysis 2B. It is clear from the spline model, however, that our data is not strictly linear. A spline may be more appropriate as a predictive model, but is difficult to interpret purely as a measure of association. If we were more interested in a purely predictive model, the spline may be more appropriate.

B. The study cannot completely randomize individuals into “treatment” and “control” groups, i.e. low PSA and high PSA groups. Because the study is observational, it is possible that an unobserved variable is causing higher PSA and higher likelihood of relapse.