8 Modeling Survival Data with Categorical Covariates

We shall first consider the case where there is no a-priori ordering expected between the categories and the outcome of interest (survival in this case). For example, geographical region, day of week, color of eyes; etc.

In regression modeling, including proportional hazards regression, a useful way of modeling such categorical covariates and their effect on outcome is by the use of dummy variables. Specifically, if there are k categories, we would define k dummy variables, $D_1, ..., D_k$ where

$$D_j = \begin{cases} 1 & \text{if individuals fall into the } j\text{th category,} \\ 0 & \text{otherwise,} \end{cases} \qquad \text{for } j = 1, ..., k.$$

In a proportional hazards model, if we were interested in modeling the effect of such a categorical covariate on the hazard function, we may consider the following model:

$$\lambda(t|\cdot) = \lambda_0(t)\text{exp}(D_1\theta_1 + \cdots + D_{k-1}\theta_{k-1} + z_1\phi_1 + \cdots + z_q\phi_q)$$

Note: There are only $(k-1)$ of the dummy variables in the model to avoid overparametrization. The category that is left out (category k) is called the reference category. At most only one of $D_1, \cdots, D_{k-1}$ may be equal to one, and all are equal to zero when an individual falls into the reference category (*i.e.*, the kth category).

Category	D_1	D_2	$\cdots$	D_{k-1}
1	1	0	$\cdots$	0
2	0	1	$\cdots$	0
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
$k-1$	0	0	$\cdots$	1
k	0	0	$\cdots$	0

The parameters $\theta_1, ..., \theta_{k-1}$ are used to measure the degree of effect that the categorical covariate has on the hazard rate. We may want to include other covariates $(z_1, ..., z_q)$ in the model to adjust for their effects.

The interpretation of θ_j is the log hazard ratio between an individual in category j and an individual in the reference category (the kth category) assuming all other covariates were the same.

This is easily seen by noting that

$$\frac{\lambda(t|cat = j, z)}{\lambda(t|cat = k, z)} = \frac{\lambda_0(t)\exp(\theta_j + z^T\phi)}{\lambda_0(t)\exp(0 + z^T\phi)} = \exp(\theta_j).$$

If we want the hazard ratio between category j and category j' $(1 \le j, j' \le (k-1))$, then we use the following

$$\frac{\lambda(t|cat = j, z)}{\lambda(t|cat = j', z)} = \frac{\lambda_0(t)\exp(\theta_j + z^T\phi)}{\lambda_0(t)\exp(\theta_{j'} + z^T\phi)} = \exp(\theta_j - \theta_{j'}).$$

The hypothesis corresponding to no effect of the categorical variable on survival is given by

$$H_0 : \theta_1 = \theta_2 = \cdots = \theta_{k-1} = 0.$$

Under this null hypothesis, the hazard function is the same regardless what category an individual was in.

The null hypothesis could be tested using the Wald test, score test, or likelihood ratio test. Since our null hypothesis considers fixed values (*i.e.*, 0) for $(k-1)$ of the parameters in the model, the distribution of all the tests above would be chi-square with $(k-1)$ degrees of freedom if the null hypothesis were true. P-values can be computed by evaluating the probability that a χ^2_{k-1} random variable exceeds the observed value of the test statistics.

Note: If we are testing the null hypothesis of no effect of a categorical variable with k categories, using a proportional hazards model with $(k-1)$ dummy variables and not adjusting for additional covariates, then the score test derived from this partial likelihood will be identical to the k-sample log rank test if there were no ties in the survival data. This extends the results we noted for the two-sample log rank test.

Let us illustrate the use of dummy variables for coding categorical variables in our dataset `CAL8082.dat` of breast cancer patients. We shall focus on the effect that the number of nodes involved at randomization has on survival.

Since the number of nodes ranges from 1 to 57, we broke it down into 7 categories (1, 2, 3, 4, 5–10, 11–15, > 15). We created dummy variables for the first six categories leaving the category (> 15) as the reference category.

The first model considered:

$$\lambda(t|\cdot) = \lambda_0(t)\exp(DN_1\theta_1 + DN_2\theta_2 + DN_3\theta_3 + DN_4\theta_4 + DN_{510}\theta_5 + DN_{1015}\theta_6).$$

The corresponding Wald test, score test and likelihood ratio test of the null hypothesis

$$H_0 : \theta_1 = \theta_2 = \theta_3 = \theta_4 = \theta_5 = \theta_6 = 0,$$

or no effect of these category of the nodes on survival were equal to

$$\text{Wald} = 100.4, \quad \text{score} = 108.5, \quad \text{LR} = 96.03$$

respectively.

All of these, compared to a chi-square with 6 degrees of freedom, yielded highly significant results.

More interesting is the ability to assess the degree of effect. For example, θ_1 corresponds to the log hazard ratio for patients with one node affected *vs.* patients with > 15 nodes (reference category).

In this example, the estimate of θ_1 and its standard error are

$$\hat{\theta}_1 = -1.283 \quad (\mathrm{e}^{\hat{\theta}_1} = 0.28), \quad \mathrm{se}(\hat{\theta}_1) = 0.174,$$

so a 95% CI for θ_1 is

$$\hat{\theta}_1 \pm 1.96 * \text{se}(\hat{\theta}_1) = -1.283 \pm 1.96 * 0.174 = [-1.624, -0.942].$$

The corresponding 95% CI for the hazard ratio is

$$[\exp(-1.624), \exp(-0.942)] = [0.197, 0.390].$$

Suppose we want to estimate the hazard ratio between the categories (nodes=1) *vs.* (nodes=3). We compute this hazard ratio to be

$$\exp(\theta_1 - \theta_3).$$

The estimate of $\theta_1 - \theta_3$ is equal to

$$\hat{\theta}_1 - \hat{\theta}_3 = -1.283 - (-1.213) = -0.070.$$

Therefore, the corresponding hazard ratio estimate is

$$\exp(-0.070) = 0.932.$$

To find the confidence interval for $\theta_1 - \theta_3$, we need to compute $\text{se}(\hat{\theta}_1 - \hat{\theta}_3)$:

$$\text{Var}(\hat{\theta}_1 - \hat{\theta}_3) = \text{Var}(\hat{\theta}_1) + \text{Var}(\hat{\theta}_3) - 2 * \text{Cov}(\hat{\theta}_1, \hat{\theta}_3) = 0.03037 + 0.04446 - 2 * 0.01588 = 0.04307.$$

So

$$\text{se}(\hat{\theta}_1 - \hat{\theta}_3) = \sqrt{0.04307} = 0.2075.$$

<u>Note</u>: We don't need to do above calculation to get the standard error of $\hat{\theta}_1 - \hat{\theta}_3$. We just need to rerun the model using category 3 as the reference category. That is, we use all dummy variables except the dummy for category 3. Then the parameter estimate corresponding to category 1 is $\hat{\theta}_1 - \hat{\theta}_3$ with its standard error being $\text{se}(\hat{\theta}_1 - \hat{\theta}_3)$.

To get a better understanding of the relationship of the various categories to survival, it is useful to plot the log hazard ratio and hazard ratio as a function of the categories. For example,

Figure 8.1: *Log hazard ratio as a function of category*

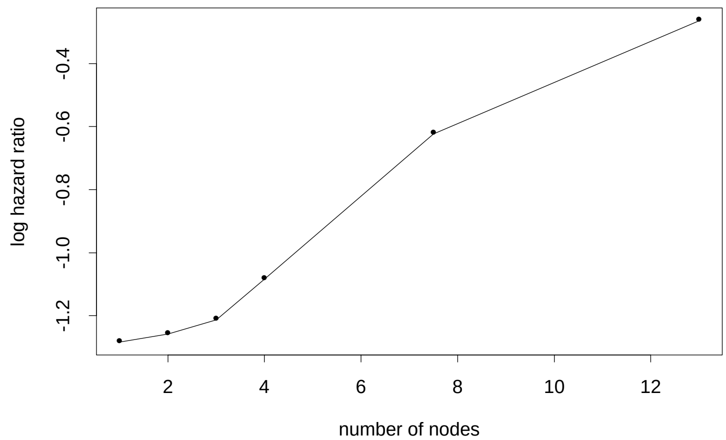


Figure 8.1 presents the relationship of log hazard ratio and the categories and Figure 8.2 presents the relationship of hazard ratio and the categories.

We also included a model when we adjust for the effect of menopausal status, tumor size, and estrogen receptor status. The adjusted effects of number of nodes changed very little.

For the model

$$\lambda(t|\cdot) = \lambda_0(t)\mathrm{e}^{DN_1\theta_1+DN_2\theta_2+DN_3\theta_3+DN_4\theta_4+DN_{510}\theta_5+DN_{1015}\theta_6+MN\phi_1+TS\phi_2+ER\phi_3},$$

we can construct a likelihood ratio test for the null hypothesis

$$H_0 : \theta_1 = \theta_2 = \theta_3 = \theta_4 = \theta_5 = \theta_6 = 0.$$

We compute

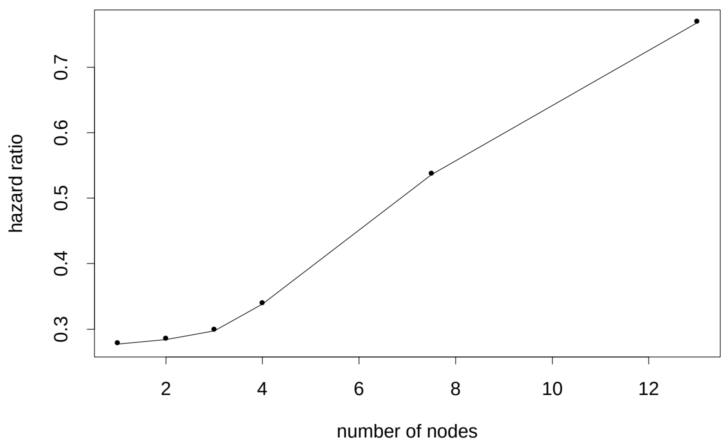
$$\left[-2\ell(\hat{\phi}(\theta = 0)) - (-2\ell(\hat{\theta}, \hat{\phi}))\right]$$

and compare this to a chi-square with 6 degrees of freedom.

Using the output, we get:

$$LR = 4791.872 - 4728.493 = 63.38, \quad \text{Score} = 71.668.$$

Figure 8.2: *Hazard ratio as a function of category*



These give strong evidence against H_0 (we can also calculate Wald statistic to be 67.12).

<u>Ordered Categorical Covariates and Trend Tests</u>

When we model the effect of a categorical covariate using dummy variables in a proportional hazards model, we are assuming no implicit ordering of the categories on their effect on survival. For example, in the model

$$\lambda(t|\cdot) = \lambda_0(t)\exp(D_1\theta_1 + \cdots + D_{k-1}\theta_{k-1})$$

the hazard ratio between the jth and j'th category is equal to

$$\begin{array}{ll} \exp(\theta_j - \theta_{j'}) & \text{if } j, j' \neq k, \\ \exp(\theta_j) & \text{if } j' = k. \end{array}$$

Since θ_j and $\theta_{j'}$ are not restricted, this hazard ratio can vary from 0 to infinity regardless of j and j'.

In some cases, however, we might expect the effect of category on survival to follow some natural ordering. In our breast cancer example, we might expect the hazard rate to increase as the "number of nodes" defining the categories gets larger.

For ordered categorical covariates, it may be easier if we label the K categories as categories

$0, 1, \cdots, k-1$, and let category 0 be the reference category. In which case we consider the model

$$\lambda(t|\cdot) = \lambda_0(t)\exp(D_1\theta_1 + \cdots + D_{k-1}\theta_{k-1})$$

If there is an ordered effect on survival, we might expect that

$$0 < \theta_1 < \theta_2 \cdots < \theta_{k-1},$$

or

$$0 > \theta_1 > \theta_2 \cdots > \theta_{k-1}.$$

However, the model above puts no restrictions on the values $\theta_1, \cdots, \theta_{k-1}$. Consequently, the multiparameter tests of

$$H_0 : \theta_1 = \theta_2 = \cdots = \theta_{k-1} = 0$$

we have discussed so far (all of which have a chi-square distribution with $(k-1)$ degrees of freedom) are considering omnibus alternatives, that is, any deviation from the null hypothesis. Because of this, these tests are not especially powerful in detecting alternatives which have an implied natural ordering.

For such situations, we may prefer to use a trend test.

In a trend test, we assign a score to the ordered categories. For example, we may use $1, 2, \cdots, k-1$ for the $k-1$ ordered categories. In the breast cancer example, the score is average number of nodes for each of the categories, *i.e.*,

$$1 = 1, 2 = 2, 3 = 3, 4 = 4, (5-10) = 7.5, (11-15) = 13, (> 15) = 20 \quad \text{(approximately)}$$

We then consider the model

$$\lambda(t|\cdot) = \lambda_0(t)\exp(Sc\theta),$$

where Sc corresponds to the ordered score, and test the hypothesis

$$H_0 : \theta = 0 \quad vs. \quad H_A : \theta \neq 0.$$

Under this alternative, the hazard increases or decreases as the score of the category increases depending on whether or not $\theta > 0$ or $\theta < 0$.

Remark:

- The null hypothesis for the trend test is the same null hypothesis as for the omnibus test; that is, the hazard function does not depend on category.
- The trend test is distributed as a chi-square with one degree of freedom under H_0 whereas the omnibus test is distributed as a chi-square with $(k-1)$ degrees of freedom under H_0.
- In general, the trend test has greater power to detect differences in categories which are ordered and have an ordered effect. However, the trend test may have less power to find deviations from the null hypothesis that are not ordered compared to the omnibus test.
- Any of the large sample tests (Wald, score, likelihood ratio) may be used to test H_0.
- We can also adjust for other covariates that may be potential confounders.

For the `CALGB 8082` example, the trend test yields

$$\begin{array}{ll} \text{Wald test :} & 102.3 \\ \text{score test :} & 106.9 \\ \text{LR test :} & 89.6 \end{array}$$

All of these are to be compared to a chi-square with one d.f.

We can contrast these values with the results from the omnibus test:

$$\begin{array}{ll} \text{Wald test :} & 100.4 \\ \text{score test :} & 108.5 \\ \text{LR test :} & 96.6 \end{array}$$

These numbers are similar to the numbers from the trend test, but they are to be compared to a chi-square distribution with 6 d.f. yielding weaker evidence against H_0 (although the evidence is still strong in this case).

When we adjust for menopausal status, estrogen receptor status and tumor size, we get for the trend test:

$$\begin{array}{ll} \text{Wald test}: & 67.97 \\ \text{LR test}: & 4791.87 - 4732.07 = 59.80 \\ \text{score test}: & 70.51 \end{array}$$

to be compared to a chi-square with one d.f.

The Philosophy of Model Building

When trying to build models and understand the relationships that these models imply, it is useful to work up hierarchically considering increasingly more complex structures of nested models. Likelihood ratio test is preferred to used in deciding which variables (or structures) are or are not important (LR test is usually more stable and easily constructed).

We should strive to find "parsimonious models", *i.e.*, the model that adequately explain the structure of the data with as simple a structure as possible. It is especially helpful to get feedback from a subject matter scientist.

Modeling Continuous Covariates

Suppose we have a covariate Z which is continuous and we want to model the hazard function to Z using a proportional hazards model. The simplest model we could consider is

$$\lambda(t|Z) = \lambda_0(t)\exp(Z\beta).$$

This model specifies a very specific structure on the relationship of the hazard to the covariate

Z. Namely,

$$\frac{\lambda(t|Z=z+1)}{\lambda(t|Z=z)} = \frac{\lambda_0(t)\exp((z+1)\beta)}{\lambda_0(t)\exp(z\beta)} = \exp(\beta),$$

regardless of z. That is, a unit increase in covariate Z will yield a proportional increase in the hazard of $\exp(\beta)$.

If this relationship is an adequate representation of the truth then the interpretation that we can give to the parameter β is easy to understand. Of course, this assumption may or may not be "adequate".

Checking Adequacy of the Covariate Relationship in the Proportional Hazards Model

Using the above model building philosophy, we shall assess whether a particular covariate relationship is reasonable by embedding the proposed model into a more complex model and then testing if the more complex structure gives sufficiently better fit.

There are two ways that we suggest for considering more complex structures for modeling a continuous variable.

1. Assume the relationship follows a higher order polynomial: For example, we may consider the model

   $$\lambda(t|Z) = \lambda_0(t)\exp(\beta_1 Z + \beta_2 Z^2).$$

   A test of the hypothesis $H_0 : \beta_2 = 0$ may be used to assess the adequacy of the model

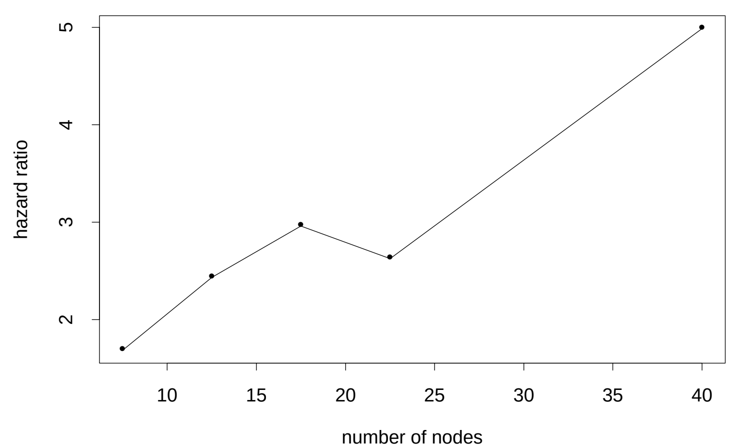
   $$\lambda(t|Z) = \lambda_0(t)\exp(\beta Z).$$

   Example: In `CALGB 8082`, nodal status seemed to be an important prognostic factor. Since the number of nodes varies from 1 to 57 it may be reasonable to think this variable as approximately a continuous variable and try to find the approximate relationship of this variable to the hazard function.

   Consider the `SAS` output as we examine a linear and quadratic relationship.

2. Discretizing (or categorizing) Continuous Covariate to Assess Models: The values of the parameters in a higher order polynomial are difficult to interpret. It may be easier to break up the continuous covariate into several categories and then use methods we developed for categorical covariates. Plots of the parameter estimates for the effects of different categories versus the mid-value defining the categories may be helpful to assess fit or suggest different models. Let us illustrate through an example. Here we will discretize number of nodes into intervals of length 5 (except the last interval, which is > 25) and use 1–5 as the reference category. The plot is presented in Figure 8.3.

Figure 8.3: *Log-hazard ratio as a function of category midpoint*



Interaction (Effect Modification)

When studying the effect of a variable on survival we showed how to control for the possible confounding effects of other prognostic factors by including these in the proportional hazards model as well.

For example, in Chapter 6 we discussed the relationship of drinking on survival controlling for smoking, age and sex by looking at the model:

$$\lambda(t|\cdot) = \lambda_0(t)\exp(\theta D + \phi_1 S + \phi_2 A + \phi_3 Sx),$$

where D is the drinking indicator, S is the smoking indicator, A is age and Sx is sex indicator.

This model assumes that the hazard ratio for a drinker compared to a non drinker is $\exp(\theta)$ regardless of their smoking status, age and sex. Therefore, if the effect of drinking on survival is measured through the hazard ratio, the above model does not allow for "effect modification", *i.e.*, where the effect of drinking on survival might change or vary by different smoking, age or sex categories.

Effect modification may be accommodated in a proportional hazards model by including interaction terms; *i.e.*, a product of the variables that are thought to be <u>effect modifiers</u>.

<u>Remark</u>: "Effect modification" is a term used in epidemiology. In statistics, we use the term "interaction" to denote the same concept.

For example, suppose we suspected that smoking was as effect modifier for the relationship of drinking to survival, then we may consider the following model

$$\lambda(t|\cdot) = \lambda_0(t)\exp(\theta D + \phi_1 S + \phi_2 A + \phi_3 Sx + \gamma(D \times S))$$

where $D \times S$ is the interaction term and its coefficient γ measures the degree of effect modification. For such a model, the hazard ratio of a drinker $(D = 1)$ compared to a non-drinker $(D = 0)$ for a given smoking status, sex and age is given by

$$\frac{\lambda(t|D=1,\cdots)}{\lambda(t|D=0,\cdots)} = \frac{\lambda_0(t)\exp(\theta + \phi_1 S + \phi_2 A + \phi_3 Sx + \gamma S)}{\lambda_0(t)\exp(\phi_1 S + \phi_2 A + \phi_3 Sx)} = \exp(\theta + \gamma S)$$

This would imply that the hazard ratio for a drinker to a non-drinker is $\exp(\theta + \gamma)$ among smokers and $\exp(\theta)$ among non-smokers.

One could test for effect modification of smoking on the relationship of drinking to survival by testing the null hypothesis

$$H_0 : \gamma = 0$$

for this multiparamter proportional hazards model.

Of course, we could also consider age or sex as effect modifiers for drinking by including terms $D \times A$ and $D \times Sx$ in the proportional hazards model.

Let us go back to our `CALGB 8082` data set and consider interaction terms:

Model	$-2\log L$	$d.f.$
All main effects	4739.69	5
All main effects + all interactions	4716.67	15
All main effects + trt × er	4734.56	6
All main effects + trt × er + tumor size × er	4721.30	7

Note: Two potentially important interactions between treatment and ER status, between tumor size and ER were surfaced that may warrant further investigation.

From the model where we have "All main effects + trt × er + tumor size × er", we get

$$\frac{\lambda(t|Rx=1,\cdots)}{\lambda(t|Rx=0,\cdots)} = \frac{\lambda_0(t)\exp(0.288+\cdots-0.449ER)}{\lambda_0(t)\exp(0+\cdots+0)} = \exp(0.288-0.449ER)$$

Thus for ER positive patients (ER=1), hazard ratio for `trt1=1` *vs.* `trt1=0` is $\exp(0.288 - 0.449) = \exp(-0.161) = 0.85$, while for ER negative patients (ER=0), hazard ratio for `trt1=1` *vs.* `trt1=0` is $\exp(0.288) = 1.33$.

Neither of these estimates are highly significant and given the fact that this relationship was discovered among many possible relationships considered in a post-hoc analysis, one must be cautious of the problem of multiple comparisons. Nonetheless, it may be worth investigating this issue further and bringing this finding to the attention of the collaborators.

Appendix: SAS Program and output

The following is the `SAS` program for the analyses on pages 153-156.

```
options ps=72 ls=72;

data bcancer;
  infile "cal8082.dat";
  input days cens trt meno tsize nodes er;
  trt1 = trt - 1;

  if nodes=0 or nodes=. then delete;
```

```
  dn1 = (nodes=1);
  dn2 = (nodes=2);
  dn3 = (nodes=3);
  dn4 = (nodes=4);
  dn510 = (4.5<nodes<10.5);
  dn1015 = (10.5<nodes<15.5);
  dn15 = (nodes>15.5);

  dnscore = nodes;
  if dn510=1 then
    dnscore=7.5;
  else if dn1015=1 then
    dnscore=13;
  else if dn15=1 then
    dnscore=20;

  label days="(censored) survival time in days"
    cens="censoring indicator"
    trt="treatment"
    meno="menopausal status"
    tsize="size of largest tumor in cm"
    nodes="number of positive nodes"
    er="estrogen receptor status"
    trt1="treatment indicator";
run;

data bcancer1; set bcancer;
  if meno = . or tsize = . or nodes = . or er = . then delete;
run;

proc freq data=bcancer;
  tables nodes;
run;

title "Unadjusted analysis of nodes effect using whole sample";
proc phreg data=bcancer;
  model days*cens(0) = dn1 dn2 dn3 dn4 dn510 dn1015 / covb;
run;

title "Unadjusted analysis of nodes effect using whole sample";
proc phreg data=bcancer;
  model days*cens(0) = dn1 dn2 dn4 dn510 dn1015 dn15;
run;

title "Unadjusted analysis of nodes effect using subsample";
proc phreg data=bcancer1;
  model days*cens(0) = dn1 dn2 dn3 dn4 dn510 dn1015;
run;

title "Analysis of adjusted nodes effect using subsample";
proc phreg data=bcancer1;
  model days*cens(0) = dn1 dn2 dn3 dn4 dn510 dn1015 meno tsize er /covb;
run;

title "Model with only meno tsize er";
proc phreg data=bcancer1;
  model days*cens(0) = meno tsize er;
run;

title "Score test for nodes effect adjusting for other covariates";
proc phreg data=bcancer1;
  model days*cens(0) = meno tsize er dn1 dn2 dn3 dn4 dn510 dn1015
```

```
    / selection=forward detail include=3 slentry=0;
run;

title1 "Trend test for number of nodes";
title2 "Unadjusted analysis of nodes effect using whole sample";
proc phreg data=bcancer;
  model days*cens(0) = dnscore;
run;

title2 "Analysis of adjusted nodes effect using subsample";
proc phreg data=bcancer1;
  model days*cens(0) = dnscore meno tsize er;
run;

title2 "Score test for nodes effect adjusting for other covariates";
proc phreg data=bcancer1;
  model days*cens(0) = meno tsize er dnscore
    / selection=forward detail include=3 slentry=0;
run;
```

The following is the corresponding output:

```
                             The SAS System                              1
                                           16:16 Monday, April 7, 2003

                           The FREQ Procedure

                        number of positive nodes

                                                 Cumulative    Cumulative
       nodes    Frequency      Percent     Frequency      Percent
       ---------------------------------------------------------------
           1         174        19.44           174         19.44
           2         140        15.64           314         35.08
           3          78         8.72           392         43.80
           4          74         8.27           466         52.07
           5          58         6.48           524         58.55
           6          53         5.92           577         64.47
           7          42         4.69           619         69.16
           8          37         4.13           656         73.30
           9          34         3.80           690         77.09
          10          26         2.91           716         80.00
          11          21         2.35           737         82.35
          12          20         2.23           757         84.58
          13          20         2.23           777         86.82
          14          16         1.79           793         88.60
          15          20         2.23           813         90.84
          16           7         0.78           820         91.62
          17          11         1.23           831         92.85
          18           8         0.89           839         93.74
          19           8         0.89           847         94.64
          20           6         0.67           853         95.31
          21           5         0.56           858         95.87
          22           6         0.67           864         96.54
          23           6         0.67           870         97.21
          24           1         0.11           871         97.32
          25           6         0.67           877         97.99
          26           3         0.34           880         98.32
          27           4         0.45           884         98.77
          28           2         0.22           886         98.99
          29           1         0.11           887         99.11
```

```
         31            1          0.11           888        99.22
         33            1          0.11           889        99.33
         34            1          0.11           890        99.44
         35            1          0.11           891        99.55
         38            1          0.11           892        99.66
         43            2          0.22           894        99.89
         57            1          0.11           895       100.00


         Unadjusted analysis of nodes effect using whole sample        2
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                         The PHREG Procedure

                          Model Information

Data Set                WORK.BCANCER
Dependent Variable      days            (censored) survival time in days
Censoring Variable      cens            censoring indicator
Censoring Value(s)      0
Ties Handling           BRESLOW


          Summary of the Number of Event and Censored Values

                                                  Percent
                Total        Event    Censored    Censored

                  895          489         406       45.36


                         Convergence Status

            Convergence criterion (GCONV=1E-8) satisfied.


                        Model Fit Statistics

                                Without          With
                Criterion     Covariates    Covariates

                -2 LOG L        6251.265      6155.232
                AIC             6251.265      6167.232
                SBC             6251.265      6192.386


                Testing Global Null Hypothesis: BETA=0

        Test                    Chi-Square       DF     Pr > ChiSq

        Likelihood Ratio           96.0334        6         <.0001
        Score                     108.5044        6         <.0001
        Wald                      100.4176        6         <.0001


                Analysis of Maximum Likelihood Estimates

                Parameter     Standard                                  Hazard
 Variable  DF    Estimate        Error  Chi-Square  Pr > ChiSq           Ratio

 dn1        1    -1.28437      0.17426     54.3251      <.0001          0.277
 dn2        1    -1.25842      0.18123     48.2173      <.0001          0.284
```

```
 dn3          1     -1.21370      0.21085      33.1338         <.0001      0.297
 dn4          1     -1.08482      0.21264      26.0262         <.0001      0.338
 dn510        1     -0.62394      0.14893      17.5510         <.0001      0.536
 dn1015       1     -0.26508      0.17134       2.3933         0.1219      0.767


                      Estimated Covariance Matrix

     Variable              dn1               dn2               dn3

     dn1           0.0303656699      0.0158794030      0.0158743801
     dn2           0.0158794030      0.0328433110      0.0158873234
     dn3           0.0158743801      0.0158873234      0.0444580750
     dn4           0.0158321124      0.0158403749      0.0158365471
     dn510         0.0157822736      0.0157910332      0.0157887547
     dn1015        0.0157102878      0.0157179826      0.0157169949


         Unadjusted analysis of nodes effect using whole sample        3
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                      Estimated Covariance Matrix

     Variable              dn4             dn510            dn1015

     dn1           0.0158321124      0.0157822736      0.0157102878
     dn2           0.0158403749      0.0157910332      0.0157179826
     dn3           0.0158365471      0.0157887547      0.0157169949
     dn4           0.0452171683      0.0157584925      0.0156986869
     dn510         0.0157584925      0.0221809786      0.0156817871
     dn1015        0.0156986869      0.0156817871      0.0293588001


         Unadjusted analysis of nodes effect using whole sample        4
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                          The PHREG Procedure

                           Model Information

Data Set                 WORK.BCANCER
Dependent Variable       days              (censored) survival time in days
Censoring Variable       cens              censoring indicator
Censoring Value(s)       0
Ties Handling            BRESLOW


           Summary of the Number of Event and Censored Values

                                                       Percent
                 Total         Event     Censored     Censored

                   895           489          406        45.36


                           Convergence Status

             Convergence criterion (GCONV=1E-8) satisfied.
```

```
                        Model Fit Statistics

                                  Without           With
                 Criterion     Covariates     Covariates

                 -2 LOG L        6251.265       6155.232
                 AIC             6251.265       6167.232
                 SBC             6251.265       6192.386


                 Testing Global Null Hypothesis: BETA=0

         Test                 Chi-Square       DF     Pr > ChiSq

         Likelihood Ratio        96.0334        6         <.0001
         Score                  108.5044        6         <.0001
         Wald                   100.4176        6         <.0001


                 Analysis of Maximum Likelihood Estimates

                         Parameter    Standard                                 Hazard
 Variable   DF       Estimate       Error  Chi-Square  Pr > ChiSq      Ratio

 dn1         1       -0.07068     0.20755      0.1160      0.7335      0.932
 dn2         1       -0.04472     0.21337      0.0439      0.8340      0.956
 dn4         1        0.12888     0.24084      0.2864      0.5926      1.138
 dn510       1        0.58976     0.18725      9.9202      0.0016      1.804
 dn1015      1        0.94862     0.20587     21.2322      <.0001      2.582
 dn15        1        1.21370     0.21085     33.1338      <.0001      3.366


           Unadjusted analysis of nodes effect using subsample          5
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                         The PHREG Procedure

                          Model Information

Data Set                 WORK.BCANCER1
Dependent Variable       days               (censored) survival time in days
Censoring Variable       cens               censoring indicator
Censoring Value(s)       0
Ties Handling            BRESLOW


            Summary of the Number of Event and Censored Values

                                                      Percent
                  Total        Event     Censored     Censored

                    723          391          332        45.92


                          Convergence Status

             Convergence criterion (GCONV=1E-8) satisfied.


                        Model Fit Statistics
```

Criterion	Without Covariates	With Covariates
-2 LOG L	4833.945	4764.954
AIC	4833.945	4776.954
SBC	4833.945	4800.766

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	68.9916	6	<.0001
Score	77.8626	6	<.0001
Wald	72.4992	6	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
dn1	1	-1.21094	0.19315	39.3037	<.0001	0.298
dn2	1	-1.26069	0.20165	39.0842	<.0001	0.283
dn3	1	-1.17723	0.23237	25.6654	<.0001	0.308
dn4	1	-1.00578	0.24002	17.5597	<.0001	0.366
dn510	1	-0.60345	0.17061	12.5111	0.0004	0.547
dn1015	1	-0.33276	0.19337	2.9614	0.0853	0.717

Analysis of adjusted nodes effect using subsample 6
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Model Information

Data Set	WORK.BCANCER1	
Dependent Variable	days	(censored) survival time in days
Censoring Variable	cens	censoring indicator
Censoring Value(s)	0	
Ties Handling	BRESLOW	

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
723	391	332	45.92

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates

```
              -2 LOG L        4833.945      4728.493
              AIC             4833.945      4746.493
              SBC             4833.945      4782.212


              Testing Global Null Hypothesis: BETA=0

      Test                  Chi-Square      DF     Pr > ChiSq

      Likelihood Ratio        105.4518       9         <.0001
      Score                   115.3524       9         <.0001
      Wald                    109.3568       9         <.0001


              Analysis of Maximum Likelihood Estimates

                  Parameter      Standard
Variable    DF     Estimate         Error    Chi-Square    Pr > ChiSq

dn1          1     -1.19408       0.19574       37.2135        <.0001
dn2          1     -1.20719       0.20415       34.9666        <.0001
dn3          1     -1.16259       0.23449       24.5813        <.0001
dn4          1     -1.03819       0.24114       18.5357        <.0001
dn510        1     -0.60950       0.17210       12.5431        0.0004
dn1015       1     -0.32581       0.19445        2.8074        0.0938
meno         1      0.40551       0.10820       14.0459        0.0002

             Analysis of Maximum Likelihood Estimates

                      Hazard
         Variable      Ratio    Variable Label

         dn1           0.303
         dn2           0.299
         dn3           0.313
         dn4           0.354
         dn510         0.544
         dn1015        0.722
         meno          1.500    menopausal status


          Analysis of adjusted nodes effect using subsample          7
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              Analysis of Maximum Likelihood Estimates

                  Parameter      Standard
Variable    DF     Estimate         Error    Chi-Square    Pr > ChiSq

tsize        1      0.02298       0.01945        1.3963        0.2373
er           1     -0.54446       0.10475       27.0157        <.0001

             Analysis of Maximum Likelihood Estimates

                      Hazard
         Variable      Ratio    Variable Label

         tsize         1.023    size of largest tumor in cm
         er            0.580    estrogen receptor status
```

```
                      Estimated Covariance Matrix

Variable                                        dn1             dn2

dn1                                    0.0383145537    0.0216371781
dn2                                    0.0216371781    0.0416773678
dn3                                    0.0215804368    0.0215943509
dn4                                    0.0212539145    0.0212273511
dn510                                  0.0212225418    0.0212180900
dn1015                                 0.0210776688    0.0210965424
meno         menopausal status         -.0001772870    0.0000821671
tsize        size of largest tumor in cm 0.0006074631  0.0006114021
er           estrogen receptor status  -.0000041378    -.0006272171

                      Estimated Covariance Matrix

Variable                                        dn3             dn4

dn1                                    0.0215804368    0.0212539145
dn2                                    0.0215943509    0.0212273511
dn3                                    0.0549853099    0.0213140081
dn4                                    0.0213140081    0.0581490154
dn510                                  0.0212533597    0.0210335278
dn1015                                 0.0211331931    0.0209323786
meno         menopausal status         -.0011395951    -.0012567326
tsize        size of largest tumor in cm 0.0005472880  0.0003777127
er           estrogen receptor status  -.0004634995    0.0001294100

                      Estimated Covariance Matrix

Variable                                      dn510          dn1015

dn1                                    0.0212225418    0.0210776688
dn2                                    0.0212180900    0.0210965424
dn3                                    0.0212533597    0.0211331931
dn4                                    0.0210335278    0.0209323786
dn510                                  0.0296173567    0.0209108008
dn1015                                 0.0209108008    0.0378115889
meno         menopausal status         -.0008123275    -.0007730645
tsize        size of largest tumor in cm 0.0004003289  0.0003517206
er           estrogen receptor status  -.0001460574    -.0004473206

                      Estimated Covariance Matrix

Variable                                       meno           tsize

dn1                                    -.0001772870    0.0006074631
dn2                                    0.0000821671    0.0006114021
dn3                                    -.0011395951    0.0005472880
dn4                                    -.0012567326    0.0003777127


           Analysis of adjusted nodes effect using subsample          8
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                      Estimated Covariance Matrix

Variable                                       meno           tsize
```

```
dn510                                            -.0008123275    0.0004003289
dn1015                                           -.0007730645    0.0003517206
meno         menopausal status                   0.0117072729    0.0000769842
tsize        size of largest tumor in cm         0.0000769842    0.0003781367
er           estrogen receptor status            -.0014632745    -.0001378757

                      Estimated Covariance Matrix

        Variable                                                    er

        dn1                                               -.0000041378
        dn2                                               -.0006272171
        dn3                                               -.0004634995
        dn4                                               0.0001294100
        dn510                                             -.0001460574
        dn1015                                            -.0004473206
        meno         menopausal status                    -.0014632745
        tsize        size of largest tumor in cm          -.0001378757
        er           estrogen receptor status             0.0109726802


                       Model with only meno tsize er                          9
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                            The PHREG Procedure

                             Model Information

Data Set                 WORK.BCANCER1
Dependent Variable       days               (censored) survival time in days
Censoring Variable       cens               censoring indicator
Censoring Value(s)       0
Ties Handling            BRESLOW


           Summary of the Number of Event and Censored Values

                                                    Percent
                 Total        Event     Censored    Censored

                   723          391          332       45.92


                             Convergence Status

             Convergence criterion (GCONV=1E-8) satisfied.


                           Model Fit Statistics

                                 Without           With
                Criterion     Covariates     Covariates

                -2 LOG L        4833.945       4791.872
                AIC             4833.945       4797.872
                SBC             4833.945       4809.779


                Testing Global Null Hypothesis: BETA=0

        Test                  Chi-Square       DF     Pr > ChiSq
```

```
       Likelihood Ratio        42.0728        3         <.0001
       Score                   44.3354        3         <.0001
       Wald                    43.9297        3         <.0001


               Analysis of Maximum Likelihood Estimates

                      Parameter      Standard
 Variable     DF       Estimate         Error    Chi-Square    Pr > ChiSq

 meno          1        0.41662       0.10758       14.9962        0.0001
 tsize         1        0.05245       0.01914        7.5127        0.0061
 er            1       -0.54977       0.10446       27.6995        <.0001

              Analysis of Maximum Likelihood Estimates

                          Hazard
          Variable         Ratio    Variable Label

          meno             1.517    menopausal status
          tsize            1.054    size of largest tumor in cm
          er               0.577    estrogen receptor status


      Score test for nodes effect adjusting for other covariates     10
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                           The PHREG Procedure

                            Model Information

Data Set                   WORK.BCANCER1
Dependent Variable         days                (censored) survival time in days
Censoring Variable         cens                censoring indicator
Censoring Value(s)         0
Ties Handling              BRESLOW


           Summary of the Number of Event and Censored Values

                                                      Percent
                 Total        Event     Censored     Censored

                   723          391          332        45.92

The following variable(s) will be included in each model:

         meno  tsize  er


                            Convergence Status

              Convergence criterion (GCONV=1E-8) satisfied.


                          Model Fit Statistics

                                 Without           With
                 Criterion     Covariates     Covariates

                 -2 LOG L        4833.945       4791.872
                 AIC             4833.945       4797.872
```

```
              SBC              4833.945       4809.779


              Testing Global Null Hypothesis: BETA=0

        Test                    Chi-Square       DF     Pr > ChiSq

        Likelihood Ratio           42.0728        3         <.0001
        Score                      44.3354        3         <.0001
        Wald                       43.9297        3         <.0001


              Analysis of Maximum Likelihood Estimates

                    Parameter      Standard
 Variable    DF      Estimate         Error    Chi-Square    Pr > ChiSq

 meno         1       0.41662       0.10758       14.9962        0.0001
 tsize        1       0.05245       0.01914        7.5127        0.0061
 er           1      -0.54977       0.10446       27.6995        <.0001

             Analysis of Maximum Likelihood Estimates

                        Hazard
          Variable       Ratio    Variable Label

          meno           1.517    menopausal status
          tsize          1.054    size of largest tumor in cm
          er             0.577    estrogen receptor status


      Score test for nodes effect adjusting for other covariates     11
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              Analysis of Variables Not in the Model

                    Score
  Variable    Chi-Square    Pr > ChiSq    Label

  dn1            10.5788        0.0011
  dn2             9.0532        0.0026
  dn3             3.9337        0.0473
  dn4             1.6003        0.2059
  dn510           5.9467        0.0147
  dn1015         14.8804        0.0001


                          Residual Chi-Square Test

                       Chi-Square       DF     Pr > ChiSq

                          71.6681        6         <.0001


NOTE: No (additional) variables met the 0 level for entry into the
      model.


                       Trend test for number of nodes                  12
          Unadjusted analysis of nodes effect using whole sample
```

```
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                          The PHREG Procedure

                           Model Information

Data Set                 WORK.BCANCER
Dependent Variable       days             (censored) survival time in days
Censoring Variable       cens             censoring indicator
Censoring Value(s)       0
Ties Handling            BRESLOW


           Summary of the Number of Event and Censored Values

                                                    Percent
                 Total        Event    Censored    Censored

                   895          489         406       45.36


                           Convergence Status

             Convergence criterion (GCONV=1E-8) satisfied.


                         Model Fit Statistics

                                Without           With
                Criterion    Covariates     Covariates

                -2 LOG L       6251.265       6161.650
                AIC            6251.265       6163.650
                SBC            6251.265       6167.843


                Testing Global Null Hypothesis: BETA=0

        Test                    Chi-Square       DF     Pr > ChiSq

        Likelihood Ratio           89.6150        1         <.0001
        Score                     106.9318        1         <.0001
        Wald                      102.3116        1         <.0001


                Analysis of Maximum Likelihood Estimates

                Parameter    Standard                                  Hazard
 Variable  DF    Estimate       Error  Chi-Square  Pr > ChiSq     Ratio

 dnscore    1     0.07245     0.00716    102.3116      <.0001     1.075


                     Trend test for number of nodes                  13
           Analysis of adjusted nodes effect using subsample
                                             08:41 Tuesday, April 8, 2003

                          The PHREG Procedure

                           Model Information

Data Set                WORK.BCANCER1
```

Dependent Variable	days	(censored) survival time in days
Censoring Variable	cens	censoring indicator
Censoring Value(s)	0	
Ties Handling	BRESLOW	

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
723	391	332	45.92

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	4833.945	4732.068
AIC	4833.945	4740.068
SBC	4833.945	4755.943

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	101.8775	4	<.0001
Score	114.2136	4	<.0001
Wald	110.7178	4	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
dnscore	1	0.06774	0.00822	67.9694	<.0001
meno	1	0.41281	0.10780	14.6631	0.0001
tsize	1	0.02268	0.01885	1.4467	0.2291
er	1	-0.54589	0.10464	27.2166	<.0001

Analysis of Maximum Likelihood Estimates

Variable	Hazard Ratio	Variable Label
dnscore	1.070	
meno	1.511	menopausal status
tsize	1.023	size of largest tumor in cm
er	0.579	estrogen receptor status

Trend test for number of nodes 14
Score test for nodes effect adjusting for other covariates
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```
                          The PHREG Procedure

                           Model Information

Data Set                 WORK.BCANCER1
Dependent Variable       days              (censored) survival time in days
Censoring Variable       cens              censoring indicator
Censoring Value(s)       0
Ties Handling            BRESLOW


           Summary of the Number of Event and Censored Values

                                                    Percent
                 Total        Event    Censored    Censored

                   723          391         332       45.92

The following variable(s) will be included in each model:

         meno  tsize  er


                           Convergence Status

             Convergence criterion (GCONV=1E-8) satisfied.


                         Model Fit Statistics

                                Without           With
                Criterion     Covariates     Covariates

                -2 LOG L        4833.945       4791.872
                AIC             4833.945       4797.872
                SBC             4833.945       4809.779


                Testing Global Null Hypothesis: BETA=0

        Test                   Chi-Square       DF     Pr > ChiSq

        Likelihood Ratio          42.0728        3         <.0001
        Score                     44.3354        3         <.0001
        Wald                      43.9297        3         <.0001


                Analysis of Maximum Likelihood Estimates

                       Parameter      Standard
 Variable     DF        Estimate         Error    Chi-Square    Pr > ChiSq

 meno          1         0.41662       0.10758       14.9962        0.0001
 tsize         1         0.05245       0.01914        7.5127        0.0061
 er            1        -0.54977       0.10446       27.6995        <.0001

               Analysis of Maximum Likelihood Estimates

                          Hazard
           Variable        Ratio    Variable Label
```