Longer Life Foundation –Project Report

Project Title: Disease Comorbidity and Survival in the NHLBI Family Heart Study (FHS)
Investigator: Michael A. Province, Ph.D.
Grant period: 9/01-2/02

Applicant's Summary: The NHLBI Family Heart Study (FHS) is a large, multicenter, population-based study of the familial and genetic determinants of coronary heart disease (CHD), atherosclerosis, and cerebral vascular disease (CVD) risk factors. Vital status, medical histories and lifestyle factors were collected on approximately 25,000 first degree relatives from 3,000 three generation pedigrees selected from 4 geographically diverse field centers (Winston-Salem, NC; Minneapolis, MN; Framingham MA; and Salt Lake City, UT) from 1992-1996. Conditions assessed included MI, CHD, stroke, hypertension, diabetes, high cholesterol, cancer, and asthma. Ages ranged from 0-103 years at that time. Approximately half of the families at each center were selected randomly, and the remaining were selected for high rates of early, familial CHD. A subset of over 5,000 subjects in 1,200 pedigrees (half random, half high risk) were further extensively examined clinically in all major risk domains for CHD, including demographics, diet, exercise, personal habits, concurrent medication use, anthropometry, lipid profile, biochemistries, ECG, pulmonary function, and carotid artery ultrasound measures of preclinical atherosclerosis. Washington University has been the Coordinating Center for FHS from the beginning (Province, PI) so these data are readily at hand and well understood.

We propose to conduct National Death Index (NDI) searches to update current vital status, and then study the relationship between prevalent disease and survival within individuals as well as within pedigree units using a variety of state of the art statistical models. Family Risk Score (FRS) methods (Williams et al., 2001) will allow us to quantify the extent of excess familial clustering of each family for each co-morbid condition. The degree to which these FRS scores are correlated across disease conditions within the same families will allow us to characterize the excess sharing of familial risk for clusters of diseases. We have also developed extensions of statistical frailty models for families (Siegmund et al., 1998, 1999) and bootstrapping methods (Province et al., 2000, 2001), which will allow us to assess the impact of disease and risk factors on survival in related (non-independent) samples. Finally, our general structural equations software designed for familial and genetic quantitative traits (SEGPATH: Province et al., 1995; 2001) will be extended to include survival.

These data will allow us to assess the degree of familial clustering of each co-morbid condition and risk factor, to assess the degree to which they co-cluster within individuals as well as families, and to evaluate the independent contributions of each of these to overall survival. By having both a large random sample as well as a high risk sample, we can readily translate inferences and estimates of risk factor effects on mortality from high risk subgroups to the population as a whole. This unique resource will allow examination of the interplay between complex disease co-morbidities and risk factors on survival in a unique, large, population based samples of individuals and pedigrees.

Six-Month Report: Because funding was restricted to $50K, the NDI search itself will consume practically all of the Longer Life funds granted to us for the first year of this project. Without these data, the project is not doable. So, unfortunately, we have made only limited progress.

We applied for and obtained formal approval from the National Death Index [NDI] to conduct the death certificate search in January 2002 (this was a several month process). We are currently waiting until the death certificate record data are released for 2000 calendar deaths (expected in March 2002), so that our search may be as complete as possible, since in practicality we have only one opportunity to conduct this search. This will give us up to 8 years of follow-up on the FHS families, which will form the primary outcomes for our analyses. We have created the file of the 25,000 relatives on whom death certificate information will be requested, formatted in as required by the NDI, so we are ready to conduct the search as soon as the 2000 data become available to us.

In the meantime, we have finalized the creation of all Family Risk Scores (FRS) for all disease conditions, which will form the key independent variables in our analyses (along with traditional, individual risk factors that are already in the database on each subject). We have created FRS for CHD, stroke, angina, high cholesterol, hypertension, obesity, syndrome X, diabetes, and each of the major cancers. We have examined the correlations of these FRS within families, both in the random samples, as well as in the high-CHD risk families. We are in preparation of a manuscript to an epidemiology journal of these results.