Commentary (Burke): Prostate Cancer Risk Assessment Program

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Bruner and colleagues describe a comprehensive, long-term research program designed to understand, model, and modify prostate cancer risk. According to the investigators, the main problem with early prostate cancer risk screening is the discovery of nonlethal tumors. Their solution is to establish a screening program, enroll the screened population in a registry and clinic, and use the information acquired from these individuals to help select those at risk for lethal prostate cancer. One emphasis of this research program is the identification and understanding of the environmental and genetic risk factors that occur early in the disease process and the modification of these factors.

Screening for Future vs Current Disease
There are two types of screening relevant to this research: (1) screening for individuals who currently do not have evidence of invasive disease but who may exhibit invasive disease at some point in the future (individuals at risk for future disease), and (2) screening for individuals who are not symptomatic but in whom disease can be detected if one searches for it (individuals with current disease). Although the detection of nonlethal tumors is a problem associated with screening for current disease, it is not the primary impediment to screening aimed at identifying individuals who are at risk for future disease.

Ostensibly, the researchers are interested in screening for current disease, but their objectives and aims suggest that their main interest is in identifying men who do not have detectable disease at present but who are at risk for developing the disease over a specified time interval. This type of risk screening is difficult because few powerful early risk factors currently exist. Early risk factors are rare even in high-risk populations, and by the time powerful predictive factors occur and are detectable, the disease has usually become invasive.

Three Program Objectives
The three objectives of this research program are as follows:

1. To establish a prostate cancer risk registry for men at high risk for prostate cancer. This registry contains the health history, family history, clinical information, quality-of-life and risk data, as well as expanded family and medical history, and, when possible, pathologic confirmation of familial cancer for men with at least three or more affected members.

2. To study the genetics of prostate cancer, including the creation of a serum bank.

3. To develop tools for intervention and primary prevention of prostate cancer in men at high risk for the disease.

Avoiding Biases in the Study Population
A critical component of this program is the study population. Questions of interest include: From which population is the high-risk study group drawn? How are individuals selected for inclusion in the study? What is the actual rate of enrollment of high-risk men? The researchers identify the following factors as placing individuals at higher risk for prostate cancer: age, family history, race, and lifestyle risk factors (eg, animal fat intake, tobacco exposure, and cadmium exposure). Their study inclusion criteria are: men under the age of 35 years who have at least one first-degree relative with prostate cancer; African-American men under the age of 35 years; and all men 35 to 69 years of age, especially those with one first-degree relative with prostate cancer.
and those of African-American descent. The men will be recruited for participation through relatives diagnosed and treated for prostate cancer at Fox Chase Cancer Center and from a database and follow-up clinic maintained by the Department of Radiation Oncology.

It should be noted that if men at low risk are allowed to enter the study group, the population may not be at high enough risk for the study to have sufficient power to detect and assess prostate cancer risk factors. Also, if enrollment is biased, the study results may also be biased.

The study’s population may not be at “high risk” even when it is compared to those men who are screened in current practice, ie, those over 50 years of age. In fact, if anything, the study inclusion criteria seem to dramatically expand the screening population, resulting in a rather low-risk population. The effect of this risk dilution is a need to increase the size of the population in order to maintain predictive power. In addition, the researchers target special subpopulations for collection. If all the collected cases are combined, the population will not be a representative one; rather, it will be biased.

One way to avoid this bias is to analyze all of the subpopulations separately and to generalize the results only to those subpopulations that were analyzed. The problem with this approach is that each subpopulation must be very large. The original sample size for the overall population becomes the sample size for each subpopulation. Thus, the study may require thousands to tens-of-thousands of participants.

**Computer Storage of Registry Information**

The computer storage of registry information must also be considered.[1] Anyone who set up a medical database more than 10 years ago knows how difficult it is to maintain and upgrade a computer-based medical information system.

This research program will presumably want to maintain its information for at least 20 years. A great deal of thought must given to how such a system is designed, implemented, and maintained so that it can function over the life of the study.[1] Furthermore, sufficient funds must be allocated to the system.

**Which Specimens Should Be Banked?**

Specimen banks play a critical role in research on prognostic factors since they save years of follow-up time.[1] This research program intends to create a serum bank for future genetic testing of oncogenes and tumor-suppresser genes potentially involved in the near-Mendelian transmission of prostate cancer. Familial prostate cancer is thought to account for no more than a small percentage of all prostate cancers; therefore, this type of genetic testing may be relevant only to a small part of the domain of prostate cancer.

It might be wiser to store biopsy specimens taken from men at high risk of prostate cancer who do not demonstrate invasive disease on biopsy, possibly a biopsy that showed only prostatic intraepithelial neoplasia (PIN) or genetic abnormalities. The morphologic and genetic profiles of those patients who later develop invasive disease can be compared to the invasive disease genetic profile and genetic risk factors may be identified.[2]

**Summary**

In summary, the study envisioned by Bruner and colleagues seems ambitious and requires serious thought to overcome some potential problems. However, this type of study is necessary for the proper investigation of risk factors and the modification of disease pathways through prevention programs.

**References:**


Links: