

THE *PROGRESS* REPORT



Volume 15

Spring/Summer 2006

Welcome to the 15th edition of The Progress Report, a newsletter for participants enrolled in *PROGRESS*, the Prostate Cancer Genetic Research Study. We are continuing our work to try to discover the genes and genetic mutations associated with hereditary prostate cancer in families. The goal of the newsletter is to keep you updated on our latest research findings and other news related to prostate cancer, and we hope you find it both informative and helpful. We really appreciate your ongoing help with the study. If you have any questions about this newsletter or your participation, please call us toll-free at 1-800-777-3035.

Analyses of Clinical Features of Prostate Cancer

In our last newsletter we mentioned grouping *PROGRESS* families on the basis of clinical information provided by the prostate cancer-related medical records of study participants. The findings from the linkage analysis have now been published in the journal "The Prostate", and we would like to provide you with a summary of the results. The main aim of the analysis was to see whether more aggressive forms of prostate cancer are associated with particular chromosomal regions, which could further help to pinpoint the gene(s) involved in a subset of hereditary prostate cancer (HPC) families. "More aggressive" prostate cancer was defined by one or more of the following features at diagnosis: regional or distant stage, a Gleason score of 7 or higher, a prostate-specific antigen (PSA) level of 20 or higher, or death from metastatic prostate cancer before age 65 (See the Glossary for a more detailed explanation of these criteria).

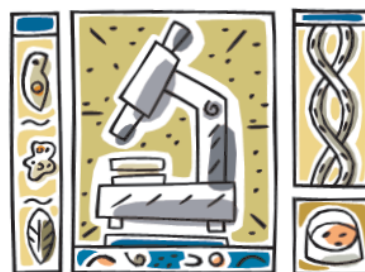
Out of the 254 families in the overall genome-wide scan, 123 *PROGRESS* families contained at least 2 men with "more aggressive" prostate cancer features, including a total of 297 cases.

The strongest linkage signal from our analysis was found at chromosome 22q11, with a LOD score of 2.18. The LOD score increased to 2.75 among families with evidence of male-to-male transmission of prostate cancer (passed from father to son). The second largest signal was found at chromosome 22q12-13, among families with a younger mean age at diagnosis of prostate cancer (<65 years). Interestingly, another recent study that focused on men with more aggressive prostate cancer also reported a LOD score of 2.1 at region 22q13 (Chang et al., *The Prostate* 2005; 64: 356). Region 22q12 was

also identified as "significant" (LOD score of 3.57) in the combined genome-wide scan of 1,233 families carried out by the International Consortium for Prostate Cancer Genetics (ICPCG) last year, based on a subset of 269 families with 5 or more affected men with prostate cancer (Xu et al., *Am J Hum Genet* 2005; 77: 219). The ICPCG group recently completed a linkage analysis of families with at least 3 men with more aggressive prostate cancer (*PROGRESS* contributed family-level data for 38 such families), and a manuscript is in press at the journal "Human Genetics". We will provide you with an update of the findings once the paper is published.

The overlap in the research findings summarized above suggests a possible association between more aggressive prostate cancer in HPC families and a fairly large region of chromosome 22q. More detailed investigations of this region are required to try and narrow the region of linkage that may be responsible for this signal. Along with other groups we are currently genotyping denser genetic markers on chromosome 22q.

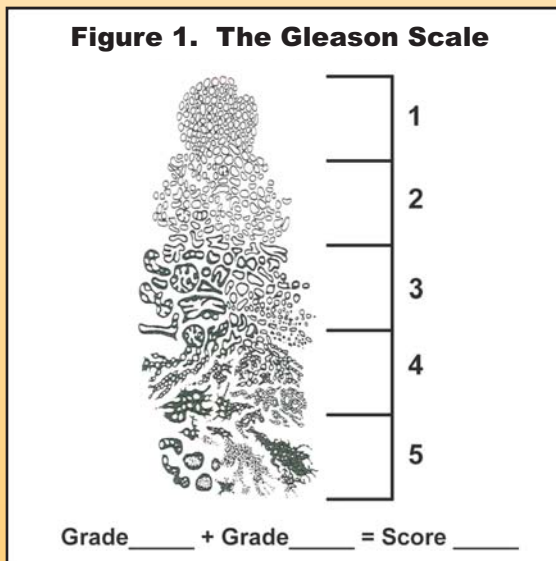
At this point we would like again to thank all the study participants who returned their Medical Record Release Forms, allowing us to send for the medical records that provided the crucial clinical data for this analysis. If any of you have not yet done so, we would be most grateful if you could return your release form as soon as possible.



GLOSSARY OF TERMS

Tumor Grade (Gleason Score): Tissue removed during a prostate biopsy or surgery is studied under a microscope and using the Gleason grading system, a number ranging from 1-5 is assigned to the two largest areas of cancer in the sample. The number is based on the degree of differentiation of the cells, with 1 indicating “well-differentiated” and 5 indicating “poorly differentiated” disease. As shown in the Gleason Scale (see Figure 1), grade 1 cells most closely resemble normal prostate tissue, and the cell pattern is orderly with well-defined borders. In stark contrast, grade 5 signifies a complete loss of normal cell structure or architecture, with the cells appearing fused and grouped together in tumor-like clusters. The final Gleason Score is created by summing the two individual Gleason grades or patterns. The lowest possible combined score is therefore 2, and the highest possible combined score is 10, which indicates the most advanced, aggressive tumors. A Gleason Score of 7 or higher is considered an indicator of a more aggressive form of prostate cancer.

Figure 1. The Gleason Scale



Tumor Stage: The stage at diagnosis is a measure of how far the prostate cancer extends or has grown, indicating whether it remains within the prostate or has spread beyond the prostate. Localized prostate cancer (Stages A and B) is confined to the prostate, while regional disease (Stage C) has spread beyond (outside) the prostate to the surrounding tissues, including the seminal vesicles. In metastatic or distant stage (Stage D) disease, prostate cancer has spread to organs beyond the prostate such as bones, the liver, or lungs. Stage of disease is used to assess prognosis and to determine the most suitable treatment options.

African-American Recruitment -We Need More Families

Along with age and family history, being African-American is one of the strongest risk factors for developing prostate cancer. Compared to other ethnic groups, African-American men have a younger median age at diagnosis of prostate cancer, have an incidence rate that is approximately 60% higher than Caucasian-Americans, and they are twice as likely to die from the disease. In fact, *African-American men have the highest rates of prostate cancer in the world*, and it is very important to try and understand why.

Genetic factors are likely to play a role, but are not yet well-understood, and further research is required. There are currently only 12 African-American families participating in *PROGRESS*, which severely limits our ability to examine possible genetic loci that may underlie HPC in this high-risk group. So we would really like to recruit more African-American families into the study. Previous recruitment efforts included a national advertising campaign in minority-owned newspapers and magazines, and mailings to members of the National Medical Association (NMA) and heads of professional organizations with mainly African-American membership.

Our latest efforts include hiring an African-American consultant with extensive links to the community here in Seattle. He helped us to develop a new study brochure, which is specifically targeted at the African-American population. We have sent copies of the new brochure to local barber shops, churches, and community health clinics. Finally, we are consulting with local community leaders on the best ways to reach out to African-American men, including attendance at health fairs and support groups, giving public presentations at appropriate local venues, and making contact through the well-attended health ministries provided by several prominent churches.

As a result of these efforts, we hope to increase enrollment of African-American families in *PROGRESS*. We would welcome any suggestions from existing *PROGRESS* participants that may help us to achieve this goal.

Follow-Up Survey Update

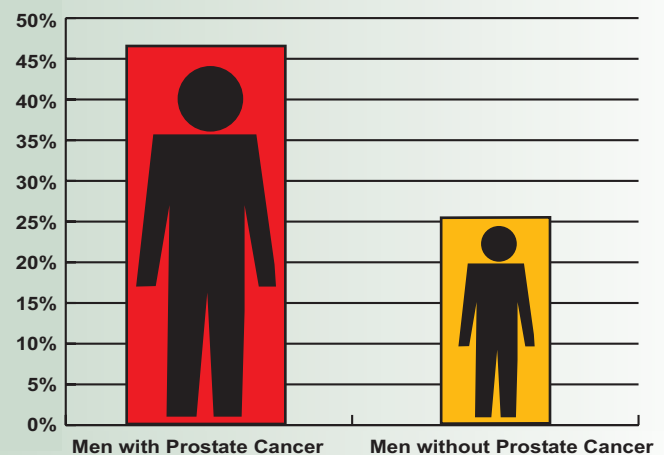
We would like to report the final results from the 1,640 follow-up surveys we mailed out to *PROGRESS* participants beginning in July 2002. We received a total of 1,422 completed surveys (87%), which is a great response rate. Once again, we would like to thank everyone who participated. All of the information you provided will be valuable for further analyses and provides us with crucial updates regarding the current health status of *PROGRESS* family members. The questions on the follow-up survey relating to level of interest in a future test to determine genetic risk for prostate cancer have been evaluated and the preliminary findings were presented at the American Society of Preventive Oncology (ASPO) 30th Annual Meeting in Bethesda, Maryland in February 2006. Based on the responses of over 900 male family members, the results showed that approximately equal proportions of men with prostate cancer and men without prostate cancer (45% versus 43%) would “definitely” be interested in taking a genetic test for prostate cancer risk, if one became available.

However, more men with prostate cancer reported having read or heard a “fair amount or more” about genetic testing compared to their male relatives without prostate cancer (46% versus 25% - See Figure 2). In addition, men over the age of 75 years were less likely to be interested in genetic testing compared to younger men, in both groups. Further analyses of these data are underway and a manuscript summarizing the results will be drafted for publication later this year.

One very important goal of the follow-up survey was to identify new cancer diagnoses in members of *PROGRESS* families. There were 14 men who reported that they had

been newly diagnosed with prostate cancer, and there were approximately 64 reports of new prostate cancer diagnoses in other family members. Men who were already participating in *PROGRESS* were sent a self-report form to confirm their diagnosis, and/or a Medical Record Release form allowing us to send for their clinical information. Male relatives who were not yet known to the study were sent an Introductory Packet inviting them to join *PROGRESS*. So far, we have added 13 new participants to our existing families. As with all longitudinal studies conducted over a period of years, ongoing data collection is critical to the success of *PROGRESS*. Therefore, we are working on a second follow-up survey that we plan to begin mailing out early next year. We will send you more details nearer to the time, but wanted you to know that this is planned. In anticipation of our next survey, now would be the perfect time to let us know about any changes in your current address.

Figure 2. Percentage of men who reported having read or heard a “fair amount or more” about genetic testing for prostate cancer



Linkage Analyses Based on Other Cancers

As we have mentioned in previous newsletters, one way of grouping HPC families into more homogeneous or “alike” subsets is via the presence of other cancers in the family. We used this approach to find a linkage region on the short arm of chromosome 1 (CAPB) in families with a history of both prostate cancer and primary brain cancer. Based on reports of other cancers in the baseline and follow-up *PROGRESS* surveys, we recently identified 13 families with a history of prostate cancer and primary kidney cancer. All of the kidney cancer cases

were either prostate cancer cases themselves or were first-degree relatives to prostate cancer cases. Linkage analyses demonstrated LOD scores above 3.0 at four markers on chromosome 11q12. This is a strong linkage signal and supports our approach of grouping HPC families according to the presence of other cancers. A manuscript summarizing these results will be completed within the next few months and submitted for publication. We have also identified 12 families with a history of prostate cancer and primary pancreatic cancer, and linkage analyses of these families are underway. The initial process of identifying HPC families who reported colon cancer in either the baseline or follow-up survey has begun, and once we have confirmed which families have members with colon cancer, linkage analyses will be carried out. We may be contacting some of you to clarify details of these reports of other cancers in family members.

Extension of Family Pedigrees – Enrollment of New Participants

Many of you have recently been contacted by us for the first time, to see if you would be willing to participate in *PROGRESS*. The reason for this is that we are trying to expand our family pedigrees to include family members from generations who are approaching the at-risk ages for prostate cancer. Current affection status in male relatives and additional DNA samples from both male and female family members contribute to the accuracy of linkage analyses, as they provide important information relating to the family's genetic background.

Linkage analysis looks for regions in the human genome where the men diagnosed with prostate cancer within a family inherited the same chromosome (see Figure 3). Most families in *PROGRESS* have multiple siblings who have been diagnosed with prostate cancer. However, the genetic information from the parents is not typically available because prostate cancer is a later-onset disease. In this case, the linkage analysis program must estimate the likelihood that the men diagnosed with prostate cancer within each family share the same chromosome. If the program knew the parents' actual chromosomes (as in Figure 3), it would not have to estimate the inheritance pattern. The best way to improve this estimation is to include genetic information from other members of the family. The unaffected

brothers, sisters or children may help to reconstruct the parental genetic information and improve our ability to successfully identify the chromosome regions that may contain prostate cancer susceptibility genes.

A separate recruitment effort is being conducted in a group of men with prostate cancer, who reported a family history of the disease and who were originally interviewed for another study of prostate cancer in men under age 65 years at diagnosis. The family members of these men were not included in the original genome-wide scan, and have not been consistently followed-up. So far, 26 families from this group have been identified as eligible for future analyses and have been added to the main group of *PROGRESS* families. We recently sent a follow-up survey to participating members from these 26 families requesting updated family information, including any new diagnoses of prostate cancer. We would like to thank those participants who have already returned their surveys for your speedy response and willingness to help, and to encourage those who have not yet done so, to return their surveys as soon as possible. The incorporation of these families into *PROGRESS* has increased the total number of participating families to 300! This means that *PROGRESS* is one of the largest extended family studies of hereditary prostate cancer in the world.

Figure 3. Inheritance of Chromosomes in Families



The brother without prostate cancer has inherited the green chromosome from his father whereas all of the brothers with prostate cancer share the blue chromosome. This suggests that there may be a gene for hereditary prostate cancer somewhere on the blue chromosome in this family.

Contact Information

If you would like additional information regarding the study, or a copy of any of our papers, please let us know. Also if you have any questions or would like to report any family updates, please contact us.

Mailing Address:

Fred Hutchinson Cancer Research Center
P.O. Box 19024, Mailstop M4-A402
Seattle, WA 98109-1024

Toll-Free Number:

1-800-777-3035

E-mail:

progress@fhcrc.org

Web-site:

http://www.fhcrc.org/phs/progress_study/index.html