Greetings

Welcome to the 18th edition of The Progress Report, a newsletter for participants in the Prostate Cancer Genetic Research Study or PROGRESS. The goal of the newsletter is to keep you updated on our latest research findings. Our hope is that you will find it both informative and helpful. We really appreciate your ongoing participation and 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. We are always pleased to hear from you. Wishing you a Happy and Healthy New Year from all of us here at the study.

Study Updates

Genome-wide SNP Linkage Scan and Focus on Chromosome 15

The results from our genome-wide SNP (single nucleotide polymorphism) linkage scan of approximately 6,000 genetic markers, have now been published (Stanford et al., Hum Mol Genet 2009; 18: 1839). Overall results for the 301 PROGRESS families included in the main analyses found evidence of “suggestive” linkage peaks at chromosomes 7q21, 8q22 and 15q13-q14. Suggestive peaks point to regions of the genome which warrant further analyses.

As mentioned in previous newsletters, one way to fine-tune our overall findings is to subset families by shared characteristics, which aims to create groups of families with a more similar genetic risk profile. Using the SNP data, we looked at families with at least 2 men with more clinically aggressive prostate cancer. There were suggestive signals for this group of families on chromosomes 11q25, 15q26 and 17q12. However, the strongest result of all was found when we grouped families by average age at diagnosis of prostate cancer. Among families with an average age at diagnosis of less than 65 years, there was a significant signal at chromosome 15q13-q14. This finding reinforces one of the overall findings from the genome-wide SNP scan and suggests that the long arm of chromosome 15 is a region of particular interest that requires further investigation.

Indeed, as you may remember, we are part of an international research collaboration, called the International Consortium for Prostate Cancer Genetics (ICPCG). Along with the 13 other groups in the ICPCG, we contributed data from members of PROGRESS families who had given consent to be included in ICPCG analyses. In the past year, these families were included in a genome-wide included in a genome-wide SNP scan of over 700 families. Analyses of this large dataset are still ongoing and we are hoping that a paper will be submitted for publication by the end of this year. By combining relevant data from this larger SNP scan with our own SNP scan data we intend to try and further narrow down
the critical region of interest on chromosome 15q. As always we will keep you up-to-date on our findings once they become available.

Co-occurrence of Other Cancers

One way of grouping prostate cancer families into smaller, more similar groups is by the presence of another type of cancer. We are continuing to look at subsets of families who also have a history of another type of cancer that has been shown to co-occur in some prostate cancer families, including colon, brain, pancreas, breast, ovarian and kidney cancers. This approach aims to identify the location of genes that may be giving rise to the development of prostate cancer, as well as the other cancer in those families. This is known as a “pleiotropic” effect where the same underlying gene mutation (a change in the DNA sequence) may cause cancers to develop in different organ sites within members of the same family.

We recently conducted a genome-wide SNP linkage analysis of 96 prostate-colon cancer families from PROGRESS. In the main analysis we obtained suggestive linkage peaks on chromosomes 11q25, 15q11-14 and 18q21. All of these regions have also been identified in previous linkage studies of either prostate cancer or colon cancer. When only families with at least two or more members with colon cancer were analyzed, a total of 27 families, the signal on chromosome 15q11-14 became even stronger. Having multiple cases of another type of cancer therefore appears to make the degree of similarity among prostate cancer families even greater, leading to more robust results. A paper describing the results of the analyses of prostate-colon cancer families has been submitted for publication. This result also supports our finding on the long arm of chromosome 15 in our genome-wide SNP scan described above. One of our ongoing aims is to look at this region in more detail to see if it contains a genetic mutation that may be responsible for causing not only prostate cancer, but also colon cancer in some families.

We are also planning to conduct similar analyses of PROGRESS families whose members reported other primary cancers such as breast, ovarian and kidney cancers, using the highly informative data from the genome-wide SNP linkage scan (see above). We may be contacting some of you for more details as part of the initial effort of identifying and confirming the families who reported other cancers in their baseline or follow-up surveys. As always your cooperation is greatly appreciated.

Interest in Genetic Testing Update

Few studies have examined the issue of what men with a strong family history of prostate cancer know about personal levels of genetic risk for this disease or their interest in genetic testing. You may recall that in our first follow-up survey, both men with prostate cancer and their male relatives who had not been diagnosed with prostate cancer were asked questions about how much they had heard about genetic testing for prostate cancer, their perceived level of risk, and whether they would be interested in taking a genetic test for prostate cancer if such a test were available. These results were recently published (Harris et al., Genetics in Medicine 2009; 11: 344).

Based on the responses of over 900 PROGRESS family members, the results showed that a larger percentage of men without prostate cancer than men with prostate cancer (56% versus 45%) would “definitely” be interested in taking a genetic test for prostate cancer risk, if and when 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%). This combination of a
greater level of interest yet lower rates of familiarity with genetic testing among men who have not been diagnosed with prostate cancer highlights the need for increased educational efforts.

There was also a clear relationship between age and interest in genetic testing, with men over the age of 65 years less likely to be interested in genetic testing compared to younger men. This may be due to the fact that younger men are more likely to have sons who have not yet been diagnosed with prostate cancer making them more concerned about any future benefits from a potential genetic test. When asked about personal risk, nearly half of the men without prostate cancer (47%) thought that they had a higher than average risk of developing prostate cancer. These findings suggest that male relatives who have not been diagnosed with prostate cancer may be insufficiently informed about their real level of risk.

**Other News**

**PSA Screening and Prostate Cancer Mortality**

The results from two large randomized trials looking at the effect of annual prostate-specific antigen (PSA) screening on prostate cancer mortality rates were published earlier this year. The benefits versus the risks of PSA screening are largely unknown, yet the level of PSA screening in the US has increased dramatically since 1988.

The first trial was part of the Prostate, Lung, Colorectal and Ovarian (PLCO) Screening Trial conducted at 10 study centers in the US from 1993 through 2001 (Andriole et al., N Engl J Med 2009; 360: 1797). Over 76,000 men were randomly assigned either to a “screening” group, which received annual PSA tests for 6 years and digital rectal exams (DRE) for 4 years, or to a “usual care” control group. The rate for PSA testing in the screening group was 85% compared to 40% in the usual care group, which went up to 52% by the sixth year of the study. After seven years of follow-up the number of prostate cancers diagnosed was 22% higher in the screening group than in the control group, 116 cases versus 95 cases. However, during the same follow-up period there was no significant difference in the mortality rate from prostate cancer, with very low rates in both groups (50 deaths in the screening group versus 44 deaths in the control group).

The European Randomized Study of Screening for Prostate Cancer was also a multi-center trial conducted in seven European countries (Schröder et al., N Engl J Med 2009; 360: 1320). The primary aim of the study was to see whether deaths from prostate cancer could be reduced by 25% as a result of PSA screening. A group of over 162,000 men aged between 55-69 years of age were randomly assigned either to a group that was offered PSA screening an average of once every 4 years, or to a control group that did not receive PSA screening; 82% of men in the screening group accepted at least one offer of PSA screening and after nine years of follow-up, the rate of prostate cancer diagnoses was 8% in the screened group compared to 5% in the control group.

As in the US study, prostate cancer-specific mortality was low, 214 deaths in the screened group versus 326 deaths in the control group. This difference represents a 20% reduction in prostate cancer mortality in the screening group, close to the proposed 25% reduction in deaths from prostate cancer. However, in spite of this apparent difference, these results raised the issue of over-diagnosis. In order to prevent one death from prostate cancer, 1,410 men would have to be screened and 48 men would have to be treated. Thus, although PSA screening reduced the rate of prostate cancer deaths in this trial, it also resulted in many more men being diagnosed and treated than needed to be. These findings strengthen the need for continued research into prostate cancer biomarkers that are superior to PSA for detecting clinically significant prostate cancer.
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If you would like copies of our earlier newsletters or for additional information regarding the study, including a list of published study-related articles, please visit our website: http://www.fhcrc.org/phs/progress_study/index.html.

If you would like a copy of any of our recent or upcoming papers, or if you have any questions, or would like to report any family updates or changes in your current address or phone information, please feel free to contact us.