Greetings

Welcome to the 20th edition of The Progress Report, a newsletter for participants in the Prostate Cancer Genetic Research Study or PROGRESS. This is an exciting and proud milestone for the study and of course for study participants, many of whom have been involved in this research for over a decade. Some of you joined back in 1995 when the project was first launched. We really appreciate your ongoing participation and help with the study over this extended period of time. The goal of the newsletter is to keep in touch with you and to provide updates on our latest research findings. We hope you will find it both informative and helpful. If you have any questions about this newsletter or your participation, please call us toll-free at 1-800-777-3035 or email us at progress@fhcrc.org. We are always pleased to hear from you.

Family Study Updates

Whole-exome sequencing pilot study

As we outlined in the last edition of The Progress Report, whole-exome sequencing (WES) involves examining the coding regions of genes known as exons, which provide the instructions for creating proteins. Exons make up only about 1% of the human genome, but genetic changes or mutations in these regions can lead to changes in the amount or structure of an encoded protein, which may have direct biological implications in terms of increasing an individual’s risk of developing cancer or other diseases.

For our WES pilot project we selected 91 members from 19 PROGRESS families with the highest number of men diagnosed with a more clinically advanced form of the disease (e.g., a tumor Gleason score of 8 or above) and/or the highest number of men with an earlier age at diagnosis of prostate cancer (PCa). By studying families with evidence of more aggressive or early onset disease, we hoped to discover some of the genes with mutations responsible for increasing risk for hereditary prostate cancer (HPC). To date, many chromosomal regions, candidate genes, and genetic variants for HPC have been identified in both family-based linkage and genome-wide association studies, but confirming these results and establishing which genetic alterations in specific genes are actually responsible for causing the disease has proved difficult.
Our initial WES findings highlighted 130 potential genetic variants or changes of interest, which we then set out to replicate in a larger set of 270 PROGRESS families. These analyses showed that two variants in a gene on the short arm of chromosome 6 were significantly more frequent in men with PCa. Ten of 12 men with the disease in 2 of the original 19 WES families carried one or both of these genetic variants, and several men with the disease in 9 additional PROGRESS families were carriers. Importantly, none of the men in these 11 families who did not have PCa carried either variant. We then genotyped over 2,400 study participants from two large population-based case-control studies conducted in Washington State. The first study enrolled men diagnosed with PCa between 1993-1996, or between 2002-2005 in the second study, and a similar number of men without PCa were enrolled as controls during each time period. The results showed that double the number of men with PCa (2%) had one or both of the genetic variants on chromosome 6 compared to age-matched control subjects without PCa (0.9%).

To summarize, as well as being associated with prostate cancer in HPC families these two genetic mutations are significantly associated with an increased risk of developing PCa in the general population. However, these mutations are relatively rare (less than 1% of men without PCa from the general population carried at least one of the genetic changes) and not all the men with PCa who were genotyped in the 11 PROGRESS families of interest carried either variant. This is an exciting initial finding using whole-exome sequencing data, but further studies of larger sets of HPC families are going to be required to see if these initial findings are confirmed. Our group is currently fine-mapping the entire region on chromosome 6 that encompasses the gene of interest, not just the exons, to see if other genetic alterations in this gene region are also more common among men with PCa. We have submitted a paper describing our results, which we hope will be published shortly. As always we will keep you updated on any further results and let you know when these findings become available.

The HOXB13 gene

Also in the past year, a rare variant in the HOXB13 gene on chromosome 17 was discovered in a study of 94 HPC families from Johns Hopkins and the University of Michigan (Ewing et al., N Engl J Med 2012; 366: 141-9). Initially, the man with the youngest age at diagnosis of PCa from each family was included in the study, which involved sequencing of exons in 202 candidate genes across a region of interest on chromosome 17. Four men with PCa were found to be carrying the same genetic variant in HOXB13, known as G84E, all of whom were diagnosed with PCa at age 55 or younger. The remaining members of these 4 families, who had DNA samples available, were then genotyped to see if they also carried this variant. All 18 family members with PCa were carriers compared to only one of the men without PCa, providing initial support for G84E as a causative genetic mutation in approximately 4% of the HPC families evaluated.

As a follow-up effort, the International Consortium for Prostate Cancer Genetics (ICPCG), to which we belong, looked for evidence of the G84E mutation in a combined group of 2,443 HPC families from around the world. The genetic variant was present in 194 men with PCa and 89 men without PCa from 112 HPC families (4.6% of the HPC families tested). Although the genetic variant was also found in men without a diagnosis of PCa, a significantly higher number of men with PCa were carriers. This finding from the ICPCG confirms the HOXB13 mutation as being associated with risk of developing prostate cancer in approximately 4-5% of HPC families of European descent.
Other Prostate Cancer Research Findings

Fried foods and prostate cancer risk

Our group recently reported findings utilizing survey data on dietary intake collected from the study participants in Dr. Stanford’s two large population-based case-control studies described above. We found that men who ate deep fried foods, including French fries, fried chicken, fried fish and doughnuts, at least once a week had a 30-37% higher risk of developing PCa compared to men who ate these foods less than once a month.

Possible explanations for the findings are that potentially carcinogenic compounds are released when foods such as meat and carbohydrates are cooked at high temperatures. In addition, the cooking oil itself generates potentially toxic compounds when heated which are absorbed by the food being fried in it, and which increase with reuse and length of frying time. Another possible explanation is that these foods are often consumed outside of the home in fast food restaurants, where the food may also contain high levels of other potentially harmful ingredients such as salt, sugar and chemical additives. (Stott-Miller et al., Prostate 2013; (EPub ahead of print))

Coffee and tea intake and prostate cancer risk and outcomes

In analyses that used the same dietary survey data from one of our two completed population-based studies (approximately 900 men with a diagnosis of PCa and 850 control subjects without PCa), we observed interesting results relating to coffee and tea consumption and PCa:

• Men who reported drinking at least 2 cups of tea per day had a 37% reduced risk of developing PCa, compared to men who drank less than one cup of tea per week. This finding is supported by results from similar studies carried out in the Netherlands and Canada. The most likely explanation is that tea (both green and black teas) contains chemical compounds called polyphenols, which have anti-cancer properties such as anti-oxidation and anti-inflammation effects.

• Coffee consumption did not affect risk of developing PCa, but among men with PCa those who reported drinking at least 4 cups of coffee per day had a 59% reduced risk of their cancer recurring or progressing, compared to men who drank less than 1 cup per week. Our definition of recurrence/progression included men who died from PCa, developed metastasis, received secondary treatment for PCa, or had a rising PSA. Coffee contains several chemical compounds that may be responsible for this finding, including caffeine, which has been shown to delay metastasis and to have an anti-proliferative effect on cancer cells. (Geybels et al., Cancer Causes Control 2013; 24(5): 941-8)

We thought you would be interested in these diet-related findings. If you would like a paper copy please let us know.

Health Status Updates

In order to keep family and clinical records up to date and to maximize the accuracy and power of study analyses, it is very important that you keep us informed about any changes in your current health status. We would particularly like to know of any new diagnosis of prostate cancer or any other type of cancer in your family. Such information would be very useful for the continuing efforts of the study to try and identify the genetic mutations that contribute to development of hereditary prostate cancer. You can reach us via any of the methods listed in the “Contact Information” section below. Your help is always very much appreciated and we would like to thank you for your ongoing participation in the PROGRESS study.
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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: https://www.fhcrc.org/en/labs/phs/projects/progress-study.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.