PCPT P01 – Biology of the Prostate Cancer Prevention Trial (PCPT)

In the program concept phase, which began in 1998, an executive scientific review committee received and evaluated proposals solicited from a widely circulated RFA from investigators across the US and Canada for studies of genetic factors and other variables that affect an individual's risk of prostate cancer and the effect of the intervention with finasteride. Proposals were evaluated for their scientific merit, relevance of the project to the original PCPT study hypotheses, judicious use of biospecimens from this unique population, and the previous scientific accomplishment and experience of the investigators. The proposals need not have been related to the planned secondary objectives of the PCPT and other than hypotheses related to the grade of carcinoma and the role of diet they were not. Because of a numerous common themes across the accepted proposals, they were assembled into a program project (P01) application rather than released for submission as independent R01 applications. Proposals that were not accepted as part of the P01 still had the potential to move forward but would need to do so under a separate funding source (R01). Another year was spent refining the projects, identifying laboratoriess, performing pilot studies, and assembling the final P01 application that was submitted to the National Cancer Institute. Ultimately, the application received a favorable score, and the notice of funding was received in December 2004. This Program Project is now complete. A paper describing the transition of the PCPT clinical trial into a resource for translational medicine was published in Cancer Prevention Research (Cancer Prev Res; 3(12); 523-33)

Risk-Modeling Program Theme

The theme unifying the five key areas (or "studies") within this P01 is the genetic, metabolic and environmental factors associated with the risks of prostate cancer overall and high grade prostate cancer specifically; and the effects of these factors on the efficacy of finasteride as a cancer preventive agent. The P01 also includes studies to better understand the mechanisms underlying these risk factor associations. Two major elements of this theme are (1) the study of genetic polymorphisms to identify molecular prostate cancer risk factors, from which we expect to determine pharmacogenetic profiles of men most likely to benefit from finasteride; and (2) the study of somatic mutations to discover the mechanisms underlying the increased risk of high grade prostate cancer associated with finasteride use. Identifying factors or mutation which can distinguish aggressive or high grade tumors in an era where there is concern about the overdection of prostate cancer will prove beneficial, and while the concern over the increase of high grade disease in the finasteride arm has been tempered by subsequent research since the inception of this project, there is still interest in finding biologic results which support the detection bias finding.

Five Inter-Related Research Projects

Project 1 ("Androgen Metabolism in the PCPT")

This project directly examines the mechanisms underlying the primary hypothesis of the PCPT: whether inhibiting conversion of T to DHT, the primary steroid driving cell growth in the prostate, reduces the risk of prostate cancer. The overall Project 1 hypothesis is that genetic variations in the steroid metabolic genes and variations in hormone levels are associated with both prostate cancer risk and the efficacy of finasteride in preventing prostate cancer. Project 1 exemplifies the new field of "preventive pharmacogenetics," or the study of genetic factors that account for inter-individual

variability in response to a preventive agent. Another hypothesis of Project 1 is that long-term finasteride exposure, which results in a DHT-starved environment, selects for the growth of high grade prostate cancer cells. This is being investigated by determining rates of somatic mutations in high grade lesions to see if they differ between the finasteride and placebo arms. Project 1 also examines whether rates of specific somatic mutations differ across normal and neoplastic prostate tissues. Finally, this project measures post-baseline finasteride concentrations in the intervention arm using LC/MS. These data will provide insight into the adherence to the intervention and will be used in secondary analyses.

Project 2 ("Diet and Diet-Related Factors in the PCPT")

This project improves the understanding of (1) the associations of diet and diet-related factors such as obesity with prostate cancer risk and (2) the role favorable dietary patterns or use of dietary supplements may play in enhancing the efficacy of finasteride as a prostate cancer preventive agent. This project investigates dietary factors that affect steroid hormone and insulin-like growth factor (IGF) metabolism, such as obesity, glycemic index and dairy foods, as well as dietary factors that affect oxidative load through pro-oxidant, antioxidant and anti-inflammatory effects, such as lycopene, ώ-3 fatty acids, glucosinolates and tocopherols.

Project 3 ("Insulin-like Growth Factor Axis and Insulin Resistance in the PCPT")

This project provides information regarding the hypothesis that circulating levels of IGF-1, IGF-2, IGFBP3 (total and intact), IGFBP2, leptin and C-peptide, considered jointly as well as individually, are related to prostate cancer risk. The metabolic factors tested in Project 3 are IGFs, peptide growth factors known to play important roles in regulating cell proliferation, differentiation and death. Suggestive evidence from human population studies show that IGF-1 and insulin resistance increase risk for prostate cancer, while IGF-BP3 decreases risk. Project 3 is also assessing whether IGFs and IGF signaling in prostate tissue is related to measures of cell renewal dynamics. If IGF-insulin receptor signaling is found to be associated with aggressive prostate cancer, one model to account for the PCPT results regarding increased risk of high grade lesions in the finasteride arm is that the reduction of androgen receptor signaling associated with finasteride use results in selective pressure for neoplasms that are, at least in part, stimulated by growth factors other than androgens.

Project 4 ("Genotypic and Phenotypic Studies of Inflammation in the PCPT")

This project tests the hypothesis that inflammation and focal atrophy, possible environmental contributors (serum antibodies against infectious agents), and genetics (polymorphisms in genes involved in the innate and adaptive immune response) influence prostate cancer risk. Given that inflammation is a clear target for intervention, we anticipate that this work will have important implications for prostate cancer prevention. This study is the first to systematically examine focal atrophy lesions in men with and without prostate cancer. Prostate tissue is not typically available for middle-aged men who do not have an indication for biopsy, such as an elevated serum PSA. For this reason, it is unknown how the presence and extent inflammation correlate with the occurrence of prostate cancer. This study is the first to evaluate this association in a large sample of men with a known negative prostate cancer status.

Project 5 ("Oxidative Damage and DNA Repair in the PCPT")

This project evaluates hypotheses related to oxidative stress and DNA repair and prostate carcinogenesis. This study investigates whether variations in genes encoding enzymes that generate reactive oxygen species (ROS), neutralize ROS, and repair DNA damage are associated with risk of prostate cancer and high grade cancer. Serum levels of oxidized proteins, a biomarker of oxidative damage, are measured to determine if baseline levels of oxidative stress are elevated in those who go on to develop cancer and if so, whether the association is modified by finasteride.