**SESSION 3**

## Preclinical Models with Relevance to Clinical Cancer Prevention

# S5. Preclinical Models Relevant to Diet, Exercise and Cancer Risk

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International variation in prostate cancer (PCa) mortality and the migration studies suggest that lifestyle factors play an important role in the development of this disease. The lifestyle factors that have received the most attention are dietary fat and physical inactivity. We developed a bioassay to study the effect of serum changes on prostate cancer cells grown in culture and tested the hypothesis that serum changes with a very-low-fat diet and exercise program would slow the growth of PCa cells. Studies were conducted with LNCaP and LAPC-4, androgen-dependent cell lines and PC-3 an androgen-independent cell line. Results showed that LNCaP cell growth was reduced by 30% after 11 days of diet and exercise and with long term compliance LNCaP growth was reduced by an additional 15%. Similar results were observed with the LAPC-4 cells but no effect was observed with the PC-3 cell line. Serum insulin, estradiol and free testosterone were all reduced following the intervention but when they were added back to the diet and exercise serum they accounted for only 50% of the reduction in LNCaP cell growth. We next hypothesized that the IGF axis might be involved. Serum IGF-I was reduced and IGFBP-1 increased following diet and exercise and there was a substantial increase in apoptosis in the LNCaP cells. When we added IGF-I back to the diet and exercise serum we eliminated the reduction in LNCaP growth as well as the increase in apoptosis. When we added IGFBP-1 to the control serum, LNCaP cell growth was reduced and apoptosis increased. With exercise alone, serum changes were significant but not as great as with diet and exercise. There was reduced LNCaP growth with increased apoptosis but less than with diet and exercise. We hypothesized that the decrease in LNCaP cell growth and the increase in apoptosis might involve stabolization of p53 protein, known to arrest the cell cycle and induce apoptosis. p53 protein was doubled in the exercise-serum-stimulated cells compared to control and p21, a downstream effector of p53, was also increased. If the observations in the cell cultures could occur in vivo, then a low-fat diet and exercise should be of value for treating PCa. Men on "watchful waiting" were randomized to control or diet and exercise intervention. Cell culture studies showed results similar to healthy men. After one year 6 of 43 men in the control group have gone on to conventional treatment compared to zero of 41 in the diet and exercise group.