S6. Models of Hormonal Manipulation as a Strategy for Cancer Risk Reduction for Specific Classes of At-Risk Individuals

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Major prevention trials such as the finasteride prostate cancer prevention trial and the various SERM breast cancer prevention trials have shown efficacy, but it may be simplistic to assume that all individuals within a population at risk for neoplasia will derive the same degree of benefit from a particular chemoprevention intervention. Identification of individuals for whom a specific intervention may be particularly effective (or useless) could result in "individualization" of prevention strategies, and would be a major step forward in preventative oncology. While there has been progress towards the goal of predictive testing to estimate future risk of cancer in individuals, predictive testing to determine if a particular hormonal prevention intervention would be likely to reduce risk for a particular individual is in its infancy. In standard chemoprevention models, efficacies of a number of candidate agents are compared by examining their effects on cancer incidence in a standardized genetic predisposition or chemical carcinogeneis model. To study host characteristics that predict chemoprevention efficacy, the host is varied and the prevention intervention is held constant. Recently, Medina and Kittrell (Cancer Res, 2003) used this approach to show that p53 function within at-risk tissue is necessary for the hormonal changes of early pregnancy to reduce mammary carcinogenesis. We tested the hypothesis that the efficacy of tamoxifen as a chemopreventative would not vary between strains of mice that differed in their circulating IGF-I level. All mice were exposed to DMBA starting at 6 weeks, and to tamoxifen or vehicle starting at 11 weeks, and were scored for tumor incidence at 28 weeks. Mice with higher levels of IGF-I showed a modestly higher incidence of cancer following DMBA exposure. The reduction in tumor incidence achieved by tamoxifen was greater in low IGF-I mice (84% reduction) than high IGF-I mice (30% reduction ($p=0.05$). This early result suggests that efficacy of of tamoxifen as a chemopreventative may vary with host circulating IGF-I concentration. This line of investigation should be accelerated by translational research: prospective collection of DNA, serum, and possibly tissue samples from participants in prevention trials will allow comparisons between those subjects for whom the intervention failed to prevent cancer and those for whom it was apparently successful.