

Presented at- Cancer Risk Prediction Models: A Workshop on Development, Evaluation, and Application, Washington, DC, May 20-21, 2004.

Title: Breast Cancer Risk Associated with Common Weakly Penetrant Polymorphisms May Be Strongly Influenced by Patient Age

David Ralph¹, Venkateswarlu Kondragunta¹, Dominique Lalo¹, Sharmila Manjeshwar^{1,2}, Christopher Aston^{1,3}, Ena Bromley⁴, Craig Shimasaki¹, John Mulvihill⁵ and Eldon Jupe^{1,2,6,7}

¹InterGenetics Incorporated, Oklahoma City, OK; ²Immunobiology and Cancer Program, ³Arthritis and Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK; ⁴BioStat Solutions LLC, Mount Airy, MD 21771, ⁵Departments of Pediatrics, ⁶Surgery and ⁷Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK.

The risk of developing sporadic breast cancer is likely to involve interactions between many common but weakly penetrant genetic variants and numerous environmental and/or personal history factors. Our goal is to construct a comprehensive breast cancer risk model with both genetic and environmental/personal history measures to predict a woman's age specific risk of developing breast cancer in the absence of highly penetrant familial cancer predisposition syndromes. Towards this end, we are engaged in a case/control associative study which currently has enrolled over 7400 participants. We report on the analysis of common SNPs in a subset of the study comprised of 3742 Caucasian women of which 1286 have been diagnosed with breast cancer (cases) and 2456 have never been diagnosed with any cancer (controls). Fifty-nine candidate SNPs were selected based on their alteration of functional activities in gene products likely to be important in breast tumorigenesis. Most candidate SNPs changed the amino acid sequences of their respective proteins. Genotypes were determined by multiplex allele specific primer extension (ASPE) using the Luminex 100 flow cytometer. The χ^2 test was used for categorical variables to test the hypothesis that the distribution of genotype frequencies was the same for cases and controls. The associations between various SNP genotypes and breast cancer were expressed in terms of odds ratios (ORs) with corresponding p-values and confidence intervals calculated. Hardy-Weinberg Equilibrium (HWE) was tested by a goodness-of-fit χ^2 test to compare observed genotype frequencies within the case-control groups to the expected genotype frequencies. Exact test was used to test Linkage Disequilibrium between SNPs of a given gene locus. In overall analyses, genotypes from eight polymorphisms were associated with breast cancer risk at a $p \leq 0.05$. Furthermore, ORs were very modest in the range of 0.8-1.2. We divided the study participants into three subgroups based on their age following the hypothesis that genetic determinants of risk may be more influential in younger women. These age groups were ≤ 44 , 45-54 and ≥ 55 . Strikingly, for many of the genes involved in hormone metabolism, the risks associated with several SNPs partitioned into only one age group. In the youngest group, the G allele of the *COMT* polymorphism at Val(158/108)Met was associated with increased risk (G/*, OR = 1.5, $p = 0.004$) and carrying the C allele in codon 10 of the *ER α* gene was associated with decreased risk (C/*, OR = 0.8, $p = 0.03$; C/C, OR = 0.7, $p = 0.2$). Carriers of the G allele (G/*) of the *SULT1A1* polymorphism Arg(213)His exhibited decreased risk only in the youngest age group (OR = 0.8, $p = 0.001$; G/A, OR = 0.6, $p = 0.001$). In the extreme case, the alternative allele (A) of the *SULT1A1* polymorphism was associated with increased risk in the women over 55 (A/*, OR = 1.3, $p = 0.02$). An example of a polymorphism exclusive to the group ≥ 55 is the G allele of the *CYP1B1* polymorphism at R48G with the GG homozygote which is associated with increased risk (OR = 1.5, $p = 0.03$). We conclude that patient age is an important determinant of the breast cancer risks associated with some weakly penetrant polymorphisms.