

Presented at the 2008 Annual Meeting of the American Association for Cancer Research in San Diego, CA.

Session Title: Genetic Epidemiology 1: Breast and Ovarian Cancer, Presentation #1916 on Monday, April 14, 2008.

Presentation Title: Influence of single nucleotide polymorphisms on cytomorphology of benign breast epithelial cells acquired by random periareolar fine needle aspiration

Bruce F. Kimler¹, Carol J. Fabian¹, Jennifer Roweton¹, Carola M. Zalles², Thomas W. Pugh³, Sharmila Manjeshwar³, Bobby A. Gramling³, Daniele C. Defreese³, Laura Blaylock³, Eldon R. Jupe³

¹University of Kansas Medical Center, Kansas City, KS; ²Yale University, New Haven, CT; ³InterGenetics Incorporated, Oklahoma City, OK.

Introduction: The primary purpose of this study was to assess potential associations between common functional polymorphisms in candidate genes and benign breast tissue cytomorphology in postmenopausal women at increased risk for breast cancer. **Methods:** Breast tissue was sampled by random periareolar fine needle aspiration (RPFNA) and the epithelial cells characterized as to whether they exhibited hyperplasia with atypia (a known major risk factor for development of breast cancer). Women were categorized as taking hormone replacement therapy (HRT) at the time of aspiration and/or taking no HRT at the time of aspiration. Buccal cells (collected via an oral rinse with mouthwash) were obtained from all participants. DNA was isolated from these cells for assessment of 117 common single nucleotide polymorphisms (SNPs) by high throughput, PCR-ASPE, microbead-based SNP genotyping on the Luminex100 platform. Candidate SNPs included those likely to be associated with risk for breast cancer because of their involvement in steroid hormone metabolism and receptor function, cell cycle control, DNA repair, and/or carcinogen metabolism. Logistic regression analysis was conducted to identify specific SNPs that were associated with 1) atypia while on HRT; 2) atypia while not on HRT; and/or 3) atypia while on HRT when it was not observed in the absence of HRT. **Results:** A total of 212 women were genotyped and had at least one RPFNA performed. Of these, 87 were aspirated only while on HRT, 75 were aspirated only while off HRT, and 44 were aspirated both on and off HRT. The frequency of atypia in the 212 women was higher in women homozygous for the G/G genotype of Transferrin Receptor (S142G) (59%) than women with the G/A (42%) or A/A (30%) genotype ($p=0.01$). Evidence of atypia in the 131 women aspirated while on HRT was more prevalent in women with an A/C genotype in the promoter region of E-Cadherin ($p=0.01$). Evidence of atypia in the 119 women aspirated while off HRT was least prevalent in women with the C/T genotype for Kallikrein 2 (R226W) ($p=0.006$); but women homozygous for C/C were more likely to exhibit atypia if they also were heterozygous (C/T) in the coding region for Integrin B3 ($p=0.039$). Finally, for the 44 women aspirated both on and off HRT, women without atypia when off HRT were more likely to exhibit atypia on HRT if their genotype for XRCC2 (R188H) was G/A (67%) vs. G/G (33%) ($p=0.049$); or if they had the G/A or G/G genotype for Pinin (S671G) (89%) vs. the A/A genotype (32%) ($p=0.006$). **Conclusions:** These preliminary results indicate that genetic background may influence the development of abnormal cytomorphology associated with breast cancer risk. Specific SNPs may predict which high risk post-menopausal women are more likely to exhibit atypia as a consequence of using hormone replacement therapy.