

Presented at the 32nd Annual San Antonio Breast Cancer Symposium, December 11, 2009

Abstract Number: 3057, Session 3: Risk, Epidemiology, and Prevention: Epidemiology – Genetic and Molecular (http://www.abstracts2view.com/sabcs09/view.php?nu=SABCS09L_1831&terms=)

Title: Breast Cancer Risk Assessment in the High Risk Marin County Population Using OncoVue® Compared to SNPs from Genome Wide Association Studies.

Kathie M. Dalessandri¹, Rei Miike¹, Margaret R. Wrensch¹, John K. Wiencke¹, Georgianna Farren², Daniele C. DeFreese³, Sharmila Manjeshwar³, Thomas W. Pugh³, Christopher C. Benz⁴, Eldon R. Jupe³

¹University of California San Francisco, San Francisco, CA; ²Zero Breast Cancer, San Rafael, CA;

³InterGenetics Incorporated, Oklahoma City, OK; ⁴Buck Institute for Age Research, Novato, CA.

Background: Models for accurate assessment of individualized risk of developing breast cancer are important for effectively guiding clinical decisions regarding early detection and prevention. Marin County (MC), California (located immediately north of San Francisco) has long been recognized as a population with high incidence rates of breast cancer. In a population-based case-control study conducted from 1997 to 1999 in MC, no classical epidemiological risk factors such as age at menarche, age at first live birth, number of first-degree relatives with breast cancer, and history/outcome of previous breast biopsies were associated with breast cancer risk. Thus, the widely used National Cancer Institute-Breast Cancer Risk Assessment Tool (BCRAT) or Gail Model is not an effective risk assessment tool for this population. Recently, we found that a new breast cancer risk assessment model (OncoVue) that integrates information from 22 single nucleotide polymorphisms (SNPs) and 5 personal risk factors effectively stratified risk in the MC population. Several genome wide association studies (GWAS) have also recently derived a consensus of seven independent candidate SNPs strongly associated with breast cancer risk that are not included in the OncoVue model. Here we have evaluated these SNPs from GWAS to determine their utility in risk estimation and stratification of the high risk MC population.

Materials and Methods: Study DNAs were genotyped for the following SNPs in seven genes: rs2981582 (FGFR2), rs3817198 (LSP1), rs889312 (MAP3K), rs4415084 (MRPS30), rs13281615 (POU5F1P1), rs13387042 (TNP1), and rs3803662 (TOX3, formerly TNRCR9). The analyses were performed on white women ages 30-69 and included 164 cases and 173 controls that were genotyped for all seven SNPs. Association of individual genotypes with breast cancer risk was evaluated by calculating odds ratios (ORs). Composite risk for each individual in the study was calculated by assigning risks from published studies for each genotype and multiplying them. The clinical utility of composite risk scores was evaluated by calculating positive likelihood ratios (PLR) as the proportion of patients with breast cancer with an elevated risk estimate divided by the proportion of disease-free individuals with an elevated risk estimate.

Results: Carriers of the rare allele for FGFR2, MAP3K, and TNP1 exhibited statistically significant associations with breast cancer risk. Over a range of risk levels, composite risk scores exhibited PLRs of approximately 1.0 but at the highest end of the risk spectrum a PLR of 2.3 indicates useful risk stratification. The women at this risk level represent <10% of the control population.

Conclusions: In the high risk MC population the seven GWAS SNPs stratify risk at the highest end of the risk. In contrast, overall OncoVue exhibits higher PLRs at high risk levels and may prove to be more clinically useful for directing prevention and screening decisions.