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Title: Genetics-based risk assessment models for sporadic breast cancer

David A. Ralph¹, Eldon R. Jupe¹, Venkateswarlu Kondragunta¹, Ena Bromley², Christopher E. Aston³, Dominique P. Lalo¹, Sharmila Manjeshwar¹, John J. Mulvihill⁴ and Craig D. Shimasaki¹.
¹InterGenetics, Oklahoma City, OK 73104; ²BioStat Solutions, Mount Airy, MD 21771; ³Arthritis and Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK 73104 and ⁴Department of Pediatrics, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104.

Background: For the majority of women, the genetic components of breast cancer risk cannot be attributed to familial predisposition syndromes involving mutations in single, highly penetrant genes, such as *BRCA1/2*. We hypothesized that weakly penetrant polymorphisms in many genes and gene-gene interactions, in conjunction with various personal history measures (PHMs), contribute to breast cancer risk. The combination of these genetic influences with certain PHMs in a logistic regression model may broadly stratify the age-specific risk of developing breast cancer. **Methods:** A case-control associative study of 5076 Caucasian women, 1812 breast cancer cases and 3264 cancer-free controls, was analyzed for 65 common polymorphisms in genes involved in hormone metabolism and signaling, DNA repair pathways, immune modulation, extracellular matrix, and cell cycle control. All polymorphisms were known to or likely to cause functional alterations and most resulted in non-synonymous amino acid substitutions. Genotyping was performed using allele-specific primer extension on the Luminex 100 flow cytometer. Overall analyses and stratification into likely pre-, peri- and post-menopausal age groups (30-44, 45-54 and ≥ 55 , respectively) were performed. Breast cancer risk associations were identified by χ^2 and logistic regression analyses and expressed as odds ratios (ORs). Genetic main effects and personal history measures were used to develop an age-specific risk model for women 30-44. **Results:** Overall, 14 polymorphisms (21%) displayed risk associations with $p \leq 0.05$. However, significant ORs were modest and ranged from 0.8 to 1.3. Partitioning the study into the three age groups revealed stronger associations that were frequently confined to only one age group. In total, 35 polymorphisms (54%) were associated with risk in at least one age group. The ORs observed in the age-stratified analysis varied over a broader range (0.7-1.6) than was observed in the overall analyses and generally were more significant with p values ranging down to 0.001. Some polymorphisms displayed a risk pattern in which one genotype was associated with increased risk in the youngest age group while the disparate genotype was associated with increased risk in the oldest age group. Risk associated with polymorphisms in steroid hormone metabolism and DNA repair pathways tended to partition into the youngest age group. Information from 17 gene polymorphisms and three PHMs were combined in a logistic regression based model of breast cancer risk in women ages 30-44. This model stratified risk over an 11-fold range (0.27-3.0) between the 5% of women at highest risk and the 5% at lowest risk and a 57-fold range at the extremes. **Discussion:** Breast cancer risk is impacted by common polymorphisms in genes involved in physiologic pathways involved in the development of breast carcinoma. Individually, they were weakly penetrant but when combined a prototype breast cancer risk model was created that broadly stratified risk in women ages 30-44. Such models provide a means to estimate a woman's age-specific and lifetime risk of being diagnosed with breast cancer with high discriminatory accuracy and could contribute to improved clinical management of breast cancer by directing women towards the most risk appropriate diagnostic and/or chemopreventative protocols.