

**Title.** Breast Cancer Risk Associated With Common Weakly Penetrant Polymorphisms May Be Strongly Influenced by Patient Age

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The risk of developing sporadic breast cancer is likely to involve interactions among 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 that utilizes both genetic and environmental/personal history information to predict women'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 more than 7,400 participants. We report on the analysis of common SNPs in a subset of the study comprised of 3,742 Caucasian women of whom 1,286 have been diagnosed with breast cancer (cases) and 2,456 have never been diagnosed with any cancer (controls).

Fifty-nine candidate SNPs were selected based on their likely alteration of enzymatic activities of genes thought to be important for breast tumorigenesis. Most candidate SNPs alter the amino acid sequences of their respective proteins. SNP genotypes were determined by multiplex allele-specific primer extension (ASPE) using the Luminex 100 flow cytometer. An  $\chi^2$  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 genotypes of the various SNPs and breast cancer were expressed in terms of odds ratios (ORs) and p-values, and its confidence intervals were calculated. Hardy-Weinberg Equilibrium (HWE) was tested by a goodness-of-fit  $\chi^2$  test to compare observed genotype frequencies within the case-control groups to the expected genotype frequencies. Exact testing was used to test Linkage Disequilibrium between SNPs of a given gene locus.

When the entire study was taken into consideration, only eight polymorphisms displayed genotypes that were associated with breast cancer risk at a  $p \leq 0.05$ . Furthermore, ORs were very modest, in the range of 1.15 to 1.3.

We divided the study participants into three subgroups based on age, following the hypothesis that genetic determinants of risk may be more influential in younger women. These age groups were <45, 45–54, and  $\geq 55$ . Strikingly, for several 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 an OR of 1.5 ( $p=0.004$ ). Similarly, the G allele of the SULT1A1 polymorphism Arg(213)His was associated with an OR of 1.5 ( $p=0.001$ ) as was the C>T polymorphism in codon 10 of the ER $\alpha$  gene (OR=1.5;  $p=0.017$ ). None of these polymorphisms was associated with risk in other age groups. In the extreme case, the alternative (A) allele of the SULT1A1 polymorphism was associated with risk in the women over 55 (OR=1.3;  $p=0.02$ ). The G allele of the Cyp1B1 polymorphism at R48G followed a similar trend with the GG homozygote being associated with risk—but only in the oldest age group (OR=1.5,  $p=0.03$ ). We conclude that patient age is an important determinant of the risks associated with some weakly penetrant polymorphisms.