Abstract category: CL02 Pediatric Cancer – Clinical Investigations

Abstract subclassification: Survivorship Research

Title: Genome-wide association study identifies two susceptibility loci that modify radiation-related risk for breast cancer after childhood cancer: A report from the Childhood Cancer Survivor Study and St. Jude Lifetime Cohort

Short title: GWAS of second breast cancer

Background: Childhood cancer survivors treated with chest radiotherapy have substantially elevated risk for developing breast cancer. Although numerous breast cancer susceptibility variants have been established, genetic predisposition for breast cancer after childhood cancer remains poorly understood.

Methods: We conducted the first genome-wide association study of subsequent breast cancer in female childhood cancer survivors within two large-scale cohorts with detailed treatment data and systematic, long-term follow-up: the Childhood Cancer Survivor Study [CCSS; 178 breast cancer cases, 2200 controls (survivors without subsequent neoplasm) of European descent] and the St. Jude Lifetime Cohort (SJLIFE; 29 cases, 574 controls). Genotyping on the Illumina HumanOmni5MExome (CCSS) or Affymetrix 6.0 (SJLIFE) array and imputation based on the 1000 Genomes Project yielded >16 million high quality genotyped or imputed variants available in both studies. Assuming an additive genetic model, we used multivariate Cox regression to quantify the effect of each variant in the overall population and stratified by receipt of ≥10 Gray (Gy) or <10 Gy radiation exposure to the chest.

Results: We identified two loci associated with breast cancer risk among children who received ≥10 Gy radiation to the chest (131 cases, 493 controls): one at 1q41 [rs4342822, risk allele frequency (RAF)=0.46 in controls, pooled per allele hazard ratio (HR)=1.94, 95% confidence interval (CI)=1.50-2.51, $P_{exact}=1.20\times10^{-8}$] and another at 11q23 (rs74949440, RAF=0.02 in controls, HR=3.71, 95%CI=2.18-6.32, $P_{exact}=2.00\times10^{-9}$). Neither locus was associated with breast cancer risk among children who received <10 Gy radiation to the chest (69 cases, 2144 controls; rs4342822: HR=1.03, 95%CI=0.75-1.44; rs74949440: HR=1.21, 0.41-3.54). Results were consistent in the two studies, and the associations did not appear to be related to type of first primary childhood cancer. Both loci fall in or near biologically plausible candidate genes: the variant rs4342822 lies near *PROX1*, which is amplified in >10% of breast cancers in The Cancer Genome Atlas data. The variant rs74949440 is intronic to *TAGLN*, whose expression levels have been associated with breast cancer prognosis and altered cell death resistance following irradiation in human carcinoma cell lines.

Conclusion: These findings represent the first evidence outside of identified high-risk cancer susceptibility genes that certain individuals are genetically predisposed to developing breast cancer after radiotherapy and suggest that radiation exposure may interact with germline genetics to modify breast cancer risk.