Type 2 Diabetes Susceptibility Variants Contribute to Breast Cancer Risk

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Type 2 diabetes mellitus (T2DM) is a known risk factor for breast cancer (BC), but whether the conditions share a common genetic etiology remains to be elucidated. Analyses to date have focused mainly on T2DM GWAs-identified intronic or intergenic variants. Recently, exome analysis in ~100,000 individuals detected 21 coding variants predisposing to T2DM. We performed whole exome sequencing in 9,639 BC cases and 3,988 controls, among patients referred for genetic testing at a single laboratory in 2012-2015, and leveraged this vast collection of genotype and phenotype data to investigate the contribution of these coding variants to risk for and clinical features of BC. We also used 1000 Genomes (G1K) as a reference population to confirm our findings. All models were conducted within genetically inferred G1K-defined populations and adjusted for sex and 3 ancestry PCs. Among Europeans (n=7,235 BC, 2,666 controls), *PPARG* P12A Pro (RAF=94.2%) was associated with BC at genome-wide significance (OR_{add}=1.49, p=3.9x10^{-10}). BC was also associated with *PPIP5K2* S1207G (RAF=2.5%, p=2.4x10^{-6}), *PAM* D563G (RAF=3.0%, p=9.5x10^{-5}) and *ASCC2* V123I (RAF=93.8%, p=8.0x10^{-4}). P12A was significantly associated with HR^+, HR^-, and $HER2^-$ BC. D563G and S1207G were significantly associated with $HER2^-$ and V123I with $HER2^+$ BC only. P12A results comparing cases to G1K (n=501) were consistent (OR_{add}=1.78, p=1.5x10^{-6}). Risk estimates from G1K comparisons for the other 3 variants were nearly identical to those from internal controls, but not significant due to sample size. Among Mexicans, Central and South Americans (n=809 BC, 768 controls, 334 G1K), *PPARG* Pro (RAF=94.3%) was associated with BC in comparisons with controls (OR_{add}=1.98, p=1.9x10^{-6}) and G1K (OR_{add}=1.90, p=0.001). Among South Asians (n=105 BC, 99 controls, 479 G1K), *PPARG* Pro (RAF=95.9%) was linked to BC in comparisons with G1K (OR_{add}=3.38, p=0.003); internal control sample size was too small for risk estimation. No associations were detected among Africans (n=968 BC, 293 controls, 639 G1K) or East Asians (n=522 BC, 162 controls, 502 G1K). Results were similar when excluding males and/or those carrying cancer gene mutations. Genetic risk scores assessing cumulative effects across 21 variants were not associated with BC in any racial/ethnic group. These data suggest that *PPARG* P12A and other T2DM variants confer risk for BC and its clinical subtypes, with potentially important implications for clinical screening and management.

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