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Abstract: Early-onset breast cancer (EOBC) causes substantial loss of life and
productivity, creating a major burden among women worldwide. We analyzed 1,265,548 Hapmap3 single-nucleotide polymorphisms (SNP) among a discovery set of 3,523 EOBC incident cases and 2,702 population control women ages <= 51 years. The SNPs with smallest P values were examined in a replication set of 3,470 EOBC cases and 5,475 control women. We also tested EOBC association with 19,684 genes by annotating each gene with putative functional SNPs, and then combining their P values to obtain a gene-based P value. We examined the gene with smallest P value for replication in 1,145 breast cancer cases and 1,142 control women. The combined discovery and replication sets identified 72 new SNPs associated with EOBC (P< 4 × 10(-8)) located in six genomic regions previously reported to contain SNPs associated largely with later-onset breast cancer (LOBC). SNP rs2229882 and 10 other SNPs on chromosome 5q11.2 remained associated (P< 6 × 10(-4)) after adjustment for the strongest published SNPs in the region. Thirty-two of the 82 currently known LOBC SNPs were associated with EOBC (P< 0.05). Low power is likely responsible for the remaining 50 unassociated known LOBC SNPs. The gene-based analysis identified an association between breast cancer and the phosphofructokinase-muscle (PFKM) gene on chromosome 12q13.11 that met the genome-wide gene-based threshold of 2.5 × 10(-6). In conclusion, EOBC and LOBC seem to have similar genetic etiologies; the 5q11.2 region may contain multiple distinct breast cancer loci; and the PFKM gene region is worthy of further investigation. These findings should enhance our understanding of the etiology of breast cancer.

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