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Genome-Wide Association Study in *BRCA1* Mutation Carriers Identifies Novel Loci Associated with Breast and Ovarian Cancer Risk

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Identification of a *BRCA2*-Specific Modifier Locus at 6p24 Related to Breast Cancer Risk

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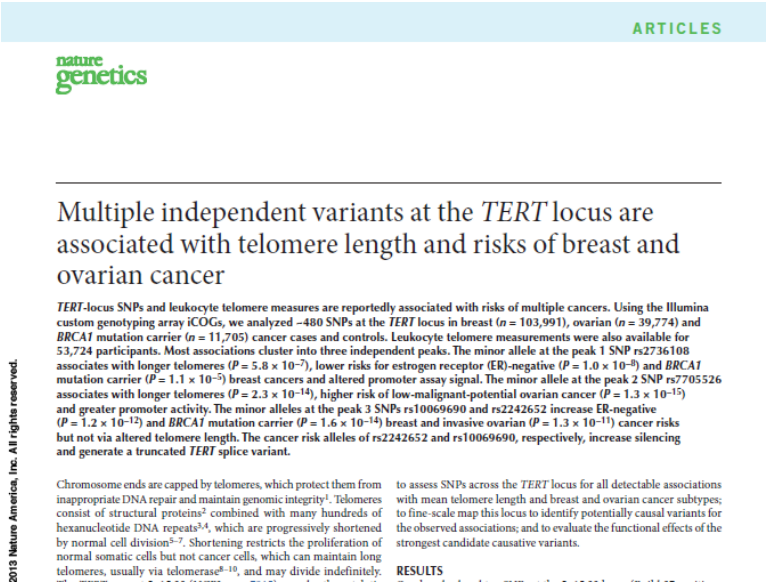

nature genetics

Multiple independent variants at the *TERT* locus are associated with telomere length and risks of breast and ovarian cancer

***TERT*-locus SNPs and leukocyte telomere measures are reportedly associated with risks of multiple cancers. Using the Illumina custom genotyping array iCOGs, we analyzed ~480 SNPs at the *TERT* locus in breast (n = 103,991), ovarian (n = 39,774) and *BRCA1* mutation carrier (n = 11,705) cancer cases and controls. Leukocyte telomere measurements were also available for 53,724 participants. Most associations cluster into three independent peaks. The minor allele at the peak 1 SNP rs2736108 associates with longer telomeres ($P = 5.8 \times 10^{-7}$), lower risks for estrogen receptor (ER)-negative ($P = 1.0 \times 10^{-8}$) and *BRCA1* mutation carrier ($P = 1.1 \times 10^{-5}$) breast cancers and altered promoter assay signal. The minor allele at the peak 2 SNP rs7705526 associates with longer telomeres ($P = 2.3 \times 10^{-14}$), higher risk of low-malignant-potential ovarian cancer ($P = 1.3 \times 10^{-15}$) and greater promoter activity. The minor alleles at the peak 3 SNPs rs10069690 and rs2242652 increase ER-negative ($P = 1.2 \times 10^{-12}$) and *BRCA1* mutation carrier ($P = 1.6 \times 10^{-14}$) breast and invasive ovarian ($P = 1.3 \times 10^{-11}$) cancer risks but not via altered telomere length. The cancer risk alleles of rs2242652 and rs10069690, respectively, increase silencing and generate a truncated *TERT* splice variant.**

Chromosome ends are capped by telomeres, which protect them from inappropriate DNA repair and maintain genomic integrity[1]. Telomeres consist of structural proteins[2] combined with many hundreds of hexanucleotide DNA repeats[3,4], which are progressively shortened by normal cell division[5–7]. Shortening restricts the proliferation of normal somatic cells but not cancer cells, which can maintain long telomeres, usually via telomerase[8–10], and may divide indefinitely.

to assess SNPs across the *TERT* locus for all detectable associations with mean telomere length and breast and ovarian cancer subtypes; to fine-scale map this locus to identify potentially causal variants for the observed associations; and to evaluate the functional effects of the strongest candidate causative variants.

RESULTS