

ARTÍCULO DE MAYOR FACTOR DE IMPACTO MARZO 2013

Couch, FJ; Wang, XS; McGuffog, L.....; **Caldes, T;**; **Romero, A; de la Hoya, M;**; Antoniou, AC. Genome-Wide Association Study in BRCA1 Mutation Carriers Identifies Novel Loci Associated with Breast and Ovarian Cancer Risk. PLOS GENETICS. MAR 2013. 9(3): doi: 10.1371/journal.pgen.1003212. Factor de Impacto: 8,694

Enlace: <http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1003212>

OPEN ACCESS [freely available online](#) PLOS GENETICS

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

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Gaudet, MM; Kuchenbaecker, KB; Vijai, J; **Caldes, T;** Offit, K. Identification of a BRCA2-Specific Modifier Locus at 6p24 Related to Breast Cancer Risk. PLOS GENETICS. MAR 2013. 9(3): doi: 10.1371/journal.pgen.1003212. Factor de Impacto: 8,694

Enlace: <http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1003173>

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

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ARTÍCULO DE MAYOR FACTOR DE IMPACTO ABRIL 2013

Bojesen, SE; Pooley, KA.....; **Caldes, T**..... G; Dunning, AM. Multiple independent variants at the *TERT* locus are associated with telomere length and risks of breast and ovarian cancer. NATURE GENETICS. APR. 2013. 45 (4): 371-384. DOI: 10.1038/ng.2566. Factor Impacto: 35,532

Enlace: <http://dx.doi.org/10.1038/ng.2566>

ARTICLES

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 (COGs), 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 ($P = 1.0 \times 10^{-9}$) 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 integrity¹. Telomeres consist of structural proteins² combined with many hundreds of hexanucleotide DNA repeats^{3,4}, which are progressively shortened by normal cell division⁵⁻⁷. Shortening restricts the proliferation of normal somatic cells but not cancer cells, which can maintain long telomeres, usually via telomerase⁸⁻¹⁰, 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