
Conference or Workshop Item:
Lindstrom, S, Kar, S, Wang, L et al. (25 more authors) (2020) Cross-cancer GWAS meta-analysis of more than 370,000 cases and 530,000 controls identifies multiple novel cancer risk regions. In: AACR Annual Meeting 2020, 27 Apr - 24 Jun 2020, Philadelphia, PA, USA.

https://doi.org/10.1158/1538-7445.AM2020-1194

Cross-cancer GWAS meta-analysis of more than 370,000 cases and 530,000 controls identifies multiple novel cancer risk regions

Sara Lindström, Siddhartha Kar, Lu Wang, Constance Turman, James MacDonald, Theo Bammler, BCAC, OCAC, PRACTICAL, Jeroen Huyghe, Stephanie Schmit, Tracy A. O'Mara, Deborah J. Thompson, Puya Gharahkhani, Stuart MacGregor, Paul Brennan, Richard S. Houlston, Beatrice S. Melin, Christopher I. Amos, James McKay, Mark M. Iles, Matthew H. Law, Alison Klein, Laufey Amundadottir, Bogdan Pasaniuc, Paul Pharoah, Rayjean J. Hung and Peter Kraft

Abstract

Genome-wide association studies (GWAS) have identified hundreds of common, low-penetrance alleles associated with cancer risk. However, known rare and common risk alleles only explain between 10% and 30% of the familial relative risk for different cancers and multiple lines of evidence indicate that many more risk alleles remain to be discovered. We have demonstrated genetic correlations between cancers, reflecting a shared genetic origin for solid tumors. These results suggest that jointly analyzing multiple cancer sites will lead to the discovery of novel risk regions.

We conducted a cross-cancer GWAS meta-analysis by leveraging GWAS summary statistics from 12 solid cancers (breast, colorectal, endometrial, esophageal, glioma, head and neck, lung, melanoma, ovarian, pancreatic, prostate and renal cancers) with a total of 373,818 cases and 532,382 controls of European ancestry. All studies had been imputed to either 1,000 Genomes or the Haplotype Reference Consortium panel. We conducted four meta-analysis using (1) fixed-effect, (2) random-effect, (3) one-sided subset (ASSET) and (4) two-sided subset (ASSET) models. The subset analysis were conducted assuming either the same direction of effects across cancers (one-sided ASSET) or allowed for opposite direction of effects across cancers (two-sided ASSET). In all analyses, we used tetrachoric correlations to account for sample overlap across cancer sites. In total, we tested 10,223,013 variants for association. We considered regions with a p-value$<1.25 \times 10-8$ in at least one of the four meta-analysis approaches and located at least 500kb away from known cancer risk SNPs as novel.

We identified eight novel regions that reached genome-wide significance. Of those eight regions, two were identified from fixed-effects meta-analysis, three from random effects meta-analysis, one from the two-sided subset analysis, and two regions (15.q15.3 and 21q22.3) were identified at $p<1.25 \times 10-8$ in three of the meta-analysis approaches. Among novel findings is a deleterious missense variant located in RREB1 previously associated with type 2 diabetes, a deleterious missense variant located in DSTYK previously associated with waist-to-hip ratio and triglycerides, and an intergenic variant in linkage disequilibrium (LD) with variants in TMEM18, previously associated with body mass index. Other potential target genes among the newly discovered regions include TP53BP1 and PCNT, both previously implicated in carcinogenesis.