INTRODUCTION

• Studies have demonstrated substantial heritability and familial clustering for many cancers, but to what extent genetic variation is unique versus shared across different cancer types is unclear.
• Genome-wide association studies (GWAS) of individual cancers have identified loci associated with multiple cancer types, and recent studies have tested single nucleotide polymorphisms (SNPs) associated with one cancer to discover pleiotropic associations.
• Recent studies evaluated genetic correlations between pairs of cancers but lack data on several cancers and aggregate studies with case-control sampling and heterogeneous populations recruited during different time periods.
• Leveraging individual-level genetic and clinical data allowed us to comprehensively interrogate shared genetic basis of susceptibility to different types.

DATA AND METHODS

• Two large, independent, and contemporary population-based cohorts unselected for phenotype yielded 475,919 individuals of European ancestry.
• UK Biobank (UKB) – 359,825 controls and 471-13,093 cases.
• Kaiser Permanente Genetic Epidemiology Research on Adult Health and Aging (GERA) – 50,525 controls and 162-3,978 cases.

RESULTS

GWAS of Individual Cancers

Table 1: Novel genome-wide significant loci from meta-analysis of UKB and GERA SNPs for each cancer site

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>SNP</th>
<th>chrom:pos</th>
<th>beta (95% CI)</th>
<th>P-value</th>
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<td>Breast</td>
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DISCUSSION

• Detected 29 novel risk variants in GWAS of 18 cancers.
• For several cancer sites, heritability estimates similar to those from twin/family studies, suggesting much of genetic risk may be due to common variation.
• Pairwise comparisons identified strongest signal for colon and rectal cancers and additional novel cancer pairs with nominal genetic correlation.
• Identified 43 pleiotropic loci, confirming known pleiotropic signals and several previously associated with specific cancers in separate studies.
• Of the 158 SNPs identified from the variant-specific approach, 27 were in 8q24 and 19 in 19A.
• HLA is critical for innate and adaptive immune response and has a complex relationship with cancer risk and 8 of these variants were omni-directional, highlighting complex relationship with cancer susceptibility.
• Majority of the 8q24 pleiotropic variants had the same direction of effect for all associated cancers, implying the existence of shared genetic mechanisms driving tumorigenesis.

ACKNOWLEDGEMENTS

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