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Article

Genome-wide analyses characterize shared heritability among cancers and identify novel cancer susceptibility regions

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Abstract

Background: The shared inherited genetic contribution to risk of different cancers is not fully known. In this study, we leverage results from 12 cancer genome-wide association studies (GWAS) to quantify pairwise genome-wide genetic correlations across cancers and identify novel cancer susceptibility loci.

Methods: We collected GWAS summary statistics for 12 solid cancers based on 376 759 participants with cancer and 532 864 participants without cancer of European ancestry. The included cancer types were breast, colorectal, endometrial, esophageal, glioma, head and neck, lung, melanoma, ovarian, pancreatic, prostate, and renal cancers. We conducted cross-cancer GWAS and transcriptome-wide association studies to discover novel cancer susceptibility loci. Finally, we assessed the extent of variant-specific pleiotropy among cancers at known and newly identified cancer susceptibility loci.

Results: We observed widespread but modest genome-wide genetic correlations across cancers. In cross-cancer GWAS and transcriptome-wide association studies, we identified 15 novel cancer susceptibility loci. Additionally, we identified multiple variants at 77 distinct loci with strong evidence of being associated with at least 2 cancer types by testing for pleiotropy at known cancer susceptibility loci.

Conclusions: Overall, these results suggest that some genetic risk variants are shared among cancers, though much of cancer heritability is cancer-specific and thus tissue-specific. The increase in statistical power associated with larger sample sizes in cross-disease analysis allows for the identification of novel susceptibility regions. Future studies incorporating data on multiple cancer types are likely to identify additional regions associated with the risk of multiple cancer types.

Some pairs of cancer types tend to co-cluster within the same family. Although this co-clustering of multiple cancer types may partly be because of shared environment (eg, similar smoking habits among family members), an increasing body of literature suggests that a component of co-clustering is because of shared genetic risk factors. Further, findings from genome-wide association studies (GWAS) have shown overlap in susceptibility loci across cancers (1), arguing that genetic variation contributing to risk of multiple cancers is not limited to rare, high-penetrant variants but also arises from (potentially shared) polygenic risk. We have previously demonstrated genome-wide genetic correlations across cancers (2,3) and conducted cross-cancer GWAS meta-analyses to identify susceptibility loci associated with more than 1 cancer type (4,5). However, these studies included at most 6 cancer types, limiting our understanding of more general patterns in the genetic architecture of cancer.

In this study, we report results from a comprehensive assessment of the shared genetic architecture of 12 cancer types: breast, colorectal, endometrial, esophageal, glioma, head and neck, lung, melanoma, ovarian, pancreatic, prostate, and renal cancers. We conduct cross-cancer GWAS and transcriptome-wide association studies (TWAS) and assess whether variants at known cancer susceptibility loci are associated with 2 or more cancer types (variant-specific pleiotropy). Our findings constitute the most comprehensive mapping of the shared germline genetic architecture across individual cancers to date, showcasing the power of cross-trait analysis for novel discovery and demonstrating widespread pleiotropy across cancers.

Methods

Detailed methods can be found in the Supplementary Methods (available online). Briefly, we collected GWAS summary statistics on 12 cancers (see Table 1), including breast (6), colorectal (7), endometrial (8), esophageal (9), glioma (10), head and neck (11), lung (12), melanoma (13), ovarian (14), pancreatic (15), prostate (16) and renal (17). In total, GWAS summary statistics were based on 376 759 cancer cases and 532 864 controls of European ancestry. Individual cancer GWAS were primarily imputed to the 1000 Genomes (1000G) reference panels (18) (Supplementary Table 1, available online).

Statistical analysis

We calculated the correlation between cancer-specific GWAS summary statistics because of overlapping controls using the tetrachoric correlation between binary-transformed GWAS

summary z scores (19,20). The tetrachoric correlations (Supplementary Table 2, available online) were then included to adjust for sample overlap in the cross-cancer GWAS, cross-cancer TWAS, and tests for pleiotropy. We used linkage disequilibrium (LD) score regression (21) to calculate pairwise genome-wide genetic correlations between cancers. To assess the importance of germline genetic variation close to cancer driver genes in cancer susceptibility, we partitioned cancer-specific heritability by creating functional annotations including single-nucleotide polymorphisms (SNPs) located in regions 100 kb around gene boundaries of 299 cancer driver genes previously identified in a pancancer tumor analysis (22).

Cross-cancer GWAS was performed by conducting meta-analysis of the summary statistics from the individual cancer GWAS. We conducted 4 sets of cross-cancer GWAS meta-analysis: 1) fixed effects, 2) random effects, 3) 1-sided subset Association analysis based on subsets (ASSET) (23), and 4) 2-sided subset (ASSET) (23) meta-analysis. We considered variants located at least 500 kb away from previously known cancer variants and with a meta-analysis P value less than 1.25×10^{-8} from at least 1 of the 4 meta-analysis approaches novel. We conducted cross-cancer TWAS using gene expression weights in noncancerous and tumor tissue. Gene expression data from noncancerous tissue were obtained from the Genotype-Tissue Expression project [GTEx v.8 (24)], and gene expression data from tumor tissue were obtained from The Cancer Genome Atlas (25) project. The pipeline for our cross-cancer TWAS is illustrated in Supplementary Figure 1 (available online) and described in detail elsewhere (26). For all TWAS analyses, we only considered genes located at least 500 kb away from previously known cancer GWAS variants or known cancer TWAS genes as potentially novel findings. To identify which cancers are credibly associated with a known cancer variant, we applied a newly developed test based on the Bayesian support region to search for evidence of pleiotropy among 60 337 variants that were associated with at least 1 of the cancers or in the cross-cancer analysis.

Table 1. Included cancer types and their GWAS sample sizes for the cross-cancer analyses[a]

Cancer	Cases	Controls
Breast	122 977	105 974
Colorectal	55 168	65 160
Endometrial	12 906	108 979
Esophageal	4112	13 663
Glioma	12 488	18 169
Head and neck	6034	6585
Lung	29 266	56 450
Melanoma	12 814	23 203
Ovarian	22 406	40 951
Pancreatic	8638	12 217
Prostate	79 166	61 106
Renal	10 784	20 406
Total	376 759	532 864

[a] GWAS = genome-wide association studies.

Results

The genetic architecture across cancers

We observed moderate genetic correlations among cancers (Figure 1; Supplementary Table 3, available online). Five pairs of cancers showed genetic correlations greater than 0.4. Lung and renal cancer showed widespread genetic correlations with multiple other cancer types, and prostate cancer had the weakest evidence of genetic correlations with other cancers. For breast and lung cancer, there were differences in genetic correlations between subtypes and other cancer types (Supplementary Table 4, Supplementary Figures 2 and 3, available online). For example, estrogen receptor–positive (ER+) breast cancer showed higher genetic correlation with endometrial cancer than ER−negative (ER−) breast cancer ($r_g = .28$ [ER+], $r_g = .03$ [ER−]). Compared with adenocarcinoma, squamous cell lung cancer showed higher genetic correlation with esophageal cancer, and lung

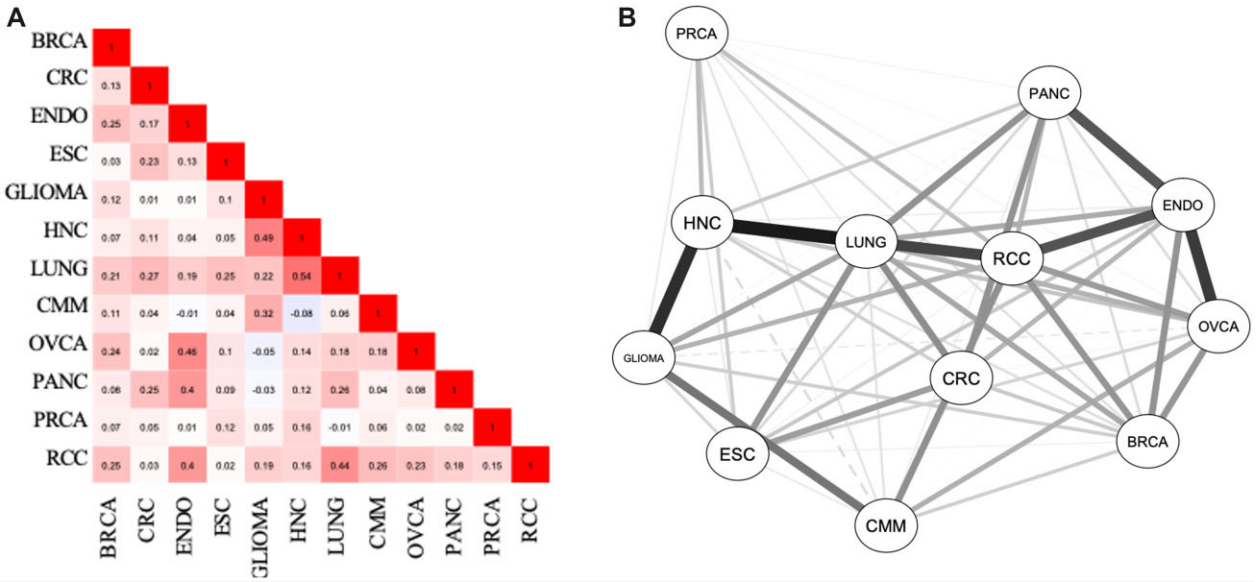

Figure 1. Pairwise genetic correlations between cancers. **(A)** Matrix of pairwise genetic correlations. **(B)** Genetic correlation network. Distance between nodes, edge shade, and edge thickness corresponds to genetic correlation magnitudes. **Dashed lines** indicate negative correlations. BRCA = breast cancer; CMM = cutaneous melanoma; CRC =colorectal cancer; ENDO = endometrial cancer; ESC = esophageal cancer; HNC = head and neck cancer; OVCA = ovarian cancer; PANC = pancreatic cancer; PRCA = prostate cancer; RCC = renal cancer (see Supplementary Table 1, available online for numerical values and corresponding P values). (Fruchterman and Reingold, 1991).

adenocarcinoma showed higher genetic correlations with renal and pancreatic cancer.

To explore if cancer driver genes are targets for germline genetic variation associated with cancer risk, we estimated the SNP heritability in regions surrounding 299 driver genes (22) (Supplementary Table 5, available online). We found that regions surrounding cancer driver genes had a 2.7-fold enrichment (95% confidence interval = 2.28 to 3.12) of SNP heritability across cancer types.

Cross-cancer GWAS

Cross-cancer GWAS was performed by conducting meta-analysis of the summary statistics from the individual cancer GWAS (Supplementary Figures 4 and 5, available online). In total, across all 4 approaches, we identified 333 distinct statistically genome-wide significant regions, of which 145 regions were statistically significant across all 4 meta-analysis approaches, and 35 regions were identified by only 1 approach (Supplementary Figure 6, available online).

We identified 7 loci that have not been reported by previous GWAS to be associated with cancer (Table 2, Figure 2; Supplementary Table 6, Supplementary Figures 7 and 8, available online). Selected novel loci are discussed below. We identified a novel association at 2p25.3, where SNPs in high LD (r^2>.8) with our lead SNP rs66906321 have been associated with multiple traits including anthropometric, type 2 diabetes, puberty timing, and osteoarthritis, among others (27). Potential nearby target genes include *TMEM18*, which has been linked to adiposity (28), and *ALKAL2*, which is hypothesized to regulate cell proliferation and transformation and has been implicated in cancer (29,30). We identified an association at 6q24.3 with lead SNP rs9379084, a missense variant (Aspartic Acid [Asp]->Asparagine [Asn]) located in a conserved region of *RREB1*, a gene involved in several aspects of cell function and often expressed in tumors (31). The A allele of this SNP has previously been associated with decreased risk type 2 diabetes. In our analysis, the A allele was associated with decreased risk of colorectal cancer but increased risk of breast cancer. The 15q15.3 locus has previously been implicated with risk of breast and ovarian cancer in a cross-cancer TWAS (32). However, this is the first time it is associated with cancer through GWAS. The association signal is in a large high-LD region with multiple potential target genes including the DNA repair gene *TP53BP1*. The lead SNP, rs533143, is an Expression quantitative trait locus (eQTL) for multiple genes in this region including *TP53BP1*, where the T allele is associated with higher gene expression and increased risk of all associated cancers. Lastly, we observed a genome-wide statistically

Table 2. Newly identified genetic variants from the cross-cancer GWAS meta-analysis ($P < 1.25 \times 10^{-8}$)

Region	Variant ID	Chr	Position[a]	Function	MAF (gnomAD EUR)	Effect allele	Other allele	P[b]
2p25.3	rs66906321	2	630070	Intergenic	0.17	T	C	1.12×10^{-8}
2q24.2	rs146071273	2	161628983	Intergenic	0.10	A	G	8.23×10^{-9}
2q32.1	rs62172372	2	188242369	Intronic (*CALCRL*)	0.22	A	G	1.21×10^{-8}
2q37.1	rs34755199	2	233516534	Intronic (*EFHD1*)	0.48	A	AAAAC	9.49×10^{-9}
6p24.3	rs9379084	6	7231843	Missense (*RREB1*)	0.12	A	G	9.10×10^{-9}
15q15.3	rs533143	15	44188854	Intron (*FRMD5*)	0.27	T	C	3.84×10^{-10}
18q21.31	rs8097764	18	55317896	Intronic (*ATP8B1*)	0.12	A	G	1.03×10^{-8}

[a] hg19. Chr = chromosome; MAF = minor allele frequency in non-Finnish European ancestry populations based on the Genome Aggregation Database (gnomAD EUR).
[b] *P* values are based on the meta-analysis approach showing the lowest *P* value.

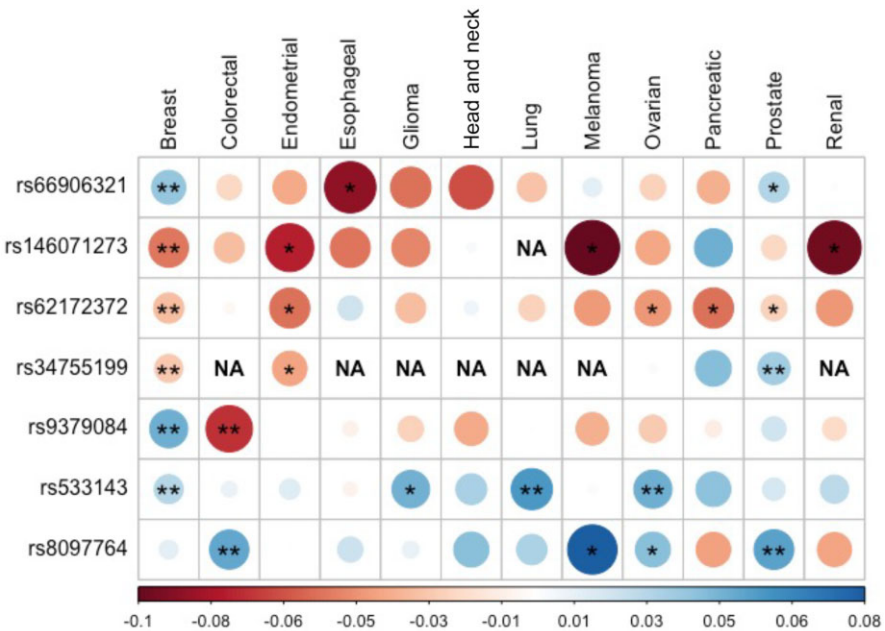

Figure 2. Cancer-specific association results for the lead single-nucleotide polymorphisms of 7 newly identified cancer susceptibility loci. The **circles** correspond to cancer-specific log(odds ratios), with color corresponding to direction of effect and size and shade corresponding to magnitude of effect. *Cancer-specific $P < .05$. **Cancer-specific $P < .001$. See Supplementary Table 5 (available online) for cancer-specific odds ratios and *P* values. NA denotes instances where the variant was not present in the corresponding cancer.

significant association at 18q21.31, with the lead SNP rs8097764 located within the proposed tumor suppressor gene *ATP8B1* (33).

We assessed cancer-specific associations of novel SNPs (Supplementary Table 7, available online) from 2 separate replication datasets (Supplementary Methods, available online): 1) a meta-analysis of the UK Biobank and Kaiser Genetic Epidemiology Research on Aging (34) cohorts and 2) FinnGen release 7 (35). Total cancer cases ranged from 692 (brain) to 31 059 (breast) (Supplementary Table 8, available online). In the discovery analysis, we detected 26 SNP-cancer pairs with a *P* value less than .05 (Supplementary Table 9, available online). Out of those, 6 (23%) replicated at a *P* value less than .05, with all 6 in the same direction of association as the discovery analysis. At 4 of the novel loci, at least 1 SNP-cancer association was statistically significant at the .05 level after Bonferroni correction, and at 2 of these loci, the directions of all tested cancer associations were consistent across the discovery and replication results. Overall, 20 (77%) associations showed consistent direction of association between the discovery and replication analyses.

Cross-cancer TWAS

To identify genes whose imputed expression is associated with cancer risk, we first conducted cross-cancer TWAS using imputed gene expression based on 49 noncancerous tissue types (GTEx v.8) as reference. To ensure that the results were not driven by a single cancer, we first removed any tissue-gene pair that was significant in the single-cancer analyses (Supplementary Methods, available online). For the single-tissue, cross-cancer TWAS (Supplementary Figure 9, Supplementary Table 10, available online), we identified 5 novel regions, each identified by a single gene: CALCRL, IKZF2, MEPCE, IGFBP3, and IGBP1P1 (Table 3). The 2q32.1 region (CALCRL) was also identified in the GWAS analysis. IGFBP3 has been implicated in cancer previously (36), but this is the first time it is observed at genome-wide statistical significance. We also identified TWAS associations with 10 genes in the previously discussed 15q15.3 region (32), including TP53BP1. In the cross-tissue, cross-cancer analyses (Supplementary Table 11, available online), we identified 3 distinct regions, each containing a single gene: ALKAL2, NEK6, and LGR4 (Table 3).

We also conducted cross-cancer TWAS using imputed gene expression based on 24 tumor tissue types from The Cancer Genome Atlas. In the single-tissue, cross-cancer TWAS (Supplementary Figure 10, Supplementary Table 12, available online), we identified 2 genes at 2 distinct loci (LOC284900 and C5; Table 3). For the cross-tissue, cross-cancer TWAS (Supplementary Table 13, available online), we observed 1 novel region (C5) that was also statistically significant in the single-tissue analysis (Table 3). The C5 gene, also known as Complement component 5, is a member of the innate immune-system and affects tumor progression through multiple mechanisms (37). Similar to the analyses based on the noncancerous tissue, we also replicated the previous observed TWAS associations (32) in the 15q15.3 region, which is also reported as a GWAS region in this study.

Cancer pleiotropy for known cancer variants

We calculated Bayesian support regions to assess whether known cancer variants show evidence of associations with more than 1 cancer type (ie, to assess variant-specific pleiotropy [see "Methods"]). No variant showed strong evidence of being associated with more than 3 cancers (Figure 3). We observed 34 genetic variants in 5 independent regions with strong evidence of being associated with 3 cancers (Supplementary Table 14, available online). These included the *TERT* region (5p15.33), the human leukocyte antigen (HLA) region at 6p21-22, 9q34.2 that includes the *ABO* gene, 9q31.1 that includes the *SMC2* gene, and 15q15 (a novel GWAS locus in this study). An additional 4967 variants distributed across 77 regions showed strong evidence of being associated with 2 cancers (Supplementary Table 15, available online). The HLA region (6p21-22) showed evidence of 2-cancer pleiotropy for 9 different cancer pairs, and the *TERT* region (5p15.33) showed evidence of 2-cancer pleiotropy for 8 different cancer pairs. Overall, we observed 28 different pairwise combinations of cancers (Supplementary Table 16, available online).

Table 3. Newly identified genes from cross-cancer TWAS analyses using either noncancerous (GTEx) tissue or tumor tissue (TCGA)[a]

Panel	Gene	Chr	Locus	Tissue	*P*
GTEx	ALKAL2	2	2p25.3	Cross-tissue	4.41×10^{-8}
GTEx	CALCRL	2	2q32.1	Aorta artery	1.12×10^{-7}
GTEx	CALCRL	2	2q32.1	Tibial nerve	8.33×10^{-8}
GTEx	IKZF2	2	2q34	Thyroid	6.28×10^{-8}
GTEx	IGFBP3	7	7p12.3	Thyroid	1.23×10^{-7}
GTEx	MEPCE	7	7q22.1	Fibroblasts	6.79×10^{-8}
GTEx	NEK6	9	9q33.3	Cross-tissue	9.69×10^{-8}
GTEx	LGR4	11	11p14.1	Cross-tissue	1.00×10^{-7}
GTEx	IGBP1P1	14	14q13.2	Pancreas	7.72×10^{-8}
TCGA	C5	9	9q33.2	Cross-tissue	4.33×10^{-7}
TCGA	C5	9	9q33.2	Prostate	2.16×10^{-7}
TCGA	LOC284900	22	22q11.21-q12.1	Renal papillary cell	1.75×10^{-7}
TCGA	LOC284900	22	22q11.21-q12.1	Stomach	2.46×10^{-7}

[a] Genes that were statistically significant for multiple tissues are listed more than once. Chr = chromosome; GTEx = Genotype-Tissue Expression project; TCGA = The Cancer Genome Atlas; TWAS = transcriptome-wide association studies.

Discussion

Studies aiming to estimate the genome-wide genetic correlations between cancers have been limited in both the number of included cancers and sizes of population samples. We report the most comprehensive effort to quantify genetic correlations between cancers to date. Although we observe a handful of strong (r_g>0.4) pairwise genetic correlations between cancers, most are modest. There are multiple potential explanations for these moderate estimates. The genetic correlations estimated here capture only correlations due to common genetic variants, ignoring any genetic correlations due to rare variation, such as pathogenic variants in cancer predisposition genes including *BRCA2* and Lynch syndrome, among others. Further, many genetic mechanisms are specific to tissue, and thus, although some of the underlying carcinogenetic mechanisms might be similar across cancers, tissue-specific germline genetic regulations could differ (24,38). Of note, endometrial and lung cancer displayed evidence of strong genetic correlations with other cancers. Lung cancer showed strong genetic correlations with head and neck and renal cancer—all 3 linked to smoking. Endometrial cancer showed strong genetic correlations with pancreatic and renal cancer—all 3 linked to obesity. Endometrial cancer also displayed genetic correlations with ER+ breast cancer and ovarian cancer, possibly because of the estrogenic pathways underlying these cancers, which are strongly driven by estrogen exposure. In contrast, lung cancer (including subtypes) showed stronger genetic correlations with ER− breast cancer. Many genetic correlations across cancer pairs were not statistically significantly

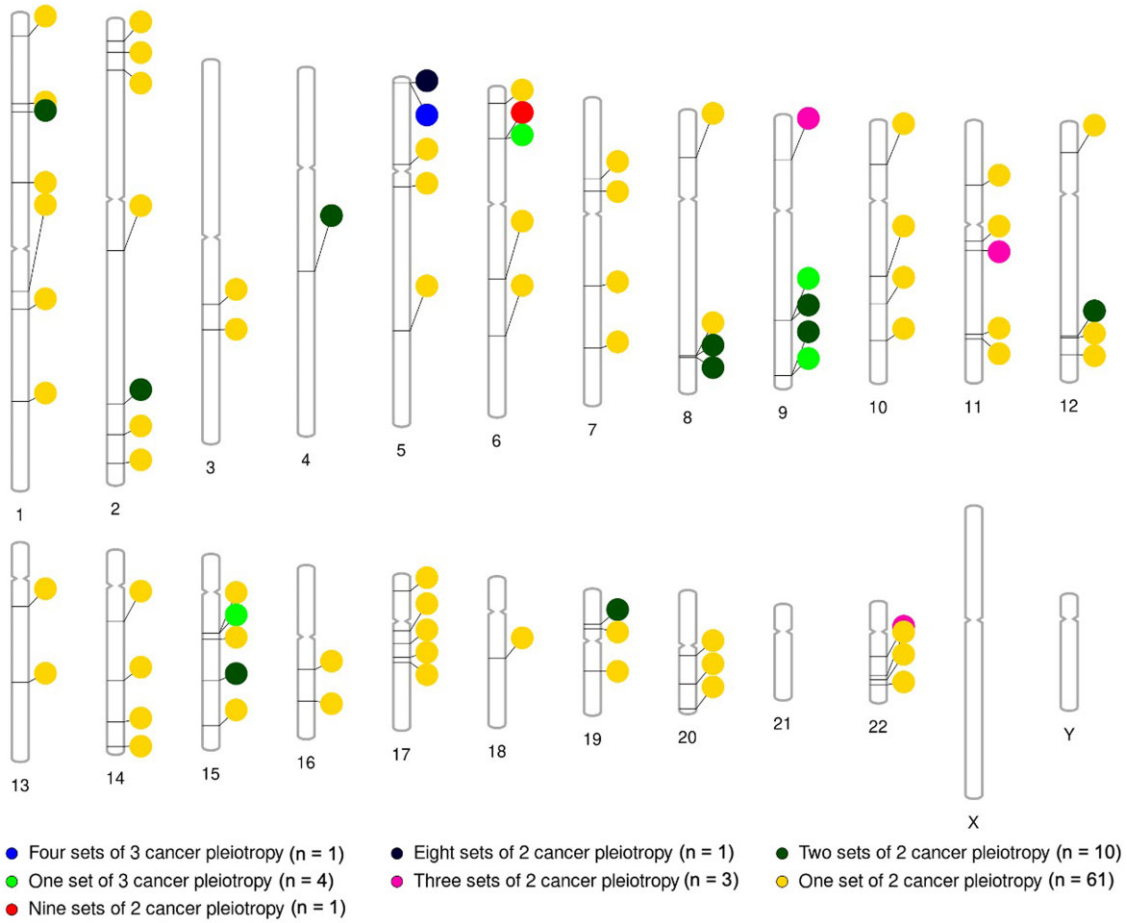

Figure 3. Regions in the genome with evidence of variant-specific pleiotropy. Colors correspond to regions with 4 sets of 3-cancer pleiotropy (**blue**), 1 combination of 3-cancer pleiotropy (**light green**), 9 combinations of pairwise cancer pleiotropy (**red**), 8 combinations of pairwise cancer pleiotropy (**black**), 3 combinations of pairwise cancer pleiotropy (**pink**), 2 combinations of pairwise cancer pleiotropy (**dark green**), and 1 combination of pairwise cancer pleiotropy (**yellow**). Full results from the pleiotropic analyses can be found in Supplementary Tables 10-12 (available online).

different than zero, likely reflecting our relatively limited sample sizes and the likely truly modest genetic correlations among cancers. We had greater than 80% power at the Bonferroni-corrected $P = .05/66 = 7.6 \times 10^{-4}$ level to detect a genetic correlation of .80 for all cancer pairs, but only a median 15% power to detect a genetic correlation of .20 (1% for glioma-head and neck and 99% for breast-prostate).

We evaluated the contribution to cancer heritability from SNPs located close to cancer driver genes and observed consistent enrichment across cancer types. This is in alignment with our previous work in breast cancer, where we demonstrated an overlap between GWAS candidate target genes and driver genes in breast tumors (6) and suggests that germline genetic variation located close to known somatic driver genes is important for cancer development.

We identified 7 novel cancer susceptibility loci in our cross-cancer GWAS. Among notable findings was an association in the *RREB1* gene (6q24.3) for which the missense SNP rs9379084 showed opposite associations with breast (odds ratio [OR] = 1.05; $P = 2.6 \times 10^{-6}$) and colorectal cancer (OR = 0.93; $P = 3.8 \times 10^{-7}$). It is not uncommon that specific SNPs show opposite associations with different cancer types. We previously mapped the 5p15.33 region (which harbors the *TERT* gene) and observed strong cancer-specific associations in opposite directions (39). Although overall genome-wide genetic correlations among cancers are exclusively positive, there are now many examples of individual variants that show strong associations with multiple cancers in opposite directions. This phenomenon could potentially be because of tissue-specific regulations of general cancer-driving mechanisms; however, such a hypothesis needs to be further studied. Alternatively, the downstream impact of the same regulatory effects can be qualitatively different. For example, genetically predicted body mass index has been associated with an increased risk of multiple cancers including bladder, cervical, colorectal, endometrial, esophageal, gallbladder and biliary tract, liver, ovary, pancreatic, renal, and stomach but with decreased risk of breast, nonmelanoma skin, and prostate cancer (40).

Our cross-cancer TWAS resulted in the discovery of 10 new regions. Of those, 2 regions (2p25.3 and 2q32.1) overlapped with our GWAS findings. Among the noteworthy TWAS findings is the insulin-like growth factor binding protein 3 (IGFBP3) gene, which binds insulin-like growth factor–1 (IGF-1) and IGF-2, can induce cell apoptosis, and is also a mediator of p53 action (41). We observed TWAS associations ($P < .01$) between IGFBP3 and colorectal, lung, ovarian, and prostate cancer. Cross-trait TWAS is more complex than cross-trait GWAS in that there is often no clear target tissue for building gene expression prediction models. This is particularly true when studying different tumor types, where the primary tissue differs. We sought to overcome this by conducting single-tissue and cross-tissue analyses as the benefits

of comprehensively capturing eQTLs across tissues outweigh the burden of an increased number of tests (42).

The 15q15.3 region, which was recently discovered in a TWAS of breast and ovarian cancer, showed genome-wide statistically significant associations in both our GWAS and TWAS, and these associations were primarily driven by breast, ovarian, and lung cancer. The 15q15.3 region displays high LD and contains multiple strong candidate genes, including TP53BP1, a prime candidate for cancer development because of its involvement in DNA repair. However, additional fine mapping and functional follow-up studies are needed to pinpoint the target gene(s) in this gene-dense region.

We assessed to what extent known cancer variants show evidence of associations with multiple cancer types. An important feature of our method is that its alternative hypothesis is a variant is associated with at least 2 traits (here cancer types) as compared with previous similar tests where the alternative hypothesis is that a particular variant is associated with at least 1 trait. Thus, we explicitly searched for variants that showed credible evidence to be associated with at least 2 of the 12 cancer types we interrogated. We observed 5 genetic regions that contained variants associated with 3 cancers, including 5p15.33 (*TERT*) and 6p21-22 (HLA), which also exhibit pairwise pleiotropy in multiple cancer combinations. In agreement with these findings, we recently found the strongest evidence of pairwise local genetic correlation among cancers in the 5p15.33 region (39), with 10 independent cancer signals showing genome-wide statistically significance. The pleiotropic variants located in 6p21-22 are part of the HLA region known to be associated with hundreds of traits. Breast, colorectal, endometrial, head and neck, lung, and prostate cancer all showed evidence of cancer-specific pleiotropy in this region. Further work is needed to understand the mechanisms driving these observed associations between single variants and multiple cancers (what we have called *variant-specific pleiotropy*): these could be because of causal effects of a single variant on multiple cancers through a shared mechanism; mediated causal effects, where a variant influences risk of 1 cancer, which then influences the risk of other cancers; or colocalization, where 2 or more variants are each causally associated with a single cancer but are in LD with each other (43). Our variant-specific pleiotropy results identify regions of the genome likely to harbor 1 or more variants associated with 2 or more cancers, but the role of individual variants in these regions is yet to be determined.

Previous cross-cancer GWAS meta-analyses have successfully identified multiple SNPs, many of which have been subsequently replicated in single cancer GWAS as single cancer study sample sizes increase. Studying multiple cancer types simultaneously not only increases statistical power to identify novel susceptibility SNPs but can also lead to a deeper understanding of the global mechanisms underlying cancer development. A weakness with the present analyses is its focus on European ancestry populations and the unbalanced sample sizes across cancer types, with many of our reported findings showing nominal statistical significance with breast cancer, which has the largest sample size. Future cross-cancer analyses aiming at identifying general cancer mechanisms will primarily benefit from increasing the sample size for cancer types with relatively limited number of samples.

In conclusion, our study provides additional insights into the shared genetic architecture of cancer. Although we observed a handful of relatively strong genome-wide genetic correlations across cancers, many correlations were low to moderate. In addition, we observed widespread evidence of cancer pleiotropy for individual variants. We also identified 15 novel loci associated with cancer, none of which has previously been identified in single cancer analyses at genome-wide statistical significance before. Overall, our results suggest that any future GWAS and/or TWAS meta-analysis of multiple cancer sites will continue to lead to the discovery of novel loci and shed further light on the shared genetic architecture underlying common cancer types.

Data availability

This study uses GWAS summary statistics from multiple cancer GWAS. For more detailed information about data access, please email the authors. Available GWAS summary statistics can be accessed at https://bcac.ccge.medschl.cam.ac.uk/bcacdata/oncoarray/oncoarray-and-combined-summary-result/gwas-summary-results-breast-cancer-risk-2017/ (breast), https://www.ebi.ac.uk/gwas/studies/GCST006465 (endometrial), http://practical.icr.ac.uk/blog/?page_id=8164 (prostate), and https://www.ebi.ac.uk/gwas/studies/GCST004418 (ovarian). For the other cancer GWAS, data can be accessed through dbGaP: colorectal cancer (accession numbers: phs001415.v1.p1, phs001078.v1.p1 and phs001856.v1.p1), esophageal cancer (accession number phs000869.v1.p1), glioma GWAS (accession numbers phs001319.v1.p1 and phs000652.v1.p1), head and neck cancer GWAS (accession number phs001202.v1.p1), lung cancer GWAS (phs001273.v3.p2, phs000876.v2.p1), melanoma GWAS (phs001868.v1.p1), pancreatic cancer GWAS (phs000206.v5.p3, phs000648.v1.p1), and renal cancer GWAS (phs001271.v1.p1, phs000351.v1.p1).

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Esophageal cancer GWAS

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Glioma GWAS

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Head and neck cancer GWAS

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Conflicts of interest

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Colorectal cancer GWAS

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