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Lindström, Sara
Wang, Lu
Feng, Helian
et al.

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Article

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

Sara Lindström, PhD,[1,2,*,‡] Lu Wang, PhD,[3,‡] Helian Feng, ScD,[4,‡] Arunabha Majumdar, PhD,[5,6,‡] Sijia Huo, MA,[4,‡] James Macdonald, MS,[3] Tabitha Harrison, MPH,[1] Constance Turman, MS,[7] Hongjie Chen, PhD,[1] Nicholas Mancuso, PhD,[8] Theo Bammler, PhD,[3] Breast Cancer Association Consortium (BCAC), Steve Gallinger, MD,[9] Stephen B. Gruber, MD,[10] Marc J. Gunter, PhD,[11] Loic Le Marchand, PhD,[12] Victor Moreno, PhD,[13,14,15,16] Kenneth Offit, MD,[17,18] Colorectal Transdisciplinary Study (CORECT), Colon Cancer Family Registry Study (CCFR), Genetics And Epidemiology Of Colorectal Cancer Consortium (GECCO), Immaculata De Vivo, PhD,[7,19,20] Tracy A. O'Mara, PhD,[21] Amanda B. Spurdle, PhD,[21] Ian Tomlinson, PhD,[22] Endometrial Cancer Association Consortium (ECAC), Rebecca Fitzgerald, MD,[23] Puya Gharahkhani, PhD,[24] Ines Gockel, MD,[25] Janusz Jankowski, MD,[26,27] Stuart Macgregor, PhD,[24] Johannes Schumacher, PhD,[28] Jill Barnholtz-Sloan, PhD,[29,30] Melissa L. Bondy, PhD,[31] Richard S. Houlston, MD,[32] Robert B. Jenkins, MD,[33] Beatrice Melin, MD,[34] Margaret Wrensch, PhD,[35] Paul Brennan, PhD,[11] David C. Christiani, MD,[7,36] Mattias Johansson, PhD,[11] James Mckay, PhD,[11] Melinda C. Aldrich, PhD,[37] Christopher I. Amos, PhD,[38] Maria Teresa Landi, MD,[29] Adonina Tardon, PhD,[39] International Lung Cancer Consortium (ILCCO), D. Timothy Bishop, MD,[40] Florence Demenais, MD,[41] Alisa M. Goldstein, PhD,[29] Mark M. Iles, PhD,[40] Peter A. Kanetsky, PhD,[42] Matthew H. Law, PhD,[24,43] Ovarian Cancer Association Consortium (OCAC), Laufey T. Amundadottir, PhD,[29] Rachael Stolzenberg-Solomon, PhD,[29] Brian M. Wolpin, MD,[44] Pancreatic Cancer Cohort Consortium (Panscan), Alison Klein, PhD,[45,46] Gloria Petersen, PhD,[47,†] Harvey Risch, MD,[48] Pancreatic Cancer Case-Control Consortium (Panc4), The PRACTICAL Consortium, Stephen J. Chanock, MD,[29] Mark P. Purdue, PhD,[29] Ghislaine Scelo, PhD,[11] Paul Pharoah, PhD,[49] Siddhartha Kar, PhD,[50] Rayjean J. Hung, PhD,[51] Bogdan Pasaniuc, PhD,[5,52,53] Peter Kraft, PhD[4,7]

[1]Department of Epidemiology, University of Washington, Seattle, WA, USA
[2]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
[3]Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, USA
[4]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[5]Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA
[6]Department of Mathematics, Indian Institute of Technology Hyderabad, Kandi, Telangana, India
[7]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[8]Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
[9]Lunenfeld Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada
[10]Department of Medical Oncology & Therapeutics Research, City of Hope National Medical Center, Duarte, CA, USA
[11]International Agency for Research on Cancer, World Health Organization, Lyon, France
[12]University of Hawaii Cancer Center, Honolulu, HI, USA
[13]Oncology Data Analytics Program, Catalan Institute of Oncology-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain
[14]CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain
[15]Department of Clinical Sciences, Faculty of Medicine, University of Barcelona, Barcelona, Spain
[16]ONCOBEL Program, Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain
[17]Clinical Genetics Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
[18]Department of Medicine, Weill Cornell Medical College, New York, NY, USA
[19]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[20]Harvard Radcliffe Institute, Cambridge, MA, USA
[21]Department of Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia
[22]Cancer Research Centre, The University of Edinburgh, Edinburgh, UK
[23]MRC Cancer Unit, Hutchison-MRC Research Centre, University of Cambridge, Cambridge, UK
[24]Statistical Genetics, QIMR Berghofer Medical Research Institute, Brisbane, Australia
[25]Department of Visceral, Transplant, Thoracic and Vascular Surgery, University Hospital of Leipzig, Leipzig, Germany
[26]Institute for Clinical Trials, University College London, Holborn, UK
[27]University of the South Pacific, Suva, Fiji
[28]Center for Human Genetics, University Hospital of Marburg, Marburg, Germany
[29]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
[30]Trans-Divisional Research Program, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
[31]Department of Epidemiology and Population Health, Stanford University, Palo Alto, CA, USA
[32]Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK
[33]Department of Laboratory Medicine and Pathology, Mayo Clinic Comprehensive Cancer Center, Mayo Clinic, Rochester, MN, USA
[34]Department of Radiation Sciences, Umeå University, Umeå, Sweden
[35]Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA, USA
[36]Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[37]Department of Thoracic Surgery, Division of Epidemiology, Vanderbilt University Medical Center, Nashville, TN, USA
[38]Institute for Clinical and Translational Research, Baylor College of Medicine, Houston, TX, USA

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[39]University Institute of Oncology of the Principality of Asturias (IUOPA), University of Oviedo and Spanish Consortium for Research on Epidemiology and Public Health (CIBERESP), Oviedo, Spain
[40]Leeds Institute for Data Analytics, University of Leeds, Leeds, UK
[41]Université Paris Cité, Institut National de la Santé et de la Recherche Médicale (INSERM), UMR-1124, Paris, France
[42]Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA
[43]School of Biomedical Sciences, Faculty of Health, and Institute of Health and Biomedical Innovation, Queensland University of Technology, Kelvin Grove, Queensland, Australia
[44]Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA
[45]Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD, USA
[46]Department of Pathology, Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins School of Medicine, Baltimore, MD, USA
[47]Department of Quantitative Health Science, Mayo Clinic, Rochester, MN, USA
[48]Yale School of Public Health, Chronic Disease Epidemiology, New Haven, CT, USA
[49]Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
[50]Medical Research Council Integrative Epidemiology Unit, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
[51]Prosserman Centre for Population Health Research, Lunenfeld-Tanenbuaum Research Institute, Sinai Health System, Toronto, ON, Canada
[52]Department of Human Genetics, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA
[53]Department of Computational Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA

*Correspondence to: Sara Lindström, PhD, Department of Epidemiology, University of Washington, Hans Rosling Population Health Building, 3980 15th Ave NE, Box 351619, Seattle, WA 98195, USA (e-mail: saralind@uw.edu).
‡These authors contributed equally to this work.
†Deceased January 8, 2023.

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

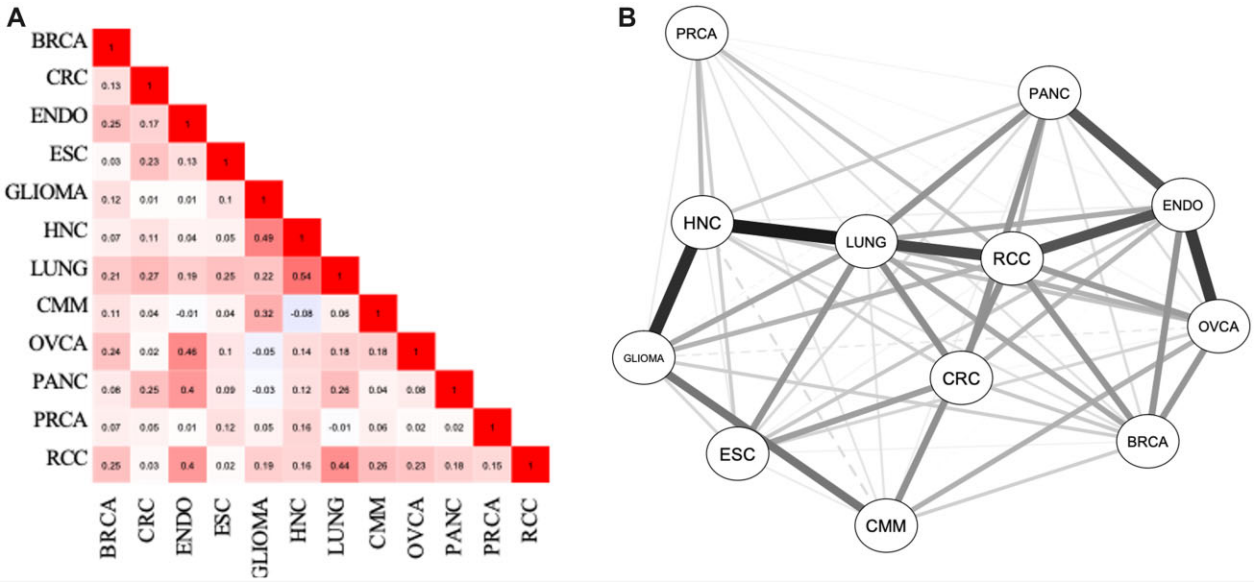

Figure 1. Pairwise genetic correlations between cancers. **(A)** Matrix of pairwise genetic correlations. **(B)** Genetic correlation network. Distance between nodes, edge shade, and edge thickness corresponds to genetic correlation magnitudes. **Dashed lines** indicate negative correlations. BRCA = 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.

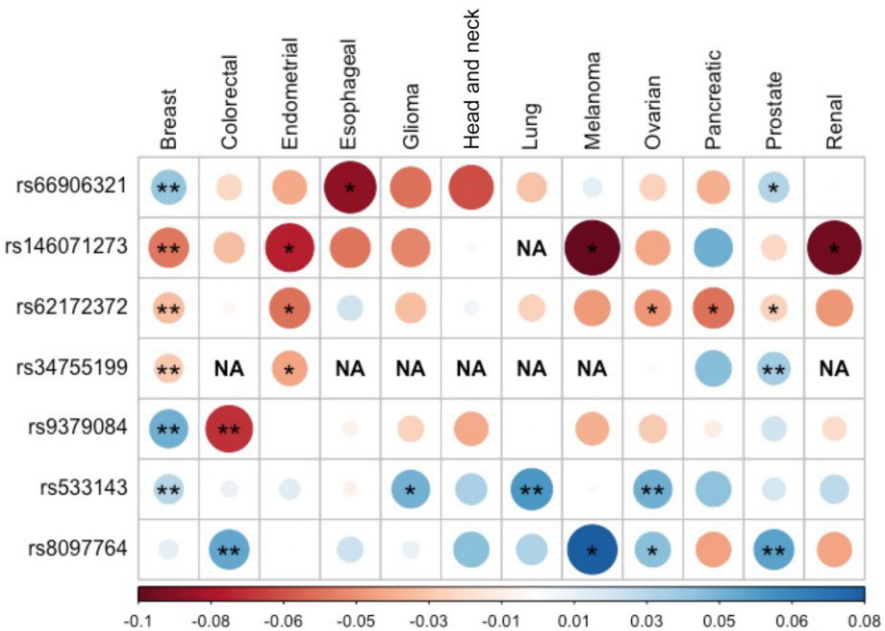

Figure 2. Cancer-specific association results for the lead single-nucleotide polymorphisms of 7 newly identified cancer susceptibility loci. The **circles** correspond to cancer-specific log(odds ratios), with color corresponding to direction of effect and size and shade corresponding to magnitude of 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

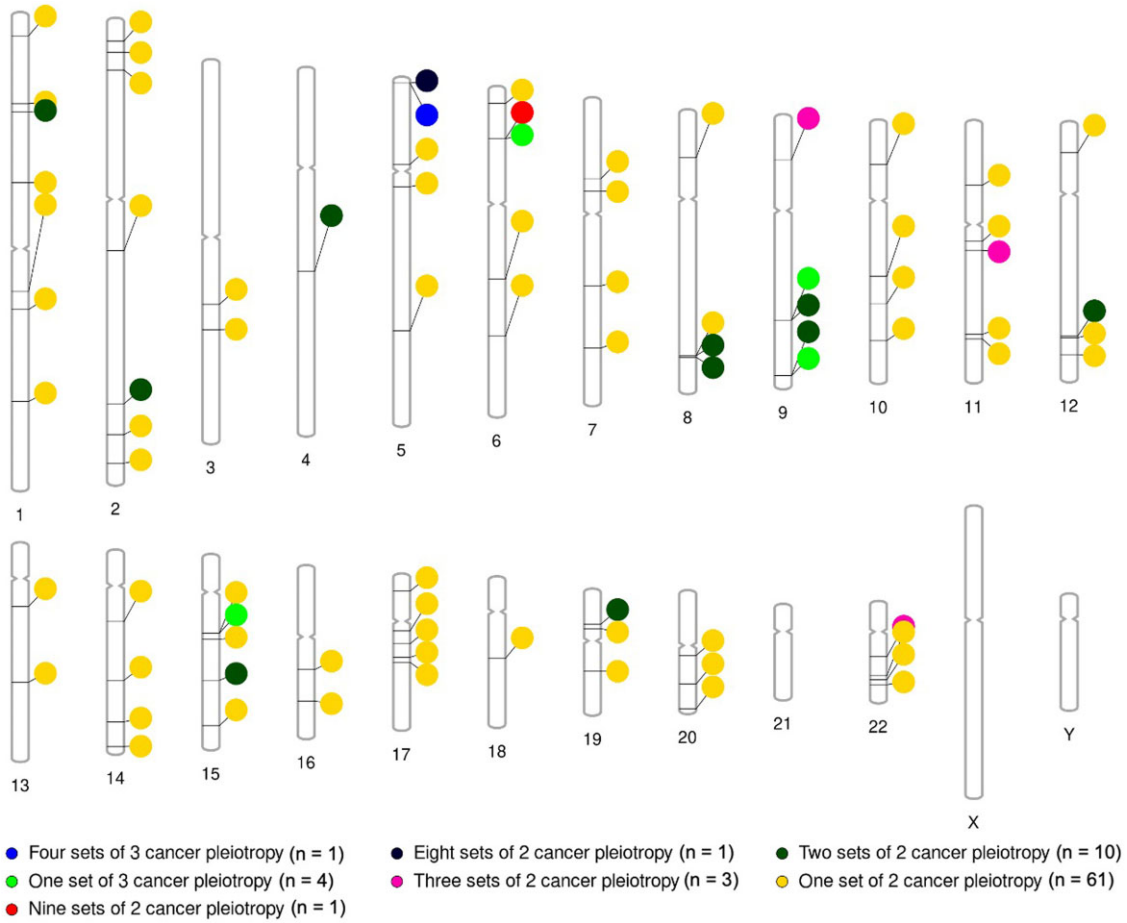

Figure 3. Regions in the genome with evidence of variant-specific pleiotropy. Colors correspond to regions with 4 sets of 3-cancer pleiotropy (**blue**), 1 combination of 3-cancer pleiotropy (**light green**), 9 combinations of pairwise cancer pleiotropy (**red**), 8 combinations of pairwise cancer pleiotropy (**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).

Author contributions

Sara Lindström (Conceptualization, Methodology, Writing—Original Draft, Writing—Review and Editing), Lu Wang (Statistical Analysis, Writing—Review and Editing), Helian Feng (Methodology, Statistical Analysis, Writing—Review and Editing), Arunabha Majumdar (Statistical Analysis, Writing—Review and Editing), Sijia Huo (Methodology, Statistical Analysis, Writing—Review and Editing), James MacDonald (Statistical Analysis, Writing—Review and Editing), Tabitha Harrison (Writing—Review and Editing), Constance Turman (Statistical Analysis, Writing—Review and Editing), Hongjie Chen (Statistical Analysis, Writing—Review and Editing), Nicholas Mancuso (Methodology, Writing—Review and Editing), Theo Bammler (Writing—Review and Editing), Breast Cancer Association Consortium (BCAC) (Data Curation, Writing—Review and Editing), Steve Gallinger (Data Curation, Writing—Review and Editing), Stephen B. Gruber (Data Curation, Writing—Review and Editing), Marc J. Gunter (Data Curation, Writing—Review and Editing), Loic Le Marchand (Data Curation, Writing—Review and Editing), Victor Moreno (Data Curation, Writing—Review and Editing), Kenneth Offit (Data Curation, Writing—Review and Editing), Colorectal Transdisciplinary Study (CORECT) (Data Curation, Writing—Review and Editing), Colon Cancer Family Registry Study (CCFR) (Data Curation, Writing—Review and Editing), Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) (Data Curation, Writing—Review and Editing), Immaculata de Vivo (Data Curation, Writing—Review and Editing), Tracy A. O'Mara (Data Curation, Writing—Review and Editing), Amanda B. Spurdle (Data Curation, Writing—Review and Editing), Ian Tomlinson (Data Curation, Writing—Review and Editing), Endometrial Cancer Association Consortium (ECAC) (Data Curation, Writing—Review and Editing), Rebecca Fitzgerald (Data

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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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Goncalo R Abecasis, Demetrius Albanes, M Henar Alonso, Kristin Anderson, Coral Arnau Collell, Volker Arndt, Christina Bamia, John A, Barron, Elizabeth L Barry, Michael C Bassik, Sonja I Berndt, Stéphane Bézieau, Stephanie Bien, D Timothy Bishop, Juergen Boehm, Heiner Boeing, Hermann Brenner, Stefanie Brezina, Stephan Buch, Daniel D Buchanan, Andrea Burnett Hartman, Bette J Caan, Qiuyin Cai, Peter T Campbell, Christopher S Carlson, Graham Casey, Jose Esteban Castelao, Sergi Castellví Bel, Andrew T Chan, Jenny Chang Claude, Stephen J Chanock, Sai Chen, Lee Soon, Maria Dolores Chirlaque, Sang Hee Cho, James Church, Gerhard Coetzee, David V Conti, Chiara Cremolini, Amanda J Cross, Marcia Cruz Correa, Katarina Cuk, Keith R Curtis, Albert de la Chapelle (deceased), Kimberly F Doheny, David Duggan, Douglas F Easton, Christopher K Edlund, Sjoerd G Elias, Faye Elliott, Dallas R English, Alfredo Falcone, Jane C Figueiredo, Liesel M FitzGerald, Charles Fuchs, Manuela Gago Dominguez, Manish Gala, Steven J Gallinger, William Gauderman, Graham G Giles, Edward Giovannucci, Jian Gong, Phyllis J Goodman, William M Grady, Peyton Greenside, Joel Greenson, John S Grove, Stephen B Gruber, Andrea Gsur, Marc J Gunter, Robert W Haile, Christopher A, Haiman, Jochen Hampe, Heather Hampel, Sophia Harlid, Tabitha A Harrison, Richard B Hayes, Volker Heinemann, Philipp Hofer, Michael Hoffmeister, John L Hopper, Wan Ling Hsu, Li Hsu, Wen Yi Huang, Thomas J Hudson, David J Hunter, Jeroen R Huyghe, Gregory E Idos, Rebecca Jackson, Mark A Jenkins, Jihyoun Jeon, Amit D Joshi, Corinne E Joshu, Hyun Min Kang, Temitope O Keku, Timothy J Key, Hyeong Rok Kim, Laurence N Kolonel, Charles Kooperberg, Tilman Kuhn, Anshul Kundaje, Sébastien Küry, Sun Seog Kweon, Susanna C Larsson, Cecelia A Laurie, Loic Le Marchand, Suzanne M Leal, Soo Chin Lee, Flavio Lejbkowicz, Heinz Josef Lenz, David M Levine, Christopher I Li, Li Li, Wolfgang Lieb, Yi Lin, Annika Lindblom, Noralane M Lindor, Hua Ling, Yun Ru Liu, Tin L Louie, Fotios Loupakis, Frank Luh, Satu Männistö, Sanford D Markowitz, Vicente Martín, Giovanna Masala, Kevin J McDonnell, Caroline E McNeil, Marilena Melas, Roger L Milne, Lorena Moreno, Victor Moreno, Bhramar Mukherjee, Victor Muñoz Garzón, Neil Murphy, Alessio Naccarati, Sarah C Nelson, Polly A Newcomb, Deborah A Nickerson (deceased), Kenneth Offit, Shuji Ogino, N Charlotte Onland Moret, Barbara Pardini, Patrick S Parfrey, Rachel Pearlman, Vittorio Perduca, Julyann Pérez Mayoral, Ulrike Peters, Paul D P Pharoah, Mila Pinchev, Elizabeth A Platz, Sarah Plummer, John D Potter, Ross L Prentice, Elizabeth Pugh, Conghui Qu, Chenxu Qu, Leon Raskin, Gad Rennert, Hedy S Rennert, Elio Riboli, Miguel Rodríguez Barranco, Jane Romm, Lori C Sakoda, Peter C Scacheri, Clemens Schafmayer, Stephanie L Schmit, Robert E Schoen, Fredrick R Schumacher, Daniela Seminara, Gianluca Severi, Mitul Shah, Tameka Shelford, David Shibata, Min Ho Shin, Xiao Ou Shu, Katerina Shulman, Erin Siegel, Sabina Sieri, Nasa A Sinnott Armstrong, Martha L Slattery, Joshua D Smith, Melissa C Southey, Zsofia K Stadler, Mariana Stern, Sebastian Stintzing, Yu Ru Su, Catherine M Tangen, Stephen N Thibodeau, Duncan C Thomas, cSushma S Thomas, Amanda E Toland, Antonia Trichopoulou, Cornelia M Ulrich, David J Van Den Berg, Franzel JB van Duijnhoven, Bethany Van Guelpen, Henk van Kranen, Joseph Vijai, Kala Visvanathan, Pavel Vodicka, Ludmila Vodickova, Veronika Vymetalkova, Michael Wainberg, Hansong Wang, Korbinian Weigl, Stephanie J Weinstein, Emily White, Lynne R Wilkens, Aung Ko Win, C Roland Wolf, Alicja Wolk, Michael O Woods, Anna H Wu, Yun Yen, Syed H Zaidi, Brent W Zanke, Wei Zheng.

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Frederic Amant, Daniela Annibali, Katie Ashton, John Attia, Paul L Auer, Matthias W, Beckmann, Amanda Black, Louise Brinton, Daniel D, Buchanan, Stephen J, Chanock, Chu Chen, Maxine M, Chen, Timothy H, T, Cheng, Linda S, Cook, Marta Crous Bous, Immaculata De Vivo, Joe Dennis, Thilo Dörk, Sean C, Dowdy, Alison M, Dunning, Matthias Dürst, Douglas F, Easton, Arif B, Ekici, Peter A, Fasching, Brooke L, Fridley, Christine M, Friedenreich, Montserrat García Closas, Mia M, Gaudet, Graham G, Giles, Dylan M, Glubb, Ellen L, Goode, Maggie Gorman, Christopher A, Haiman, Susan E, Hankinson, Catherine S, Healey, Alexander Hein, Peter Hillemanns, Shirley Hodgson, Erling Hoivik, Elizabeth G, Holliday, David J, Hunter, Angela Jones, Peter Kraft, Camilla Krakstad, Diether Lambrechts, Loic Le Marchand, Xiaolin Liang, Annika Lindblom, Jolanta Lissowska, Jirong Long, Lingeng Lu, Anthony M, Magliocco, Lynn Martin, Mark McEvoy, Roger L, Milne, Miriam Mints, Rami Nassir, Tracy A, O'Mara, Irene Orlow, Geoffrey Otton, Claire Palles, Paul D, P, Pharoah, Loreall Pooler, Jennifer Prescott, Tony Proietto, Timothy R, Rebbeck, Stefan P, Renner, Harvey A, Risch, Matthias Ruebner, Ingo Runnebaum, Carlotta Sacerdote, Gloria E, Sarto, Fredrick Schumacher, Rodney J, Scott, V, Wendy Setiawan, Mitul Shah, Xin Sheng, Xiao Ou Shu, Melissa C, Southey, Amanda B, Spurdle, Emma Tham, Deborah J, Thompson, Ian Tomlinson, Jone Trovik, Constance Turman, David Van Den Berg, Zhaoming Wang, Penelope M, Webb, Nicolas Wentzensen, Stacey J Winham, Lucy Xia, Yong Bing Xiang, Hannah P, Yang, Herbert Yu, Wei Zheng.

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Puya Gharahkhania, Rebecca C Fitzgerald, Thomas L Vaughan, Claire Palles, Ines Gockel, Ian Tomlinson, Matthew F Buas, Andrea May, Christian Gerges, Mario Anders, Jessica Becker, Nicole Kreuser, Tania Noder, Marino Venerito, Lothar Veits, Thomas Schmidt, Hendrik Manner, Claudia Schmidt, Timo Hess, Anne C Böhmer, Jakob R Izbicki, Arnulf H Hölscher, Hauke Lang, Dietmar Lorenz, Brigitte Schumacher, Andreas Hackelsberger, Rupert Mayershofer, Oliver Pech, Yogesh Vashist, Katja Ott, Michael Vieth, Josef Weismüller, Markus M Nöthen, Barrett's and Esophageal Adenocarcinoma Consortium (BEACON), Esophageal Adenocarcinoma GenEtics Consortium (EAGLE), Wellcome Trust Case Control Consortium (WTCCC), Stephen Attwood, Hugh Barr, Laura Chegwidden, John de Caestecker, Rebecca Harrison, Sharon B Love, David MacDonald, Paul Moayyedi, Hans Prenen, R G Peter Watson, Prasad G Iyer, Lesley A Anderson, Leslie Bernstein, Wong Ho Chow, Laura J Hardie, Jesper Lagergren, Geoffrey Liu, Harvey A Risch, Anna H Wu, Weimin Ye, Nigel C Bird, Nicholas J Shaheen, Marilie D Gammon, Douglas A Corley, Carlos Caldas, Susanne Moebus, Michael Knapp, Wilbert H M Peters, Horst Neuhaus, Thomas Rösch, Christian Ell, Stuart MacGregor, Paul Pharoah, David C Whiteman, Janusz Jankowski, Johannes Schumacher.

Glioma GWAS

Melissa L Bondy, Ryan T Merrell, Daniel Lachance, Georgina N Armstrong, Margaret R Wrensch, Dora Il'yasova, Elizabeth B Claus, Jill S Barnholtz Sloan, Joellen Schildkraut, Siegal Sadetzki, Christoffer Johansen, Richard S Houlston, Robert B Jenkins, Jonine L Bernstein, Rose Lai, Beatrice Melin.

Lung cancer GWAS

International lung cancer consortium (ILCCO) members

Demetrios Albanes, Melinda C Aldrich, Christopher I Amos, Angeline Andrew, Susanne Arnold, Heike Bickeböller, Stig E Bojesen, Paul Brennan, Hans Brunnström, Neil Caporaso, Chu Chen, David Christiani, Angela Cox, John K Field, Kjell Grankvist, Rayjean J Hung, Mattias Johansson, Mikael Johansson, Lambertus A Kiemeney, Stephen Lam, Maria Teresa Landi, Philip Lazarus, Geoffrey Liu, James MacKay, Loic Le Marchand, Olle Melander, Gadi Rennert, Angela Risch, Matthew B Schabath, Sanjay S Shete, Adonina Tardon, H, Erich Wichmann, Shan Zienolddiny Narut.

Melanoma GWAS consortium members

The list of Melanoma GWAS Consortium Members and affiliations shown in this document are co-authors of reference (13). More details on additional members associated to the Melanoma GWAS consortium, acknowledgements and funding can be found in reference (13).

Matthew H Law, D Timothy Bishop, Jeffrey E Lee, Myriam Brossard, Nicholas G Martin, Eric K Moses, Fengju Song, Jennifer H Barrett, Rajiv Kumar, Douglas F Easton, Paul D P Pharoah, Anthony J Swerdlow, Katerina P Kypreou, John C Taylor, Mark Harland, Juliette Randerson Moor, Lars A Akslen, Per A Andresen, Marie Françoise Avril, Esther Azizi, Giovanna Bianchi Scarrà, Kevin M Brown, Tadeusz Dębniak, David L Duffy, David E Elder, Shenying Fang, Eitan Friedman, Pilar Galan, Paola Ghiorzo, Elizabeth M Gillanders, Alisa M Goldstein, Nelleke A Gruis, Johan Hansson, Per Helsing, Marko Hočevar, Veronica Höiom, Christian Ingvar, Peter A Kanetsky, Wei V Chen, GenoMEL Consortium, Essen Heidelberg Investigators, The SDH Study Group, Q MEGA and QTWIN Investigators, AMFS Investigators, ATHENS Melanoma Study Group, Maria Teresa Landi, Julie Lang, G Mark Lathrop, Jan Lubiński, Rona M Mackie, Graham J Mann, Anders Molven, Grant W Montgomery, Srdjan Novaković, Håkan Olsson, Susana Puig, Joan Anton Puig Butille, Abrar A Qureshi, Graham L Radford Smith, Nienke van der Stoep, Remco van Doorn, David C Whiteman, Jamie E Craig, Dirk Schadendorf, Lisa A Simms, Kathryn P Burdon, Dale R Nyholt, Karen A Pooley, Nick Orr, Alexander J Stratigos, Anne E Cust, Sarah V Ward, Nicholas K Hayward, Jiali Han, Hans Joachim Schulze, Alison M Dunning, Julia A Newton Bishop, Florence Demenais, Christopher I Amos, Stuart MacGregor & Mark M Iles.

Ovarian cancer GWAS

Katja KH Aben, Kathryn Alsop, Natalia N Antonenkova, Gerassimos Aravantinos, Elisa V Bandera, Yukie Bean, Matthias W Beckmann, Alicia Beeghly Fadiel, Jonathan Beesley, Sabine Behrens, Javier Benitez, Andrew Berchuck, Marina Bermisheva, Line Bjorge, Amanda Black, Clara Bodelon, Natalia V Bogdanova, James D Brenton, Per Broberg, Angela Brooks Wilson, Fiona Bruinsma, Clareann H Bunker, Ralf Butzow, Michael E Carney, Ilana Cass, Jenny Chang Claude, Stephen J Chanock, Y Ann Chen, Zhihua Chen, Georgia Chenevix Trench, Linda S Cook, Daniel W Cramer, Julie M Cunningham, Kara L Cushing Haugen, Cezary Cybulski, Fanny Dao, Joe Dennis, Brenda B Diergaarde, Suzanne Dixon, Jennifer A Doherty, Thilo Dörk, Laure Dossus, Andreas du Bois, Matthias Dürst, Todd Edwards, Arif B Ekici, Svend Aage Engelholm, Peter A Fasching, Zachary C Fogarty, Renee T Fortner, Florentia Fostira, George Fountzilas, Jan Gawełko, Graham G Giles, Ellen L Goode, Marc T Goodman, Jacek Gronwald, AOCS Group, OPAL Study Group, Christopher A Haiman, Holly R Harris, Philipp Harter, Alexander Hein, Florian Heitz, Betrand Hemon, Michelle AT Hildebrandt, Peter Hillemanns, Estrid Hogdall, Claus K Hogdall, Alison Hopkins, Ruea Yea Huang, Chad Huff, Edwin S Iversen, Mats Jennertz, Allan Jensen, Sharon E Johnatty, Michael E Jones, Pääivy Kannistö, Siddhartha Kar, Beth Y Karlan, Linda E Kelemen, Melissa Kellar, Elza Khusnutdinova, Lambertus A Kiemeney, Susanne K Kjaer, Martin Köbel, Reidun K Kopperud, Bridget Kruszka, Diether Lambrechts, Nhu D Le, Loic Le Marchand, Shashikant B Lele, Jenny Lester, Douglas A Levine, Andrew J Li, Dong Liang, Clemens Liebrich, Hui Yi Lin, Loren Lipworth, Jolanta Lissowska, Karen H Lu, Jan Lubiński, Lene Lundvall, Jeffrey R, Marks, Melissa Merritt, Roger L Milne, Stacey Missmer, Francesmary Modugno, Melissa Moffitt, Alvaro N Monteiro, Patricia G Moorman, Carl Morrison, Kirsten B, Moysich, Lotte Nedergaard, Heli Nevanlinna, Katie O'Brien, Kunle Odunsi, Sara H Olson, Håkan Olsson, Irene Orlow, Nick Orr, Ana Osorio, Lisa E, Paddock, Tjoung Won Park Simon, Tanja Pejovic, Liisa M Pelttari, Paul DP Pharoah, Anna Piskorz, Darya Prokofyeva, Megan S Rice, Marjorie J Riggan, Harvey A Risch, Cristina Rodriguez Antona, Isabelle Romieu, Mary Anne Rossing, Ingo Runnebaum, Dina D Sakaeva, Joellen M Schildkraut, Minouk J Schoemaker, Ira Schwaab, V Wendy Setiawan, Helen Steed, Lara Sucheston, Anthony J Swerdlow, Ingvild L Tangen, Kathryn L Terry, Pamela J Thompson, Liv Cecilie Vestrheim Thomsen, Linda Titus, Mary K Townsend, Britton Trabert, Shelley S Tworoger, Jonathan P Tyrer, Anne M van Altena, Els Van Nieuwenhuysen, Adriaan Vanderstichele, Digna Velez Edwards, Ignace Vergote, Roel CH Vermeulen, Allison F Vitonis, Frances Wang, Shan Wang Gohrke, Penelope M Webb, Nicolas Wentzensen, Stacey J Winham, Hannah P Yang, Drakoulis Yannoukakos, Hoda Anton Culver, Marcus Q Bernardini, Alison H Brand, Robert Brown, Agnieszka Budzilowska, Hui Cai, Ian Campbell, Karen Carty, Yoke Eng Chiew, Agnieszka Dansonka Mieszkowska, Anna deFazio, Diana M Eccles, Ailith Ewing, Anna Felisiak Golabek, Sarah Ferguson, James M Flanagan, Bo Gao, Simon A Gayther, Aleksandra Gentry Maharaj, Rosalind Glasspool, Niclas Håkansson, Sandra D Halverson, Paul R Harnett, David G Huntsman, Anthony Karnezis, Stanley B Kaye, Catherine J Kennedy, Stefan Kommoss, Bozena Konopka, Björg Kristjansdottir, Jolanta Kupryjanczyk, Kate Lawrenson, Alice W Lee, Radoslaw Madry, Taymaa May, Jessica McAlpine, Valerie McGuire, John R McLaughlin, Iain A McNeish, Usha Menon, Joanna Moes Sosnowska, Steven A Narod, Ying Ng, Celeste L, Pearce, Malcolm C Pike, Judith Pike, Joanna Plisiecka Halasa, Agnieszka Podgorska, Susan J Ramus, Joseph H Rothstein, Iwona K Rzepecka, Dale P Sandler, Jennifer Santos, Wlodzimierz Sawicki, Janine Senz, Nadeem Siddiqui, Weiva Sieh, Beata Spiewankiewicz, Daniel O Stram, Karin Sundfeldt, Rebecca Sutphen, Lukasz Szafron, Jack A Taylor, Rachel T Teten, Agnieszka Timorek, Anne Tinker, Alicia Tone, David Van Den Berg, Birgitta Weijdegård, Clarice R Weinberg, Emily White, Alice S Whittemore, Alicja Wolk, Michelle Woo, Anna H Wu, Wei Zheng, Argyrios Ziogas.

Pancreatic cancer GWAS

Pancreatic cancer cohort consortium (PanScan) authors

Demetrius Albanes, Gabriella Andreotti, Alan A Arslan, Laura Beane Freeman, Sonja I Berndt, Julie Buring, Federico Canzian, Neal D Freedman, J. Michael Gaziano, Graham G Giles, Edward Giovannucci, Phyllis J Goodman, Christopher Haiman, Eric J Jacobs, Verena Katzke, Manolis Kogevinas, Charles Kooperberg, Peter Kraft, Loic LeMarchand, Núria Malats, Marjorie L McCullough, Roger L Milne, Alpa V Patel, Ulrike Peters, Miguel Porta, Elio Riboli, Xiao Ou Shu, Malin Sund, Anne Tjønneland, Kala Visvanathan, Jean Wactawski Wende, Emily White, Anne Zeleniuch Jacquotte, Wei Zheng, Jun Zhong, Stephen J Chanock, Brian M Wolpin, Rachael Z Stolzenberg Solomon, Laufey T Amundadottir.

Pancreatic cancer case control consortium (PanC) authors

Alison P. Klein, Erica J. Childs, Paige M. Bracci, Steven Gallinger, Rachel E. Neale, Mengmeng Du, William R. Bamlet, Paul Brennan, Kari G. Rabe, Manal Hassan, Elizabeth A. Holly, Rayjean J. Hung, Michael Goggins, Robert C. Kurtz, Stephen Van Den Eeden, Sandra Perdomo, Gloria M. Petersen, Harvey A. Risch, Donghui Li.

Prostate cancer GWAS

The PRACTICAL consortium (http://practical.icr.ac.uk/)

Rosalind A. Eeles, Christopher A. Haiman, Zsofia Kote Jarai, Fredrick R. Schumacher, Sara Benlloch, Ali Amin Al Olama, Kenneth R. Muir, Sonja I. Berndt, David V. Conti, Fredrik Wiklund, Stephen Chanock, Ying Wang, Catherine M. Tangen, Jyotsna Batra, Judith A. Clements, APCB BioResource (Australian Prostate Cancer BioResource), Henrik Grönberg, Nora Pashayan, Johanna Schleutker, Demetrius Albanes, Stephanie J. Weinstein, Alicja Wolk, Catharine M. L. West, Lorelei A. Mucci, Géraldine Cancel Tassin, Stella Koutros, Karina Dalsgaard Sørensen, Eli Marie Grindedal, David E. Neal, Freddie C. Hamdy, Jenny L. Donovan, Ruth C. Travis, Robert J. Hamilton, Sue Ann Ingles, Barry S. Rosenstein, Yong Jie Lu, Graham G. Giles, Robert J. MacInnis, Adam S. Kibel, Ana Vega, Manolis Kogevinas, Kathryn L. Penney, Jong Y. Park, Janet L. Stanford, Cezary Cybulski, Børge G. Nordestgaard, Sune F. Nielsen, Hermann Brenner, Christiane Maier, Jeri Kim, Esther M. John, Manuel R. Teixeira, Susan L. Neuhausen, Kim De Ruyck, Azad Razack, Lisa F. Newcomb, Davor Lessel, Radka Kaneva, Nawaid Usmani, Frank Claessens, Paul A. Townsend, Jose Esteban Castelao, Ron H.N. van Schaik, Florence Menegaux, Kay Tee Khaw, Lisa Cannon Albright, Hardev Pandha, Stephen N. Thibodeau, David J. Hunter, Peter Kraft, William J. Blot, Elio Riboli.

Renal cancer GWAS

Ghislaine Scelo, Mark P Purdue, Kevin M Brown, Mattias Johansson, Zhaoming Wang, Jeanette E Eckel Passow, Yuanqing Ye, Jonathan N Hofmann, Jiyeon Choi, Matthieu Foll, Valerie Gaborieau, Mitchell J Machiela, Leandro M Colli, Peng Li, Joshua N Sampson, Behnoush Abedi Ardekani, Celine Besse, Helene Blanche, Anne Boland, Laurie Burdette, Amelie Chabrier, Geoffroy Durand, Florence Le Calvez Kelm, Egor Prokhortchouk, Nivonirina Robinot, Konstantin G Skryabin, Magdalena B Wozniak, Meredith Yeager, Gordana Basta Jovanovic, Zoran Dzamic, Lenka Foretova, Ivana Holcatova, Vladimir Janout, Dana Mates, Anush Mukeriya, Stefan Rascu, David Zaridze, Vladimir Bencko, Cezary Cybulski, Eleonora Fabianova, Viorel Jinga, Jolanta Lissowska, Jan Lubinski, Marie Navratilova, Peter Rudnai, Neonila Szeszenia Dabrowska, Simone Benhamou, Geraldine Cancel Tassin, Olivier Cussenot, Laura Baglietto, Heiner Boeing, Kay Tee Khaw, Elisabete Weiderpass, Borje Ljungberg, Raviprakash T Sitaram, Fiona Bruinsma, Susan J Jordan, Gianluca Severi, Ingrid Winship, Kristian Hveem, Lars J Vatten, Tony Fletcher, Kvetoslava Koppova, Susanna C Larsson, Alicja Wolk, Rosamonde E Banks, Peter J Selby, Douglas F Easton, Paul Pharoah, Gabriella Andreotti, Laura E Beane Freeman, Stella Koutros, Demetrius Albanes, Satu Männistö, Stephanie Weinstein, Peter E Clark, Todd L Edwards, Loren Lipworth, Susan M Gapstur, Victoria L Stevens, Hallie Carol, Matthew L Freedman, Mark M Pomerantz, Eunyoung Cho, Peter Kraft, Mark A Preston, Kathryn M Wilson, J Michael Gaziano, Howard D Sesso, Amanda Black, Neal D Freedman, Wen Yi Huang, John G Anema, Richard J Kahnoski, Brian R Lane, Sabrina L Noyes, David Petillo, Bin Tean Teh, Ulrike Peters, Emily White, Garnet L Anderson, Lisa Johnson, Juhua Luo, Julie Buring, I Min Lee, Wong Ho Chow, Lee E Moore, Christopher Wood, Timothy Eisen, Marc Henrion, James Larkin, Poulami Barman, Bradley C Leibovich, Toni K Choueiri, G Mark Lathrop, Nathaniel Rothman, Jean Francois Deleuze, James D McKay, Alexander S Parker, Xifeng Wu, Richard S Houlston, Paul Brennan, Stephen J Chanock.

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