OXFORD

JNCI: Journal of the National Cancer Institute, 2023, **115(6)**, 712–732

https://doi.org/10.1093/jnci/djad043
Advance Access Publication Date: 17 March 2023
Article

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

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Received: June 15, 2022. **Revised:** November 07, 2022. **Accepted:** February 14, 2023
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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

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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

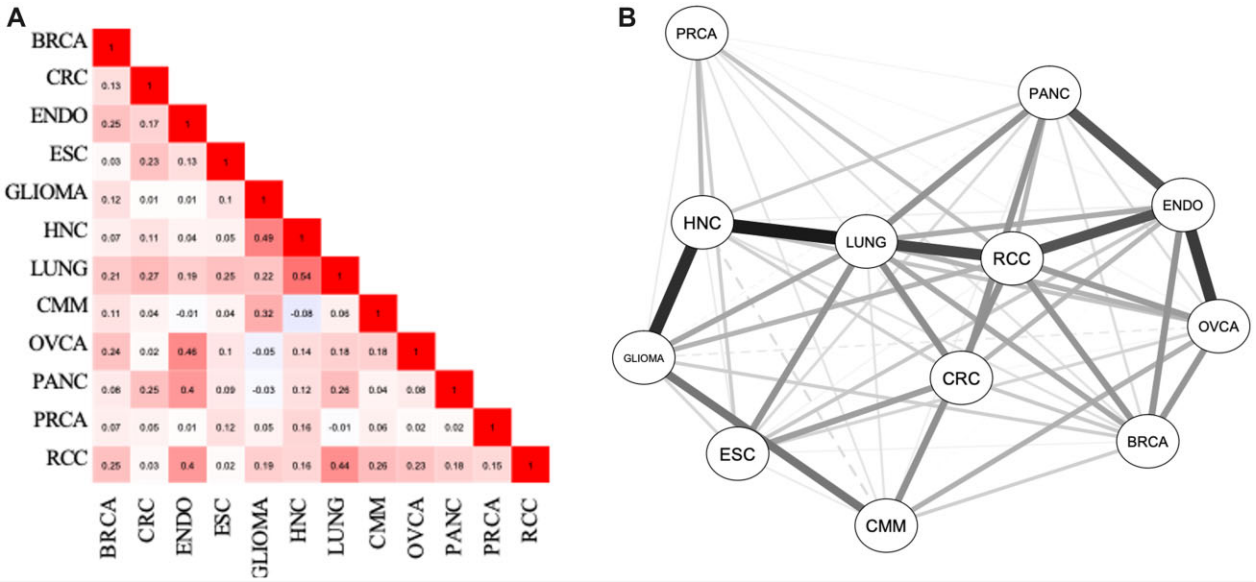

Figure 1. Pairwise genetic correlations between cancers. **(A)** Matrix of pairwise genetic correlations. **(B)** Genetic correlation network. Distance between nodes, edge shade, and edge thickness corresponds to genetic correlation magnitudes. **Dashed lines** indicate negative correlations. BRCA =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

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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.

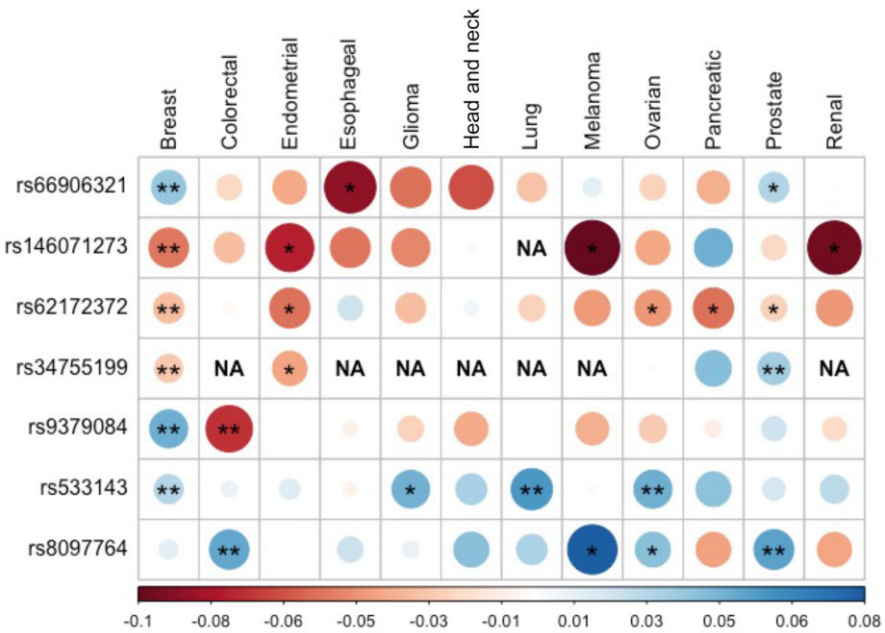

Figure 2. Cancer-specific association results for the lead single-nucleotide polymorphisms of 7 newly identified cancer susceptibility loci. The **circles** correspond to cancer-specific log(odds ratios), with color corresponding to direction of effect and size and shade corresponding to magnitude of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

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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

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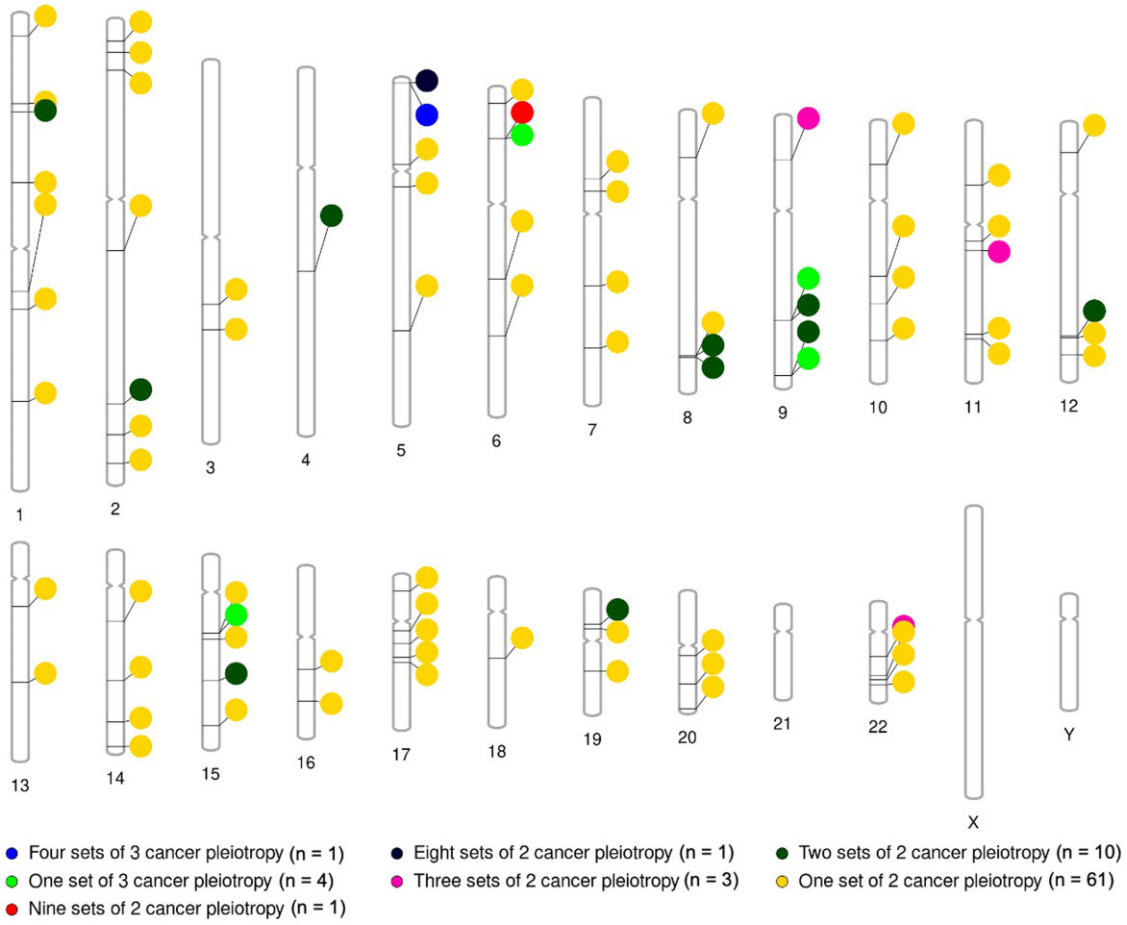

Figure 3. Regions in the genome with evidence of variant-specific pleiotropy. Colors correspond to regions with 4 sets of 3-cancer pleiotropy (**blue**), 1 combination of 3-cancer pleiotropy (**light green**), 9 combinations of pairwise cancer pleiotropy (**red**), 8 combinations of pairwise cancer pleiotropy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

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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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Curation, Writing—Review and Editing), Puya Gharahkhani (Data Curation, Writing—Review and Editing), Ines Gockel (Data Curation, Writing—Review and Editing), Janusz Jankowski (Data Curation, Writing—Review and Editing), Stuart MacGregor (Data Curation, Writing—Review and Editing), Johannes Schumacher (Data Curation, Writing—Review and Editing), Jill Barnholtz-Sloan (Data Curation, Writing—Review and Editing), Melissa L. Bondy (Data Curation, Writing—Review and Editing), Richard S. Houlston (Data Curation, Writing—Review and Editing), Robert B. Jenkins (Data Curation, Writing—Review and Editing), Beatrice Melin (Data Curation, Writing—Review and Editing), Margaret Wrensch (Data Curation, Writing—Review and Editing), Paul Brennan (Data Curation, Writing—Review and Editing), David C Christiani (Data Curation, Writing—Review and Editing), Mattias Johansson (Data Curation, Writing—Review and Editing), James McKay (Data Curation, Writing—Review and Editing), Melinda C. Aldrich (Data Curation, Writing—Review and Editing), Christopher I. Amos (Data Curation, Writing—Review and Editing), Maria Teresa Landi (Data Curation, Writing—Review and Editing), Adonina Tardon (Data Curation, Writing—Review and Editing), International Lung Cancer Consortium (ILCCO) (Data Curation, Writing—Review and Editing), D Timothy Bishop (Data Curation, Writing—Review and Editing), Florence Demenais (Data Curation, Writing—Review and Editing), Alisa M Goldstein (Data Curation, Writing—Review and Editing), Mark M Iles (Data Curation, Writing—Review and Editing), Peter A Kanetsky (Data Curation, Writing—Review and Editing), Matthew H Law (Data Curation, Writing—Review and Editing), Ovarian Cancer Association Consortium (OCAC) (Data Curation, Writing—Review and Editing), Laufey T Amundadottir (Data Curation, Writing—Review and Editing), Rachael Stolzenberg-Solomon (Data Curation, Writing—Review and Editing), Brian M Wolpin (Data Curation, Writing—Review and Editing), Pancreatic Cancer Cohort Consortium (PanScan) (Data Curation, Writing—Review and Editing), Alison Klein (Data Curation, Writing—Review and Editing), Gloria Petersen (Data Curation, Writing—Review and Editing), Harvey Risch (Data Curation, Writing—Review and Editing), Pancreatic Cancer Case-Control Consortium (PanC4) (Data Curation, Writing—Review and Editing), The PRACTICAL consortium (Data Curation, Writing—Review and Editing), Stephen J. Chanock (Data Curation, Writing—Review and Editing), Mark P. Purdue (Data Curation, Writing—Review and Editing), Ghislaine Scelo (Data Curation, Writing—Review and Editing), Paul Pharoah (Conceptualization, Methodology, Data Curation, Writing—Review and Editing), Siddhartha Kar (Conceptualization, Methodology, Data Curation, Writing—Review and Editing), Rayjean J. Hung (Conceptualization, Methodology, Data Curation, Writing—Review and Editing), Bogdan Pasaniuc (Methodology, Writing—Review and Editing), Peter Kraft (Conceptualization, Methodology, Data Curation, Writing—Original Draft, Writing—Review and Editing).

Funding

This work was supported by CA194393.

Breast cancer GWAS (BCAC)

The breast cancer genome-wide association analyses were supported by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research, the "Ministère de l'Économie, de la Science et de l"Innovation du Québec" through Genome Québec and grant PSR-SIIRI-701, The National Institutes of Health (U19 CA148065, X01HG007492), Cancer Research UK (C1287/A10118, C1287/A16563, C1287/A10710) and The European Union (HEALTH-F2-2009-223175 and H2020 633784 and 634935). All studies and funders are listed in Michailidou et al (Nature, 2017).

Colorectal cancer GWAS (CCFR-CORECT-GECCO)

GECCO: Genetics and Epidemiology of Colorectal Cancer Consortium: National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services (U01 CA164930, U01 CA137088, R01 CA059045, R21 CA191312, R01201407). Genotyping/Sequencing services were provided by the Center for Inherited Disease Research (CIDR) contract number HHSN2682017000006I and HHSN2682012000008I. This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA015704. Scientific Computing Infrastructure at Fred Hutch funded by ORIP grant S10OD028685. ASTERISK: a Hospital Clinical Research Program (PHRC-BRD09/C) from the University Hospital Center of Nantes (CHU de Nantes) and supported by the Regional Council of Pays de la Loire, the Groupement des Entreprises Françaises dans la Lutte contre le Cancer (GEFLUC), the Association Anne de Bretagne Génétique and the Ligue Régionale Contre le Cancer (LRCC). The ATBC Study is supported by the Intramural Research Program of the U.S. National Cancer Institute, National Institutes of Health. CLUE II funding was from the National Cancer Institute (U01 CA86308, Early Detection Research Network; P30 CA006973), National Institute on Aging (U01 AG18033), and the American Institute for Cancer Research. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government. Maryland Cancer Registry (MCR) Cancer data was provided by the Maryland Cancer Registry, Center for Cancer Prevention and Control, Maryland Department of Health, with funding from the State of Maryland and the Maryland Cigarette Restitution Fund. The collection and availability of cancer registry data is also supported by the Cooperative Agreement NU58DP006333, funded by the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services. ColoCare: This work was supported by the National Institutes of Health (grant numbers R01 CA189184 (Li/Ulrich), U01 CA206110 (Ulrich/Li/Siegel/Figueireido/Colditz, 2P30CA015704- 40 (Gilliland), R01 CA207371 (Ulrich/Li)), the Matthias Lackas-Foundation, the German Consortium for Translational Cancer Research, and the EU TRANSCAN initiative. The Colon Cancer Family Registry (CCFR, www.coloncfr.org) is supported in part by funding from the National Cancer Institute (NCI), National Institutes of Health (NIH) (award U01 CA167551). Support for case ascertainment was provided in part from the Surveillance, Epidemiology, and End Results (SEER) Program and the following U.S. state cancer registries: AZ, CO, MN, NC, NH; and by the Victoria Cancer Registry (Australia) and Ontario Cancer Registry (Canada). The CCFR Set-1 (Illumina 1M/1M-Duo) and Set-2 (Illumina Omni1-Quad) scans were supported by NIH awards U01 CA122839 and R01 CA143237 (to GC). The CCFR Set-3 (Affymetrix Axiom CORECT Set array) was supported by NIH award U19 CA148107 and R01 CA81488 (to SBG). The CCFR Set-4 (Illumina OncoArray 600K SNP array) was supported by NIH award U19 CA148107 (to SBG) and by the Center for Inherited Disease Research (CIDR), which is funded by the NIH to the Johns Hopkins University, contract number HHSN2682012000008I.

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Additional funding for the OFCCR/ARCTIC was through award GL201-043 from the Ontario Research Fund (to BWZ), award 112746 from the Canadian Institutes of Health Research (to TJH), through a Cancer Risk Evaluation (CaRE) Program grant from the Canadian Cancer Society (to SG), and through generous support from the Ontario Ministry of Research and Innovation. The SFCCR Illumina HumanCytoSNP array was supported in part through NCI/NIH awards U01 CA074794 (to JDP) and/U24 CA074794 and R01 CA076366 (to PAN). The content of this manuscript does not necessarily reflect the views or policies of the NCI, NIH or any of the collaborating centers in the Colon Cancer Family Registry (CCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government, any cancer registry, or the CCFR. COLON: The COLON study is sponsored by Wereld Kanker Onderzoek Fonds, including funds from grant 2014/1179 as part of the World Cancer Research Fund International Regular Grant Programme, by Alpe d'Huzes and the Dutch Cancer Society (UM 2012-5653, UW 2013-5927, UW2015-7946), and by TRANSCAN (JTC2012-MetaboCCC, JTC2013-FOCUS). The Nqplus study is sponsored by a ZonMW investment grant (98-10030); by PREVIEW, the project PREVention of diabetes through lifestyle intervention and population studies in Europe and around the World (PREVIEW) project which received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant no. 312057; by funds from TI Food and Nutrition (cardiovascular health theme), a public–private partnership on precompetitive research in food and nutrition; and by FOODBALL, the Food Biomarker Alliance, a project from JPI Healthy Diet for a Healthy Life. Colorectal Cancer Transdisciplinary (CORECT) Study: The CORECT Study was supported by the National Cancer Institute, National Institutes of Health (NCI/NIH), U.S. Department of Health and Human Services (grant numbers U19 CA148107, R01 CA081488, P30 CA014089, R01 CA197350; P01 CA196569; R01 CA201407; R01 CA242218),National Institutes of Environmental Health Sciences, National Institutes of Health (grant number T32 ES013678) and a generous gift from Daniel and Maryann Fong. CORSA: "Österreichische Nationalbank Jubiläumsfondsprojekt" (12511) and Austrian Research Funding Agency (FFG) grant 829675. CPS-II: The American Cancer Society funds the creation, maintenance, and updating of the Cancer Prevention Study-II (CPS-II) cohort. This study was conducted with Institutional Review Board approval. CRCGEN: Colorectal Cancer Genetics & Genomics, Spanish study was supported by Instituto de Salud Carlos III, co-funded by FEDER funds –a way to build Europe– (grants PI14-613 and PI09-1286), Agency for Management of University and Research Grants (AGAUR) of the Catalan Government (grant 2017SGR723), and Junta de Castilla y León (grant LE22A10-2). Sample collection of this work was supported by the Xarxa de Bancs de Tumors de Catalunya sponsored by Pla Director d'Oncología de Catalunya (XBTC), Plataforma Biobancos PT13/0010/0013 and ICOBIOBANC, sponsored by the Catalan Institute of Oncology. Czech Republic CCS: This work was supported by the Czech Science Foundation (20-03997S) and by the Grant Agency of the Ministry of Health of the Czech Republic (grants NV18/03/00199 and NU21-07-00247). DACHS: This work was supported by the German Research Council (BR 1704/6-1, BR 1704/6-3, BR 1704/6-4, CH 117/1-1, HO 5117/2-1, HE 5998/2-1, KL 2354/3-1, RO 2270/8-1 and BR 1704/17-1), the Interdisciplinary Research Program of the National Center for Tumor Diseases (NCT), Germany, and the German Federal Ministry of Education and Research (01KH0404, 01ER0814, 01ER0815, 01ER1505A and 01ER1505B). DALS: National Institutes of Health (R01 CA48998 to M. L. Slattery). EDRN: This work is funded and supported by the NCI, EDRN Grant (U01 CA 84968-06). EPIC: The coordination of EPIC is financially supported by the European Commission (DGSANCO) and the International Agency for Research on Cancer. The national cohorts are supported by Danish Cancer Society (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid, German Cancer Research Center (DKFZ), Federal Ministry of Education and Research (BMBF), Deutsche Krebshilfe, Deutsches Krebsforschungszentrum and Federal Ministry of Education and Research (Germany); the Hellenic Health Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro-AIRCItaly and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (the Netherlands); ERC-2009-AdG 232997 and Nordforsk, Nordic Centre of Excellence programme on Food, Nutrition and Health (Norway); Health Research Fund (FIS), PI13/00061 to Granada, PI13/01162 to EPIC-Murcia, Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra, ISCIII RETIC (RD06/0020) (Spain); Swedish Cancer Society, Swedish Research Council and County Councils of Skåne and Västerbotten (Sweden); Cancer Research UK (14136 to EPIC-Norfolk; C570/A16491 and C8221/A19170 to EPIC-Oxford), Medical Research Council (1000143 to EPIC-Norfolk, MR/M012190/1 to EPICOxford) (United Kingdom). The EPIC-Norfolk study (https://doi.org/10.22025/2019.10.105.00004) has received funding from the Medical Research Council (MR/N003284/1 and MC-UU_12015/1) and Cancer Research UK (C864/A14136). The genetics work in the EPIC-Norfolk study was funded by the Medical Research Council (MC_PC_13048). Metabolite measurements in the EPIC-Norfolk study were supported by the MRC Cambridge Initiative in Metabolic Science (MR/L00002/1) and the Innovative Medicines Initiative Joint Undertaking under EMIF grant agreement no. 115372. EPICOLON: This work was supported by grants from Fondo de Investigación Sanitaria/FEDER (PI08/0024, PI08/1276, PS09/02368, PI11/00219, PI11/00681, PI14/00173, PI14/00230, PI17/00509, 17/00878, PI20/00113, PI20/00226, Acción Transversal de Cáncer), Xunta de Galicia (PGIDIT07PXIB9101209PR), Ministerio de Economia y Competitividad (SAF07-64873, SAF 2010-19273, SAF2014-54453R), Fundación Científica de la Asociación Española contra el Cáncer (GCB13131592CAST), Beca Grupo de Trabajo "Oncología" AEG (Asociación Española de Gastroenterología), Fundación Privada Olga Torres, FP7 CHIBCHA Consortium, Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR, Generalitat de Catalunya, 2014SGR135, 2014SGR255, 2017SGR21, 2017SGR653), Catalan Tumour Bank Network (Pla Director d'Oncologia, Generalitat de Catalunya), PERIS (SLT002/16/00398, Generalitat de Catalunya), CERCA Programme (Generalitat de Catalunya) and COST Actions BM1206 and CA17118. CIBERehd is funded by the Instituto de Salud Carlos III. ESTHER/VERDI. This work was supported by grants from the Baden-Württemberg Ministry of Science, Research and Arts and the German Cancer Aid. Harvard cohorts (HPFS, NHS, PHS): HPFS is supported by the National Institutes of Health (P01 CA055075, UM1 CA167552, U01 CA167552, R01 CA137178, R01 CA151993, R35 CA197735, K07 CA190673, and P50 CA127003), NHS by the National Institutes of Health (R01 CA137178, P01 CA087969, UM1 CA186107, R01 CA151993, R35 CA197735, K07CA190673, and P50 CA127003) and PHS by the

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National Institutes of Health (R01 CA042182). Hawaii Adenoma Study: NCI grants R01 CA72520. HCES-CRC: the Hwasun Cancer Epidemiology Study–Colon and Rectum Cancer (HCES-CRC; grants from Chonnam National University Hwasun Hospital, HCRI15011-1). Kentucky: This work was supported by the following grant support: Clinical Investigator Award from Damon Runyon Cancer Research Foundation (CI-8); NCI R01CA136726. LCCS: The Leeds Colorectal Cancer Study was funded by the Food Standards Agency and Cancer Research UK Programme Award (C588/A19167). Melbourne Collaborative Cohort Study (MCCS) cohort recruitment was funded by VicHealth and Cancer Council Victoria. The MCCS was further augmented by Australian National Health and Medical Research Council grants 209057, 396414 and 1074383 and by infrastructure provided by Cancer Council Victoria. Cases and their vital status were ascertained through the Victorian Cancer Registry and the Australian Institute of Health and Welfare, including the National Death Index and the Australian Cancer Database. Multiethnic Cohort (MEC) Study: National Institutes of Health (R37 CA54281, P01 CA033619, R01 CA063464 and U01 CA164973). MECC: This work was supported by the National Institutes of Health, U.S. Department of Health and Human Services (R01 CA081488, R01 CA197350, U19 CA148107, R01 CA242218, and a generous gift from Daniel and Maryann Fong. MSKCC: The work at Sloan Kettering in New York was supported by the Robert and Kate Niehaus Center for Inherited Cancer Genomics and the Romeo Milio Foundation. Moffitt: This work was supported by funding from the National Institutes of Health (grant numbers R01 CA189184, P30 CA076292), Florida Department of Health Bankhead-Coley Grant 09BN-13, and the University of South Florida Oehler Foundation. Moffitt contributions were supported in part by the Total Cancer Care Initiative, Collaborative Data Services Core, and Tissue Core at the H. Lee Moffitt Cancer Center & Research Institute, a National Cancer Institute-designated Comprehensive Cancer Center (grant number P30 CA076292). NCCCS I & II: We acknowledge funding support for this project from the National Institutes of Health, R01 CA66635 and P30 DK034987. NFCCR: This work was supported by an Interdisciplinary Health Research Team award from the Canadian Institutes of Health Research (CRT 43821); the National Institutes of Health, U.S. Department of Health and Human Services (U01 CA74783); and National Cancer Institute of Canada grants (18223 and 18226). The authors wish to acknowledge the contribution of Alexandre Belisle and the genotyping team of the McGill University and Génome Québec Innovation Centre, Montréal, Canada, for genotyping the Sequenom panel in the NFCCR samples. Funding was provided to Michael O. Woods by the Canadian Cancer Society Research Institute. NSHDS: Swedish Research Council; Swedish Cancer Society; Cutting-Edge Research Grant and other grants from Region Västerbotten; Knut and Alice Wallenberg Foundation; Lion's Cancer Research Foundation at Umeå University; the Cancer Research Foundation in Northern Sweden; and the Faculty of Medicine, Umeå University, Umeå, Sweden. OSUMC: OCCPI funding was provided by Pelotonia and HNPCC funding was provided by the NCI (CA16058 and CA67941). PLCO: Intramural Research Program of the Division of Cancer Epidemiology and Genetics and supported by contracts from the Division of Cancer Prevention, National Cancer Institute, NIH, DHHS. Funding was provided by National Institutes of Health (NIH), Genes, Environment and Health Initiative (GEI) Z01 CP 010200, NIH U01 HG004446, and NIH GEI U01 HG 004438. SEARCH: The University of Cambridge has received salary support in respect of PDPP from the NHS in the East of England through the Clinical Academic Reserve. Cancer Research UK (C490/A16561); the UK National Institute for Health Research Biomedical Research Centres at the University of Cambridge. SELECT: Research reported in this publication was supported in part by the National Cancer Institute of the National Institutes of Health under Award Numbers U10 CA37429 (CD Blanke), and UM1 CA182883 (CM Tangen/IM Thompson). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. SMS and REACH: This work was supported by the National Cancer Institute (grant P01 CA074184 to J.D.P. and P.A.N., grants R01 CA097325, R03 CA153323, and K05 CA152715 to P.A.N., and the National Center for Advancing Translational Sciences at the National Institutes of Health (grant KL2 TR000421 to A.N.B.-H.) The Swedish Low-risk Colorectal Cancer Study: The study was supported by grants from the Swedish research council; K2015-55X-22674-01-4, K2008-55X-20157-03-3, K2006-72X-20157-01-2 and the Stockholm County Council (ALF project). Swedish Mammography Cohort and Cohort of Swedish Men: This work is supported by the Swedish Research Council/Infrastructure grant, the Swedish Cancer Foundation, and the Karolinska Institutés Distinguished Professor Award to Alicja Wolk. UK Biobank: This research has been conducted using the UK Biobank Resource under Application Number 8614 VITAL: National Institutes of Health (K05 CA154337). WHI: The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C.

Endometrial cancer GWAS

The endometrial cancer genome-wide association analyses were supported by the National Health and Medical Research Council of Australia (APP552402, APP1031333, APP1109286, APP1111246 and APP1061779), the U.S. National Institutes of Health (R01-CA134958), European Research Council (EU FP7 Grant), Wellcome Trust Centre for Human Genetics (090532/Z/09Z) and Cancer Research UK. OncoArray genotyping of ECAC cases was performed with the generous assistance of the Ovarian Cancer Association Consortium (OCAC), which was funded through grants from the U.S. National Institutes of Health (CA1X01HG007491-01 (C.I. Amos), U19-CA148112 (T.A. Sellers), R01-CA149429 (C.M. Phelan) and R01-CA058598 (M.T. Goodman); Canadian Institutes of Health Research (MOP-86727 (L.E. Kelemen)) and the Ovarian Cancer Research Fund (A. Berchuck). OncoArray genotyping of the BCAC controls was funded by Genome Canada Grant GPH-129344, NIH Grant U19 CA148065, and Cancer UK Grant C1287/A16563. All studies and funders are listed in O'Mara et al (2018).

Esophageal cancer GWAS

S.M. is supported by Australian National Health and Medical Research Council Fellowship. P.G. is supported by a NHMRC Investigator Grant (#1173390). The laboratory of R.C.F. is funded by a Core Programme Grant from the Medical Research Council (RG84369). The Barrett's and Esophageal Adenocarcinoma Genetic Susceptibility Study (BEAGESS) was funded by grant R01 CA136725 from the National Cancer Institute. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute. Bonn (Germany): this work was supported by

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funding from the Else Kröner Fresenius Stiftung (EKFS) (grant number 2013_A118 awarded to I.G. and J.S.). M.M.N. is a member of the DFG funded Excellence Cluster ImmunoSensation. The Heinz Nixdorf Recall cohort was established with the generous support of the Heinz Nixdorf Foundation, Germany. Cambridge (UK): the UK Barrett's oesophagus gene study was funded by a Medical Research Council Programme grant. The UK SOCS study was funded by CRUK as well as funding from the Cambridge NIHR biomedical research centre and the Cambridge Experimental Cancer Medicine Centre. Genotyping of Cambridge samples was supported by funding from the US National Cancer Institute at the National Institutes of Health (grant number R01CA136725 awarded to T.L.V and D.C.W). This study made use of data generated by the Wellcome Trust Case Control Consortium: Funding for the project was provided by the Wellcome Trust under award 076113; a full list of the investigators who contributed to the generation of the data is available from the website (http://www.wtccc.org.uk/). Oxford (UK): this work was supported by the Esophageal Adenocarcinoma GenE Consortia incorporating the ChOPIN project (grant C548/A5675), the Inherited Predisposition of neoplasia analysis of genomic DNA (IPOD) from AspECT and BOSS clinical trials project (grant MGAG1G7R), Cancer Research UK (AspECT, grants C548/A4584 and D9612L00090), the Histological AssessmeNt Determining EpitheliaL Response (HANDEL) (grant C548/A9085), the AstraZeneca UK educational grant, the University Hospitals of Leicester R and D grant, and AspECT (T91 5211 University of Oxford grant HDRMJQ0).

Glioma GWAS

GICC: The Glioma International Case Control Consortium (GICC) was supported by grants from the US National Institutes of Health (NIH) (R01 CA139020).

Head and neck cancer GWAS

Head neck cancer GWAS consortium: Genotyping of cases and controls included was performed at the Center for Inherited Disease Research (CIDR) and funded by the US National Institute of Dental and Craniofacial Research (NIDCR; 1X01HG007780-0). Genotyping for shared controls with the Lung OncoArray initiative was funded through grant X01HG007492-0.

Head neck cancer GWAS individual studies: ARCAGE: The Alcohol-Related Cancers and Genetic Susceptibility Study in Europe (ARCAGE) was funded by the European Commission's fifth framework programme (QLK1-2001-00182), the Italian Association for Cancer Research, Compagnia di San Paolo/FIRMS, Region Piemonte and Padova University (CPDA057222). CHANCE: The Carolina Head and Neck Cancer Study (CHANCE) was supported by the National Cancer Institute (R01CA90731). HN5000: The HN5000 study was funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research scheme (RP-PG-0707-10034); the views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the UK Department of Health. Core funding was also provided through awards from Above and Beyond, University Hospitals Bristol Research Capability Funding and the NIHR Senior Investigator award to Professor Andy Ness. Human papillomavirus (HPV) serology was supported by a Cancer Research UK Programme Grant, the Integrative Cancer Epidemiology Programme (grant number: C18281/A19169). Pitt: The University of Pittsburgh head and neck cancer case–control study is supported by US National Institutes of Health grants P50CA097190 and P30CA047904. Toronto: The Toronto study was funded by the Canadian Cancer Society Research Institute (020214) and the National Cancer Institute (U19CA148127) and by the Cancer Care Ontario Research Chair. EPIC: Coordination of the EPIC study is financially supported by the European Commission (DG SANCO) and the International Agency for Research on Cancer. IARC Oral Cancer: The IARC Oral Cancer Multicenter study was funded by grant S06 96 202489 05F02 from Europe against Cancer; grants FIS 97/0024, FIS 97/0662 and BAE 01/5013 from Fondo de Investigaciones Sanitarias, Spain; the UICC Yamagiwa-Yoshida Memorial International Cancer Study; the National Cancer Institute of Canada; Associazione Italiana per la Ricerca sul Cancro; and the Pan-American Health Organization. IARC Central Europe: The IARC Central Europe study was supported by the European Commission's INCO-COPERNICUS Program (IC15-CT98-0332), US NIH/National Cancer Institute grant CA92039 and World Cancer Research Foundation grant WCRF 99A28. Rome: The Rome Study was supported by the Associazione Italiana per la Ricerca sul Cancro (AIRC) awards IG 2011 10491 and IG 2013 14220 to Stefania Boccia and by Fondazione Veronesi to Stefania Boccia. GENCAPO: Genome Project (GENCAPO) was supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP; grants 04/12054-9 and 10/51168-0). IARC Latin American study: The IARC Latin American study was funded by the European Commission INCO-DC programme (IC18-CT97-0222), with additional funding from Fondo para la Investigación Científica y Tecnológica (Argentina) and the Fundação de Amparo à Pesquisa do Estado de São Paulo (01/01768-2).

Lung cancer GWAS

ILCCO: This work was supported by CA194393 and CA182821. Lung cancer GWAS from the International Lung Cancer Consortium (ILCCO) was supported by NIH U19 CA203654 and U19 CA148127 and the data harmonization was supported by Canada Research Chair to R. J. H. This work has been supported by the Intramural Research Program (IRP) of the Division of Cancer Epidemiology and Genetics, National Cancer Institute, US National Institutes of Health. The content of this publication does not necessarily reflect the views or policies of the US Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government.

Melanoma GWAS

Melanoma GWAS Consortium: Please see reference 13. The GenoMEL study (http://www.genomel.org/) was funded by the European Commission under the 6th Framework Programme (contract no. LSHC-CT-2006-018702), by Cancer Research UK Programme Awards (C588/A4994 and C588/A10589), by a Cancer Research UK Project Grant (C8216/A6129) and by a grant from the US National Institutes of Health (R01CA83115). This research was also supported by the intramural Research Program of the NIH, National Cancer Institute (NCI), Division of Cancer Epidemiology and Genetics. Mark Iles is supported in part by the National Institute for Health and Care Research (NIHR) Leeds Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Ovarian cancer GWAS

OCAC: The Ovarian Cancer Association Consortium is supported by a grant from the Ovarian Cancer Research Fund thanks to donations by the family and friends of Kathryn Sladek Smith

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(PPD/RPCI.07). The scientific development and funding for this project were in part supported by the US National Cancer Institute GAME-ON Post-GWAS Initiative (U19-CA148112). This study made use of data generated by the Wellcome Trust Case Control consortium that was funded by the Wellcome Trust under award 076113. The results published here are in part based upon data generated by The Cancer Genome Atlas Pilot Project established by the National Cancer Institute and National Human Genome Research Institute (dbGap accession number phs000178.v8.p7). The OCAC OncoArray genotyping project was funded through grants from the U.S. National Institutes of Health (CA1X01HG007491-01 (C.I.A.), U19-CA148112 (T.A.S.), R01-CA149429 (C.M.P.) and R01-CA058598 (M.T.G.); Canadian Institutes of Health Research (MOP-86727 (L.E.K.) and the Ovarian Cancer Research Fund (A.B.). The COGS project was funded through a European Commission's Seventh Framework Programme grant (agreement number 223175 - HEALTH-F2-2009-223175).

OCAC Individual Studies: AAS: National Institutes of Health (RO1-CA142081); AUS: The Australian Ovarian Cancer Study (AOCS) was supported by the U.S. Army Medical Research and Materiel Command (DAMD17-01-1-0729), National Health & Medical Research Council of Australia (199600, 400413 and 400281), Cancer Councils of New South Wales, Victoria, Queensland, South Australia and Tasmania and Cancer Foundation of Western Australia (Multi-State Applications 191, 211 and 182). AOCS gratefully acknowledges additional support from Ovarian Cancer Australia and the Peter MacCallum Foundation; BAV: ELAN Funds of the University of Erlangen-Nuremberg; BEL: National Kankerplan; BGS: Breast Cancer Now, Institute of Cancer Research; BVU: Vanderbilt University Medical Center's BioVU is supported by the 1S10RR025141-01 instrumentation award and Vanderbilt CTSA grant from the National Institutes of Health (NIH)/National Center for Advancing Translational Sciences (NCATS) (ULTR000445); CAM: National Institutes of Health Research Cambridge Biomedical Research Centre and Cancer Research UK Cambridge Cancer Centre; CHA: Innovative Research Team in University (PCSIRT) in China (IRT1076); CNI: Instituto de Salud Carlos III (PI 12/01319); Ministerio de Economía y Competitividad (SAF2012); DKE: Ovarian Cancer Research Fund; DOV: National Institutes of Health R01-CA112523 and R01-CA87538; EPC: The coordination of EPIC is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by Danish Cancer Society (Denmark) (EMC 2014-6699); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid, German Cancer Research Center (DKFZ), Federal Ministry of Education and Research (BMBF) (Germany); the Hellenic Health Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (the Netherlands); ERC-2009-AdG 232997 and Nordforsk, Nordic Centre of Excellence programme on Food, Nutrition and Health (Norway); Health Research Fund (FIS), PI13/00061 to Granada, PI13/01162 to EPIC-Murcia, Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra, ISCIII RETIC (RD06/0020) (Spain); Swedish Cancer Society, Swedish Research Council and County Councils of Skåne and Västerbotten (Sweden); Cancer Research UK (14136 to EPIC-Norfolk; C570/A16491 and C8221/A19170 to EPIC-Oxford), Medical Research Council (1000143 to EPIC-Norfolk, MR/M012190/1 to EPIC-Oxford) (United Kingdom); GER: German Federal Ministry of Education and Research, Programme of Clinical Biomedical Research (01 GB 9401) and the German Cancer Research Center (DKFZ); GRC: This research has been co-financed by the European Union (European Social Fund—ESF) and Greek national funds through the Operational Program "Education and Lifelong Learning" of the National Strategic Reference Framework (NSRF) - Research Funding Program of the General Secretariat for Research & Technology: SYN11_10_19 NBCA. Investing in knowledge society through the European Social Fund; GRR: Roswell Park Cancer Institute Alliance Foundation, P30 CA016056; HAW: U.S. National Institutes of Health (R01-CA58598, N01-CN-55424 and N01-PC-67001); HJO: German Research Foundation (DFG Do761/15-1); Rudolf-Bartling Foundation; HMO: German Research Foundation (DFG Do761/15-1); Rudolf-Bartling Foundation; HOC: Helsinki University Hospital Research Fund; HOP: University of Pittsburgh School of Medicine Dean's Faculty Advancement Award (F. Modugno), Department of Defense (DAMD17-02-1-0669) and NCI (K07-CA080668, R01-CA95023, P50-CA159981 MO1-RR000056 R01-CA126841); HUO: German Research Foundation (DFG Do761/15-1); Rudolf-Bartling Foundation; JPN: Grant-in-Aid for the Third Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare; KRA: This study (Ko-EVE) was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), and the National R&D Program for Cancer Control, Ministry of Health & Welfare, Republic of Korea (HI16C1127; 0920010); LAX: American Cancer Society Early Detection Professorship (SIOP-06-258-01-COUN) and the National Center for Advancing Translational Sciences (NCATS), Grant UL1TR000124; LUN: ERC-2011-AdG 294576-risk factors cancer, Swedish Cancer Society, Swedish Research Council, Beta Kamprad Foundation; MAC: National Institutes of Health (R01-CA122443, P30-CA15083, P50-CA136393); Mayo Foundation; Minnesota Ovarian Cancer Alliance; Fred C. and Katherine B. Andersen Foundation; Fraternal Order of Eagles; MAL: Funding for this study was provided by research grant R01- CA61107 from the National Cancer Institute, Bethesda, MD, research grant 94 222 52 from the Danish Cancer Society, Copenhagen, Denmark; and the Mermaid I project; MAS: Malaysian Ministry of Higher Education (UM.C/HlR/MOHE/06) and Cancer Research Initiatives Foundation; MAY: National Institutes of Health (R01-CA122443, P30-CA15083, P50-CA136393); Mayo Foundation; Minnesota Ovarian Cancer Alliance; Fred C. and Katherine B. Andersen Foundation; MCC: MCCS cohort recruitment was funded by VicHealth and Cancer Council Victoria. Cancer Council Victoria, National Health and Medical Research Council of Australia (NHMRC) grants number 209057, 251533, 396414, and 504715; MDA: DOD Ovarian Cancer Research Program (W81XWH-07-0449); MEC: NIH (CA54281, CA164973, CA63464); MOF: Moffitt Cancer Center, Merck Pharmaceuticals, the state of Florida, Hillsborough County, and the city of Tampa; NCO: National Institutes of Health (R01-CA76016) and the Department of Defense (DAMD17-02-1-0666); NEC: National Institutes of Health R01-CA54419 and P50-CA105009 and Department of Defense W81XWH-10-1-02802; NHS: UM1 CA186107, P01 CA87969, R01 CA49449, R01-CA67262, UM1 CA176726; NJO: National Cancer Institute (NIH-K07 CA095666, R01-CA83918, NIH-K22-CA138563, and P30-CA072720) and the Cancer Institute of New Jersey; NOR: Helse Vest, The

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Norwegian Cancer Society, The Research Council of Norway; NTH: Radboud University Medical Centre; OPL: National Health and Medical Research Council (NHMRC) of Australia (APP1025142) and Brisbane Women's Club; ORE: Sherie Hildreth Ovarian Cancer (SHOC) Foundation; OVA: This work was supported by Canadian Institutes of Health Research grant (MOP-86727) and by NIH/NCI 1 R01CA160669-01A1; PLC: Intramural Research Program of the National Cancer Institute; POC: Pomeranian Medical University; POL: Intramural Research Program of the National Cancer Institute; PVD: Canadian Cancer Society and Cancer Research Society GRePEC Program; RBH: National Health and Medical Research Council of Australia; RMH: Cancer Research UK, Royal Marsden Hospital; RPC: National Institute of Health (P50 CA159981, R01CA126841); SEA: Cancer Research UK (C490/A10119 C490/A10124); UK National Institute for Health Research Biomedical Research Centres at the University of Cambridge; SIS: The Sister Study (SISTER) is supported by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences (Z01-ES044005 and Z01-ES049033); SMC: The Swedish Cancer Foundation and the Swedish Research Council (VR 2017-00644) grant for the Swedish Infrastructure for Medical Population-based Life-course Environmental Research (SIMPLER); SRO: Cancer Research UK (C536/A13086, C536/A6689) and Imperial Experimental Cancer Research Centre (C1312/A15589); STA: NIH grants U01 CA71966 and U01 CA69417; SWH: NIH (NCI) grant R37-CA070867; TBO: National Institutes of Health (R01-CA106414-A2), American Cancer Society (CRTG-00-196-01-CCE), Department of Defense (DAMD17-98-1-8659), Celma Mastry Ovarian Cancer Foundation; TOR: NIH grants R01 CA063678 and R01 CA063682; UCI: NIH R01-CA058860 and the Lon V Smith Foundation grant LVS-39420; UHN: Princess Margaret Cancer Centre Foundation-Bridge for the Cure; UKO: The UKOPS study was funded by The Eve Appeal (The Oak Foundation) with investigators supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre; UKR: Cancer Research UK (C490/A6187), UK National Institute for Health Research Biomedical Research Centres at the University of Cambridge; USC: P01CA17054, P30CA14089, R01CA61132, N01PC67010, R03CA113148, R03CA115195, N01CN025403, and California Cancer Research Program (00-01389 V-20170, 2II0200); VAN: BC Cancer Foundation, VGH & UBC Hospital Foundation; VTL: NIH K05-CA154337; WMH: National Health and Medical Research Council of Australia, Enabling Grants ID 310670 & ID 628903. Cancer Institute NSW Grants 12/RIG/1-17 & 15/RIG/1-16; WOC: National Science Centre (N N301 5645 40), The Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland.

Pancreatic cancer GWAS

PanC4: This PANC4 GWAS was supported by R01CA154823 and P50CA062924 (PI: A.P. Klein). The IARC/Central Europe study was supported by a grant from the US National Cancer Institute at the National Institutes of Health (R03 CA123546-02) and grants from the Ministry of Health of the Czech Republic (NR 9029-4/2006, NR9422-3, NR9998-3, MH CZ-DRO-MMCI 00209805). The work at Johns Hopkins University was supported by the NCI Grants P50CA062924 and R01CA97075. Additional support was provided by the Lustgarten Foundation, Susan Wojcicki and Dennis Troper and the Sol Goldman Pancreas Cancer Research Center. This work was supported by U01CA247283 RO1 CA154823 and federal funds from the National Cancer Institute (NCI), US National Institutes of Health (NIH) under contract number HHSN261200800001E. The Mayo Clinic Biospecimen Resource for Pancreas Research study is supported by the Mayo Clinic SPORE in Pancreatic Cancer (P50 CA102701). The Memorial Sloan Kettering Cancer Center Pancreatic Tumor Registry is supported by P30CA008748, the Geoffrey Beene Foundation, the Arnold and Arlene Goldstein Family Foundation, and the Society of MSKCC. The PACIFIC Study was supported by RO1CA102765, Kaiser Permanente and Group Health Cooperative. The Queensland Pancreatic Cancer Study was supported by a grant from the National Health and Medical Research Council of Australia (NHMRC) (Grant number 442302). RE Neale is supported by a NHMRC Senior Research Fellowship (#1060183). The UCSF pancreas study was supported by NIH-NCI grants (R01CA1009767, R01CA109767-S1 and R0CA059706) and the Joan Rombauer Pancreatic Cancer Fund. Collection of cancer incidence data was supported by the California Department of Public Health as part of the statewide cancer reporting program; the NCI's SEER Program under contract HSN261201000140C awarded to CPIC; and the CDC's National Program of Cancer Registries, under agreement #U58DP003862-01 awarded to the California Department of Public Health. The Yale (CT) pancreas cancer study is supported by National Cancer Institute at the U.S. National Institutes of Health, grant 5R01CA098870.

PanScan: This project has been funded in whole or in part with Federal funds from the National Cancer Institute, National Institutes of Health, under NCI Contract No. 75N910D00024. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. The American Cancer Society (ACS) funds the creation, maintenance, and updating of the Cancer Prevention Study II cohort. The coordination of EPIC is financially supported by International Agency for Research on Cancer (IARC) and by the Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London which has additional infrastructure support provided by the NIHR Imperial Biomedical Research Centre (BRC). Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization. The Health Professionals Follow-up Study is supported by NIH grant UM1 CA167552. from the National Cancer Institute, Bethesda, MD USA. The Melbourne Collaborative Cohort Study (MCCS) cohort recruitment was funded by VicHealth and Cancer Council Victoria. The MCCS was further augmented by Australian National Health and Medical Research Council grants 209057, 396414 and 1074383 and by infrastructure provided by Cancer Council Victoria. Nurses' Health Study is supported by NIH grants UM1 CA186107, P01 CA87969, and R01 CA49449 from the National Cancer Institute, Bethesda, MD USA. The NYU study (AZJ and AAA) was funded by NIH R01 CA098661, UM1 CA182934 and center grants P30 CA016087 and P30 ES000260. The PANKRAS II Study in Spain was supported by research grants from Instituto de Salud Carlos III-FEDER, Spain: Fondo de Investigaciones Sanitarias (FIS) (#PI13/00082 and #PI15/01573) and Red Temática de Investigación Cooperativa en Cáncer, Spain (#RD12/0036/0050); and European Cooperation in Science and Technology (COST Action #BM1204: EU_Pancreas), Ministerio de Ciencia y Tecnología (CICYT SAF 2000-0097), Fondo de Investigación Sanitaria (95/0017), Madrid, Spain; Generalitat de Catalunya (CIRIT—SGR); "Red temática de

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investigación cooperativa de centros en Cáncer" (C03/10), "Red temática de investigación cooperativa de centros en Epidemiología y salud pública" (C03/09), and CIBER de Epidemiología (CIBERESP), Madrid. The Physicians' Health Study was supported by research grants CA-097193, CA-34944, CA-40360, HL-26490, and HL-34595 from the National Institutes of Health, Bethesda, MD USA. The SELECT study is supported by National Institutes of Health grant award number U10 CA37429 (CD Blanke), and UM1 CA182883 (CM Tangen/IM Thompson). The Shanghai Men's Health Study is supported by NIH grant UM1CA173640. The Shanghai Women's Health Study is supported by NIH grant UM1CA182910. The Women's Health Study was supported by research grants CA182913, CA-047988, HL-043851, HL-080467, and HL-099355 from the National Institutes of Health, Bethesda, MD USA. The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts 75N92021D00001, 75N92021D00002, 75N92021D00003, 75N92021D00004, 75N92021D00005.

Prostate cancer GWAS

CRUK and PRACTICAL consortium: This work was supported by the Canadian Institutes of Health Research, European Commission's Seventh Framework Programme grant agreement n° 223175 (HEALTH-F2-2009-223175), Cancer Research UK Grants C5047/A7357, C1287/A10118, C1287/A16563, C5047/A3354, C5047/A10692, C16913/A6135, and The National Institute of Health (NIH) Cancer Post-Cancer GWAS initiative grant: No. 1 U19 CA 148537-01 (the GAME-ON initiative). We would also like to thank the following for funding support: The Institute of Cancer Research and The Everyman Campaign, The Prostate Cancer Research Foundation, Prostate Research Campaign UK (now PCUK), The Orchid Cancer Appeal, Rosetrees Trust, The National Cancer Research Network UK, The National Cancer Research Institute (NCRI) UK. We are grateful for support of NIHR funding to the NIHR Biomedical Research Centre at The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, and Manchester NIHR Biomedical Research Centre. The Prostate Cancer Program of Cancer Council Victoria also acknowledge grant support from The National Health and Medical Research Council, Australia (126402, 209057, 251533, 396414, 450104, 504700, 504702, 504715, 623204, 940394, 614296), VicHealth, Cancer Council Victoria, The Prostate Cancer Foundation of Australia, The Whitten Foundation, PricewaterhouseCoopers, and Tattersall's. EAO, DMK, and EMK acknowledge the Intramural Program of the National Human Genome Research Institute for their support. Genotyping of the OncoArray was funded by the US National Institutes of Health (NIH) [U19 CA 148537 for ELucidating Loci Involved in Prostate cancer SuscEptibility (ELLIPSE) project and X01HG007492 to the Center for Inherited Disease Research (CIDR) under contract number HHSN268201200008I]. Additional analytic support was provided by NIH NCI U01 CA188392 (PI: Schumacher). Research reported in this publication also received support from the National Cancer Institute of the National Institutes of Health under Award Numbers U10 CA37429 (CD Blanke), and UM1 CA182883 (CM Tangen/IM Thompson). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Funding for the iCOGS infrastructure came from: the European Community's Seventh Framework Programme under grant agreement n° 223175 (HEALTH-F2-2009-223175) (COGS), Cancer Research UK (C1287/A10118, C1287/A 10710, C12292/A11174, C1281/A12014, C5047/A8384, C5047/A15007, C5047/A10692, C8197/A16565), the National Institutes of Health (CA128978) and Post-Cancer GWAS initiative (1U19 CA148537, 1U19 CA148065 and 1U19 CA148112 - the GAME-ON initiative), the Department of Defence (W81XWH-10-1-0341), the Canadian Institutes of Health Research (CIHR) for the CIHR Team in Familial Risks of Breast Cancer, Komen Foundation for the Cure, the Breast Cancer Research Foundation, and the Ovarian Cancer Research Fund.

BPC3: The BPC3 was supported by the U.S. National Institutes of Health, National Cancer Institute (cooperative agreements U01-CA98233 to D.J.H., U01-CA98710 to S.M.G., U01-CA98216 to E.R., and U01-CA98758 to B.E.H., and Intramural Research Program of NIH/National Cancer Institute, Division of Cancer Epidemiology and Genetics).

CAPS: CAPS GWAS study was supported by the Cancer Risk Prediction Center (CRisP), a Linneus Centre (Contract ID 70867902) financed by the Swedish Research Council, (grant no K2010-70X-20430-04-3), the Swedish Cancer Foundation (grant no 09-0677), the Hedlund Foundation, the Soederberg Foundation, the Enqvist Foundation, ALF funds from the Stockholm County Council. Stiftelsen Johanna Hagstrand och Sigfrid Linner's Minne, Karlsson's Fund for urological and surgical research.

PEGASUS: PEGASUS was supported by the Intramural Research Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health.

Renal cancer GWAS

The coordination and a proportion of the genotyping for the RCC GWAS was funded by CA155309.

Renal Cancer GWAS Studies: AHS: This research was supported by the Intramural Research Program of the NIH, National Cancer Institute, Division of Cancer Epidemiology and Genetics (Z01CP010119). ATBC: The ATBC Study was supported by funding provided by the Intramural Research Program of the NCI, NIH, and through U.S. Public Health Service contracts (N01-CN-45165, N01-RC-45035 and N01-RC-37004) from the NCI. BioVU: The dataset used in the analyses described were obtained from the Vanderbilt University Medical Center resource BioVU, which is supported by institutional funding, the 1S10RR025141-01 instrumentation award, and by the Vanderbilt CTSA grant UL1 TR000445 from NCATS/NIH. Sample processing and phenotyping algorithm development was supported by institutional funding for TLE. Center "Bioengineering" of the Russian Academy of Sciences/Kurchatov Scientific Center: The work conducted for this study was supported by the grant Russian Scientific Fund 14-14- 01202. ConFIRM/MCCS: The ConFIRM study, also known as CARES, was supported by the Victorian Cancer Agency (PTCB08_05), the Australian National Health and Medical Research Council (Project Grant 1011626). The Melbourne Collaborative Cohort Study (MCCS) recruitment was funded by VicHealth and Cancer Council Victoria. The MCCS was further supported by Australian NHMRC grants 209057, 251553 and 504711 and by infrastructure provided by Cancer Council Victoria. CPS-II: The Cancer Prevention Study II Nutrition Cohort is supported by the American Cancer Society. Health Professionals Follow-up Study (HPFS) and Nurses' Health Study (NHS): The HPFS is supported by National Institutes of Health, National Cancer Institute grant UM1 CA167552. The NHS is supported by National Institutes of Health, National Cancer Institute grants UM1 CA186107 and P01 CA87969. The authors assume full responsibility for analyses and interpretation of these data. K2 study: This study was supported by the EU FP7 under grant agreement number 241669 (the CAGEKID project). In Czech Republic,

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this work was also supported by MH CZ—DRO (MMCI, 00209805) and by the project MEYS—NPS I—LO1413, Czech Republic. Leeds Cohort: The infrastructure support from Cancer Research UK as part of the Leeds Centre and Experimental Cancer Medicine Centre funding is gratefully acknowledged. Mayo Clinic: This study was partially supported by National Institutes of Health: R21CA176422 (JEEP) and R01CA134466 (ASP). MD Anderson: This work was supported in part by the NIH (grant R01 CA170298) and the Center for Translational and Public Health Genomics, Duncan Family Institute for Cancer Prevention and Risk Assessment, The University of Texas MD Anderson Cancer Center. NCI/IARC RCC Study in Central Europe (CE): This project was supported by the Intramural Research Program of the NIH and the National Cancer Institute. Physicians' Health Study (PHS): This study was supported by grants CA 097193, CA 34944, CA 40360, HL 26490, and HL 34595 from the National Institutes of Health, Bethesda, MD. PLCO: This research was supported by the Intramural Research Program of the National Cancer Institute and by contracts from the Division of Cancer Prevention, National Cancer Institute, NIH, DHHS. SEARCH: This study is funded by Cancer Research UK (C490/A16651). UK GWAS: We acknowledge support from the Medical Research Council (MRC), Cancer Research UK, an educational grant from Bayer and NHS funding for the Royal Marsden Biomedical Research Centre and Cambridge University Health Partners. JL is supported by the NIHR RM/CR Biomedical Research Centre for Cancer. US Kidney Cancer Study: The NCI United Stated Kidney Cancer Study was supported by the Intramural Research Program of the National Institutes of Health and the National Cancer Institute under the following contracts: N02-CP-10128 (Westat, Inc.), N02-CP-11004 (Wayne State University), and N02-CP- 11161 (University of Illinois at Chicago). Women's Health Initiative (WHI): The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C. Women's Health Study (WHS): The study is supported by grants CA-047988, HL-043851, HL-080467, HL-099355, and UM1CA182913 from the National Institutes of Health, Bethesda, MD.

Conflicts of interest

BMW reports Grants from Celgene, Eli Lilly; Consulting for BioLineRx, Celgene, Grail; outside of the presented work. No other conflicts of interest exist.

Stephen J. Chanock and Harvey Risch, *JNCI* Associate Editors and coauthors on this manuscript, were not involved in the editorial review or decision to publish the article.

Acknowledgements

The funders had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Where authors are identified as personnel of the International Agency for Research on Cancer–World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer–World Health Organization.

Part of this work was presented as a poster presentation at the Annual Meeting of the American Association of Cancer Research, April 2020 (Abstract no. 1194).

GTEx data: The Genotype-Tissue Expression (GTEx) Project was supported by the Common Fund of the Office of the Director of the National Institutes of Health (commonfund.nih.gov/GTEx). Additional funds were provided by the NCI, NHGRI, NHLBI, NIDA, NIMH, and NINDS. Donors were enrolled at Biospecimen Source Sites funded by NCI\Leidos Biomedical Research, Inc. subcontracts to the National Disease Research Interchange (10XS170), Roswell Park Cancer Institute (10XS171), and Science Care, Inc. (X10S172). The Laboratory, Data Analysis, and Coordinating Center (LDACC) was funded through a contract (HHSN268201000029C) to the Broad Institute, Inc. Biorepository operations were funded through a Leidos Biomedical Research, Inc subcontract to Van Andel Research Institute (10ST1035). Additional data repository and project management were provided by Leidos Biomedical Research, Inc.(HHSN261200800001E). The Brain Bank was supported supplements to University of Miami grant DA006227. Statistical Methods development grants were made to the University of Geneva (MH090941 & MH101814), the University of Chicago (MH090951, MH090937, MH101825, & MH101820), the University of North Carolina—Chapel Hill (MH090936), North Carolina State University (MH101819),Harvard University (MH090948), Stanford University (MH101782), Washington University (MH101810), and to the University of Pennsylvania (MH101822). The datasets used for the analyses described in this manuscript were obtained from dbGaP at http://www.ncbi.nlm.nih.gov/gap through dbGaP accession number phs000424.v7.p2.

TCGA data: The results published here are in part based upon data generated by the TCGA Research Network: https://www.cancer.gov/tcga.

We want to acknowledge the participants and investigators of the FinnGen study.

Colorectal cancer GWAS

ASTERISK: We are very grateful to Dr Bruno Buecher without whom this project would not have existed. We also thank all those who agreed to participate in this study, including the patients and the healthy control persons, as well as all the physicians, technicians and students. CCFR: The Colon CFR graciously thanks the generous contributions of their study participants, dedication of study staff, and the financial support from the U.S. National Cancer Institute, without which this important registry would not exist. The authors would like to thank the study participants and staff of the Seattle Colon Cancer Family Registry and the Hormones and Colon Cancer study (CORE Studies). CLUE II: We thank the participants of Clue II and appreciate the continued efforts of the staff at the Johns Hopkins George W. Comstock Center for Public Health Research and Prevention in the conduct of the Clue II Cohort Study. COLON and NQplus: the authors would like to thank the COLON and NQplus investigators at Wageningen University & Research and the involved clinicians in the participating hospitals. CORSA: We kindly thank all those who contributed to the screening project Burgenland against CRC. Furthermore, we are grateful to Doris Mejri and Monika Hunjadi for laboratory assistance. CPS-II: The authors thank the CPS-II participants and Study Management Group for their invaluable contributions to this research. The authors would also

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like to acknowledge the contribution to this study from central cancer registries supported through the Centers for Disease Control and Prevention National Program of Cancer Registries, and cancer registries supported by the National Cancer Institute Surveillance Epidemiology and End Results program. Czech Republic CCS: We are thankful to all clinicians in major hospitals in the Czech Republic, without whom the study would not be practicable. We are also sincerely grateful to all patients participating in this study. DACHS: We thank all participants and cooperating clinicians, and Ute Handte-Daub, Utz Benscheid, Muhabbet Celik and Ursula Eilber for excellent technical assistance. EDRN: We acknowledge all the following contributors to the development of the resource: University of Pittsburgh School of Medicine, Department of Gastroenterology, Hepatology and Nutrition: Lynda Dzubinski; University of Pittsburgh School of Medicine, Department of Pathology: Michelle Bisceglia; and University of Pittsburgh School of Medicine, Department of Biomedical Informatics. EPIC: Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization. The EPIC-Norfolk study: we are grateful to all the participants who have been part of the project and to the many members of the study teams at the University of Cambridge who have enabled this research. EPICOLON: We are sincerely grateful to all patients participating in this study who were recruited as part of the EPICOLON project. We acknowledge the Spanish National DNA Bank, Biobank of Hospital Clínic–IDIBAPS and Biobanco Vasco for the availability of the samples. The work was carried out (in part) at the Esther Koplowitz Centre, Barcelona. Harvard cohorts (HPFS, NHS, PHS): The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required. We acknowledge Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital as home of the NHS. We would like to thank the participants and staff of the HPFS, NHS and PHS for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data. Interval: The academic coordinating center would like to thank blood donor center staff and blood donors for participating in the INTERVAL trial. Kentucky: We would like to acknowledge the staff at the Kentucky Cancer Registry. LCCS: We acknowledge the contributions of Jennifer Barrett, Robin Waxman, Gillian Smith and Emma Northwood in conducting this study. NCCCS I & II: We would like to thank the study participants, and the NC Colorectal Cancer Study staff. NSHDS investigators thank the Biobank Research Unit at Umeå University, the Västerbotten Intervention Programme, the Northern Sweden MONICA study and Region Västerbotten for providing data and samples and acknowledge the contribution from Biobank Sweden, supported by the Swedish Research Council (VR 2017-00650). PLCO: The authors thank the PLCO Cancer Screening Trial screening center investigators and the staff from Information Management Services Inc and Westat Inc. Most importantly, we thank the study participants for their contributions that made this study possible. SEARCH: We thank the SEARCH team. SELECT: We thank the research and clinical staff at the sites that participated on SELECT study, without whom the trial would not have been successful. We are also grateful to the 35 533 dedicated men who participated in SELECT. UK Biobank: We would like to thank the participants and researchers UK Biobank for their participation and acquisition of data. WHI: The authors thank the WHI investigators and staff for their dedication, and the study participants for making the program possible. A full listing of WHI investigators can be found at: https://www.whi.org/doc/WHI-Investigator-Long-List.pdf.

Endometrial cancer GWAS

We thank the many individuals who participated in the Endometrial Cancer Association Consortium and the numerous institutions and their staff who supported recruitment. We particularly thank the efforts of Cathy Phelan. We particularly thank the efforts of Deborah Thompson.

Esophageal cancer GWAS

A subset of the controls used with the Barrett's and Oesophageal Adenocarcinoma data were obtained from dbGaP. The MD Anderson controls were drawn from study accession phs000187.v1.p1. Genotyping of these controls were done through the University of Texas MD Anderson Cancer Center (UTMDACC) and the Johns Hopkins University Center for Inherited Disease Research (CIDR). We acknowledge the principal investigators of this study: Christopher Amos, Qingyi Wei, and Jeffrey E Lee. Controls from the Genome-Wide Association Study of Parkinson Disease were obtained from dbGaP (study accession: phs000196.v2.p1). This work, in part, used data from the National Institute of Neurological Disorders and Stroke (NINDS) dbGaP database from the CIDR: NeuroGenetics Research Consortium Parkinson's disease study. We acknowledge the principal investigators and coinvestigators of this study: Haydeh Payami, John Nutt, Cyrus Zabetian, Stewart Factor, Eric Molho, and Donald Higgins. Controls from the Chronic Renal Insufficiency Cohort (CRIC) were drawn from dbGaP (study accession: phs000524.v1.p1). The CRIC study was done by the CRIC investigators and supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Data and samples from CRIC reported here were supplied by NIDDK Central Repositories. This report was not prepared in collaboration with investigators of the CRIC study and does not necessarily reflect the opinions or views of the CRIC study, the NIDDK Central Repositories, or the NIDDK. We acknowledge the principal investigators and the project officer of this study: Harold I Feldman, Raymond R Townsend, Lawrence J Appel, Mahboob Rahman, Akinlolu Ojo, James P Lash, Jiang He, Alan S Go, and John W Kusek.

Lung cancer GWAS

We would like to thank all investigators who have contributed to the individual cancer GWAS. We thank the study PIs for the data contribution to lung cancer summary statistics.

Pancreatic cancer GWAS

PanC4: The cooperation of 30 Connecticut hospitals, including Stamford Hospital, in allowing patient access, is gratefully acknowledged. The Connecticut Pancreas Cancer Study was approved by the State of Connecticut Department of Public Health Human Investigation Committee. Certain data used in that study were obtained from the Connecticut Tumor Registry in the Connecticut Department of Public Health. The authors assume full responsibility for analyses and interpretation of these data.

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PanScan: The authors acknowledge the research contributions of the Cancer Genomics Research Laboratory, National Cancer Institute, National Institutes of Health, for their expertise, execution, and support of this research in the areas of project planning, wet laboratory processing of specimens, and bioinformatics analysis of generated data. Cancer incidence data for CLUE were provided by the Maryland Cancer Registry, Center for Cancer Surveillance and Control, Department of Health and Mental Hygiene, 201 W. Preston Street, Room 400, Baltimore, MD 21201, https://health.maryland.gov/phpa/cancer/pages/home.aspx, 410-767-4055. We acknowledge the State of Maryland, the Maryland Cigarette Restitution Fund, and the National Program of Cancer Registries of the Centers for Disease Control and Prevention for the funds that support the collection and availability of the cancer registry data. We thank all the CLUE participants. MCCS cases and their vital status were ascertained through the Victorian Cancer Registry and the Australian Institute of Health and Welfare, including the National Death Index and the Australian Cancer Database. The authors thank the site investigators and staff and, most importantly, the participants from PCPT and SELECT who donated their time to this trial.

Renal cancer GWAS

Centre National de Genotypage, France: We thank Jean Guillaume Garnier and Delphine Bacq-Daian for their work on the IARC-2 scan. ConFIRM/MCCS: We acknowledge the contribution of Professor Graham Giles in supporting this work and of Ms Olive Schmid and Ms Jennifer Walsh for the project management. CPS-II: The authors thank all of the men and women in the Cancer Prevention Study II Nutrition Cohort for their many years of dedicated participation in the study. Health Professionals Follow-up Study (HPFS) and Nurses' Health Study (NHS): We would like to thank the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. Leeds Cohort: The Leeds Multidisciplinary Research Tissue Bank, all patients who consented to take part in the research studies and the staff of the Urology and Oncology Departments in Leeds Teaching Hospitals Trust. Mayo Clinic: The authors acknowledge the Mayo Clinic Comprehensive Cancer Center Biospecimens Accessioning and Processing Shared Resource and the Pathology Research Core Shared Resource. Van Andel Research Institute (VARI): The authors would like to thank Dr Kyle Furge for his role in this project as well as Drs. Anthony Avallone, John Ludlow and Philip Wise for contributing samples for this project. Women's Health Initiative (WHI): For a list of all the investigators who have contributed to WHI science, please visit: https://www.whi.org/doc/WHI-Investigator-Long-List.pdf.

The authors acknowledge the contribution of all the investigators including the consortia members listed below, who contributed to the cancer-specific GWAS, making these analyses possible.

Breast cancer GWAS (BCAC)

Kyriaki Michailidou, Sara Lindström, Joe Dennis, Jonathan Beesley, Penny Soucy, Manjeet K. Bolla, Qin Wang, Renske Keeman, Sabine Behrens, Thomas U. Ahearn, Kristiina Aittomäki, Hoda Anton Culver, Natalia N. Antonenkova, Volker Arndt, Kristan J. Aronson, Banu K. Arun, Marina Bermisheva, Heiko Becher, Matthias W. Beckmann, Javier Benitez, Marina Bermisheva, Carl Blomqvist, Natalia V. Bogdanova, Stig E. Bojesen, Bernardo Bonanni, Hiltrud Brauch, Michael Bremer, Hermann Brenner, Ian W. Brock, Annegien Broeks, Angela Brooks Wilson, Sara Y. Brucker, Thomas Brüning, Barbara Burwinkel, Katja Butterbach, Saundra S. Buys, Qiuyin Cai, Hui Cai, Daniele Campa, Sander Canisius, Federico Canzian, Angel Carracedo, Jose E. Castelao, Tsun L. Chan, Ting Yuan David Cheng, Kee Seng Chia, Ji Yeob Choi, Hans Christiansen, Christine L. Clarke, J. Margriet Collée, Emilie Cordina Duverger, Sten Cornelissen, Angela Cox, Simon S. Cross, Kamila Czene, Mary B. Daly, Arcangela De Nicolo, Peter Devilee, Thilo Dörk, Laure Dossus, Martine Dumont, Lorraine Durcan, Miriam Dwek, Diana M. Eccles, A. Heather Eliassen, Christoph Engel, Mikael Eriksson, Peter A. Fasching, Jonine D. Figueroa, Dieter Flesch Janys, Olivia Fletcher, Henrik Flyger, Lin Fritschi, Marike Gabrielson, Manuela Gago Dominguez, Yu Tang Gao, José A. García Sáenz, Jürgen Geisler, Vassilios Georgoulias, Graham G. Giles, Gord Glendon, Mark S. Goldberg, Anna González Neira, Grethe I. Grenaker Alnæs, Mervi Grip, Jacek Gronwald, Anne Grundy, Pascal Guénel, Lothar Haeberle, Eric Hahnen, Christopher A. Haiman, Niclas Håkansson, Ute Hamann, Susan E. Hankinson, Jaana M. Hartikainen, Mikael Hartman, Alexander Hein, Peter Hillemanns, Dona N. Ho, Weang Kee Ho, Antoinette Hollestelle, Maartje J. Hooning, Reiner Hoppe, John L. Hopper, Ming Feng Hou, Richard S. Houlston, Chia Ni Hsiung, Guanmengqian Huang, Dezheng Huo, Junko Ishiguro, Hidemi Ito, Motoki Iwasaki, Hiroji Iwata, Anna Jakubowska, Wolfgang Janni, Esther M. John, Nichola Johnson, Michael E. Jones, Audrey Jung, Rudolf Kaaks, Daehee Kang, Yoshio Kasuga, Michael J. Kerin, Elza K. Khusnutdinova, Johanna I. Kiiski, Sung Won Kim, Julia A. Knight, Veli Matti Kosma, Vessela N. Kristensen, Ute Krüger, Allison W. Kurian, Ava Kwong, James V. Lacey, Inge M.M. Lakeman, Diether Lambrechts, Loic Le Marchand, Jong Won Lee, Min Hyuk Lee, Flavio Lejbkowicz, Jingmei Li, Annika Lindblom, Jolanta Lissowska, Wing Yee Lo, Sibylle Loibl, Jirong Long, Artitaya Lophatananon, Jan Lubiński, Michael P. Lux, Edmond S.K. Ma, Robert J. MacInnis, Tom Maishman, Enes Makalic, Arto Mannermaa, Siranoush Manoukian, Sara Margolin, Shivaani Mariapun, Maria Elena Martinez, Keitaro Matsuo, Dimitrios Mavroudis, Catriona McLean, Hanne E.J. Meijers Heijboer, Usha Menon, Nicola Miller, Nur Aishah Mohd Taib, Kenneth Muir, Anna Marie Mulligan, Claire Mulot, Taru A. Muranen, Rachel A. Murphy, Heli Nevanlinna, Patrick Neven, Sune F. Nielsen, Dong Young Noh, Børge G. Nordestgaard, Aaron Norman, Katie M. O'Brien, Olufunmilayo I. Olopade, Janet E. Olson, Sue K. Park, Tjoung Won Park Simon, Alpa V. Patel, Paolo Peterlongo, Kelly Anne Phillips, Dijana Plaseska Karanfilska, Ross Prentice, Nadege Presneau, Darya Prokofyeva, Katri Pylkäs, Brigitte Rack, Paolo Radice, Muhammad U. Rashid, Gad Rennert, Valerie Rhenius, Atocha Romero, Thomas Rüdiger, Matthias Ruebner, Emiel J. Th. Rutgers, Emmanouil Saloustros, Dale P. Sandler, Elinor J. Sawyer, Daniel F. Schmidt, Rita K. Schmutzler, Andreas Schneeweiss, Fredrick Schumacher, Peter Schürmann, Rodney J. Scott, Christopher Scott, Mitul Shah, Priyanka Sharma, Chen Yang Shen, Martha J. Shrubsole, Xiao Ou Shu, Ann Smeets, Christof Sohn, Melissa C. Southey, Christa Stegmaier, Jennifer Stone, Daniel O. Stram, Harald Surowy, Rulla M. Tamimi, William J. Tapper, Jack A. Taylor, Maria Tengström, Soo Hwang Teo, Lauren R. Teras, Mary Beth Terry, Somchai Thanasitthichai, Heather Thorne, Rob A.E.M. Tollenaar, Ian Tomlinson, Diana Torres, Thérèse Truong, Chiu Chen Tseng, Shoichiro Tsugane, Hans Ulrich Ulmer, Michael Untch, Celine M. Vachon, Christi J. van Asperen, David Van Den Berg, Ans M.W. van den Ouweland, Lizet E. van der Kolk, Philippe Wagner, Sophia S. Wang, Barbara Wappenschmidt, Clarice R. Weinberg, Camilla Wendt, Hans Wildiers, Walter Willett, Stacey J. Winham, Robert Winqvist, Alicja Wolk, Anna H.

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Wu, Pei Ei Wu, Taiki Yamaji, Xiaohong R. Yang, Cheng Har Yip, Keun Young Yoo, Jyh Cherng Yu, Wei Zheng, Ying Zheng, Argyrios Ziogas, Elad Ziv, AOCS Group, ABCTB Investigators, CTS Consortium, kConFab Investigators, NBCS Collaborators, SGBCC Investigators, Antonis C. Antoniou, Arnaud Droit, Irene L. Andrulis, Fergus J. Couch, Paul D.P. Pharoah, Jenny Chang Claude, Per Hall, David J. Hunter, Roger L. Milne, Montserrat García Closas, Marjanka K. Schmidt, Stephen J. Chanock, Alison M. Dunning, Georgia Chenevix Trench, Jacques Simard, Peter Kraft, Douglas F. Easton.

Colorectal cancer GWAS (CCFR, CORECT, GECCO)

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.

Endometrial cancer GWAS

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Esophageal cancer GWAS

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