

Table S2: Odds ratio and 95% confidence limits for cancers associated with variants with pleiotropic associations. Bold indicates risk allele.

Region	SNP [†]	Gene	Alleles	EAF	Cancer site	GAME-ON		Validation		Combined
						OR (95% CI)	P-value	OR (95% CI)	P-value	P-value
1q22	rs1057941	<i>MTX1</i>	G/A	0.41	Breast	1.07 (1.04-1.11)	6.08 x 10 ⁻⁵	1.03 (1.01-1.05)	0.004	1.10 x 10 ⁻⁵
					Lung SqCC	1.10 (1.04-1.16)	0.001	1.12 (1.01-1.23)	0.03	1.21 x 10 ⁻⁴
					Aggressive prostate	1.09 (1.03-1.15)	0.004	-- ^a	-- ^a	-- ^a
13q13.1	rs11571833	<i>BRCA2</i>	A/T	0.01	Serous ovarian	1.76 (1.30-2.39)	2.50 x 10 ⁻⁴	1.45 (1.22-1.72)	3.08 x 10 ⁻⁵	3.95 x 10 ⁻⁸
					Lung (known)	1.91 (1.60-2.28)	1.23 x 10 ⁻¹²	-- ^b	-- ^b	-- ^b
2q33.1	rs13016963	<i>ALS2CR12</i>	A/G	0.61	Prostate	1.08 (1.04-1.13)	3.05 x 10 ⁻⁵	1.05 (1.03-1.08)	7.62 x 10 ⁻⁵	1.90 x 10 ⁻⁸
	rs1830298		T/C	0.29	Breast (known)	1.11 (1.07-1.15)	1.02 x 10 ⁻⁷	-- ^b	-- ^b	-- ^b
9p21.3	rs62560775	<i>CDKN2B-AS1</i>	A/G	0.09	Lung Adenocarcinoma	1.19 (1.08-1.31)	2.77 x 10 ⁻⁴	1.16 (1.03-1.30)	0.01	1.01 x 10 ⁻⁵
	rs1011970		G/T	0.17	Prostate	1.10 (1.05-1.15)	7.29 x 10 ⁻⁵	1.05 (1.02-1.09)	0.001	9.51 x 10 ⁻⁷
	rs1333040		T/C	0.43	Lung Squamous cell (known)	1.14 (1.08-1.20)	2.17 x 10 ⁻⁶	-- ^b	-- ^b	-- ^b

^aData not available; ^bpreviously known locus, thus did not include in the replication analysis.

Analysis Flowchart

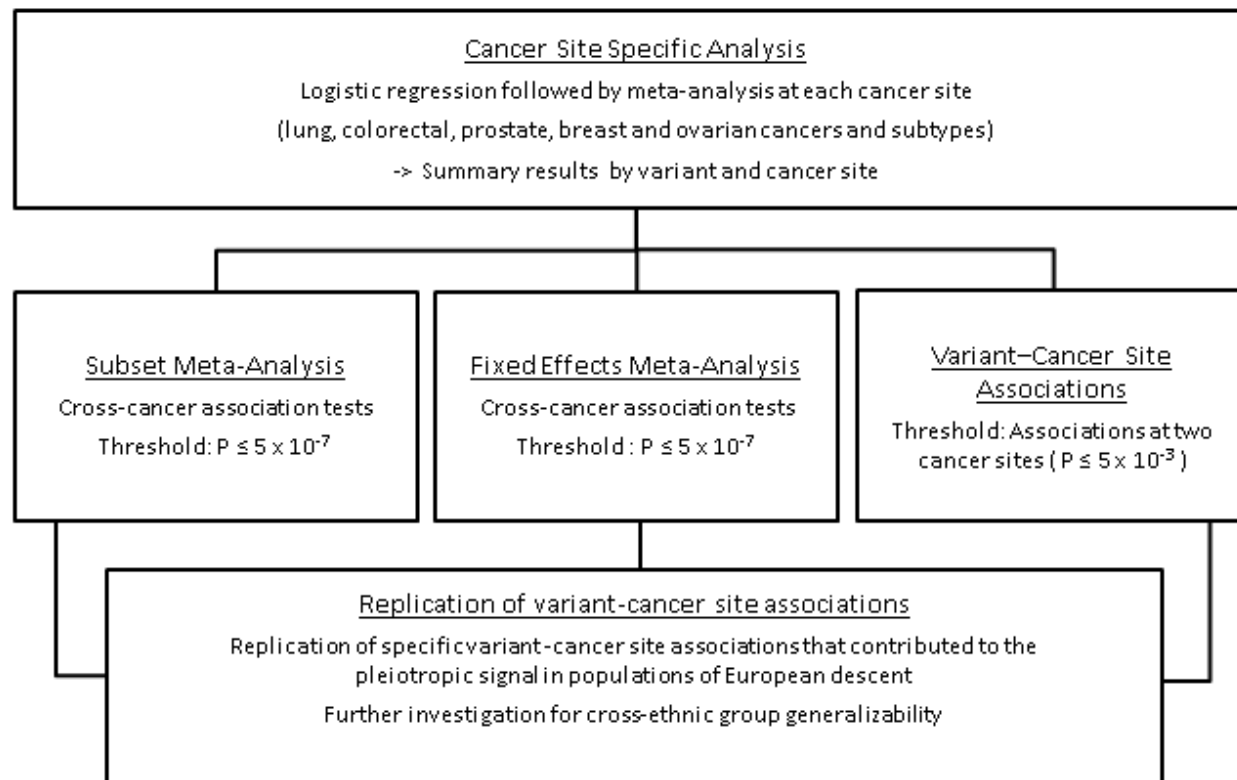


Figure S1: Flowchart showing analysis steps with first level showing initial logistic regression and meta-analysis to produce summary results for individual cancer sites, second level describing discovery analysis to find variants associated with subsets of cancers and the third level describing replication of specific variant cancer site associations from the identified subsets.

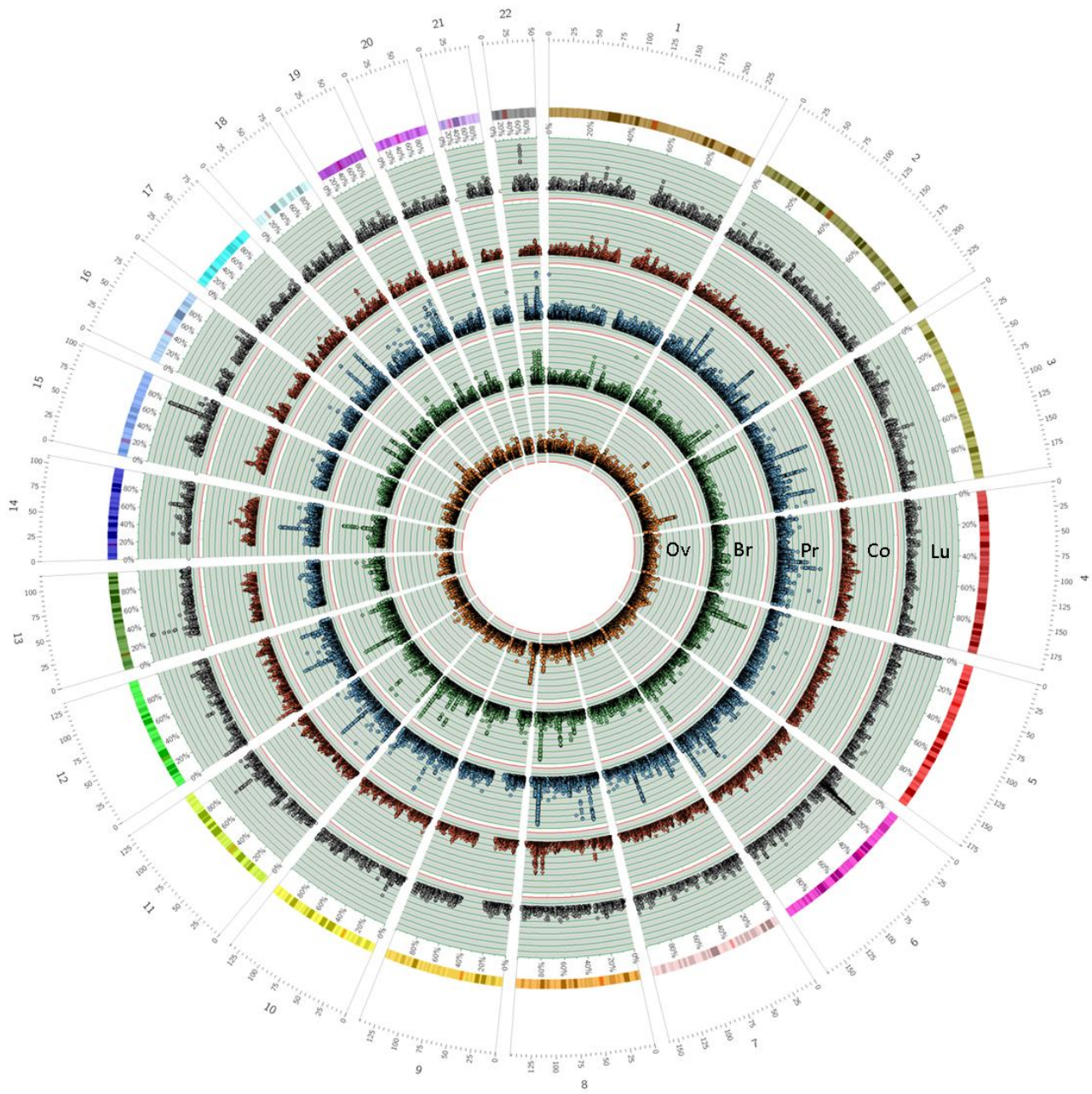


Figure S2. Manhattan plots ($-\log_{10}(p)$) by chromosome for individual cancer sites (innermost to outermost ring – ovary(Ov) breast (Br), prostate (PR), colorectal/GECCO (Co), Lung (Lu)).

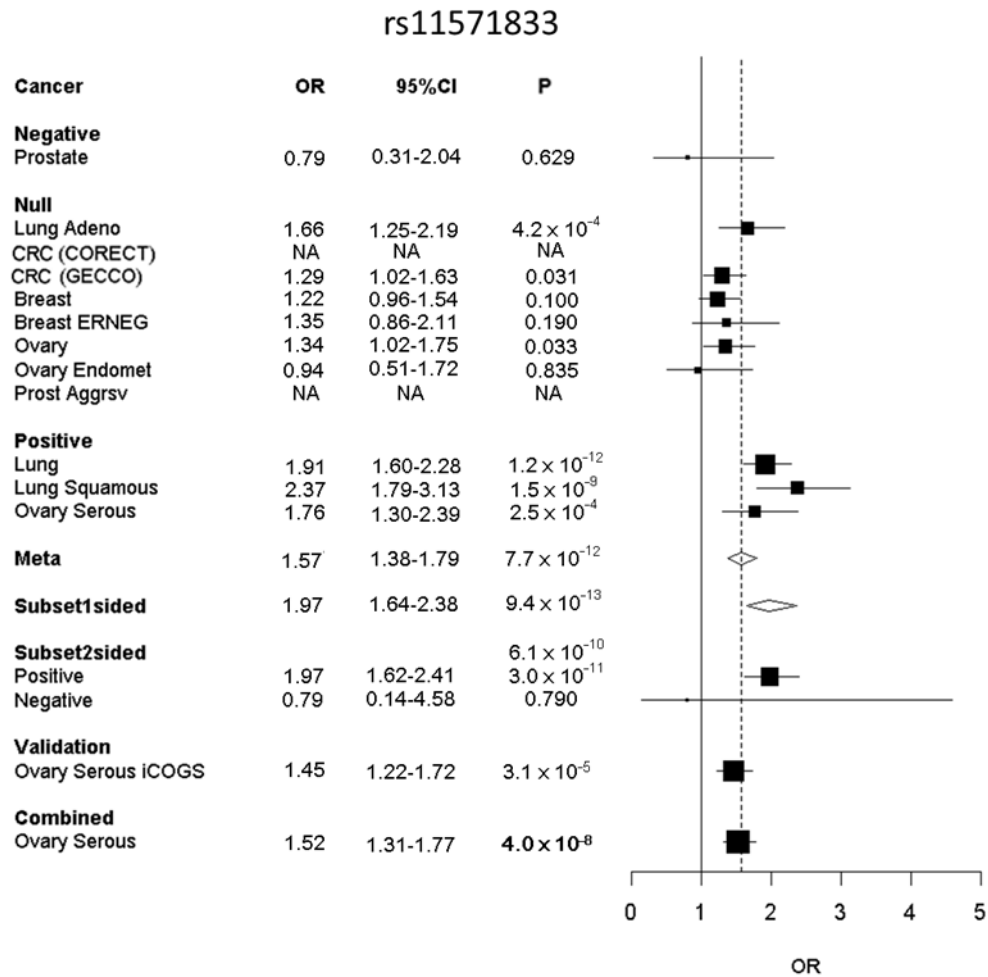
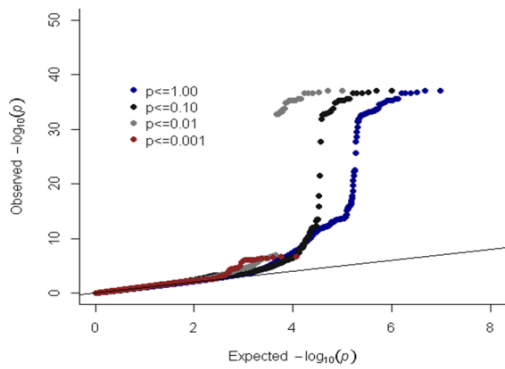
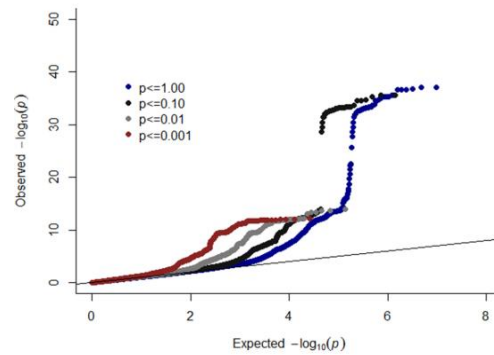


Figure S3. Results for rs11571833 **(A)** Forest plot showing per allele ORs for risk allele T of (T/A). Standard fixed effects meta-analysis (also indicated by dashed line), and subset meta-analysis results (two-sided, one-sided and positive and negative subset associations) are shown. **(B)** Regional plot showing two sided P values from ASSET subset meta-analysis at region 13q13.1 using GAME-ON/GECCO discovery set data. Peak is at *BRCA2*. rs11571815 and rs11571818 (partially obscured by rs11571833) have nearly identical association signals. Abbreviations - CRC: colorectal, ERNEG: estrogen receptor negative, Aggrsv: aggressive, Adeno: Adenocarcinoma.

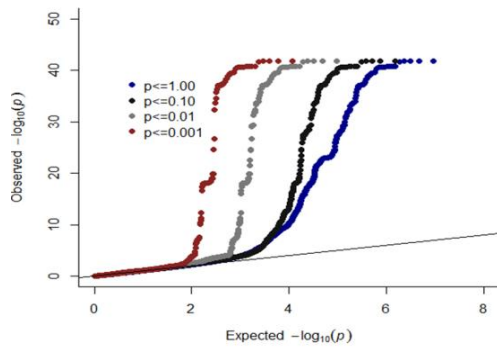
A) Breast conditioned on ovary



B) Breast conditioned on prostate



C) Prostate conditioned on colorectal



D) Prostate conditioned on ovary

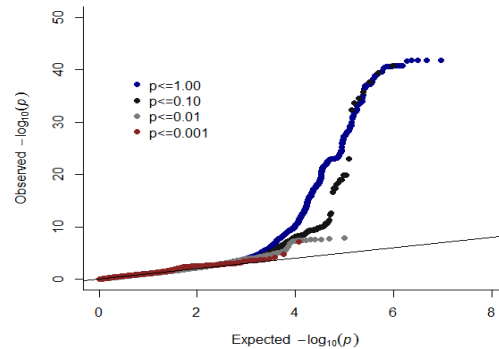


Figure S4: Conditional QQ-plots. **A** through **C** provide evidence for pleiotropic association. Panel **D** (prostate and ovary) gives an example where no pleiotropic association is observed (no leftward deflection of the curve with decreasing p-value category of the conditioning cancer).