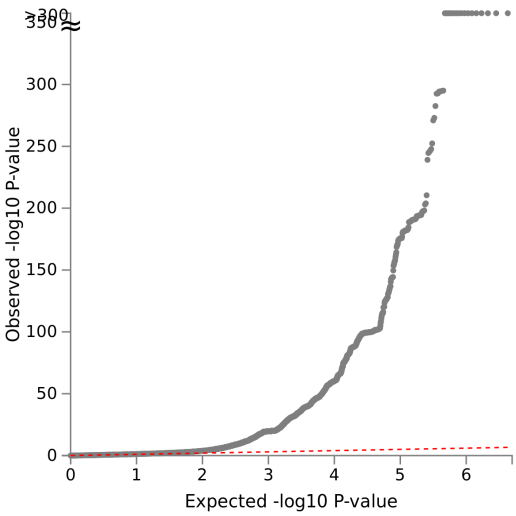
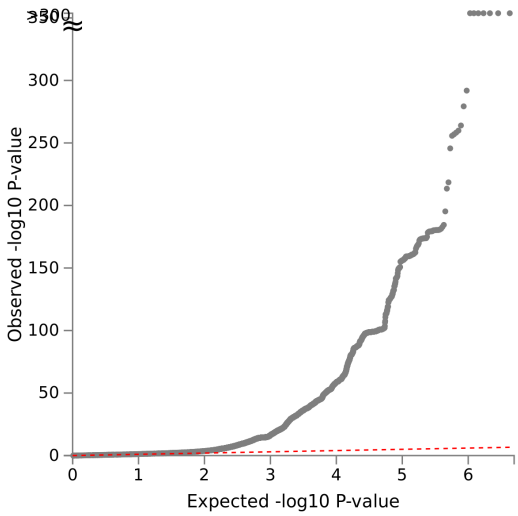
Supplementary Figures

Supplementary Figure 1. Quantile-quantile plots from the (a) main and the (b) subtype-focused meta-analyses. Negative logarithm (base 10) *P*-values from each meta-analysis are plotted on the Y-axis. For **(a)** λ = 1.11 and λ_{1000} = 1.00. For **(b)** λ = 1.15 and λ_{1000} = 1.00. Lambda, λ, is the genomic control inflation statistic and λ_{1000} is the same statistic scaled for 1,000 cases and 1,000 controls.

a

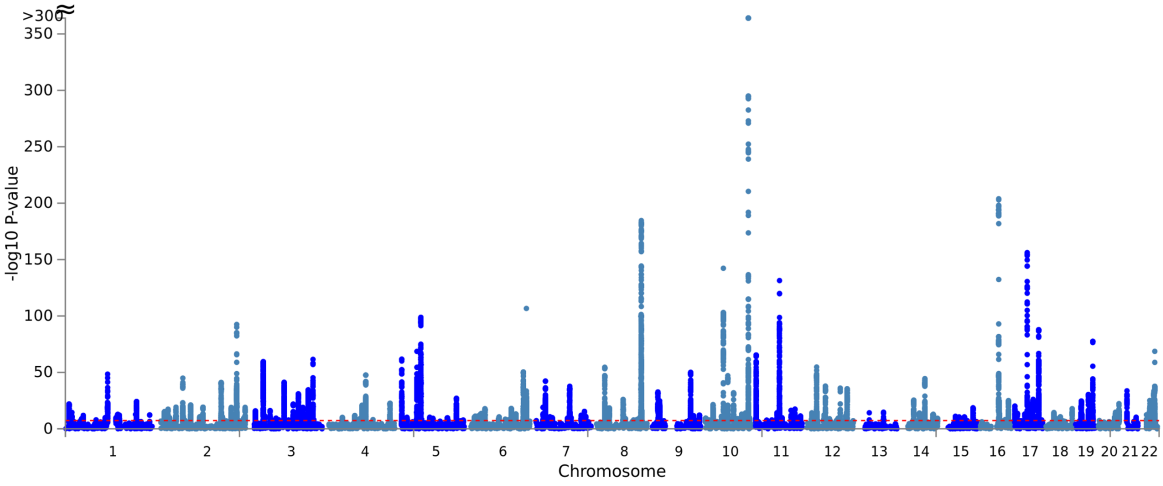


b

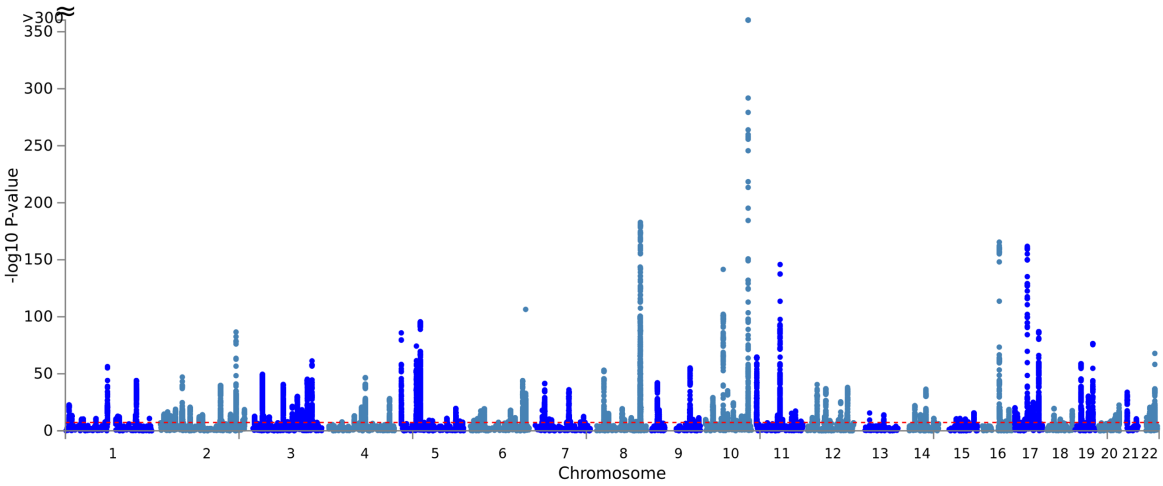


Supplementary Figure 2. Manhattan plots of genome-wide association results from the (a) main and the (b) subtype-focused meta-analyses. Negative logarithm (base 10) *P*-values from the meta-analysis are plotted on the Y-axis. The red dashed line indicates genome-wide significance ($P < 5 \times 10^{-8}$).

a



b



Supplementary Note 1

Gene-level MAGMA association analyses also revealed candidate multi-cancer susceptibility genes likely acting via diverse but fundamental carcinogenic processes. SNPs in or near *BSN* are highly pleiotropic and known to be associated at genome-wide significance ($P < 5 \times 10^{-8}$) with circulating levels of the inflammatory marker, C-reactive protein[1], and with multiple chronic inflammatory diseases[2]. *SIK2* encodes a centrosome kinase essential for bipolar mitotic spindle formation[3]. The kinase positively regulates cell-cycle progression and negatively regulates the proto-oncogene *CREB1* in prostate cancer cells[4]. *INTS10* codes for a component of Integrator, a complex involved in the transcription and processing of the small nuclear RNAs *U1* and *U2*[5]. Recurrent somatic mutations in *U1*, which regulates alternative splicing of cancer driver genes, have recently been identified in multiple tumor types[6]. *UQCC1* polymorphisms are associated at genome-wide significance with non-melanoma skin cancer[7]. *CLIC6* encodes a chloride intracellular channel and its expression has been shown to differ by *TP53* mutation and ER status in breast tumors[8]. *ATP5B* encodes a subunit of mitochondrial ATP synthase, the core enzyme of oxidative phosphorylation. The enzyme is downregulated across cancers[9], a reflection of the "Warburg effect" wherein cancer cells, regardless of their tissue of origin, favour glycolysis over oxidative phosphorylation even under aerobic conditions[10]. *IKZF2* encodes the hematopoietic-specific transcription factor "Helios" that is involved in the regulation of lymphocyte development. Helios-dependent regulation of gene expression and lymphocyte reprogramming is particularly observed in the tumor microenvironment[11]. *PYGB* encodes brain-type glycogen phosphorylase that helps metabolize glycogen as an energy source under hypoxic conditions. *PYGB* knockdown has been shown to reduce the wound-healing capability of MCF-7 breast cancer cells and the invasive potential of MDA-MB-231 breast cancer cells[12]. *PYGB* silencing in PC3 prostate cancer cells supresses growth and promotes apoptosis via NF-κB/Nrf2 signaling[13]. *PRDM5*, which encodes an epigenetic modifier that acts as a tumor suppressor, has a CpG island promoter that is silenced in multiple tumor types[14,15]. Inherited genetic variation in *LAMC1* is associated at genome-wide significance with colorectal cancer[16] and with the hormone-related traits of acne[17] and male-pattern baldness[18]. *GLIS1* was identified in our study based on its association with breast and prostate cancer. GLIS1 is a hypoxia-inducible transcription factor that regulates gene expression related to cell migration and invasion in breast cancer cells, specifically transcriptional activation of the Wnt/β-catenin pathway[19,20]. *CDKN1A* and *TIAL1* were identified at gene-level genome-wide significance ($P_{MAGMA} < 2.62 \times 10^{-6}$) for breast cancer alone and in the combined data, with the breast cancer association underlying the combined signal. Variants in/near these genes are associated at sub-genome-wide significance levels ($5 \times 10^{-8} < P_{lead\ SNP} \leq 10^{-7}$), with breast cancer susceptibility in the Michailidou et al. data set.[21] *TIAL1* encodes nucleolysin TIAR that has roles in G1/S phase cell-cycle arrest and caspase-dependent apoptosis[22]. *CDKN1A* expression is tightly controlled by TP53 and mediates the G1/S phase arrest in response to a range of stress stimuli[23]. These genes add to a list of candidate breast cancer susceptibility genes identified by GWAS,

including *CCND1*[24] and *CCNE1*[25], that collectively underscore the importance of the G1/S checkpoint as a major functional effector of inherited breast cancer risk.

Supplementary Note 2

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