Supplementary Materials

Supplementary Table 1. Demographic information for TCGA-UCEC and TCGA-BRCA cohorts using self-reported race.

Characteristic	TCGA-UCEC (endometrial cancer)		TCGA-BRCA (breast cancer) – female patients	
	All genotyped patients No. (%)	Patients with subtype classified No. (%)	All genotyped patients No. (%)	Patients with subtype classified No. (%)
Self-reported race				
American Indian or Alaska Native	3 (0.5)	3 (0.6)	1 (0.1)	1 (0.1)
Asian	20 (3.7)	20 (4.0)	59 (5.6)	58 (6.1)
Black	108 (19.8)	101 (20.0)	173 (16.5)	152 (16.0)
Native Hawaiian or other Pacific Islander	9 (1.6)	9 (1.8)	--	--
White	374 (68.5)	342 (67.6)	725 (69.1)	657 (69.2)
Not available	32 (5.9)	31 (6.1)	91 (8.7)	81 (8.5)
Total number of patients	546	506	1,049	949
Age – mean (range)	63.9 (31-90)	63.8 (31-90)	58.4 (26-90)	58.2 (31-90)

Supplementary Table 2. Demographic information and genetic ancestry breakdowns by genomic subtype for TCGA-UCEC patients with subtype classified.[a]

Characteristic	CN-high No. (%)	CN-low No. (%)	MSI No. (%)	POLE No. (%)
Self-reported race				
American Indian or Alaska Native	1 (0.6)	1 (0.7)	1 (0.7)	0 (0.0)
Asian	2 (1.2)	7 (4.8)	6 (4.1)	5 (10.2)
Black	51 (31.3)	19 (12.9)	23 (15.6)	8 (16.3)
Native Hawaiian or other Pacific Islander	3 (1.8)	2 (1.4)	2 (1.4)	2 (4.1)
White	93 (57.1)	115 (78.2)	108 (73.5)	26 (53.1)
Not available	13 (8.0)	3 (2.0)	7 (4.8)	8 (16.3)
Genetic ancestry				
African	52 (31.9)	21 (14.3)	25 (17.0)	9 (18.4)
East Asian	4 (2.5)	8 (5.4)	9 (6.1)	8 (16.3)
European	102 (62.6)	114 (77.6)	111 (75.5)	29 (59.2)
Native American	4 (2.5)	3 (2.0)	2 (1.4)	3 (6.1)
Other	1 (0.6)	1 (0.7)	0 (0.0)	0 (0.0)
Age: mean (range)	68.7 (33-87)	61.6 (31-90)	63.0 (35-88)	56.0 (33-87)

[a]CN: copy number; MSI: microsatellite instability hypermutated; POLE: *POLE* hypermutated

Supplementary Table 3. Demographic information and genetic ancestry breakdowns by genomic subtype for TCGA-BRCA patients with subtype classified.

Characteristic	Basal No. (%)	Her2 enriched No. (%)	Luminal A No. (%)	Luminal B No. (%)	Normal No. (%)
Self-reported race					
American Indian or Alaska Native	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	7 (4.3)	14 (18.4)	20 (4.1)	16 (8.5)	1 (2.8)
Black	49 (30.4)	15 (19.7)	56 (11.5)	23 (12.2)	9 (25.0)
White	100 (62.1)	36 (47.4)	375 (77.0)	121 (64.0)	25 (69.4)
Not available	5 (3.1)	10 (13.2)	36 (7.4)	29 (15.3)	1 (2.8)
Genetic ancestry					
African	50 (31.1)	14 (18.4)	56 (11.5)	24 (12.7)	9 (25.0)
East Asian	7 (4.3)	14 (18.4)	17 (3.5)	16 (8.5)	1 (2.8)
European	101 (62.7)	45 (59.2)	396 (81.3)	147 (77.8)	24 (66.7)
Native American	3 (1.9)	2 (2.6)	12 (2.5)	2 (1.1)	2 (5.6)
Other	0 (0.0)	1 (1.3)	6 (1.2)	0 (0.0)	0 (0.0)
Age: mean (range)	55.9 (29-90)	58.6 (32-90)	59.1 (26-90)	58.6 (27-90)	55.1 (35-90)

Supplementary Table 4. TCGA-UCEC Clinicopathological characteristics by *HSD3B1* genotype for samples from subjects of African ancestry.

Variable	Genotype	No. (%)	p-value
Stage			
I	AA	53 (85.5)	0.46
	AC	8 (12.9)	
	CC	1 (1.6)	
≥ II	AA	44 (84.6)	
	AC	6 (11.5)	
	CC	2 (3.9)	
Histologic diagnosis			
Endometrioid	AA	62 (84.9)	0.87 (serous vs. endometrioid)
	AC	8 (11.0)	
	CC	3 (4.1)	
Mixed serous and endometrioid	AA	7 (100.0)	
	AC	0 (0.0)	
	CC	0 (0.0)	
Serous	AA	28 (82.4)	
	AC	6 (17.6)	
	CC	0 (0.0)	
Grade (endometrioid only)			
1 or 2	AA	34 (82.9)	0.31
	AC	4 (9.8)	
	CC	3 (7.3)	
3	AA	28 (87.5)	
	AC	4 (12.5)	
	CC	0 (0.0)	

Supplementary Table 5. Summary information for the TCGA-OV ovarian cancer cohort.

Characteristic	All genotyped patients No. (%)
Genetic ancestry	
African	32 (7.4)
East Asian	10 (2.3)
European	367 (84.8)
Native American	10 (2.3)
Other	7 (1.6)
Not classified	7 (1.6)
Total number of patients	433
Age – mean (range)	59.6 (26-89)

Supplementary Table 6. Breakdown of TCGA-OV samples by subtype and *HSD3B1* genotype.

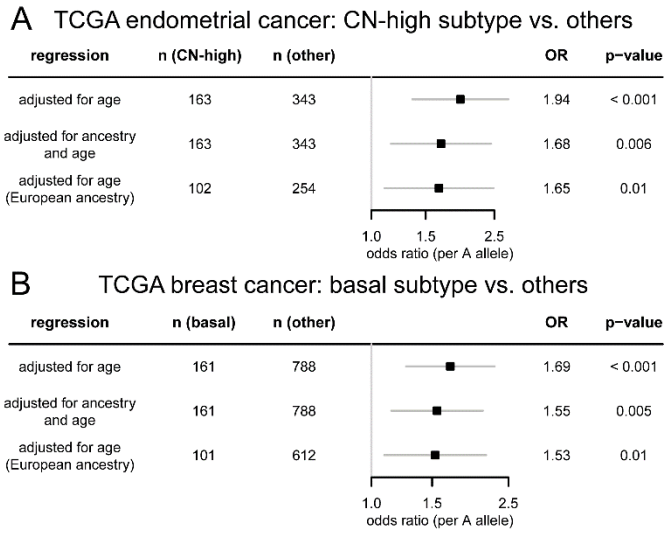
Subtype[a]	Genotype	All TCGA-OV No. (%)	European ancestry No. (%)
low-grade serous	AA	31 (55.4)	24 (51.1)
	AC	21 (37.5)	19 (40.4)
	CC	4 (7.1)	4 (8.5)
high-grade serous	AA	171 (47.0)	138 (44.5)
	AC	168 (46.2)	149 (48.1)
	CC	25 (6.9)	23 (7.4)
serous (any grade)	AA	210 (48.5)	168 (45.8)
	AC	194 (44.8)	172 (46.9)
	CC	29 (6.7)	27 (7.4)

[a]Grade 1 or 2 was considered low-grade and grade 3 was considered high grade. Note that the numbers for serous (any grade) are not the exact sums of low-grade plus high-grade due to some samples lacking grade classification.

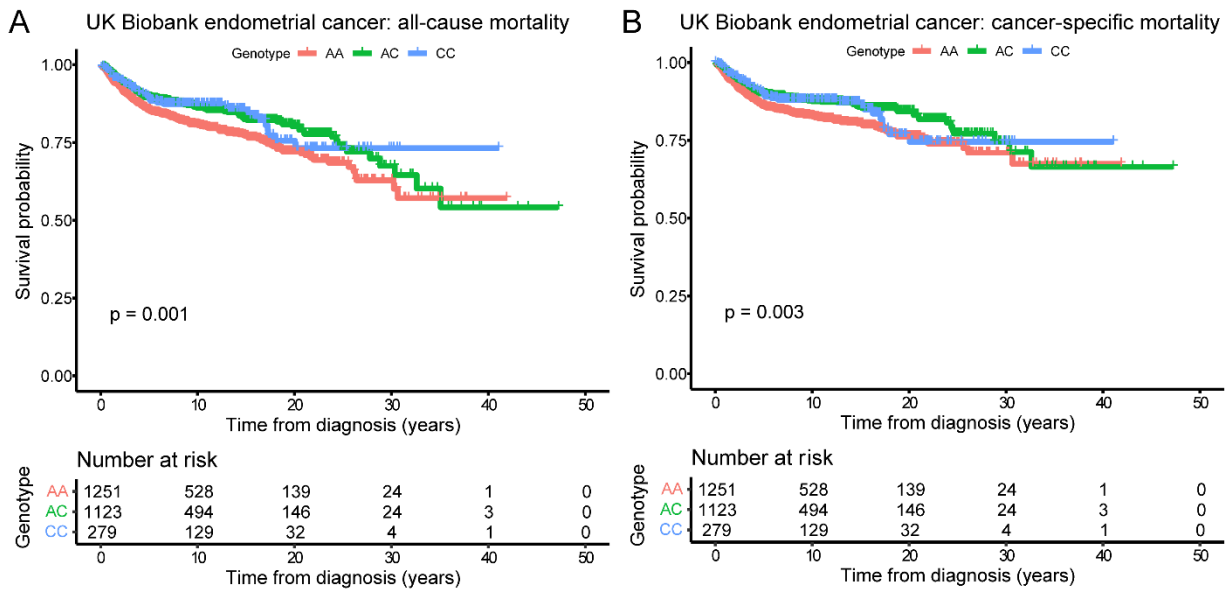
Supplementary Table 7. Results from testing of proportional hazards assumptions[a] for Cox regression models for survival of UK Biobank subjects with endometrial cancer diagnoses.

outcome	regression model	p-value for genotype variable	global p-value
all-cause mortality	univariate regression against genotype	0.38	0.38
	genotype + diagnosis age + BMI	0.32	0.19
	genotype + diagnosis age + BMI + first ten genetic principal components	0.33	0.54
cancer-specific mortality	univariate regression against genotype	0.31	0.31
	genotype + diagnosis age + BMI	0.28	0.40
	genotype + diagnosis age + BMI + first ten genetic principal components	0.29	0.71

[a]Testing of proportional hazards assumptions was performed using the cox.zph function of R package survival. BMI: body mass index



Supplementary Figure 1. Adrenal-restrictive *HSD3B1* genotype is associated with hormone independent subtypes of endometrial and breast cancer in age-adjusted models. Odds ratios (per A allele) with 95% confidence intervals for having **(A)** CN-high endometrial cancer vs. other genomic subtypes of endometrial cancer and **(B)** basal breast cancer vs. other genomic subtypes of breast cancer among subjects in the TCGA-UCEC and TCGA-BRCA projects, respectively, whose tumors had genomic subtype classified. Results are shown from binomial logistic regressions: a regression of (subtype = CN-high/basal) against number of A alleles adjusted for diagnosis age, a regression adjusted for genetic ancestry classification and diagnosis age, and a regression adjusted for diagnosis age and restricted to subjects classified as having European ancestry.



Supplementary Figure 2. Homozygous adrenal-restrictive *HSD3B1* genotype is associated with worse endometrial cancer outcomes. Kaplan-Meier curves of **(A)** all-cause mortality and **(B)** cancer-specific mortality for UK Biobank subjects who were diagnosed with endometrial cancer. Endometrial cancer patients were identified using the UK Biobank's cancer registry with additional diagnosed patients identified using inpatient hospital records (ICD10 code C54.1). Diagnosis dates were extracted from the cancer registry for patients in the cancer registry, and from the earliest inpatient hospital record with ICD10 code C54.1 for patients not in the cancer registry. The UK Biobank's death register was used to determine which patients died, along with causes and dates of death. P-values from log-rank tests are shown.