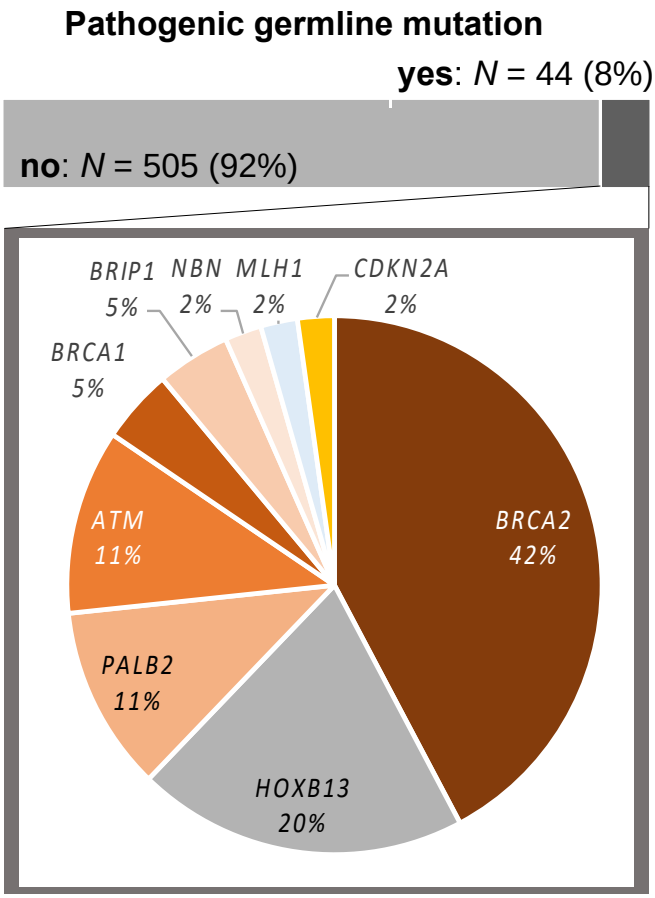
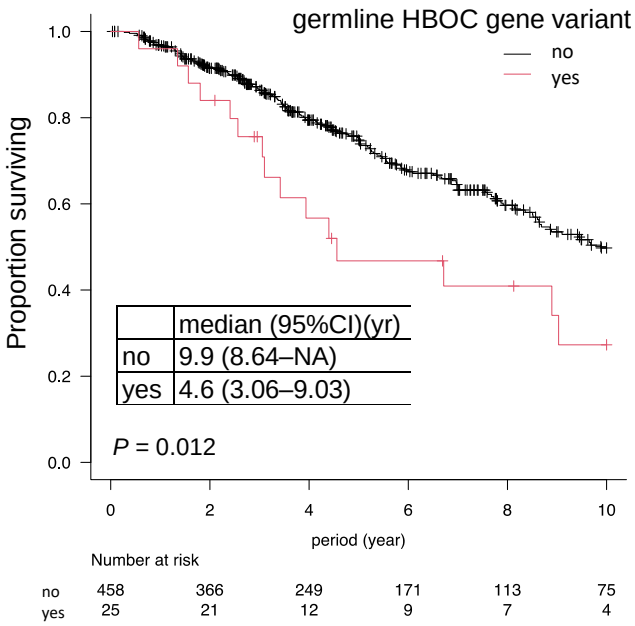


Supplementary Figure 1

Distribution of patients with pathogenic germline variants in the 27 tested genes. One case with concomitant variants in *HOXB13* and *ATM* genes was observed.

Supplementary Figure 2

(A)



(B) **Overall survival**

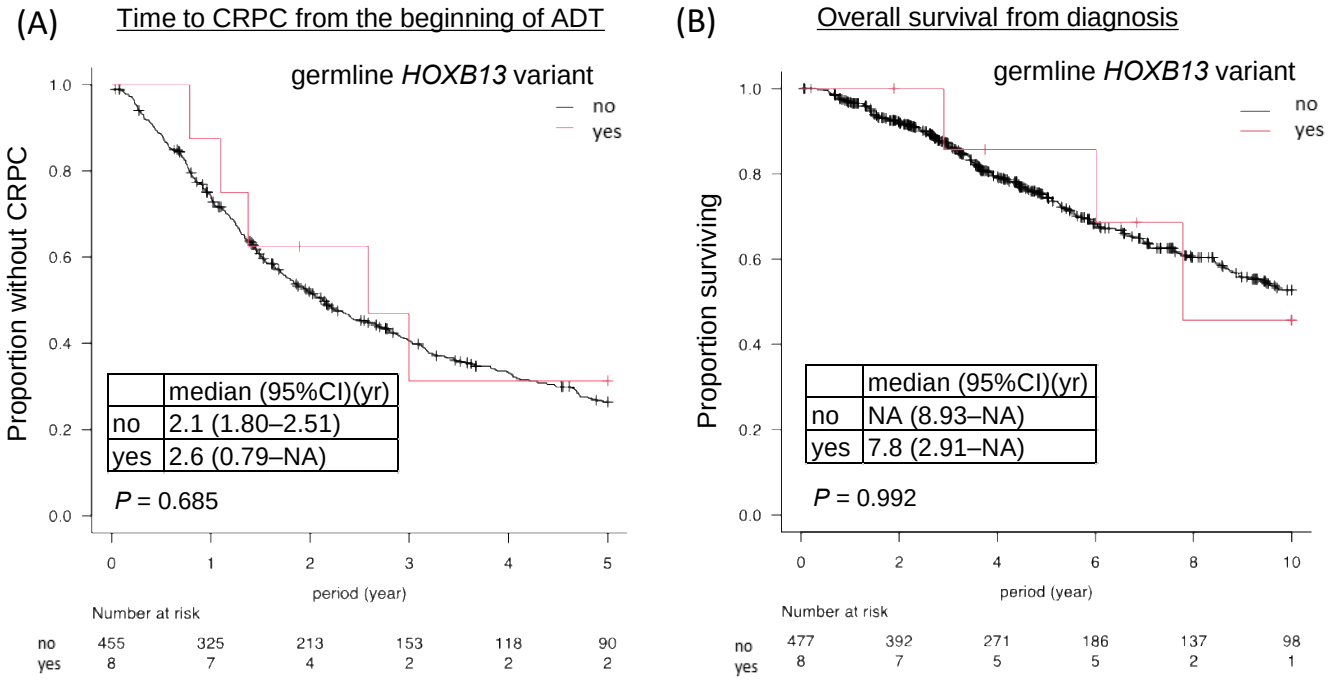
			95%CI		
		HR	lower	upper	*P*-value
Age		1.02	1.00	1.05	0.08
Initial PSA		1.00	1.00	1.00	0.32
Family history	no	Reference			
	yes	0.35	0.14	0.88	0.03 *
GG	1	Reference			0.03 *
	2	0.48	0.09	2.57	
	3	0.31	0.05	1.74	
	4	0.62	0.14	2.77	
	5	1.01	0.23	4.35	
Distant metastasis at diagnosis	no	Reference			
	yes	1.92	1.21	3.05	< 0.01 *
HBOC gene variant	no	Reference			
	yes	2.37	1.24	4.52	< 0.01 *

Supplementary Figure 2

(A) Kaplan–Meier curve showing overall survival (OS) from the initiation of androgen deprivation therapy (ADT) for patients with and without pathogenic germline variants in HBOC-associated genes.

(B) Multivariable Cox regression analysis showing the association between clinical and genetic variables and OS from the initiation of ADT. Clinical factors that showed significant association with OS in the univariate analysis were included in the multivariable analysis.

Supplementary Figure 3

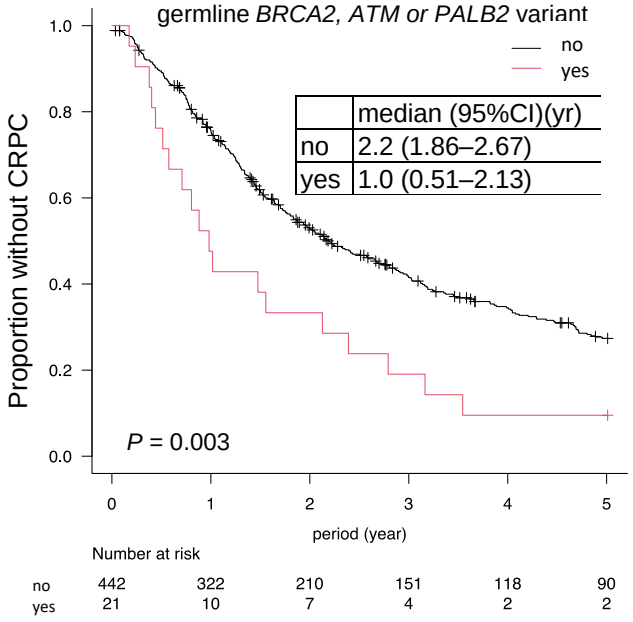


Supplementary Figure 3

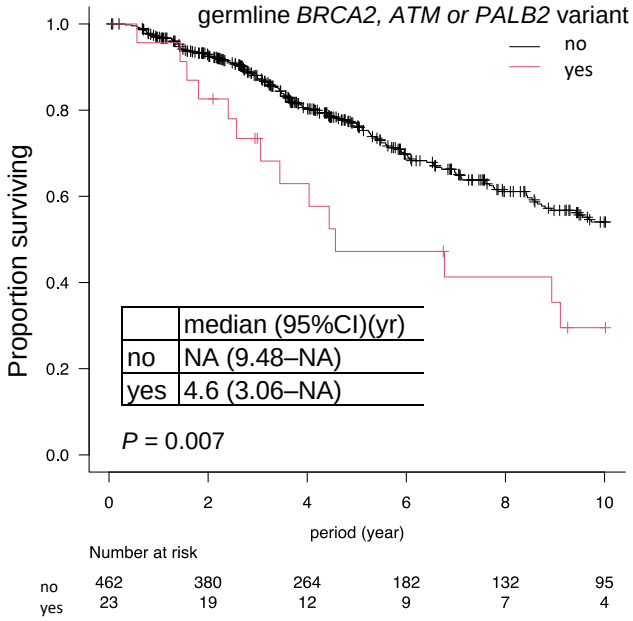
Prognostic value of pathogenic germline variants in *HOXB13* in patients treated with hormonal therapy. (A) Kaplan–Meier curve showing time to castration resistance from the initiation of androgen deprivation therapy for patients with and without pathogenic germline variants in the *HOXB13* gene. Group differences were tested by performing log-rank tests. (B) Kaplan–Meier curve showing overall survival from the time of diagnosis for patients with and without pathogenic germline variants in *HOXB13*.

Supplementary Figure 4

(A)



(B)



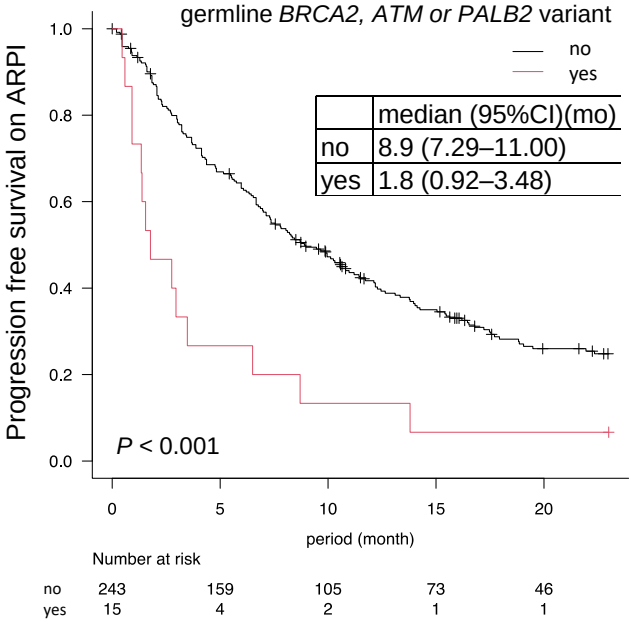
(C) **Time to CRPC**

			95%CI		
		HR	lower	upper	*P*-value
Age		1.01	1.00	1.03	0.12
Initial PSA		1.00	1.00	1.00	0.02 *
Family history	no	Reference			
	yes	0.74	0.46	1.20	0.23
GG	1	Reference			0.01 *
	2	0.48	0.13	1.83	
	3	0.60	0.17	2.11	
	4	0.82	0.25	2.70	
	5	1.17	0.36	3.78	
Distant metastasis	no	Reference			
at diagnosis	yes	1.40	1.03	1.89	0.03 *
BRCA2, ATM or PALB2	no	Reference			
variant	yes	1.87	1.06	3.30	0.03 *

(D) **Overall survival**

			95%CI		
		HR	lower	upper	*P*-value
Age		1.02	1.00	1.05	0.06
Initial PSA		1.00	1.00	1.00	0.34
Family history	no	Reference			
	yes	0.38	0.15	0.96	0.04 *
GG	1	Reference			0.01 *
	2	0.33	0.06	1.88	
	3	0.12	0.02	0.86	
	4	0.53	0.12	2.38	
	5	0.82	0.19	3.60	
Distant metastasis	no	Reference			
at diagnosis	yes	2.34	1.43	3.83	< 0.01 *
BRCA2, ATM or PALB2	no	Reference			
variant	yes	2.14	1.09	4.21	0.03 *

(E)



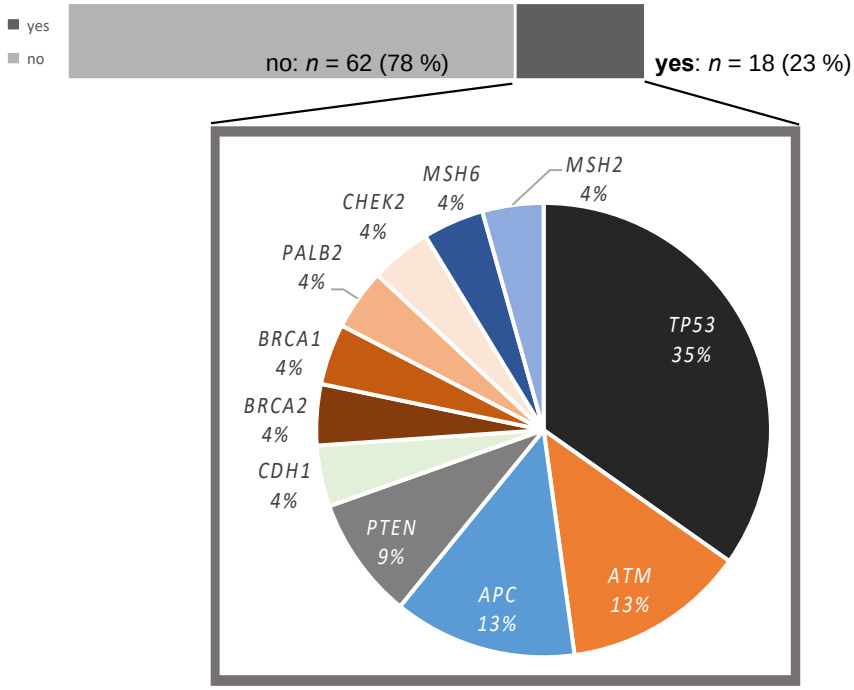
(F) **ARPI duration (univariate analysis)**

			95%CI		
		HR	lower	upper	*P*-value
Age		0.99	0.98	1.01	0.57
Initial PSA		1.00	1.00	1.00	0.18
Family history	no	Reference			
	yes	0.78	0.47	1.31	0.35
GG	1	Reference			0.07
	2	0.15	0.03	0.69	
	3	0.18	0.04	0.82	
	4	0.17	0.04	0.71	
	5	0.22	0.05	0.91	
Distant metastasis	no	Reference			
at diagnosis	yes	1.21	0.91	1.61	0.18
BRCA2, ATM or PALB2	no	Reference			
variant	yes	2.77	1.60	4.80	< 0.01 *

Supplementary Figure 4

Prognostic value of pathogenic germline variants in HBOC-associated genes excluding *BRCA1*. (A) Kaplan–Meier curve showing time to castration resistance from the initiation of androgen deprivation therapy (ADT) for patients with and without known pathogenic germline variants in HBOC-associated genes (*BRCA2*, *ATM*, and *PALB2*). Group differences were tested by performing log-rank tests. (B) Kaplan–Meier curve showing overall survival (OS) from initiation of androgen deprivation therapy (ADT) for patients with and without pathogenic germline variants in HBOC-associated genes excluding *BRCA1*. (C) Multivariable Cox regression analysis for the evaluation of the association between clinical and genetic variables and time to castration resistance from the initiation of ADT. Clinical factors that showed significant association with time to castration resistance based on the univariate analysis were included in the multivariable analysis. (D) Multivariable Cox regression analysis for the evaluation of the association between clinical and genetic variables and OS from initial diagnosis. Clinical factors that showed significant association with OS in the univariate analysis were included in the multivariable analysis. (E) Kaplan–Meier curve showing progression-free survival (PFS) for androgen receptor pathway inhibitors (ARPIs, abiraterone, or enzalutamide) for patients with and without known pathogenic germline variants in HBOC-associated genes excluding *BRCA1*. (F) Univariate Cox regression analysis for the evaluation of the association between clinical and genetic variables and PFS based on ARPIs. Multivariable analysis was not performed due to the limited number of events.

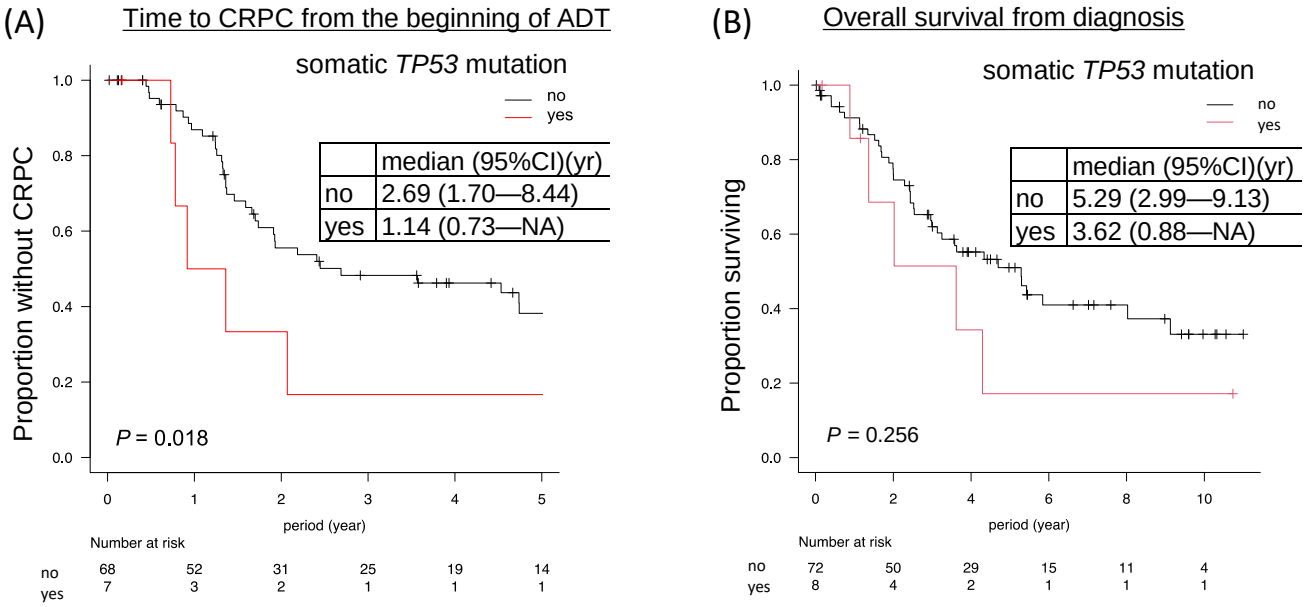
Supplementary Figure 5



Supplementary Figure 5

Proportion of patients with somatic mutations and the distribution of mutated genes.

Supplementary Figure 6



Supplementary Figure 6

Prognostic value of somatic mutations in *TP53* in patients treated with hormonal therapy. (A) Kaplan–Meier curve showing time to castration resistance from the initiation of androgen deprivation therapy for patients with and without somatic mutations in *TP53*. Group differences were determined by performing log-rank tests. (B) Kaplan–Meier curve showing overall survival from the time of diagnosis for patients with and without somatic mutations in *TP53*.