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Supplemental Data

Breast Cancer Polygenic Risk Score and Contralateral Breast Cancer Risk

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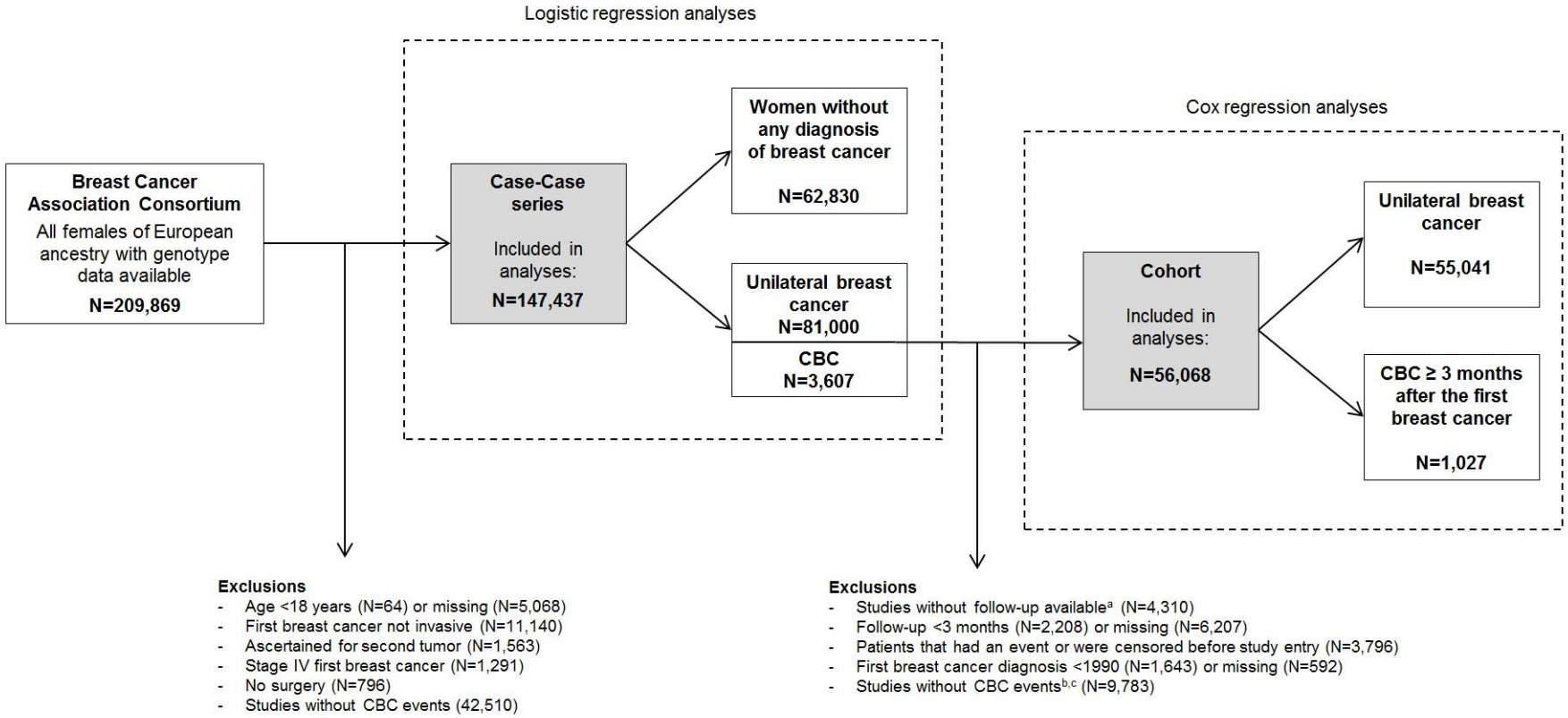
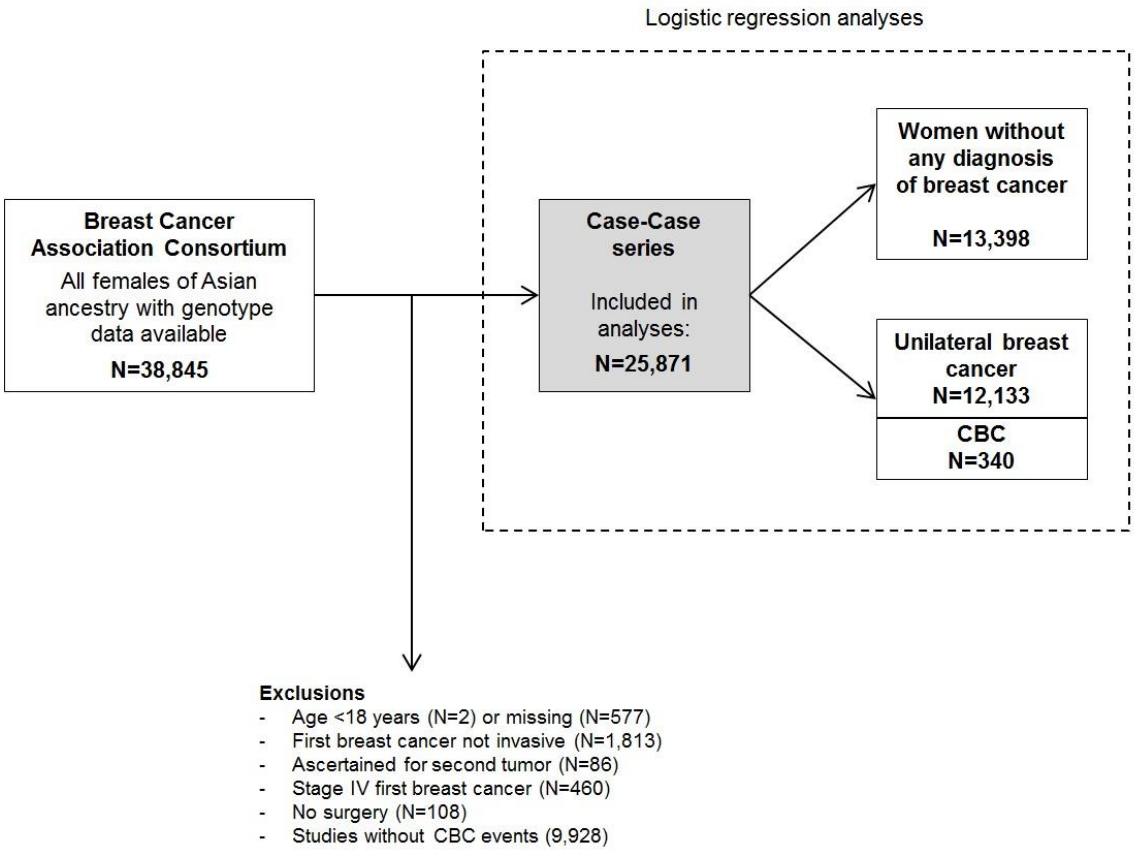
Supplemental Figures

Figure S1A. Overview of the selection of women with breast cancer and control women for the European series



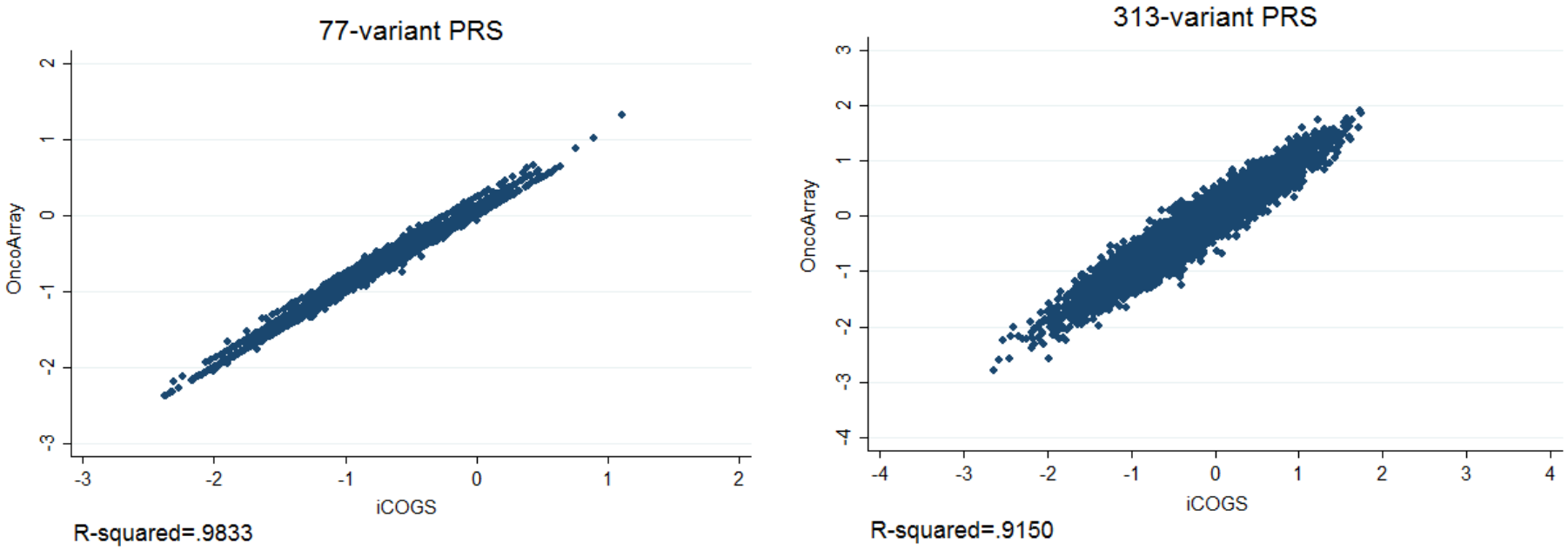
Abbreviations: CBC = contralateral breast cancer
For a complete overview of all studies see Table S1
[a] Excluded studies: CBCS, GLACIER, HMBCS, TNBCC
[b] Excluded studies: BCFR-NY, BCFR-UTAH, CNIO-BCS, DIETCOMPLYF, FHRISK, GESBC, HABCS, HUBCS, ICICLE, KBCP, MCCS, MMHS, NCBCS, PREFACE, SUCCESSB, SUCCESSC
[c] These studies dropped out because for these analyses the definition of CBC is based on the criteria that the CBC was diagnosed at least three months after the first breast cancer diagnosis

Figure S1B. Overview of the selection of women with breast cancer and control women for Asian series



Abbreviations: CBC = contralateral breast cancer

Figure S2. Correlation of total variant scores between the iCOGS array and OncoArray for the 77-variant PRS and the 313-variant PRS[a,b]

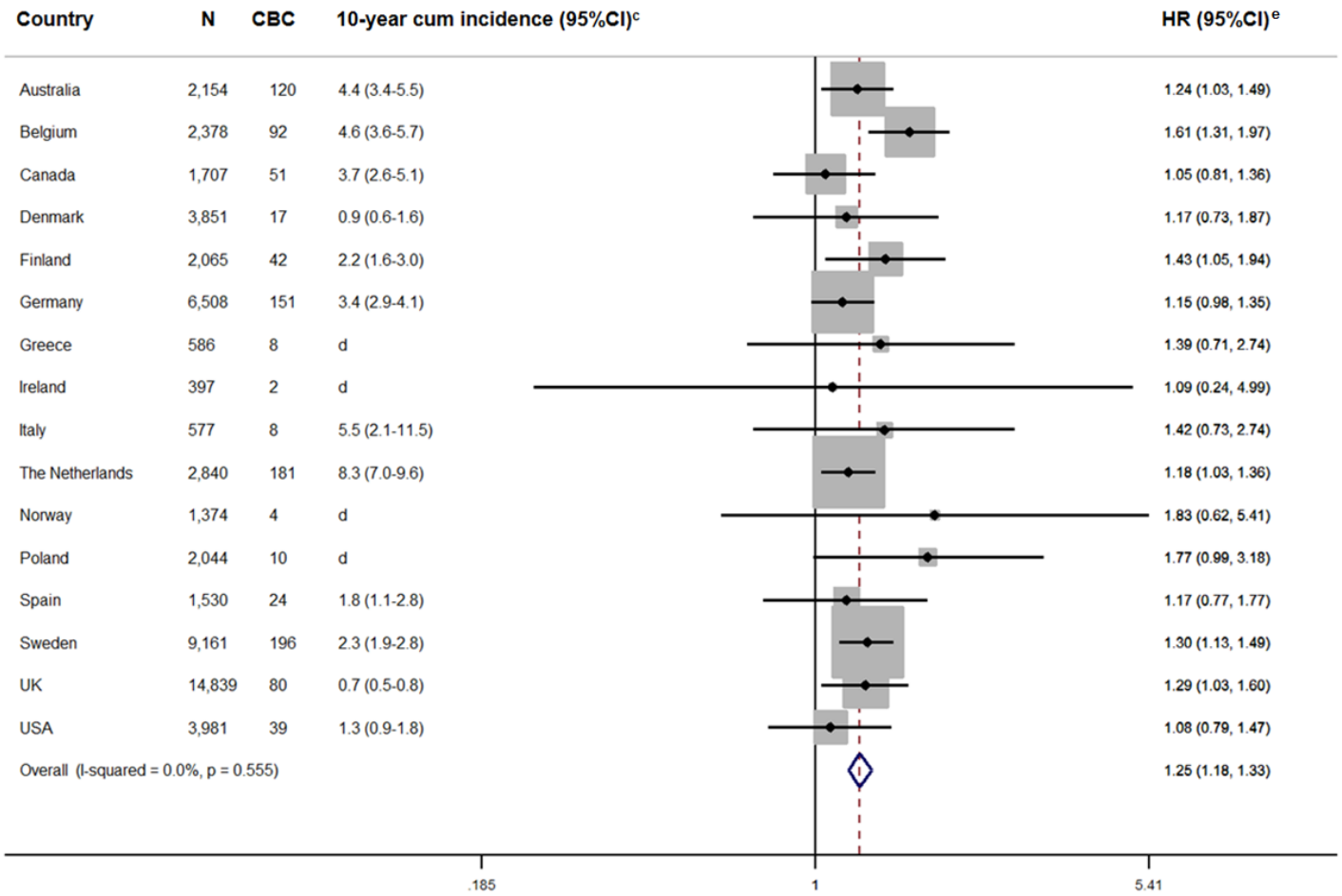


Abbreviations: PRS = polygenic risk score, SD = standard deviation

[a] We evaluated consistency between iCOGS and OncoArray using the intraclass correlation coefficient (ICC), showing a ICC of 0.99 (95%CI=0.99-0.99) for the PRS_{77}, and an ICC of 0.96 (95%CI=0.95-0.96) for the PRS_{313}, based on N=9,071 observations

[b] Coefficients to construct the PRSs are shown in Table S3. The PRSs were standardized by the same SD as was used by Mavaddat et al.[1]. The SD was 0.45 for overall breast cancer PRS_{77}, and 0.61 for overall breast cancer PRS_{313}

Figure S3. Forest plot of the association between the 313-variant PRS and contralateral breast cancer risk by country[a,b]



Abbreviations: PRS = polygenic risk score, N = number of women, CBC = contralateral breast cancer, cum = cumulative, CI = confidence interval, HR = hazard ratio, SD = standard deviation

Fixed effect meta-analysis was used to calculate I-squared and P-value for heterogeneity

[a] Republic of North Macedonia was left out this plot because of a too small sample size (N=76 women including N=2 CBC events)

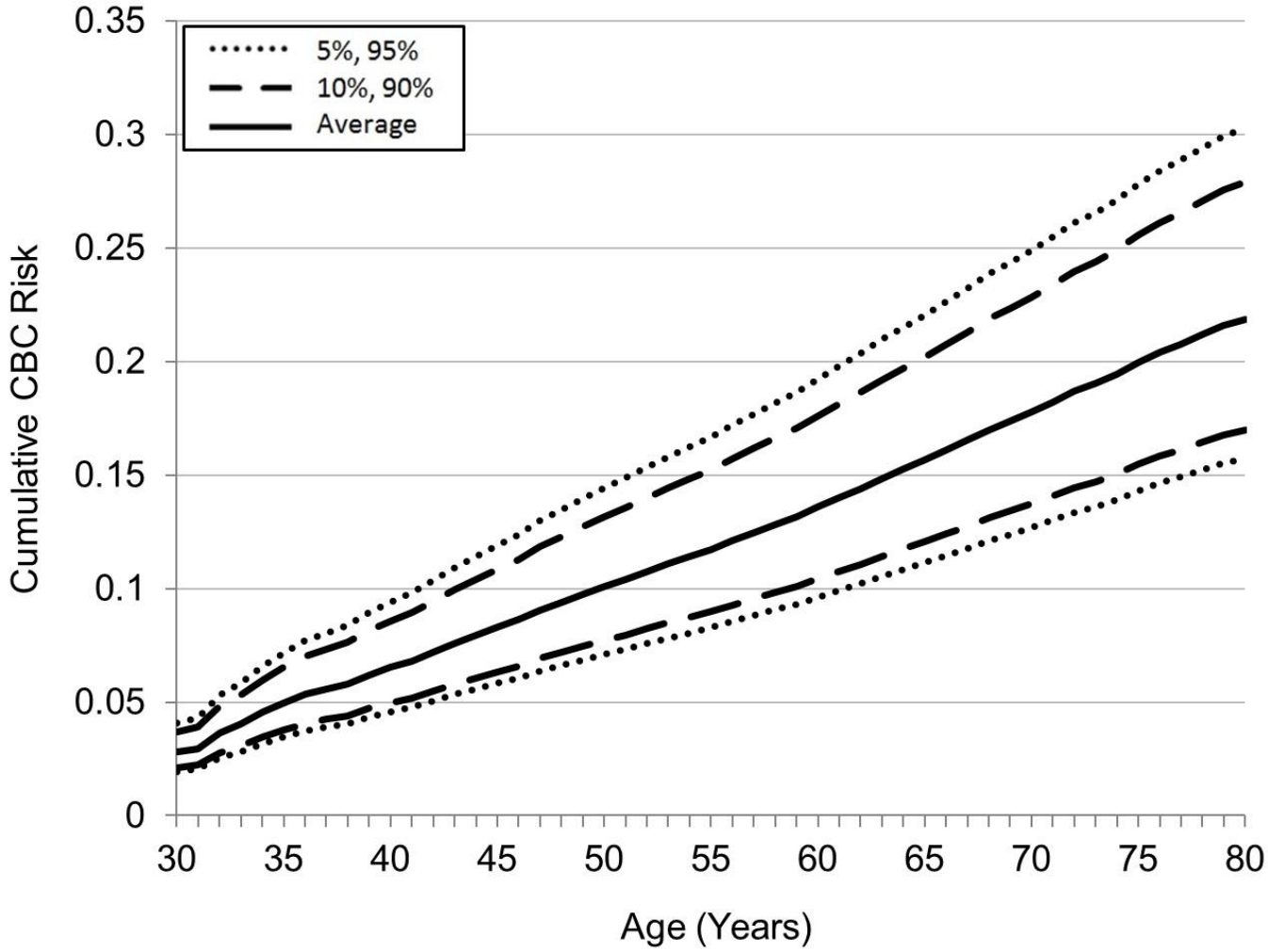
[b] Coefficients to construct the PRS_{313} are shown in Table S3. The PRS_{313} was standardized by SD=0.61, in line with Mavaddat et al.[1]

[c] The 10-year cumulative incidence of CBC was estimated with time since first breast cancer as time scale, and distant metastases (where available) and death as competing risks

[d] Follow-up too short for calculating 10-year cumulative incidence

[e] HR per SD. The analyses were performed with attained age as the time scale

Figure S4. Predicted contralateral breast cancer risk by percentile of the 313-variant PRS (PRS_{313})



Abbreviations: PRS = polygenic risk score, CBC = contralateral breast cancer

Coefficients to construct the PRS_{313} are shown in Table S3. The PRS_{313} was standardized by SD=0.61, in line with Mavaddat et al[1]. The CBC incidences were calculated based on incidence data from the Netherlands Cancer Registry[2] and relative risks estimated as described in the Material and Methods. In contrast to Figure 2, death was not taken into account as competing risk.

Supplemental Tables

Table S1. Study characteristics of included studies of the Breast Cancer Association Consortium

Table S2. Studies and samples included in the analyses using the case-case series, cohort, and validation set

	European								Asian		
	Case-case series N studies = 62			Cohort N studies = 42		Validation set N studies = 24			Case-case series N studies = 8		
Studies	Control women[a]	Unilateral BC	CBC	Unilateral BC	CBC	Control women[a]	Unilateral BC	CBC	Control women[a]	Unilateral BC	CBC
ABCFS	738	1,149	127	1,021	93	-	-	-	-	-	-
ABCS	1,567	1,047	54	519	14	-	-	-	-	-	-
ABCS-F	0	861	91	363	17	-	-	-	-	-	-
ABCTB	375	900	17	708	1	74	180	8	-	-	-
BBCC	711	845	58	766	6	49	56	5	-	-	-
BBCS	1,768	1,266	80	466	1	-	-	-	-	-	-
BCEES	-	-	-	-	-	166	133	0	-	-	-
BCFR-NY	27	340	61	-	-	-	-	-	-	-	-
BCFR-PA	0	104	14	69	4	-	-	-	-	-	-
BCFR-UTAH	0	13	87	-	-	-	-	-	-	-	-
BCINIS	-	-	-	-	-	144	262	0	-	-	-
BIGGS	49	713	50	395	2	-	-	-	-	-	-
BREOGAN	725	1,245	19	1,233	15	145	238	4	-	-	-
BSUCH	1,122	900	36	727	3	-	-	-	-	-	-
CBCS	817	530	21	-	-	163	105	4	170	238	10
CCGP	321	598	19	578	8	66	125	7	-	-	-
CGPS	5,250	4,135	60	3,834	17	142	227	3	-	-	-
CNIO-BCS	829	742	5	-	-	-	-	-	-	-	-
CTS	-	-	-	-	-	115	220	0	-	-	-
DIETCOMPLYF	0	704	1	-	-	-	-	-	-	-	-
FHRISK	0	119	2	-	-	-	-	-	-	-	-
GC-HBOC	1,732	2,690	230	1,406	47	-	-	-	-	-	-
GENICA	711	869	26	869	1	56	89	2	-	-	-
GESBC	181	303	3	-	-	-	-	-	-	-	-
GLACIER	0	1,733	230	-	-	-	-	-	-	-	-
HABCS	863	774	84	-	-	173	141	6	-	-	-
HCSC	0	362	13	273	9	-	-	-	-	-	-
HEBCS	1,060	1,632	116	1,578	41	-	-	-	-	-	-
HERPACC	-	-	-	-	-	-	-	-	1,659	756	18
HKBCS	-	-	-	-	-	-	-	-	451	403	12
HMBCS	345	729	28	-	-	-	-	-	-	-	-
HUBCS	116	198	2	-	-	-	-	-	-	-	-
ICICLE	1	138	12	-	-	-	-	-	-	-	-
KARBAC	0	761	46	443	32	-	-	-	-	-	-
KARMA	5,981	2,314	96	2,188	33	597	185	10	-	-	-
KBCP	431	516	9	-	-	-	-	-	-	-	-
KCONFAB/AOCS	898	397	83	305	26	-	-	-	-	-	-
LMBC	1,821	3,016	208	2,286	92	87	142	14	-	-	-
MABCS	88	80	9	74	2	-	-	-	-	-	-

MARIE	2,066	1,540	115	1,535	53	-	-	-	-	-	-
MBCSG	766	1,015	150	569	8				-	-	-
MCBCS	2,093	1,999	59	1,903	6	35	96	3	-	-	-
MCCS	1,207	1,034	2	-	-	142	86	0	-	-	-
MEC	1,123	1,016	38	988	23	-	-	-	-	-	-
MISS	1,529	582	6	563	3	304	83	0	-	-	-
MMHS	1,635	273	4	-	-	320	48	4	-	-	-
MYBRCA	-	-	-	-	-	-	-	-	4,197	3,652	105
NBCS	212	2,334	31	1,370	4	-	-	-	-	-	-
NBHS	-	-	-	-	-	122	79	0	-	-	-
NC-BCFR	150	614	69	602	5	-	-	-	52	391	33
NCBCS	1,006	1,988	42	-	-	-	-	-	-	-	-
OBCS	414	467	10	445	1	-	-	-	-	-	-
OFBCR	728	1,908	143	1,656	51	-	-	-	-	-	-
ORIGO	0	1,090	89	1,053	69	132	134	15	-	-	-
PBCS	2,082	1,719	40	1,625	9	331	215	2	-	-	-
PKARMA	5,435	4,81	277	4,685	124	1	4	0	-	-	-
POSH	0	1,069	19	1,063	16	-	-	-	-	-	-
PREFACE	0	2,73	90	-	-	-	-	-	-	-	-
PROCAS	1,647	488	9	422	3	-	-	-	-	-	-
RBCS	0	873	152	724	81	-	-	-	-	-	-
SASBAC	1,378	1,118	22	1,086	5	-	-	-	-	-	-
SBCS	848	748	14	691	1	-	-	-	-	-	-
SEARCH	9,056	12,423	118	12,117	59	197	628	0	-	-	-
SEBCS	-	-	-	-	-	-	-	-	2,236	2,080	21
SGBCC	-	-	-	-	-	-	-	-	4,141	1,250	124
SKKDKFZS	29	1,084	71	1,054	41	-	-	-	-	-	-
SMC	-	-	-	-	-	141	244	0	-	-	-
SUCCESSB	0	438	2	-	-	-	-	-	-	-	-
SUCCESSC	0	2,807	29	-	-	-	-	-	-	-	-
SZBCS	489	676	6	409	1	-	-	-	-	-	-
TNBCC	152	1,037	2	-	-	-	-	-	-	-	-
TWBCS	-	-	-	-	-	-	-	-	492	1,250	17
UCIBCS	258	397	1	380	1	51	61	7	-	-	-
Total	**62,830**	**81,000**	**3,607**	**55,041**	**1,027**	**3,753**	**3,781**	**94**	**13,398**	**12,133**	**340**
Characteristics											
Invasiveness in situ	-	excluded	361	excluded	104	-	3[b]	7	-	excluded	67
invasive	-	79,876	2,200	54,675	670	-	3,777	60	-	11,929	209
unknown	-	1,124	1,046	366	253	-	1	27	-	204	64
ER status negative	-	13,828	446	9,333	105	-	766	8	-	3,457	54
positive	-	52,238	2,048	37,420	289	-	3,001	47	-	7,826	163
unknown	-	14,934	1,113	8,288	633	-	14	39	-	850	123

Abbreviations: BC = breast cancer, CBC = contralateral breast cancer, ER = estrogen receptor

[a] Without any diagnosis of breast cancer

[b] Due to the use of a new freeze of the BCAC data, N=3 breast cancers were now defined as in situ, which had previously been defined as invasive; the original validation dataset contained data of two additional studies[1]

Table S3. Variant information and breast cancer risk coefficients for the 77-variant PRS, 313-variant PRS, and ER-specific PRSs; previously published in Mavaddat et al.[1; 3]

Table S4. Patient, tumor, and treatment characteristics of all women diagnosed with first invasive breast cancer since 1990 (European cohort)

Characteristics	Number of women (%)[a]
Total	56,068 (100)
Median age at first diagnosis in years (range)	56 (18-98)
Year of diagnosis	
1990-1994	3,029 (5.4)
1995-1999	10,153 (18.1)
2000-2004	18,484 (33.0)
2005-2009	17,575 (31.3)
2010-2015	6,827 (12.2)
Family history (first degree relative)	
no	33,623 (76.4)
yes	10,369 (23.6)
unknown	12,076
Nodal status	
negative	29,070 (61.9)
positive	17,903 (38.1)
unknown	9,095
Tumor size, cm	
≤2	28,057 (63.8)
(2, 5]	14,138 (32.2)
>5	1,750 (4.0)
unknown	12,123
Differentiation grade	
I	8,721 (19.5)
II	21,621 (48.3)
III	14,454 (32.3)
unknown	11,272
Morphology	
ductal	37,324 (76.6)
lobular	5,878 (12.1)
mixed (ductal and lobular)	2,174 (4.5)
other	3,344 (6.9)
unknown	7,348

ER-status	
negative	9,527 (20.0)
positive	38,090 (80.0)
unknown	8,451
PR-status	
negative	13,098 (32.6)
positive	27,044 (67.4)
unknown	15,926
HER2-status	
negative	23,787 (82.7)
positive	4,969 (17.3)
unknown	27,312
Surgery	
yes, breast saving	16,468 (42.3)
yes, mastectomy	11,315 (29.1)
yes, type unknown	11,163 (28.7)
unknown	17,122
(Neo)adjuvant chemotherapy	
no	18,110 (49.4)
yes	18,559 (50.6)
unknown	19,399
(Neo)adjuvant endocrine therapy	
no	10,781 (28.3)
yes	27,322 (71.7)
unknown	17,965
Radiotherapy	
no	11,023 (27.4)
yes	29,142 (72.6)
unknown	15,903

Abbreviations: ER = estrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor receptor 2
[a] Total may not be 100% because of rounding

Table S5. Association between the 313-variant PRS (PRS_{313}) and contralateral breast cancer risk in the European cohort

Percentile categories of the PRS_{313}	No. of women	No. of CBC	HR per unit SD[a]	95%CI	P-value
0^{th} to 10^{th}	5,607	65	0.59	0.45-0.78	<.001
10^{th} to 20^{th}	5,606	79	0.71	0.55-0.92	.01
20^{th} to 40^{th}	11,214	165	0.74	0.60-0.90	.003
40^{th} to 60^{th}	11,214	224	1.00	Ref.	-
60^{th} to 80^{th}	11,214	208	0.90	0.74-1.08	.25
80^{th} to 90^{th}	5,607	121	1.05	0.84-1.31	.69
90^{th} to 100^{th}	5,606	165	1.38	1.13-1.69	.002

Abbreviations: PRS = polygenic risk score, No = number, CBC = contralateral breast cancer, HR = hazard ratio, CI = confidence interval, SD = standard deviation
[a] The analysis was performed with attained age as time scale. Coefficients to construct the PRS_{313} are shown in Table S3. The PRS_{313} was standardized by SD=0.61, in line with Mavaddat et al.[1]

Table S6. Multivariable Cox regression models of contralateral breast cancer risk by 313-variant PRS (PRS_{313}) in all women, all women excluding studies oversampling cases with family history, and those with complete covariate information

		All patients N=56,068 (CBC=1,027)			All women excluding studies oversampling cases with family history N=51,883 (CBC=829)			Complete case N=12,065 (CBC=193)		
		HR per unit SD[a]	**95%CI**	**P-value**	**HR per unit SD[a]**	**95%CI**	**P-value**	**HR per unit SD[a]**	**95%CI**	**P-value**
Model 1										
PRS_{313}[b]		1.25	1.18-1.33	<.001	1.26	1.17-1.34	<.001	1.35	1.17-1.56	<.001
Model 2										
PRS_{313}[b]		1.23	1.16-1.31	<.001	1.25	1.17-1.34	<.001	1.33	1.15-1.54	<.001
Family history	yes vs. no	1.43	1.24-1.64	<.001	1.34	1.13-1.59	.001	1.49	1.06-2.09	.02
	unknown vs. no	0.93	0.75-0.16	.54	0.92	0.73-1.16	.47	-	-	-
Model 3										
PRS_{313}[b]		1.25	1.18-1.33	<.001	1.26	1.17-1.34	<.001	1.35	1.17-1.56	<.001
Nodal status	positive vs. negative	1.05	0.91-1.20	.50	1.07	0.92-1.25	.37	1.14	0.85-1.53	.37
	unknown vs. no	1.26	1.04-1.53	.02	1.29	1.04-1.60	.02	-	-	-
Model 4										
PRS_{313}[b]		1.25	1.18-1.33	<.001	1.26	1.18-1.35	<.001	1.35	1.17-1.56	<.001
Tumor size,	(2-5] vs. ≤2	1.08	0.92-1.25	.34	1.12	0.95-1.32	.20	0.93	0.68-1.27	.66
	>5 vs. ≤2	1.37	0.99-1.89	.06	1.45	1.02-2.07	.04	1.63	0.93-2.85	.09
	unknown vs. ≤2	1.23	1.04-1.47	.02	1.14	0.94-1.39	.18	-	-	-
Model 5										
PRS_{313}[b]		1.25	1.17-1.33	<.001	1.25	1.17-1.34	<.001	1.35	1.17-1.57	<.001
Differentiation grade	II vs. I	0.93	0.76-1.13	.45	0.99	0.80-1.24	.94	0.98	0.65-1.48	.93
	III vs. I	0.90	0.73-1.12	.35	0.97	0.76-1.24	.81	1.09	0.70-1.69	.69
	unknown vs. I	1.20	0.96-1.49	.11	1.45	1.13-1.86	.004	-	-	-
Model 6										
PRS_{313}[b]		1.25	1.17-1.33	<.001	1.25	1.17-1.34	<.001	1.33	1.16-1.54	<.001
Morphology	lobular vs. ductal	1.26	1.03-1.53	.03	1.34	1.08-1.67	.008	1.48	0.99-2.21	.05
	mixed (ductal and lobular) vs. ductal	1.28	0.94-1.73	.11	1.36	0.98-1.88	.06	1.48	0.87-2.54	.15
	other vs. ductal	1.04	0.81-1.33	.75	0.91	0.66-1.24	.55	1.24	0.69-2.21	.47
	unknown vs. ductal	1.77	1.42-2.19	<.001	1.82	1.44-2.30	<.001	-	-	-
Model 7										
PRS_{313}[b]		1.25	1.18-1.33	<.001	1.26	1.18-1.35	<.001	1.35	1.17-1.56	<.001
ER-status	positive vs. negative	0.88	0.75-1.04	.14	0.86	0.72-1.03	.11	0.90	0.62-1.32	.60
	unknown vs. negative	1.16	0.93-0.43	.19	1.11	0.86-1.43	.43	-	-	-
Model 7										
PRS_{313}[b]		1.25	1.18-1.33	<.001	1.26	1.18-1.35	<.001	1.35	1.17-1.56	<.001

PR-status	positive vs. negative	0.95	0.81-1.11	.51	0.92	0.78-1.09	.32	0.91	0.66-1.25	.56
	unknown vs. negative	1.15	0.95-1.40	.14	1.10	0.88-1.37	.40	-	-	-
Model 9										
PRS_{313}[b]		1.25	1.18-1.33	<.001	1.26	1.17-1.34	<.001	1.34	1.16-1.55	<.001
HER2-status	positive vs. negative	0.84	0.64-1.11	.22	0.76	0.56-1.05	.10	0.70	0.45-1.10	.12
	unknown vs. negative	1.29	1.11-1.50	.001	1.28	1.08-1.52	.004	-	-	-
Model 10										
PRS_{313}[b]		1.25	1.17-1.32	<.001	1.26	1.17-1.34	<.001	1.35	1.16-1.56	<.001
Chemotherapy	yes vs. no	0.86	0.73-1.01	.06	0.99	0.83-1.19	.92	0.89	0.64-1.25	.51
	unknown vs. no	1.09	0.91-1.31	.34	1.20	0.97-1.47	.09	-	-	-
Model 11										
PRS_{313}[b]		1.25	1.18-1.33	<.001	1.26	1.18-1.35	<.001	1.36	1.17-1.57	<.001
Endocrine therapy	yes vs. no	0.75	0.64-0.88	.001	0.92	0.75-1.12	.41	0.78	0.55-1.11	.17
	unknown vs. no	0.90	0.75-1.09	.28	1.11	0.87-1.41	.39	-	-	-
Model 12										
PRS_{313}[b]		1.25	1.17-1.32	<.001	1.26	1.17-1.34	<.001	1.35	1.17-1.56	<.001
Radiotherapy	yes vs. no	1.00	0.85-1.18	1.00	0.98	0.82-1.18	.85	1.35	0.88-2.08	.17
	unknown vs. no	1.41	1.14-1.74	.001	1.18	0.93-1.50	.17	-	-	-
Model 13										
PRS_{313}[b]		1.25	1.17-1.32	<.001	1.25	1.17-1.34	<.001	1.34	1.16-1.55	<.001
Year of first breast cancer diagnosis		0.95	0.94-0.96	<.001	0.95	0.93-0.96	<.001	0.90	0.86-0.95	<.001
Model 14										
PRS_{313}[b]	full model[c]	1.23	1.16-1.31	<.001	1.25	1.16-1.33	<.001	1.33	1.15-1.53	<.001

Abbreviations: PRS = polygenic risk score, CBC = contralateral breast cancer, HR = hazard ratio, CI = confidence interval, SD = standard deviation, ER = estrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor receptor 2

[a] All analyses were performed with attained age as the time scale

[b] Coefficients to construct the PRS_{313} are shown in Table S3. The PRS_{313} was standardized by SD=0.61, in line with Mavaddat et al.[1]

[c] Adjusted for family history, nodal status, tumor size, differentiation grade, morphology, ER status, HER2 status, chemotherapy, endocrine therapy, radiotherapy, and year of first breast cancer diagnosis

Table S7. Five- and ten-year cumulative risks of contralateral breast cancer by the 313-variant PRS (PRS_{313}) for different age groups

	5-year cumulative CBC risks (%) range by age					10-year cumulative CBC risks (%) range by age				
Age at first breast cancer diagnosis (years)	**5^{th} percentile PRS_{313}**	**10^{th} percentile PRS_{313}**	**50^{th} percentile PRS_{313}**	**90^{th} percentile PRS_{313}**	**95^{th} percentile PRS_{313}**	**5^{th} percentile PRS_{313}**	**10^{th} percentile PRS_{313}**	**50^{th} percentile PRS_{313}**	**90^{th} percentile PRS_{313}**	**95^{th} percentile PRS_{313}**
30-34	1.9-3.3	2.1-3.6	2.8-4.7	3.7-6.2	4.0-6.8	3.3-4.4	3.6-4.8	4.7-6.3	6.2-8.3	6.8-9.1
35-39	0.8-2.2	0.9-2.4	1.2-3.2	1.6-4.2	1.7-4.6	2.2-3.9	2.4-4.2	3.2-5.5	4.2-7.2	4.6-8.0
40-44	1.5-2.9	1.7-3.2	2.2-4.2	2.9-5.5	3.2-6.0	2.9-4.9	3.2-5.3	4.2-7.0	5.5-9.1	6.0-10.0
45-49	1.4-2.5	1.5-2.8	2.0-3.7	2.6-4.8	2.9-5.3	2.5-4.2	2.8-4.5	3.7-6.0	4.8-7.8	5.3-8.6
50-54	1.4-2.9	1.5-3.1	2.0-4.1	2.6-5.5	2.9-6.0	2.9-4.8	3.1-5.3	4.1-6.9	5.5-9.1	6.0-10.0
55-59	1.6-3.3	1.8-3.6	2.4-4.7	3.1-6.2	3.4-6.8	3.3-5.3	3.6-5.7	4.7-7.5	6.2-9.8	6.8-10.8
60-64	1.8-3.5	1.9-3.8	2.6-5.0	3.4-6.5	3.7-7.2	3.5-5.5	3.8-6.0	5.0-7.9	6.5-10.3	7.2-11.3
65-70	1.5-3.5	1.7-3.8	2.2-5.0	2.9-6.6	3.2-7.2	3.5-4.6	3.8-5.0	5.0-6.6	6.6-8.7	7.2-9.5

Abbreviations: PRS = polygenic risk score, CBC = contralateral breast cancer

Coefficients to construct the PRS_{313} are shown in Table S3. The PRS_{313} was standardized by SD=0.61, in line with Mavaddat et al[1]. The CBC incidences for each age group were calculated based on incidence data from the Netherlands Cancer Registry[2] and relative risks estimated as described in the Material and Methods. In contrast to Table 4, death was not taken into account as competing risk

Table S8. Estimates of unilateral- and contralateral breast cancer risk by the 313-variant PRS (PRS_{313}) in the European case-case series and the Asian case-case series

	European						Asian		
	Case-case series[a]			Validation set[b]			Case-case series[a]		
PRS_{313}[c]	**OR per unit SD**	**95%CI**	**P-value**	**OR per unit SD**	**95%CI**	**P-value**	**OR per unit SD**	**95%CI**	**P-value**
Unilateral breast cancer versus control	1.82	1.80-1.84	<.001	1.67	1.59-1.76	<.001	1.56	1.52-1.60	<.001
CBC versus unilateral breast cancer	1.30	1.26-1.35	<.001	1.39	1.13-1.70	.002	1.15	1.02-1.29	.02

Abbreviations: PRS = polygenic risk score, CBC = contralateral breast cancer, OR = odds ratio, SD = standard deviation, CI = confidence interval

[a] Adjusted for country and age. For all women with unilateral- and contralateral breast cancer we used age at first breast cancer diagnosis, and for control women without any diagnosis of breast cancer we used age at baseline questionnaire.

[b] The validation set was previously used to develop the PRS_{313}; see details in materials and methods. For analyses in the current paper, this set is nested within the case-case series. These analyses were additionally adjusted for 10 principal components for comparability with the originally published PRS_{313} overall estimates[1]

[c] Coefficients to construct the PRS_{313} are shown in Table S3. The PRS_{313} was standardized by SD=0.61, in line with Mavaddat et al.[1]

Supplemental Note

Our initial aim was to externally validate our results using the UK Biobank, which seemed the most suitable cohort given the large number of women diagnosed with breast cancer with information available on the PRS_{313},. However, when we started the analyses, it turned out that the UK Biobank had no information available on the laterality of the second breast tumor. Therefore, we were unable to distinguish between ipsilateral and contralateral breast cancer, and had to define our endpoint in these analyses as 'any second breast cancer'. In addition, in comparison to our analyses in the BCAC, we were unable to exclude patients diagnosed with stage IV invasive first breast cancer from the UK Biobank cohort, and had limited information on metastases developed during follow-up.

The association between the overall breast cancer PRS_{313} and (any) second breast cancer was evaluated among women aged ≥18 years of European ancestry from the UK Biobank cohort who had had a diagnosis of invasive first breast cancer. UK Biobank samples were genotyped using Affymetrix UK BiLEVE Axiom array and Affymetrix UK Biobank Axiom® array and imputed to the combined 1000 Genome Project v3 and UK10K reference panels using SHAPEIT3 and IMPUTE3[4]. The lowest imputation info score for the variants used in these analyses was 0.86. Samples were included for this analysis of the UK BIOBANK study on the basis of female sex (genetic and self-reported) and ethnicity filter (Europeans/White British ancestry subset). Duplicates and individuals with high degree of relatedness (samples which have >10 putative third degree relatives) were removed, and we randomly excluded one of each related pair first-degree relatives. Samples were also excluded on standard quality control criteria. The PRS_{313} was calculated as a weighted sum of the minor allele dosages; the variant selection and weights are as given by Mavaddat et al[1]. The PRS_{313} was standardized by SD=0.61, in line with our BCAC analyses and Mavaddat et al[1].

The final cohort included 10,567 women with invasive breast cancer among whom 302 registry-confirmed second breast cancers developed over 59,260 person-years of follow-up. A Cox proportional hazards model was used to assess the association between PRS_{313} and second breast cancer risk. Time at risk started three months after the age of first breast cancer diagnosis, where this was diagnosed after the baseline questionnaire date, or three months after the baseline questionnaire where first breast cancer was diagnosed before the baseline questionnaire date. Time at risk ended at the age of second breast cancer diagnosis (ipsilateral or contralateral), distant metastasis (where available), death or end of follow-up (at latest December 10, 2016). Potential effect modification of the PRS_{313} by age was evaluated by adding an interaction term (PRS_{313} x age at first breast cancer diagnosis [continuous]) in the model. We performed a separate analysis for invasive second breast cancer (241 breast cancers), where we censored on in situ second breast cancer.

The HR for a second breast cancer (in situ or invasive) per SD of PRS_{313} in the UK Biobank cohort was 1.13 (95%CI=1.01-1.26). We found no indication for interaction with age at first breast cancer diagnosis ($HR_{interaction}$=1.00, 95%CI=0.99-1.01; P=0.87). When analyses were restricted to invasive second breast cancer, the HR per SD was 1.13 (95%CI=1.00-1.29).

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Supplemental References

1. Mavaddat, N., Michailidou, K., Dennis, J., Lush, M., Fachal, L., Lee, A., Tyrer, J.P., Chen, T.H., Wang, Q., Bolla, M.K., et al. (2019). Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. American journal of human genetics 104, 21-34.

2. Kramer, I., Schaapveld, M., Oldenburg, H.S.A., Sonke, G.S., McCool, D., van Leeuwen, F.E., Van de Vijver, K.K., Russell, N.S., Linn, S.C., Siesling, S., et al. (2019). The influence of adjuvant systemic regimens on contralateral breast cancer risk and receptor subtype. J Natl Cancer Inst.

3. Mavaddat, N., Pharoah, P.D., Michailidou, K., Tyrer, J., Brook, M.N., Bolla, M.K., Wang, Q., Dennis, J., Dunning, A.M., Shah, M., et al. (2015). Prediction of breast cancer risk based on profiling with common genetic variants. J Natl Cancer Inst 107.

4. O'Connell, J., Sharp, K., Shrine, N., Wain, L., Hall, I., Tobin, M., Zagury, J.F., Delaneau, O., and Marchini, J. (2016). Haplotype estimation for Biobank-scale data sets. Nature genetics 48, 817-820.