

TITLE PAGE

Validating a breast cancer score in Spanish women. The MCC-Spain study.

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Supplementary Table 1. List of SNPs included in the genetic risk score

a) GRS24: Genetic Risk Score with 24 SNPs

SNP	Gene	Chromosome	Location	Major allele	Minor allele	Per allele odds ratio	Reference for odds ratio
rs11249433	EMBP1	1	121538815	T	G	1.14	13
rs1045485	CASP8	2	201284866	G*	C	1.04	13
rs13387042	LOC101928278 - LOC105373874	2	217041109	G*	A	1.27	13
rs4973768	SLC4A7	3	27374522	C	T	1.07	13
rs10069690	TERT	5	1279675	C	T	1.08	13
rs10941679	LOC102723839 - RN7SL383P	5	44706396	A	G	1.13	13
rs889312	LOC101928448 - LOC105378979	5	56736057	A	C	1.09	13
rs17530068	LOC105377871	6	81483392	T	C	1.06	13
rs2046210	CCDC170 - ESR1	6	151627231	C	A	1.05	13
rs1562430	CASC21 - CASC8	8	127375606	A*	C	1.11	13
rs1011970	CDKN2B-AS1	9	22062135	G	T	1.06	13
rs865686	LOC105376214	9	108126198	A/T*	G	1.09	13
rs2380205	GDI2 - TRV-TAC3-1	10	5844771	C*	T	1.06	13
rs10995190	ZNF365	10	62518923	G*	A	1.12	13
rs1250003	ZMIZ1	10	79087057	A	C	1.07	13
rs2981582	FGFR2	10	121592803	C	A	1.18	13
rs909116	TNNT3	11	1920716	T*	C	1.05	13
rs614367	LINC01488 - CCND1	11	69513996	C	T	1.13	13
rs10483813	RAD51B	14	68564567	T*	A	1.08	13
rs999737	RAD51B	14	68567965	C*	T	1.08	13
rs3803662	CASC16	16	52552429	C	A	1.21	13
rs6504950	STXBP4	17	54979110	G*	A	1.08	13
rs8170	BABAM1	19	17278895	C*	A	1.06	13
rs2284378	RALY	20	34000289	C*	T	1.04	13

GRS68: Genetic Risk Score with 68 SNPs

SNP	Gene	Chromosome	Location	Major allele	Minor allele	Per allele odds ratio	Reference for odds ratio
rs11552449	AP4B1 - DCLRE1B	1	113905767	C/G	T	1.08	17
rs12048493	OTUD7B	1	149955122	A	C	1.06	18
rs12405132	RNF115	1	145790097	C	T	1.04	18
rs4245739	MDM4	1	204549714	A	C	1.02	17
rs616488	PEX14	1	10506158	T	G	1.05	17
rs6678914	LGR6	1	202218048	G	A	1.01	17
rs72755295	EXO1	1	241870961	A	G	1.15	18
rs12710696	LOC105373455 - MIR4757	2	19121042	C	T	1.03	17
rs1550623	LOC100289479 - CDCA7	2	173348166	T*	G	1.08	17
rs16857609	DIRC3	2	217431785	C	T	1.06	17
rs2016394	DLX2-AS1	2	172108243	C*	A	1.05	17
rs4849887	LINC01101 - LOC105373585	2	120487546	C*	T	1.09	17
rs12493607	TGFBR2	3	30641447	G/T	C	1.07	17
rs6762644	ITPR1	3	4700592	A	G	1.07	17
rs6796502		3	46825376	G	A	1.08	18
rs6828523	ADAM29	4	174925275	C*	A	1.12	17
rs9790517	TET2	4	105163621	C	T	1.03	17
rs10472076	RAB3C - PDE4D	5	58888234	A/T	C	1.05	17
rs13162653	LOC401176	5	16187419	A/G	T	1.03	18
rs1353747	PDE4D	5	59041654	T*	C	1.1	17
rs1432679	EBF1	5	158817075	C	T	1.07	17
rs2012709	SUB1	5	32567626	C	T	1.05	18
rs2736108	TERT	5	1297373	G*	T	1.06	17
rs7707921	ATG10	5	82242227	A	T	1.09	18
rs11242675	FOXQ1 - LINC01394	6	1318643	T*	C	1.05	17

rs12662670	CCDC170	6	151597721	C/T	G	1.22	17
rs204247	RANBP9 - MCUR1	6	13722291	A	G	1.05	17
rs9257408		6	28958443	C	G	1.05	18
rs4593472	LINC-PINT	7	130982362	C	T	1.05	18
rs720475	ARHGEF5	7	144377836	G*	A	1.08	17
rs11780156	MIR1208 - RN7SKP226	8	128182395	C	T	1.1	17
rs13267382	LINC00536	8	116197325	A	G	1.06	18
rs13365225	RPL26P25 - LOC105379377	8	37000965	A	G	1.06	18
rs2943559	HNF4G	8	75505702	A	G	1.13	17
rs6472903	HIGD1AP6 - PKMP4	8	75318066	T*	G	1.12	17
rs9693444	RPL17P33 - LINC00589	8	29652100	C	A	1.05	17
rs10759243	LOC105376206 - LOC105376205	9	107543834	C/T	A	1.06	17
rs11199914	LOC105378523 - RN7SKP167	10	121334387	C*	T	1.04	17
rs11814448	DNAJC1 - ADIPOR1P1	10	22026914	A	C	1.19	17
rs7072776	LOC107984214 - MLLT10	10	21744013	G	A	1.06	17
rs7904519	TCF7L2	10	113014168	A	G	1.06	17
rs11820646	RPS27P20 - LINC01395	11	129591276	C*	T	1.05	17
rs554219		11	69516874			1.27	17
rs75915166		11	69564393	C	A	1.29	17
rs10771399	PTHLH - LOC105369710	12	28002147	A*	G	1.18	18
rs12422552	GNAI2P1 - RPL30P11	12	14260997	G	C	1.05	17
rs1292011	LOC105370003	12	115398717	T*	G	1.08	17
rs17356907	USP44 - PGAM1P5	12	95633983	A*	G	1.09	17
rs11571833	BRCA2	13	32398489	A	T	1.25	17
rs11627032	RIN3	14	92637727	T	C	1.04	18
rs2236007	LOC105370455 - PAX9	14	36663564	G*	A	1.09	17
rs2588809	RAD51B	14	68193711	C	T	1.09	17
rs941764	CCDC88C	14	91374725	A	G	1.06	17
rs11075995	FTO	16	53821379	T	A	1.04	17

rs13329835	CDYL2	16	80616908	A	G	1.09	17
rs17817449	FTO	16	53779455	T*	G	1.06	17
chr17:29230520:D	ATAD5	17	29230520	GGT	G	1.08	18
rs745570	CBX8 - LOC102723961	17	79807926	C	A	1.04	18
rs1436904	CHST9	18	26990703	T*	G	1.04	17
rs527616	PCAT18 - LOC105372035	18	26757460	G*	C	1.05	17
rs6507583	SETBP1	18	44819625	A	G	1.1	18
rs2363956	ANKLE1	19	17283315	T	G	1.02	17
rs3760982	KCNN4	19	43782361	G	A	1.06	17
rs4808801	ELL	19	18460331	A*	G	1.09	17
rs2823093	LOC107985483 - LOC105372739	21	15148511	G*	A	1.06	17
rs132390	EMID - LOC105372985	22	29225488	T	C	1.14	17
rs17879961	CHEK2	22	28725099	C/T	G	1.07	17
rs6001930	MKL1	22	40480230	T	C	1.14	17

Minor allele = risk allele unless major allele is marked with an asterisk

Supplementary Table 2. Linkage disequilibrium between the SNPs indicated in Supplementary Table 1 (Source: <https://analysistools.nci.nih.gov/LDlink/?tab=home>; accessed: 8 January, 2018)

Chromosome	SNP	rs72755295	rs4245739	rs6678914	rs12048493	rs12405132	rs11249433	rs11552449		
1	rs616488	0.0024	0.0003	0	0.0003	0.0011	0.0008	0.0006		
	rs11552449	0.0019	0	0.0005	0.003	0.0005	0			
	rs11249433	0.0032	0.0002	0.0003	0.0008	0.0012				
	rs12405132	0.0001	0.0007	0.0028	0					
	rs12048493	0.0022	0.0008	0.0059						
	rs6678914	0.0003	0.3417							
	rs4245739	0.0006								
2	SNP	rs16857609	rs13387042	rs1045485	rs1550623	rs2016394	rs4849887			
	rs12710696	0.0001	0.0002	0.0002	0.0018	0.0004	0.0041			
	rs4849887	0.0004	0.0001	0	0	0.001				
	rs2016394	0	0.0005	0.0021	0.0047					
	rs1550623	0.0001	0.0044	0.0009						
	rs1045485	0	0							
	rs13387042	0.0008								
3	SNP	rs6796502	rs12493607	rs4973768						
	rs6762644	0.002	0	0.0012						
	rs4973768	0.0011	0.0003							
	rs12493607	0.0006								
4	SNP	rs6828523								
	rs9790517	0.0016								
5	SNP	rs1432679	rs7707921	rs1353747	rs10472076	rs889312	rs10941679	rs2012709	rs13162653	rs2736108
	rs10069690	0.0001	0.0004	0.0011	0.0004	0.0001	0.0004	0.0001	0.0003	0.0191
	rs2736108	0	0	0.0001	0.0031	0.0001	0.0004	0.0021	0	
	rs13162653	0.0005	0.0002	0.0006	0.0004	0.0011	0.0001	0.0005		

	rs2012709	0	0.0001	0.0002	0.0001	0.001	0.0025	
	rs10941679	0.0003	0.0002	0.0014	0.0025	0.0001		
	rs889312	0.0002	0.0007	0	0.0001			
	rs10472076	0.0001	0.0009	0.0312				
	rs1353747	0.0006	0.0014					
	rs7707921	0.0003						
6	SNP	rs2046210	rs12662670	rs17530068	rs9257408	rs204247		
	rs11242675	0.0015	0.0001	0.002	0	0.003		
	rs204247	0.0013	0.0018	0.0036	0.0011			
	rs9257408	0.0007	0.0007	0.0011				
	rs17530068	0.0002	0.0007					
	rs12662670	0.1352						
7	SNP	rs720475						
	rs4593472	0.0015						
8	SNP	rs11780156	rs1562430	rs13267382	rs2943559	rs6472903	rs13365225	
	rs9693444	0.0001	0.0005	0.0006	0.001	0.0001	0.0002	
	rs13365225	0.0005	0.0012	0.0009	0.0003	0		
	rs6472903	0.0004	0.003	0.0018	0.0005			
	rs2943559	0.006	0.0009	0.0001				
	rs13267382	0	0					
	rs1562430	0.0005						
9	SNP	rs865686	rs10759243					
	rs1011970	0	0.0001					
	rs10759243	0.0043						
10	SNP	rs2981582	rs11199914	rs7904519	rs1250003	rs10995190	rs11814448	rs7072776
	rs2380205	0.0003	0.0002	0.0008	0.0001	0.0007	0.0002	0
	rs7072776	0.0024	0.0002	0	0.0001	0	0.0454	
	rs11814448	0.0014	0	0.0034	0.0005	0.0013		

	rs10995190	0	0.0003	0.0007	0.0001	
	rs1250003	0.0027	0.0012	0.0007		
	rs7904519	0.0038	0.0007			
	rs11199914	0.0006				
11	SNP	rs11820646	rs75915166	rs554219	rs614367	
	rs909116	0.0006	0	NA	NA	
	rs614367	NA	NA	NA		
	rs554219	NA	NA			
	rs75915166	0				
12	SNP	rs1292011	rs17356907	rs10771399		
	rs12422552	0	0.0026	0.0001		
	rs10771399	0.001	0.0015			
	rs17356907	0.0013				
14	SNP	rs11627032	rs941764	rs999737	rs10483813	rs2588809
	rs2236007	0.0018	0.0005	0.0001	0.0003	0.0009
	rs2588809	0	0.0009	0.0044	0.0038	
	rs10483813	0.0003	0.0006	0.9821		
	rs999737	0.0003	0.0008			
	rs941764	0.0001				
16	SNP	rs13329835	rs11075995	rs17817449		
	rs3803662	0.0014	0.002	0.0001		
	rs17817449	0.0005	0.0158			
	rs11075995	0				
17	SNP	rs745570	rs6504950			
	chr17:29230520:D	NA	NA			
	rs6504950	0.0001				
18	SNP	rs6507583	rs1436904			
	rs527616	0.0021	0.0001			

	rs1436904	0.002		
19	SNP	rs3760982	rs4808801	rs2363956
	rs8170	0.0003	0.0001	0.2609
	rs2363956	0	0.0007	
	rs4808801	0.0036		
22	SNP	rs6001930	rs132390	
	rs17879961	0.0005	0.0001	
	rs132390	0.0001		

Supplementary Table 3. Categories used in continuous variables (cut points proceed from Maas et al (2016))

Variable	Units	Category ^a									
		1	2	3	4	5	6	7	8	9	10
Age at menarche	Years	≤11	11.0- 11.5 ^b	11.5- 12.0	12.0- 13.0	13.0- 14.0	14.0- 15.0	>15.0			
Age at first birth	Years	≤19 or no children	19-22	22-23	23-25	25-27	27-30	30-34	34-38	>38	
Age at menopause	Years	≤40 or premenopausal	40-45	45-47	47-48	48-50	50-51	51-52	52-53	53-55	>55
Alcohol use	Drinks/week	0.0	0.0-0.4	0.4-0.8	0.8-1.5	1.5-3.2	3.2-5.7	5.7-9.8	>9.8		
Body mass index	kg/m ²	≤21.5	21.5- 23.0	23.0- 24.2	24.2- 25.3	25.3- 26.5	26.5- 27.8	27.8- 29.3	29.3- 31.4	31.4- 34.6	>34.6
Height	Meters	≤1.55	1.55- 1.57	1.57- 1.60	1.60- 1.61	1.61- 1.63	1.63- 1.65	1.65- 1.66	1.66- 1.68	1.68- 1.71	>1.71

^a Each category includes right end point but not left end point.

^b Age at menarche was recorded in accomplished years, so category 2 was empty.

Supplementary Table 4. Sample description according to modifiable and non-modifiable risk factors. Odds ratios (OR) and 95% confidence intervals (CI) are adjusted by age and the remaining factors in the table.

Variable	Category	Breast cancer		OR (95% CI)
		cases	Controls	
Age (years mean±sd)		56.4±12.6	59.0±13.2	0.98(0.97-0.99)
Height (m)	≤1.55	402	447	1(Ref)
	1.55-1.57	212	241	0.97(0.75-1.25)
	1.57-1.60	379	447	0.89(0.71-1.10)
	1.60-1.61	53	50	1.05(0.65-1.70)
	1.61-1.63	191	209	0.87(0.66-1.15)
	1.63-1.65	193	213	0.86(0.66-1.13)
	1.65-1.66	34	34	0.98(0.57-1.69)
	1.66-1.68	124	110	1.00(0.72-1.40)
	1.68-1.71	78	92	0.77(0.52-1.12)
	>1.71	66	61	1.13(0.74-1.75)
BMI (kg/m²)	≤21.5	276	319	1(Ref)
	21.5-23.0	210	260	0.95(0.72-1.26)
	23.0-24.2	198	223	1.16(0.87-1.55)
	24.2-25.3	170	195	1.24(0.92-1.68)
	25.3-26.5	176	175	1.49(1.10-2.03)
	26.5-27.8	164	163	1.55(1.14-2.11)
	27.8-29.3	155	150	1.77(1.29-2.43)
	29.3-31.4	176	160	1.60(1.17-2.19)
	31.4-34.6	119	140	1.36(0.97-1.90)
	>34.6	88	110	1.40(0.96-2.04)
Alcohol consumption (drinks/week)	0	486	540	1(Ref)
	0.0-0.4	127	129	0.94(0.69-1.27)
	0.4-0.8	132	134	1.03(0.76-1.40)
	0.8-1.5	148	171	0.81(0.61-1.08)
	1.5-3.2	304	342	0.89(0.71-1.12)
	3.2-5.7	265	289	0.83(0.66-1.06)
	5.7-9.8	134	166	0.82(0.62-1.10)
	>9.8	136	139	1.01(0.74-1.36)
Family history of breast cancer	No first-degree relative affected	1157	1509	1(Ref)
	First-degree relative affected	255	167	2.19(1.76-2.72)
Age at menarche	≤11	74	100	1(Ref)
	11.0-11.5	118	134	1.09(0.71-1.67)
	11.5-12.0	333	408	1.05(0.73-1.52)
	12.0-13.0	455	463	1.21(0.85-1.74)
	13.0-14.0	425	460	1.17(0.81-1.69)

	14.0-15.0	246	262	1.19(0.81-1.75)
	>15.0	81	65	1.51(0.92-2.50)
Parity	0	351	355	1(Ref)
	1	319	294	1.19(0.78-1.82)
	2	674	751	0.97(0.66-1.45)
	3	250	293	0.99(0.66-1.49)
	≥4	130	206	0.79(0.51-1.21)
Age at first delivery	≤19 or no children	441	448	1(Ref)
	19-22	201	217	1.05(0.70-1.56)
	22-23	96	111	0.90(0.57-1.43)
	23-25	228	286	0.85(0.57-1.26)
	25-27	228	265	0.86(0.58-1.28)
	27-30	249	293	0.85(0.57-1.26)
	30-34	182	186	0.89(0.58-1.35)
	34-38	78	78	0.98(0.59-1.61)
	>38	29	26	1.15(0.57-2.32)
Menopausal status	Premenopause	610	554	1.01(0.76-1.33)
	Postmenopause	1122	1356	1(Ref)
Age at menopause	≤40 or premenopausal	850	893	1(Ref)
	40-45	124	198	0.83(0.61-1.13)
	45-47	94	84	1.58(1.08-2.30)
	47-48	62	107	0.83(0.56-1.22)
	48-50	189	243	1.10(0.83-1.47)
	50-51	50	34	1.92(1.14-3.23)
	51-52	116	126	1.32(0.94-1.85)
	52-53	81	61	1.70(1.12-2.58)
	53-55	112	113	1.35(0.95-1.92)
	>55	54	51	1.63(1.03-2.58)
Hormone replacement therapy	Never	1574	1692	1(Ref)
	Ever	116	135	1.01(0.75-1.36)
	Not known	38	68	0.77(0.50-1.19)

Supplementary Table 5. Scores in breast cancer cases and controls, mean±standard deviation

Score	Controls	Breast cancer cases	p
GRS24	1.78±0.29	1.85±0.29	<0.001
GRS68	3.78±0.36	3.90±0.35	<0.001
GRS92	5.56±0.46	5.75±0.45	<0.001
NMRFS	0.29±0.45	0.44±0.48	<0.001
MRFS	0.27±0.37	0.30±0.36	0.009
RFS	0.56±0.62	0.74±0.65	<0.001
Full model	6.05±0.76	6.41±0.78	<0.001

GRS24: Genetic Risk Score with 24 SNPs

GRS68: Genetic Risk Score with 68 SNPs

GRS92: Genetic Risk Score with 92 SNPs

NMRFS: Non-modifiable Risk Factor Score

MRFS: Modifiable Risk Factor Score

RFS: Risk Factor Score

Supplementary Table 6. Pearson correlation coefficient among genetic scores, modifiable risk factor score, nonmodifiable risk factor score and full model

	GRS68	GRS24	GRS92	NMRFS	MRFS	RF
GRS24	0.01					
GRS92	0.78	0.64				
NMRFS	0.05	0.04	0.07			
MRFS	<-0.01	0.01	<0.01	0.22		
RF	0.04	0.03	0.05	0.82	0.74	
Full model	0.49	0.40	0.63	0.58	0.58	0.81

GRS24: Genetic Risk Score with 24 SNPs
 GRS68: Genetic Risk Score with 68 SNPs
 GRS92: Genetic Risk Score with 92 SNPs
 NMRFS: Non-modifiable Risk Factor Score
 MRFS: Modifiable Risk Factor Score
 RF: Risk Factor Score

Supplementary Table 7. Sensitivity analysis on imputation results: Relationship between breast cancer and GRS24 (in deciles) according on whether GRS24 was obtained by genotyping or by imputation: Odds ratios (OR) and 95% confidence intervals

GRS24 decile	OR in the whole sample	OR in 1138 cases and 1239 controls with available genotype	OR in 594 cases and 671 controls without available genotype
1	1 (reference)	1 (reference)	1 (reference)
2	1.20 (0.89 – 1.63)	0.95 (0.66 – 1.37)	1.43 (0.83 – 2.47)
3	1.13 (0.83 – 1.53)	1.04 (0.72 – 1.49)	0.85 (0.49 – 1.49)
4	1.54 (1.14 – 2.08)	1.27 (0.88 – 1.83)	1.28 (0.74 – 2.21)
5	1.31 (0.96 – 1.77)	1.38 (0.96 – 1.99)	2.00 (1.16 – 3.43)
6	1.58 (1.17 – 2.14)	1.23 (0.85 – 1.77)	1.89 (1.10 – 3.24)
7	1.49 (1.10 – 2.01)	1.21 (0.84 – 1.74)	1.66 (0.97 – 2.86)
8	1.93 (1.42 – 2.61)	1.78 (1.24 – 2.57)	1.46 (0.85 – 2.51)
9	1.83 (1.35 – 2.48)	1.58 (1.10 – 2.28)	2.40 (1.39 – 4.14)
10	2.34 (1.73 – 3.17)	1.94 (1.35 – 2.80)	2.79 (1.62 – 4.83)

Supplementary fig. 1. ROC curves of genetic and risk factor scores – breast cancer relationship.

