SUPPLEMENTARY MATERIALS

Supplementary Methods

Patient ascertainment:

Study subjects included women with breast cancer who underwent multigene panel testing between March 2012 and December 2016 at a single diagnostic laboratory (Ambry Genetics, Aliso Viejo, CA). Clinical histories were obtained from clinician-completed test requisition forms and from clinical documentation such as pedigrees and chart notes when provided. Case selection was limited to one individual per family. In the instance where multiple individuals from the same family underwent MGPT, the first family member to undergo panel testing was selected for inclusion in this study. Approximately 90% of women met the National Comprehensive Cancer Network (NCCN) criteria on germline genetic testing (1). Women reporting prior *BRCA1* and *BRCA2* and Lynch syndrome testing were excluded. The present analyses were limited to non-Hispanic Whites, Blacks, Asians, Ashkenazi-Jews and Hispanics and women with missing information on race/ethnicity or mixed ethnicity were excluded.

The process of race/ethnicity classification:

Race and ethnicity data were collected from clinician-reported information provided on test requisition forms submitted at the time testing was ordered. To classify ethnicity, categorization of these data was performed referencing the Office of Management and Budget Race and Hispanic Ethnicity Categories (OMB race categories) as defined by the Subcommittee on Standardized Collection of Race/Ethnicity Data for Healthcare Quality Improvement (2). For major race/ethnicity categories, OMB race category and our study ethnicity condensed categories were the same (Supplementary table 1). However, for some race/ethnicity categories with smaller numbers, further condensing was performed referencing the cumulative list of granular ethnicities to determine the appropriate category. With the exception of Ashkenazi Jewish ancestry, ethnicities that could not be classified under the distinct OMB race categories were labeled as 'Other' ethnicity. Although not defined

under the OMB race categories, Ashkenazi Jewish was indicated as an ethnicity condensed category due to known genetic predispositions specific to this population. If clinician-reported race/ethnicity data condensing resulted in multiple OMB race categories, the patient was categorized as having 'Mixed Ethnicity.' When data condensing resulted in both Ashkenazi Jewish and non-Hispanic White categorizations, patients were labeled as 'Ashkenazi Jewish' whereas Ashkenazi Jewish and other ethnicity condensed categories resulted in 'Mixed Ethnicity.' The present analysis was limited to non-Hispanic White, Black, Hispanic, Ashkenazi-Jewish and Asian races/ethnicities. All other categories were excluded.

Germline genetic testing and variant classification:

Mutation testing was performed by targeted custom capture and sequencing and targeted chromosomal microarray analysis, as described previously (3, 4). Patients underwent comprehensive germline analysis of 5 to 49 genes depending on the multigene panel ordered. Sanger or next-generation sequencing analysis was performed for all coding domains and well into the flanking 5' and 3' ends of all the introns and untranslated regions. Gross deletion/duplication analysis was performed for all covered exons and untranslated regions. All variants, with the exception of previously characterized benign alterations, underwent thorough assessment and review of available evidence (e.g., population frequency information, published case reports, case–control and functional studies, internal co-occurrence and cosegregation data, evolutionary conservation, and in silico predictions). A 5-tier system was used to classify variants utilizing a framework consistent with the guidelines published by American College of Medical Genetics and Association for Molecular Pathology (5). Pathogenic and likely pathogenic variants were analyzed together as pathogenic variants. All missense variants in *CHEK2* and other low penetrance PVs were excluded from analysis as the risk of breast cancer associated with these variants is undefined or lower compared to deleterious variants in *CHEK2* (3, 4, 6, 7). These included the c.1111C>T, c.1169A>C, c.1283C>T, c.1427C>T, c.349A>G, c.433C>T, c.470T>C, c.499G>A, and c.917G>C variants in *CHEK2*.

Case-control analysis:

For each ethnic or racial group, mutation frequencies by gene were compared with mutation frequencies for the same population in Genome Aggregatoin Database (gnomAD) (http://gnomad.broadinstitute.org/)(8). The gnomAD is a coalition of investigators seeking to aggregate and harmonize exome and genome sequencing data from a variety of large-scale sequencing projects, and to make summary data available for the wider scientific community. The v2 dataset (GRCh37/hg19) used in this analysis includes 125,748 exome sequences from unrelated individuals sequenced as part of various disease-specific and population genetic studies. For the present analysis, both men and women were included as controls but those with a personal history of cancer were excluded. Ashkenazi Jews were also excluded from this analysis because the population of gnomAD controls in this group was small. East Asians and South Asians in gnomAD were combined to serve as a reference group for Asians. Patients who had undergone testing for *BRCA* or Lynch genes prior to MGPT were excluded from cases. Copy number variations in all genes and gnomAD filter non-PASS variants were excluded from both cases and controls, the rationale and process for which have been described previously (9). Further case-control analysis by estrogen receptor (ER) status was performed by subsetting BC cases to estrogen receptor positive and negative cases while the control population essentially remained the same as in overall analysis.

Absolute breast cancer risk estimation for each race or ethnicity:

Absolute risk is the probability an individual with a measured set of risk factors (e.g. pathogenic variant (PV) status) and is disease free at age a will be diagnosed with the disease in the subsequent τ years (10). Let Z be the set of measured risk factors, then we can express the absolute risk as:

$$R(a, \tau, Z) = \int_a^{a+\tau} h_1(u|Z) \times \exp\left(-\int_a^u \{h_1(v|Z) + h_2(v|Z)\}\, dv\right) du$$

where $h_1(a|Z)$ is the conditional disease-specific hazard at age a and $h_2(a|Z)$ is the competing risks hazard at age a. The competing risks may include other diseases or death. The hazards can be parameterized as:

$$h_1(a|Z) = h_{10}(a)\exp(\beta Z)$$

and

$$h_2(a|Z) = h_{20}(a)\exp(\gamma Z)$$

where $h_{i0}(a)$ is the baseline hazard and β and γ represent the relative risks for each risk factor in Z for the disease of interest and competing risks, respectively. In this analysis, β was estimated in the case-control analysis and we assumed $\gamma=1$. The baseline hazards can be estimated by the following relationship between the baseline hazard and the marginal hazard

$$h_1^*(a) = h_{10}(a)E(\exp(\beta Z)) \approx \int h_{10}(a)\exp(\beta z)dF(z)$$

where $F(Z)$ denotes the distribution of the risk factors in the population. For each age, we solve for $h10(a)$ by using the expected distribution of the risk factor in the population (11, 12). We estimated race or ethnicity-specific absolute risk for a women at age a without a diagnosis with any breast cancer, and the risk factor of interest being gene specific PV carrier status, the odds ratio estimates from the Ambry cases versus gnomAD controls were used as estimates for β, and SEER race or ethnicity-specific incidence rates (13) were utilized for the estimation of the baseline hazard combined with the gnomAD PV frequency for the population frequency. In the SEER database, Non-Hispanic Whites, non-Hispanic Blacks and Hispanics were used to estimate the SEER race or ethnicity-specific incidence rates for Caucasians, African Americans and Hispanics respectively. Incidence of breast cancer for Asians were estimated by pooling data from several sub-ethnicities (Chinese, Japanese, Filipino, Hawaiian, Korean, Vietnamese, Laotian, Hmong, Kampuchean, Thai, Asian Indian, Pakistani, Micronesian, Chamorran, Guamanian, Polynesian, Tahitian, Samoan, Tongan, Melenesian, Fiji Islander, New Guinean, Other Asian not otherwise specified (NOS), and Pacific Islander, NOS). The age and

reace or ethnicity specific competing events were all cause mortality derived from the CDC WONDER database

subset to the same years and states as the corresponding SEER registries.

References:

1.	Genetic/Familial High-Risk Assessment: Breast and Ovarian [Internet]. 2019 [cited 01/29/2019]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf.

2.	Race, Ethnicity and Language Data: Standardization for Health Care Quality Improvement. Agency for Healthcare Research and Quality, Rockville, MD. Available from: https://www.ahrq.gov/research/findings/final-reports/iomracereport/index.html [

3.	Shimelis H, LaDuca H, Hu C, Hart SN, Na J, Thomas A, et al. Triple-Negative Breast Cancer Risk Genes Identified by Multigene Hereditary Cancer Panel Testing. Journal of the National Cancer Institute. 2018.

4.	Couch FJ, Shimelis H, Hu C, Hart SN, Polley EC, Na J, et al. Associations Between Cancer Predisposition Testing Panel Genes and Breast Cancer. JAMA oncology. 2017;3(9):1190-6.

5.	Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in medicine : official journal of the American College of Medical Genetics. 2015;17(5):405-24.

6.	Kilpivaara O, Vahteristo P, Falck J, Syrjäkoski K, Eerola H, Easton D, et al. CHEK2 variant I157T may be associated with increased breast cancer risk. International journal of cancer. 2004;111(4):543-7.

7.	Tung N, Domchek SM, Stadler Z, Nathanson KL, Couch F, Garber JE, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. Nature reviews Clinical oncology. 2016;13(9):581-8.

8.	Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature. 2016;536(7616):285-91.

9.	Hu C, LaDuca H, Shimelis H, Polley EC, Lilyquist J, Hart SN, et al. Multigene Hereditary Cancer Panels Reveal High-Risk Pancreatic Cancer Susceptibility Genes. JCO Precision Oncology. 2018(2):1-28.

10.	Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. Journal of the National Cancer Institute. 1989;81(24):1879-86.

11.	Costantino JP, Gail MH, Pee D, Anderson S, Redmond CK, Benichou J, et al. Validation Studies for Models Projecting the Risk of Invasive and Total Breast Cancer Incidence. JNCI: Journal of the National Cancer Institute. 1999;91(18):1541-8.

12.	Chatterjee N, Shi J, García-Closas M. Developing and evaluating polygenic risk prediction models for stratified disease prevention. Nature reviews Genetics. 2016;17(7):392-406.

13.	National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch. Surveillance, Epidemiology, and End Results (SEER) Program Research Data (2010-2015). https://www.seer.cancer.gov. April 2018 (Based on November 2017 Submission).

Supplementary Tables

Supplementary Table 1: Comparison of OMB race category and study ethnicity condensed category

OMB Race Category	Study Ethnicity Condensed Category
Asian	Asian
Black or African American	Black
Native Hawaiian or Other Pacific Islander	Asian
White	Non-Hispanic White
American Indian or Alaska Native	Native American, Alaska Native
No determinate OMB race classification	Other (e.g., Brazilian)
Hispanic or Latino	Hispanic
Other ethnicity	Other
Middle Eastern or North African	Middle Eastern
--	Ashkenazi Jewish
--	Mixed ethnicity (if multiple of the above categories, with the exception of non-Hispanic White/Ashkenazi Jewish = Ashkenazi Jewish)

OMB: Office of Management and Budget

Supplementary Table 2: Characteristics of breast cancer patients from racial and ethnic groups

	Non-Hispanic White		Ashkenazi-Jewish		Black		Hispanic		Asian	
	n	%	n	%	n	%	n	%	n	%
Total patients	57003		4798		6722		5194		4183	
Age at testing (years)										
mean (SD)	55.4 (12.1)		58.9 (12.1)		50.8 (11.8)		49.6 (11.4)		49.0 (11.3)	
<30	609	1.1	39	0.8	166	2.5	131	2.5	90	2.2
30-39	4488	7.9	223	4.6	977	14.5	791	15.2	689	16.5
40-49	14132	24.8	850	17.7	2101	31.3	1902	36.6	1702	40.7
50-59	16472	28.9	1280	26.7	1888	28.1	1363	26.2	930	22.2
>59	21301	37.4	2406	50.1	1590	23.7	1007	19.4	772	18.5
Personal History of Cancer										
Age at breast cancer diagnosis										
mean (SD)	50.2 (11.4)		52.5 (11.6)		47.0 (11.2)		46.2 (10.7)		45.5 (10.2)	
dx ≤36	5972	10.5	346	7.2	1194	17.8	888	17.1	752	18.0
dx ≤45	21040	36.9	1395	29.1	3232	48.1	2717	52.3	2364	56.5
dx ≤50	32228	56.5	2298	47.9	4420	65.8	3718	71.6	3187	76.2
dx ≤60	46214	81.1	3593	74.9	5878	87.4	4651	89.5	3802	90.9
dx >60	10789	18.9	1205	25.1	844	12.6	543	10.5	381	9.1
Multiple Breast Cancer										
No	48717	85.5	4041	84.2	5808	86.4	4683	90.2	3685	88.1
Not provided	191	0.3	17	0.4	24	0.4	48	0.9	15	0.4
Yes	8095	14.2	740	15.4	890	13.2	463	8.9	483	11.5
TNBC	6367	11.2	340	7.1	1586	23.6	743	14.3	420	10.0
ER status										
Negative	9305	16.3	530	11.0	1994	29.7	1040	20.0	671	16.0
Not provided	17601	30.9	1804	37.6	1802	26.8	1620	31.2	1145	27.4
Positive	30097	52.8	2464	51.4	2926	43.5	2534	48.8	2367	56.6
Ovarian	1206	2.1	78	1.6	79	1.2	61	1.2	56	1.3
Family History of Cancer[§]										
Breast (no ovarian)	31820	58.2	2728	58.9	3384	53.7	2108	44.5	1550	41.4
Breast & Ovarian	4859	8.9	307	6.6	455	7.2	328	6.9	203	5.4
Ovarian (no breast)	2651	4.8	202	4.4	297	4.7	278	5.9	191	5.1
No family history[#]	9684	17.7	830	17.9	1620	25.7	1523	32.2	1364	36.4
Not provided	2334	4.1	169	3.5	416	6.2	458	8.8	438	10.5

[#]No family history of breast, ovarian, colorectal, pancreatic and endometrial cancer in 1st or 2nd degree relatives
[§]Family history analysis is subset to individuals who provided information on family history of cancer

Supplementary Table 3: Gene-based frequency of variants of uncertain significance[#]

Genes	Non-Hispanic White		Ashkenazi-Jewish		Black		Hispanic		Asian	
	Women with VUS	VUS frequency (%)	Women with VUS	VUS frequency (%)	Women with VUS	VUS frequency (%)	Women with VUS	VUS frequency (%)	Women with VUS	VUS frequency (%)
Breast Cancer Predisposition Genes										
ATM	1288	3.80	76	3.80	361	8.70	163	5.30	141	5.60
BARD1	365	1.20	25	1.30	60	1.60	31	1.1	63	2.70
BRCA1	368	0.80	13	0.50	115	2.10	55	1.30	100	3.00
BRCA2	760	1.80	14	0.60	226	4.00	131	3.20	154	4.70
BRIP1	475	1.50	32	1.70	67	1.80	48	1.70	71	3.00
CDH1	313	0.70	9	0.40	70	1.30	51	1.30	57	1.80
CHEK2	597	1.80	46	2.30	43	1.00	87	2.80	48	1.90
PALB2	475	1.30	20	0.90	81	1.80	41	1.20	81	1.80
PTEN	407	0.90	19	0.80	99	1.80	63	1.50	59	1.80
RAD51C	399	1.30	16	0.80	41	1.10	15	0.50	13	0.50
RAD51D	173	0.60	3	0.20	34	0.90	14	0.50	24	1.00
TP53	175	0.40	10	0.40	27	0.50	17	0.40	39	1.20
Total frequency[$]		16.1		13.7		26.6		20.8		29
Other cancer predisposition genes										
CDKN2A	33	0.30	1	0.10	12	1.10	6	0.80	10	1.50
MLH1	159	0.80	13	1.00	26	1.20	15	0.90	30	2.00
MRE11A	369	1.20	10	0.50	66	1.80	39	1.40	29	1.20
MSH2	308	1.60	15	1.20	53	2.50	26	1.60	35	2.40
MSH6	350	1.80	17	1.30	78	3.70	31	1.90	53	3.60
NBN	371	1.20	23	1.20	129	3.40	44	1.60	57	2.40
NF1	461	1.50	30	1.60	61	1.60	48	1.70	53	2.30
PMS2	275	1.40	16	1.20	72	3.40	42	2.60	52	3.50
RAD50	482	1.50	28	1.50	118	3.10	56	2.00	122	5.20

VUS: variants of uncertain significance;

#: Breast cancer patients reporting prior *BRCA1* and *BRCA2* and Lynch syndrome testing were excluded. VUS frequencies are reported per subject for each gene.

$: Total frequency is a sum of PV frequency across all breast cancer predisposition genes.

Supplementary Table 4: Frequency of PVs in other cancer predisposition genes in different racial and ethnic groups

	Non Hispanic White	Ashkenazi-Jewish	Black	Hispanic	Asian
	PV (%)	PV (%)	PV (%)	PV (%)	PV (%)
CDKN2A	15 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
MLH1	17 (0.1%)	0 (0.0%)	1 (0.0%)	2 (0.1%)	4 (0.3%)
MRE11A	41 (0.1%)	1 (0.1%)	11 (0.3%)	1 (0.0%)	4 (0.2%)
MSH2	16 (0.1%)	3 (0.2%)	1 (0.0%)	3 (0.2%)	1 (0.1%)
MSH6	60 (0.3%)	5 (0.4%)	4 (0.2%)	2 (0.1%)	0 (0.0%)
NBN	74 (0.2%)	4 (0.2%)	1 (0.0%)	4 (0.1%)	2 (0.1%)
NF1	45 (0.1%)	3 (0.2%)	10 (0.3%)	3 (0.1%)	2 (0.1%)
PMS2	71 (0.4%)	2 (0.2%)	7 (0.3%)	4 (0.2%)	4 (0.3%)
RAD50	98 (0.3%)	3 (0.2%)	10 (0.3%)	8 (0.3%)	7 (0.3%)

PV: Pathogenic Variant;

Supplementary Table 5: Odds ratios for breast cancer risk for different ethnicities/races compared to ethnicity/race-matched controls in gnomAD[#]

Gene	Odds Ratio	95% Confidence Interval	Adjusted p-value[ε]	Cases[$]			Controls		
				PV Allele Count	Total Allele Number	PV Allele Frequency	PV Allele Count	Total Allele Number	PV Allele Frequency
Non-Hispanic White									
ATM	2.83	2.4-3.35	2.01e-36	404	67204	0.6%	218	102301	0.21%
BARD1	2.47	1.68-3.67	5.73e-06	68	63068	0.11%	44	100573	0.04%
BRCA1	7.34	5.97-9.08	1.18e-115	643	86848	0.74%	104	102451	0.1%
BRCA2	5.9	4.96-7.03	1.1e-122	782	86848	0.9%	156	101445	0.15%
BRIP1	1.45	1.1-1.92	0.013	96	63250	0.15%	107	102403	0.1%
CDH1	4.9	2.01-12.22	0.000163	25	84752	0.03%	6	99702	0.01%
CDKN2A	7.56	2.84-20.71	3.98e-05	12	21890	0.05%	7	96453	0.01%
CHEK2*	2.3	2-2.64	6.88e-32	503	67098	0.75%	331	101013	0.33%
MLH1	2.1	0.97-4.61	0.07	13	39538	0.03%	16	102283	0.02%
MRE11A	1.29	0.82-2.04	0.313	35	63068	0.06%	44	102368	0.04%
MSH2	2.13	0.9-5.01	0.104	10	39538	0.03%	12	101268	0.01%
MSH6	2.37	1.62-3.47	1.58e-05	54	39538	0.14%	58	100774	0.06%
NBN	1.62	1.15-2.28	0.00922	68	63068	0.11%	68	102072	0.07%
NF1	3.91	2.21-7.04	2.11e-06	40	61306	0.07%	17	101782	0.02%
PALB2	4.74	3.71-6.08	1.63e-42	278	70970	0.39%	85	102504	0.08%
PTEN	ND	ND	ND	26	87280	0.03%	4	101599	0%
RAD50	1.09	0.82-1.45	0.562	81	63068	0.13%	120	101953	0.12%
RAD51C	1.45	0.99-2.15	0.07	51	63250	0.08%	57	102515	0.06%
RAD51D	1.8	1.04-3.16	0.0584	27	61488	0.04%	25	102346	0.02%
TP53	4.69	2.67-8.35	2.11e-09	64	87546	0.07%	16	102541	0.02%
Black									
ATM	3.58	1.87-7.21	0.000266	28	8318	0.34%	14	14846	0.09%
BARD1	6.59	2.34-18.68	0.000211	17	7508	0.23%	5	14535	0.03%
BRCA1	27.11	13-58.75	1.11e-41	141	11178	1.26%	7	14864	0.05%
BRCA2	14.52	8.36-25.32	4.2e-39	153	11178	1.37%	14	14661	0.1%
BRIP1	1.73	0.84-3.71	0.268	14	7528	0.19%	16	14850	0.11%
CDH1	ND	ND	ND	5	10908	0.05%	1	14414	0.01%
CDKN2A	ND	ND	ND	1	2232	0.04%	2	13449	0.01%
CHEK2*	1.55	0.59-4.33	0.529	8	8306	0.1%	9	14485	0.06%
MLH1	ND	ND	ND	1	4206	0.02%	3	14801	0.02%

MRE11A	ND	ND	ND	11	7508	0.15%	3	14873	0.02%
MSH2	ND	ND	ND	1	4206	0.02%	0	14568	0%
MSH6	ND	ND	ND	3	4206	0.07%	7	14533	0.05%
NBN	ND	ND	ND	1	7508	0.01%	8	14779	0.05%
NF1	ND	ND	ND	6	7420	0.08%	3	14760	0.02%
PALB2	5.89	3.14-11.18	2.13e-09	46	8950	0.51%	13	14846	0.09%
PTEN	ND	ND	ND	7	11186	0.06%	0	14688	0%
RAD50	1.36	0.56-3.17	0.558	9	7508	0.12%	13	14731	0.09%
RAD51C	ND	ND	ND	8	7528	0.11%	4	14856	0.03%
RAD51D	ND	ND	ND	5	7440	0.07%	3	14833	0.02%
TP53	ND	ND	ND	11	11208	0.1%	1	14828	0.01%
Hispanic									
ATM	2.54	1.62-3.96	0.000317	29	6112	0.47%	64	34167	0.19%
BARD1	7.29	2.81-18.48	8.47e-05	11	5608	0.2%	9	33414	0.03%
BRCA1	18.16	11.45-29.23	4.36e-46	96	8312	1.15%	22	34214	0.06%
BRCA2	5.95	4.35-8.14	1.36e-28	101	8312	1.22%	69	33442	0.21%
BRIP1	2.86	1.17-6.6	0.0331	8	5624	0.14%	17	34188	0.05%
CDH1	ND	ND	ND	3	8128	0.04%	0	33665	0%
CDKN2A	ND	ND	ND	0	1592	0%	2	33874	0.01%
CHEK2*	2.9	1.46-5.82	0.0121	13	6106	0.21%	25	34013	0.07%
MLH1	ND	ND	ND	2	3256	0.06%	4	34057	0.01%
MRE11A	ND	ND	ND	1	5608	0.02%	13	34210	0.04%
MSH2	ND	ND	ND	2	3256	0.06%	2	33819	0.01%
MSH6	ND	ND	ND	2	3256	0.06%	16	33665	0.05%
NBN	ND	ND	ND	4	5608	0.07%	9	34171	0.03%
NF1	ND	ND	ND	3	5524	0.05%	10	34057	0.03%
PALB2	5.98	3.46-10.14	1.04e-09	30	6630	0.45%	26	34220	0.08%
PTEN	ND	ND	ND	4	8334	0.05%	2	34072	0.01%
RAD50	1.01	0.45-2.29	1	7	5608	0.12%	42	34124	0.12%
RAD51C	ND	ND	ND	11	5624	0.2%	4	34218	0.01%
RAD51D	ND	ND	ND	2	5540	0.04%	3	34199	0.01%
TP53	ND	ND	ND	9	8348	0.11%	1	34234	0%
Asian									
ATM	1.41	0.74-2.5	0.468	13	5044	0.26%	88	48103	0.18%
BARD1	4.11	1.61-9.99	0.018	7	4722	0.15%	17	47051	0.04%

Gene	OR	95% CI	p-value€	Cases PV	Cases total	Cases %	Controls PV	Controls total	Controls %
BRCA1	7.96	5.37-11.66	7.62e-23	56	6562	0.85%	52	48167	0.11%
BRCA2	8.08	5.66-11.42	8.22e-28	69	6562	1.05%	62	47204	0.13%
BRIP1	ND	ND	ND	1	4736	0.02%	35	48112	0.07%
CDH1	ND	ND	ND	4	6462	0.06%	3	47304	0.01%
CDKN2A	ND	ND	ND	0	1246	0%	1	47371	0%
CHEK2*	0.97	0.37-2.4	1	5	5048	0.1%	49	47861	0.1%
MLH1	ND	ND	ND	4	2930	0.14%	11	47991	0.02%
MRE11A	ND	ND	ND	4	4722	0.08%	22	48177	0.05%
MSH2	ND	ND	ND	1	2930	0.03%	3	47576	0.01%
MSH6	ND	ND	ND	0	2930	0%	26	47407	0.05%
NBN	ND	ND	ND	2	4722	0.04%	19	48098	0.04%
NF1	ND	ND	ND	2	4666	0.04%	5	47938	0.01%
PALB2	11.16	6.46-19.7	3.6e-15	29	5468	0.53%	23	48166	0.05%
PTEN	ND	ND	ND	1	6582	0.02%	5	47928	0.01%
RAD50	0.8	0.34-1.81	0.995	6	4722	0.13%	76	47957	0.16%
RAD51C	ND	ND	ND	2	4736	0.04%	24	48161	0.05%
RAD51D	ND	ND	ND	2	4680	0.04%	14	48121	0.03%
TP53	ND	ND	ND	8	6586	0.12%	4	48184	0.01%

ND: Not determined due to insufficient number of pathogenic variants in cases or controls (<5);

PV: pathogenic variant;

$: Copy number variants excluded from breast cancer cases;

#: Fishers exact test comparing frequency of PVs in breast cancer cases and gnomAD reference controls. PVs in *PMS2* excluded from analysis. Breast cancer patients reporting prior *BRCA1* and *BRCA2* and Lynch syndrome testing were excluded;

€: Adjusted for multiple testing by Benjamini-Hochberg method;

*: Missense and low penetrance PVs in *CHEK2* excluded from analysis;

Supplementary Table 6: Associations with estrogen receptor positive breast cancer risk for pathogenic variants in cancer predisposition genes by race and ethnicity[#]

Gene	Non-Hispanic White			Black			Hispanic			Asian		
	Odds Ratio	95% CI	Adjusted p-value[€]	Odds Ratio	95% CI	Adjusted p-value[€]	Odds Ratio	95% CI	Adjusted p-value[€]	Odds Ratio	95% CI	Adjusted p-value[€]
ATM	2.95	2.43-3.55	1.02e-27	5.52	2.73-11.08	9.55e-06	2.85	1.59-5.02	0.00242	2.11	1.07-3.99	0.104
BARD1	1.49	0.87-2.48	0.22	ND	ND	ND	ND	ND	ND	ND	ND	ND
BRCA1	3.36	2.62-4.32	1.42e-21	9.63	4.05-23.51	6.63e-08	8.41	4.54-15.59	7.91e-10	5.3	3.07-8.9	1.44e-07
BRCA2	5.43	4.5-6.56	4.02e-79	11.72	6.38-21.74	1.1e-19	6.6	4.61-9.45	4.88e-20	8.12	5.43-12.2	9.74e-18
BRIP1	1.36	0.96-1.91	0.144	1.98	0.77-4.96	0.336	ND	ND	ND	ND	ND	ND
CDH1	6.98	2.81-17.82	1.53e-05	ND	ND	ND	ND	ND	ND	ND	ND	ND
CDKN2A	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
*CHEK2**	2.44	2.08-2.86	4.21e-26	3.08	1.04-9.01	0.093	4.98	2.43-10.14	0.000449	ND	ND	ND
MLH1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
MRE11A	1.03	0.57-1.87	0.927	ND	ND	ND	ND	ND	ND	ND	ND	ND
MSH2	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
MSH6	1.82	1.1-3.03	0.0451	ND	ND	ND	ND	ND	ND	ND	ND	ND
NBN	1.96	1.32-2.87	0.00202	ND	ND	ND	ND	ND	ND	ND	ND	ND
NF1	3.08	1.56-6.07	0.004	ND	ND	ND	ND	ND	ND	ND	ND	ND
PALB2	4.22	3.21-5.6	5.5e-25	8.08	4.13-15.73	1.1e-09	6.06	3.12-11.62	5.87e-06	10.92	5.72-21.41	2.81e-09
PTEN	8.19	2.71-26.82	6.9e-05	ND	ND	ND	ND	ND	ND	ND	ND	ND
RAD50	1.16	0.82-1.64	0.559	1.73	0.59-5.06	0.471	ND	ND	ND	1.19	0.45-2.94	0.951
RAD51C	0.96	0.54-1.65	1	ND	ND	ND	ND	ND	ND	ND	ND	ND
RAD51D	1.23	0.55-2.59	0.698	ND	ND	ND	ND	ND	ND	ND	ND	ND
TP53	4.26	2.3-7.95	5.2e-06	ND	ND	ND	ND	ND	ND	16.33	4.39-64.39	0.0009

ND: Not determined due to insufficient number of pathogenic variants (PVs);

#: Fishers exact test comparing frequency of PVs in breast cancer cases and gnomAD reference controls. PVs in *PMS2* excluded from analysis. Breast cancer patients reporting prior *BRCA1* and *BRCA2* and Lynch syndrome testing were excluded;

€: Adjusted for multiple testing by Benjamini-Hochberg method;

*: Missense and low penetrance PVs in *CHEK2* excluded from analysis

Supplementary Table 7: Associations with estrogen receptor negative breast cancer risk for pathogenic variants in cancer predisposition genes by race and ethnicity[#]

Gene	Non-Hispanic White			Black			Hispanic			Asian		
	Odds Ratio	95% CI	Adjusted p-value[€]	Odds Ratio	95% CI	Adjusted p-value[€]	Odds Ratio	95% CI	Adjusted p-value[€]	Odds Ratio	95% CI	Adjusted p-value[€]
ATM	1.25	0.84-1.84	0.344	ND	ND	ND	ND	ND	ND	ND	ND	ND
BARD1	6.55	3.99-10.51	1.24e-11	12.97	4.26-39.33	1.93e-05	16.12	5.22-49.15	0.000322	18.61	6.56-52.84	9.8e-05
BRCA1	21.82	17.39-27.42	4.02e-187	56.68	26.3-124.11	1.92e-54	43.56	26.15-74.91	7.62e-43	20.64	12.48-34.02	2.64e-19
BRCA2	6.53	5.16-8.23	4.16e-49	13.94	7.54-26.44	3.41e-20	5.33	3.05-8.97	1e-06	7.28	3.6-14.48	2.49e-05
BRIP1	1.79	1.09-2.94	0.0545	ND	ND	ND	ND	ND	ND	ND	ND	ND
CDH1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
CDKN2A	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
CHEK2*	0.87	0.6-1.27	0.561	ND	ND	ND	ND	ND	ND	ND	ND	ND
MLH1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
MRE11A	1.15	0.43-2.88	0.801	ND	ND	ND	ND	ND	ND	ND	ND	ND
MSH2	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
MSH6	2.34	1.02-4.94	0.0545	ND	ND	ND	ND	ND	ND	ND	ND	ND
NBN	1.78	0.94-3.34	0.108	ND	ND	ND	ND	ND	ND	ND	ND	ND
NF1	7.24	3.35-15.72	1.19e-05	ND	ND	ND	ND	ND	ND	ND	ND	ND
PALB2	6.73	4.85-9.32	1.65e-24	4.76	2.04-10.95	0.00173	9.74	4.38-20.31	4.4e-06	17.13	7.04-40.29	7.25e-06
PTEN	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
RAD50	1.34	0.79-2.26	0.344	ND	ND	ND	ND	ND	ND	ND	ND	ND
RAD51C	1.95	0.98-3.75	0.0812	ND	ND	ND	ND	ND	ND	ND	ND	ND
RAD51D	4.11	1.84-8.65	0.00197	ND	ND	ND	ND	ND	ND	ND	ND	ND
TP53	5	2.26-10.82	0.000547	22.17	3.1-516.63	0.00428	ND	ND	ND	ND	ND	ND

ND: Not determined due to insufficient number (<5) of pathogenic variants (PVs);

#: Fishers exact test comparing frequency of PVs in breast cancer cases and gnomAD reference controls. PVs in *PMS2* excluded from analysis. Breast cancer patients reporting prior *BRCA1* and *BRCA2* and Lynch syndrome testing were excluded;

€: Adjusted for multiple testing by Benjamini-Hochberg method;

*: Missense and low penetrance variants in *CHEK2* excluded from analysis

Supplementary Table 8: Absolute lifetime risk of breast cancer by gene and ethnicity[#]

Gene	Non-Hispanic White						Black						Hispanic						Asian					
	Age/years						Age/years						Age/years						Age/years					
	30	40	50	60	70	85	30	40	50	60	70	85	30	40	50	60	70	85	30	40	50	60	70	85
ATM	<0.01	0.02	0.06	0.13	0.21	0.30	<0.01	0.03	0.08	0.16	0.24	0.32	<0.01	0.01	0.03	0.07	0.11	0.16	<0.01	0.01	0.03	0.05	0.09	0.12
BARD1	<0.01	0.02	0.06	0.11	0.19	0.27	0.01	0.05	0.14	0.26	0.39	0.50	<0.01	0.02	0.09	0.18	0.29	0.40	<0.01	0.02	0.08	0.15	0.23	0.31
BRCA1	0.01	0.04	0.16	0.29	0.45	0.59	0.03	0.17	0.44	0.68	0.81	0.85	0.01	0.06	0.20	0.37	0.55	0.68	<0.01	0.04	0.14	0.26	0.39	0.50
BRCA2	<0.01	0.04	0.13	0.24	0.38	0.51	0.01	0.09	0.27	0.47	0.63	0.73	<0.01	0.02	0.07	0.14	0.24	0.34	<0.01	0.04	0.14	0.26	0.39	0.51
CHEK2	<0.01	0.01	0.05	0.11	0.18	0.26	<0.01	0.01	0.04	0.07	0.11	0.16	<0.01	0.01	0.04	0.07	0.13	0.19	<0.01	<0.01	0.02	0.04	0.06	0.09
PALB2	<0.01	0.03	0.11	0.20	0.33	0.45	0.01	0.04	0.13	0.24	0.36	0.46	<0.01	0.02	0.07	0.15	0.24	0.34	0.01	0.05	0.19	0.34	0.50	0.62

#: Absolute lifetime risk of breast cancer (up to age 85) determined for genes with at least 5 pathogenic variants across all races/ethnicities;