

# Genetic Risk of Second Primary Cancer in Breast Cancer Survivors: The Multiethnic Cohort Study

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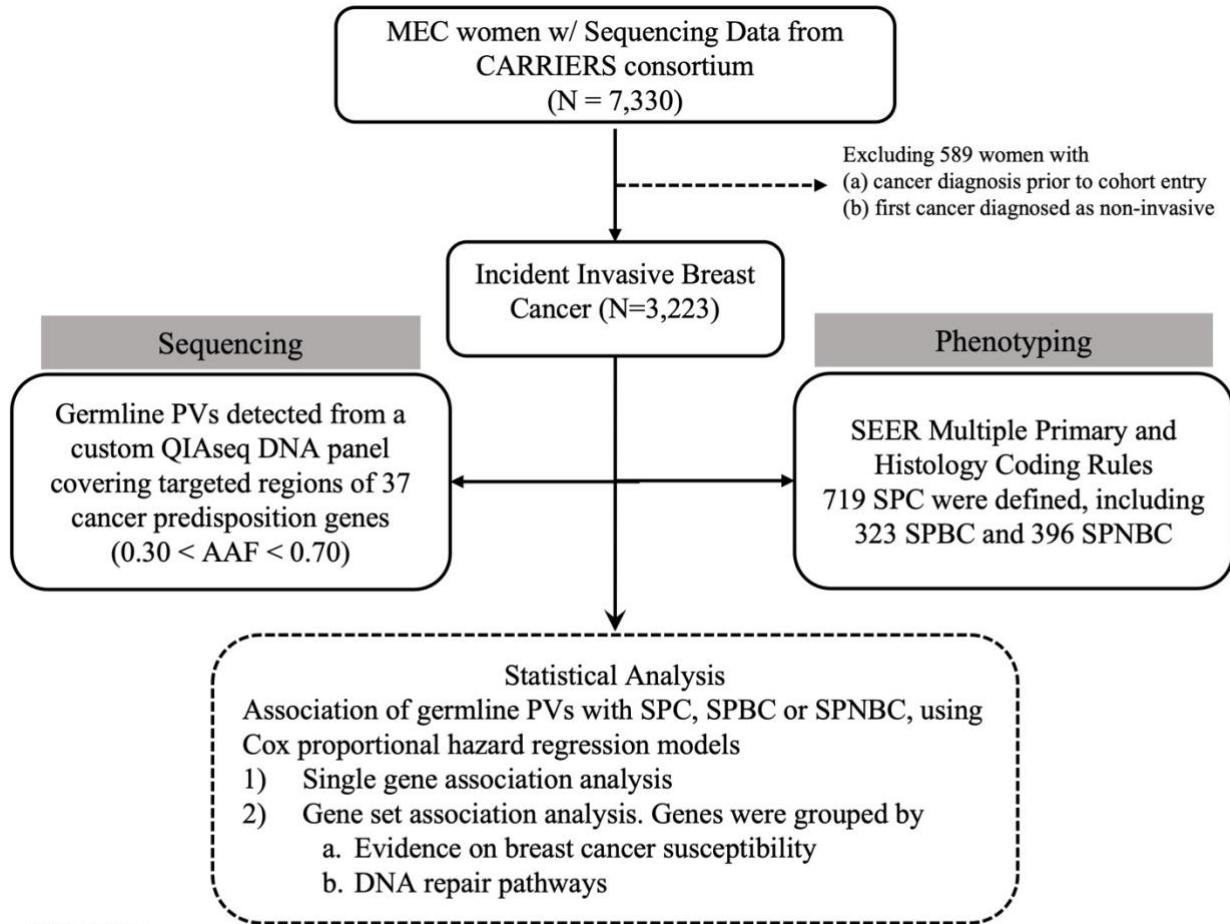
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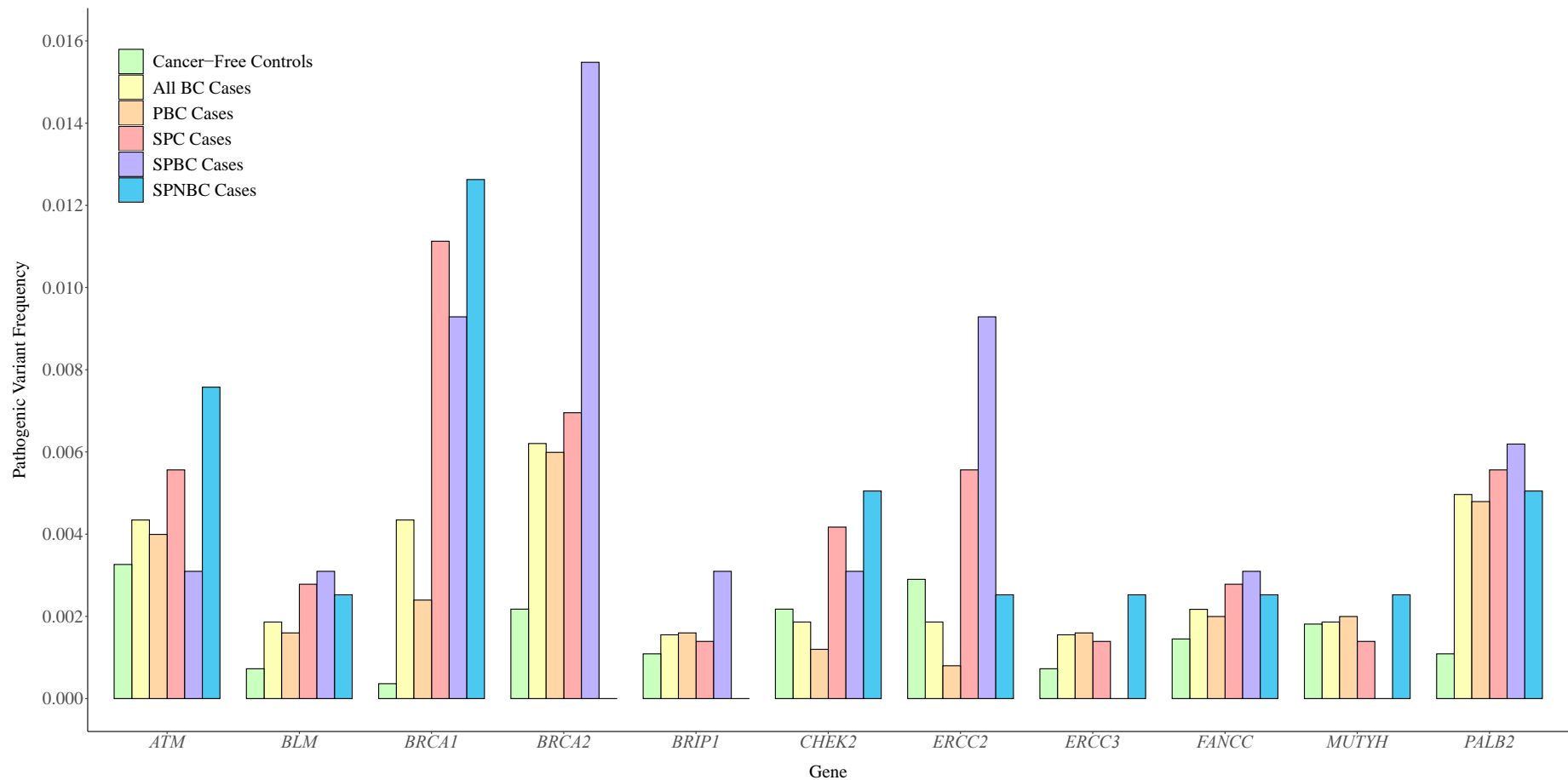
## SUPPLEMENTARY FIGURES

### Supplementary Figure 1 Overview of Study Design and Statistical Analysis



#### Abbreviations

MEC: Multiethnic Cohort Study  
CARRIERS: CAncer RiSk Estimates Related to Susceptibility Consortium  
SPC: second primary cancer  
SPBC: second primary breast cancer  
SPNBC: second primary non-breast cancer  
PVs: pathogenic variants  
AAF: alternate allele fraction



**Supplementary Figure 2 Carrier Frequency of pathogenic variants in 11 genes tested in the single-gene association analysis.**

Frequencies were estimated in 2,758 cancer-free controls, 3,223 breast cancer (BC) cases, 2,504 women with only primary breast cancer (PBC), 719 women with second primary cancer (SPC), 323 women with second primary breast cancer (SPBC) and 396 women with second primary non-breast cancer (SPNBC).

**SUPPLEMENTARY TABLES**

**Supplementary Table 1 Associations of non-genetic factors with SPC, SPBC or SPNBC**

Variables	SPC		SPBC		SPNBC	
	HR (95% CI) <sup>1</sup>	P	HR (95% CI) <sup>1</sup>	P	HR (95% CI) <sup>1</sup>	P
Age at diagnosis of 1 <sup>st</sup> BC	1.01 (1.00 - 1.03)	0.08	1.02 (0.99 - 1.04)	0.17	1.01 (0.99 - 1.03)	0.15
Family history of breast cancer						
Negative	1.00 (reference)	--	1.00 (reference)	--	1.00 (reference)	--
Positive	1.30 (1.07 - 1.56)	0.007	1.42 (1.08 - 1.88)	0.01	1.28 (0.99 - 1.64)	0.06
Race/Ethnicity						
White	1.00 (reference)	--	1.00 (reference)	--	1.00 (reference)	--
African American	0.87 (0.70 - 1.10)	0.25	0.87 (0.62 - 1.23)	0.43	0.86 (0.64 - 1.17)	0.34
Japanese American	0.76 (0.62 - 0.92)	0.006	0.87 (0.64 - 1.16)	0.34	0.65 (0.50 - 0.85)	0.002
Latino	0.69 (0.55 - 0.88)	0.002	0.59 (0.40 - 0.86)	0.006	0.75 (0.56 - 1.02)	0.06
Native Hawaiian	1.08 (0.82 - 1.42)	0.59	1.30 (0.88 - 1.92)	0.18	0.90 (0.61 - 1.33)	0.61
Tumor stage of 1 <sup>st</sup> BC						
Localized	1.00 (reference)	--	1.00 (reference)	--	1.00 (reference)	--
Regional	1.02 (0.84 - 1.24)	0.82	0.94 (0.70 - 1.26)	0.67	1.08 (0.83 - 1.41)	0.55
Distant	1.43 (0.71 - 2.89)	0.32	1.92 (0.78 - 4.70)	0.16	0.98 (0.31 - 3.09)	0.98
ER status of 1 <sup>st</sup> BC						
Negative	1.00 (reference)	--	1.00 (reference)	--	1.00 (reference)	--
Positive	1.06 (0.81 - 1.39)	0.67	0.97 (0.68 - 1.37)	0.86	1.13 (0.79 - 1.63)	0.50
PR status of 1 <sup>st</sup> BC						
Negative	1.00 (reference)	--	1.00 (reference)	--	1.00 (reference)	--
Positive	0.84 (0.67 - 1.05)	0.12	0.97 (0.68 - 1.37)	0.83	0.74 (0.55 - 1.00)	0.05
Radiotherapy for 1 <sup>st</sup> BC						
Not administered	1.00 (reference)	--	1.00 (reference)	--	1.00 (reference)	--
Administered	0.93 (0.79 - 1.09)	0.36	0.78 (0.62 - 0.99)	0.04	1.09 (0.88 - 1.34)	0.44
Chemotherapy for 1 <sup>st</sup> BC						
Not administered	1.00 (reference)	--	1.00 (reference)	--	1.00 (reference)	--
Administered	1.06 (0.87 - 1.29)	0.58	1.13 (0.85 - 1.52)	0.40	0.99 (0.75 - 1.30)	0.95
Hormonal therapy for 1 <sup>st</sup> BC						
Not administered	1.00 (reference)	--	1.00 (reference)	--	1.00 (reference)	--
Administered	0.97 (0.82 - 1.14)	0.70	0.91 (0.71 - 1.16)	0.43	1.01 (0.81 - 1.26)	0.91

<sup>1</sup> Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated from the Cox proportional hazard regression models adjusting for all variables listed in this table given each SPC phenotype.

**Supplementary Table 2 Clinical characteristics of women carrying PVs in selected genes**

Characteristics	<i>ATM</i>	<i>BRCA1</i>	<i>BRCA2</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>BLM</i>	<i>BRIP1</i>	<i>ERCC3</i>	<i>FANCC</i>	<i>ERCC2</i>	<i>MUTYH</i>
No. Carriers	14	14	20	6	16	6	5	5	7	6	6
Mean age at 1 <sup>st</sup> BC diagnosis	63.0	64.4	62.7	65.9	69.2	68.3	69.0	71.3	66.6	66.9	62.0
Mean survival years	8.7	11.0	9.8	10.1	10.7	8.5	11.8	9.5	10.0	8.6	14.7
Tumor stage of 1 <sup>st</sup> BC											
Localized	8	11	11	4	12	5	4	3	7	3	5
Regional	5	3	7	2	4	0	1	2	0	3	1
Distant	0	0	2	0	0	1	0	0	0	0	0
Missing	1	0	0	0	0	0	0	0	0	0	0
ER status of 1 <sup>st</sup> BC											
Negative	2	7	8	1	6	1	0	0	3	0	2
Positive	9	5	9	4	7	4	4	5	3	5	4
Missing	3	2	3	1	3	1	1	0	1	1	0
PR status of 1 <sup>st</sup> BC											
Negative	2	8	8	2	6	1	0	0	3	1	3
Positive	9	4	9	3	7	4	4	5	3	3	3
Missing	3	2	3	1	3	1	1	0	1	2	0
Radiation Treatment of 1 <sup>st</sup> BC <sup>1</sup>											
Not administered	7	6	11	5	10	2	2	1	4	2	3
Administered	7	8	9	1	6	4	3	4	3	4	3
Missing	0	0	0	0	0	0	0	0	0	0	0
Chemotherapy of 1 <sup>st</sup> BC <sup>1</sup>											
Not administered	6	7	8	4	11	4	3	3	7	4	4
Administered	8	7	12	2	5	2	2	1	0	1	2
Missing	0	0	0	0	0	0	0	1	0	1	0
Hormonal Therapy of 1 <sup>st</sup> BC <sup>1</sup>											
Not administered	9	10	10	3	12	4	3	2	3	4	4
Administered	4	4	9	3	4	1	2	3	3	1	2
Missing	1	0	1	0	0	1	0	0	1	1	0
Cause of Death											
Alive	10	11	12	4	11	2	4	4	4	4	4
Breast Cancer	2	1	3	1	1	2	0	0	1	1	0
Others	2	2	5	1	4	2	1	1	2	1	2

<sup>1</sup> First-course treatment from SEER cancer registry

**Supplementary Table 3 Association of germline PVs in selected genes with SPC, SPBC or SPNBC: sensitivity analyses**

Gene	Sensitivity Analyses	SPC		SPBC		SPNBC	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
<i>ATM</i>	SPA <sup>1</sup>	1.48 (0.55 - 3.98)	0.47	0.85 (0.12 - 6.29)	0.88	1.91 (0.61 - 6.00)	0.29
	Imputation <sup>2</sup>	1.52 (0.56 - 4.10)	0.41	0.86 (0.12 - 6.35)	0.88	1.99 (0.63 - 6.25)	0.24
	MSM <sup>3</sup>	1.76 (0.65 - 4.76)	0.27	1.04 (0.14 - 7.71)	0.97	2.22 (0.71 - 6.99)	0.17
<i>BRCA1</i>	SPA <sup>1</sup>	2.28 (1.11 - 4.65)	0.012	2.64 (0.82 - 8.43)	0.07	2.98 (1.21 - 7.36)	0.011
	Imputation <sup>2</sup>	2.24 (1.10 - 4.58)	0.027	2.61 (0.82 - 8.34)	0.11	2.93 (1.19 - 7.22)	0.020
	MSM <sup>3</sup>	2.65 (1.29 - 5.44)	0.008	3.15 (0.98 - 10.2)	0.06	3.48 (1.41 - 8.62)	0.007
<i>BRCA2</i>	SPA <sup>1</sup>	1.18 (0.49 - 2.88)	0.72	2.24 (0.91 - 5.55)	0.07	--	--
	Imputation <sup>2</sup>	1.14 (0.47 - 2.78)	0.77	2.14 (0.87 - 5.27)	0.10	--	--
	MSM <sup>3</sup>	1.36 (0.56 - 3.32)	0.50	2.61 (1.05 - 6.50)	0.04	--	--
<i>CHEK2</i>	SPA <sup>1</sup>	2.03 (0.64 - 6.46)	0.20	1.81 (0.24 - 13.6)	0.52	2.32 (0.56 - 9.60)	0.18
	Imputation <sup>2</sup>	2.02 (0.63 - 6.42)	0.24	1.71 (0.23 - 12.8)	0.60	2.37 (0.57 - 9.79)	0.23
	MSM <sup>3</sup>	2.47 (0.77 - 7.91)	0.13	2.11 (0.28 - 16.0)	0.47	2.84 (0.68 - 11.8)	0.15
<i>PALB2</i>	SPA <sup>1</sup>	0.89 (0.33 - 2.40)	0.80	0.96 (0.24 - 3.94)	0.95	0.95 (0.23 - 3.87)	0.94
	Imputation <sup>2</sup>	0.92 (0.34 - 2.46)	0.86	0.97 (0.24 - 3.98)	0.97	1.01 (0.25 - 4.10)	0.99
	MSM <sup>3</sup>	0.77 (0.25 - 2.43)	0.66	0.58 (0.08 - 4.20)	0.59	1.10 (0.27 - 4.47)	0.90
<i>BLM</i>	SPA <sup>1</sup>	2.50 (0.61 - 10.2)	0.30	4.12 (0.55 - 30.9)	0.32	2.74 (0.38 - 19.8)	0.44
	Imputation <sup>2</sup>	2.40 (0.59 - 9.74)	0.22	4.29 (0.58 - 32.0)	0.15	2.72 (0.38 - 19.6)	0.32
	MSM <sup>3</sup>	2.81 (0.69 - 11.5)	0.15	4.63 (0.61 - 35.2)	0.14	2.87 (0.40 - 20.8)	0.30
<i>BRIP1</i>	SPA <sup>1</sup>	1.02 (0.14 - 7.34)	0.98	1.99 (0.27 - 14.4)	0.52	--	--
	Imputation <sup>2</sup>	1.05 (0.15 - 7.55)	0.96	2.10 (0.29 - 15.2)	0.46	--	--
	MSM <sup>3</sup>	--	--	--	--	--	--
<i>ERCC3</i>	SPA <sup>1</sup>	1.24 (0.17 - 8.90)	0.86	--	--	2.21 (0.31 - 16.1)	0.51
	Imputation <sup>2</sup>	1.19 (0.17 - 8.57)	0.86	--	--	2.05 (0.28 - 14.8)	0.48
	MSM <sup>3</sup>	1.41 (0.20 - 10.2)	0.73	--	--	2.34 (0.32 - 17.0)	0.40
<i>FANCC</i>	SPA <sup>1</sup>	1.28 (0.32 - 5.16)	0.73	1.32 (0.18 - 9.52)	0.77	1.07 (0.15 - 7.66)	0.95
	Imputation <sup>2</sup>	1.32 (0.33 - 5.34)	0.69	1.36 (0.19 - 9.79)	0.76	1.11 (0.16 - 7.99)	0.91
	MSM <sup>3</sup>	1.60 (0.40 - 6.49)	0.51	1.86 (0.26 - 13.5)	0.54	1.25 (0.17 - 8.96)	0.83
<i>ERCC2</i>	SPA <sup>1</sup>	3.51 (1.29 - 9.54)	0.014	5.09 (1.58 - 16.4)	0.007	2.00 (0.27 - 14.6)	0.44
	Imputation <sup>2</sup>	3.55 (1.31 - 9.62)	0.013	4.93 (1.53 - 15.9)	0.007	2.05 (0.28 - 14.9)	0.48
	MSM <sup>3</sup>	4.42 (1.62 - 12.1)	0.004	6.84 (2.10 - 22.3)	0.001	2.35 (0.32 - 17.2)	0.40
<i>MUTYH</i>	SPA <sup>1</sup>	0.51 (0.07 - 3.65)	0.41	--	--	0.88 (0.12 - 6.30)	0.88
	Imputation <sup>2</sup>	0.50 (0.07 - 3.57)	0.49	--	--	0.87 (0.12 - 6.24)	0.89
	MSM <sup>3</sup>	0.58 (0.08 - 4.17)	0.59	--	--	0.95 (0.13 - 6.82)	0.96

<sup>1</sup> P values were estimated using a saddlepoint approximation (SPA) method implemented in Cox proportional hazard models.

<sup>2</sup> Missing value was imputed with the ethnic-specific expected value.

<sup>3</sup> Association was estimated from multi-state models (MSM) that modeled a third primary cancer as a subsequent event following the diagnosis of a SPC while accounting for competing risk of death.

**Supplementary Table 4 Gene set associations with SPC, SPBC or SPNBC excluding *BRCA1*, *BRCA2* and/or *ERCC2***

Gene Set (no. genes)	PBC No. Carriers (%)	SPC No. Carriers (%)	HR (95% CI)	P
<b>SPC</b>				
DNA repair genes (25)	96 (3.89)	21 (6.50)	1.60 (1.02 - 2.51)	0.04
<i>BRCA1</i> excluded (24)	92 (3.67)	34 (4.73)	1.26 (0.89 - 1.79)	0.19
<i>ERCC2</i> excluded (24)	96 (3.83)	38 (5.29)	1.30 (0.93 - 1.82)	0.12
Both excluded (23)	90 (3.59)	30 (4.17)	1.16 (0.80 - 1.68)	0.43
HR pathway (14)	74 (2.96)	26 (3.62)	1.18 (0.79 - 1.76)	0.42
<i>BRCA1</i> excluded (13)	68 (2.72)	18 (2.50)	0.96 (0.60 - 1.54)	0.87
FA pathway (8)	51 (2.04)	21 (2.92)	1.26 (0.81 - 1.97)	0.30
<i>BRCA1</i> excluded (7)	45 (1.80)	13 (1.81)	0.98 (0.56 - 1.71)	0.95
NER pathway (2)	6 (0.24)	5 (0.70)	2.57 (1.06 - 6.27)	0.04
<i>ERCC2</i> excluded (1)	4 (0.16)	1 (0.14)	1.24 (0.17 - 8.90)	0.83
<b>SPBC<sup>1</sup></b>				
DNA repair genes (25)	96 (3.89)	21 (6.50)	1.60 (1.02 - 2.51)	0.04
<i>BRCA1</i> excluded (24)	90 (3.64)	18 (5.57)	1.48 (0.91 - 2.40)	0.11
<i>BRCA2</i> excluded (24)	81 (3.28)	16 (4.95)	1.44 (0.86 - 2.39)	0.16
<i>ERCC2</i> excluded (24)	94 (3.80)	18 (5.57)	1.42 (0.87 - 2.30)	0.16
All excluded (22)	73 (2.95)	10 (3.10)	1.04 (0.55 - 1.97)	0.89
HR pathway (14)	72 (2.91)	14 (4.33)	1.45 (0.84 - 2.50)	0.19
<i>BRCA1</i> excluded (13)	66 (2.67)	11 (3.41)	1.27 (0.69 - 2.34)	0.44
<i>BRCA2</i> excluded (13)	57 (2.31)	9 (2.79)	1.19 (0.61 - 2.32)	0.62
Both excluded (12)	51 (2.06)	6 (1.86)	0.93 (0.41 - 2.09)	0.85
FA pathway (8)	50 (2.02)	13 (4.02)	1.76 (1.00 - 3.12)	0.05
<i>BRCA1</i> excluded (7)	44 (1.78)	10 (3.10)	1.57 (0.83 - 2.99)	0.17
<i>BRCA2</i> excluded (13)	35 (1.42)	8 (2.48)	1.51 (0.74 - 3.09)	0.25
Both excluded (12)	29 (1.17)	5 (1.55)	1.20 (0.49 - 2.92)	0.70
NER pathway (2)	6 (0.24)	3 (0.93)	3.04 (0.96 - 9.69)	0.06
<i>ERCC2</i> excluded (1)	4 (0.16)	0 (0.00)	--	--
<b>SPNBC</b>				
DNA repair genes (25)	98 (3.91)	21 (5.30)	1.32 (0.85 - 2.07)	0.22
<i>BRCA1</i> excluded (24)	92 (3.67)	16 (4.04)	1.11 (0.67 - 1.85)	0.68
<i>ERCC2</i> excluded (24)	96 (3.83)	20 (5.05)	1.30 (0.82 - 2.05)	0.26
Both excluded (23)	90 (3.59)	15 (3.79)	1.08 (0.64 - 1.82)	0.77
HR pathway (14)	74 (2.96)	12 (3.03)	1.06 (0.59 - 1.91)	0.83
<i>BRCA1</i> excluded (13)	68 (2.72)	7 (1.77)	0.72 (0.34 - 1.53)	0.40
FA pathway (8)	51 (2.04)	8 (2.02)	0.93 (0.46 - 1.89)	0.84
<i>BRCA1</i> excluded (13)	45 (1.80)	3 (0.76)	0.43 (0.14 - 1.34)	0.15
NER pathway (2)	6 (0.24)	2 (0.51)	2.11 (0.52 - 8.58)	0.30
<i>ERCC2</i> excluded (1)	4 (0.16)	1 (0.25)	2.21 (0.31 - 16.07)	0.43

<sup>1</sup> A total of 33 women with bilateral mastectomy were further excluded in the analysis of SPBC.



**Supplementary Table 5 Association of PVs in *ERCC2* Gene with Breast Cancer**

	Sample Size No. controls/No. cases	Controls No. Carriers (%)	Cases No. Carriers (%)	OR (95% CI) <sup>1</sup>	P
<b>CARRIERS</b>					
Overall	31874/36548	159 (0.50)	171 (0.47)	0.90 (0.72 – 1.12)	0.34
White	26945/28720	149 (0.55)	152 (0.53)	0.90 (0.71 – 1.13)	0.35
African American	1220/1880	1 (0.08)	7 (0.37)	4.63 (0.57 – 37.8)	0.15
Asian	1381/1929	3 (0.22)	3 (0.16)	0.56 (0.10 – 3.01)	0.50
Latino	1450/2208	3 (0.21)	4 (0.18)	1.14 (0.20 – 6.35)	0.88
<b>MEC</b>					
Overall	2758/3223	8 (0.29)	6 (0.19)	0.64 (0.22 – 1.86)	0.41
White	614/755	4 (0.65)	2 (0.26)	0.39 (0.07 – 2.16)	0.28
African American	538/600	1 (0.19)	3(0.50)	2.79 (0.29 – 27.2)	0.38
Japanese American	834/992	1 (0.12)	0 (0)	--	--
Latino	535/608	1 (0.19)	0 (0)	--	--
Native Hawaiian	237/268	1 (0.42)	1 (0.37)	0.79 (0.05 – 13.4)	0.87

<sup>1</sup> Odds ratio (OR) and 95% confidence interval (CI) were estimated from logistic regression models adjusting for age and family history of breast cancer. Race/ethnicity was also adjusted in the analysis of overall study population.

<sup>2</sup> Controls selected in the MEC were cancer-free women.