

## Supplementary Materials

**Supplementary Table 1. Baseline characteristics of index women.**

	Index women with genotyping data			Index women with sequencing data		
	Total ( <i>n</i> =28362)	Control ( <i>n</i> =21141)	Cases ( <i>n</i> =7221)	Total ( <i>n</i> =13226)	Control ( <i>n</i> =5549)	Cases ( <i>n</i> =7677)
Age <sup>a</sup> , mean (SD)	56.5 (10.0)	56.3 (10.0)	56.9 (10.2)	60.0 (9.6)	60.7 (9.2)	59.3 (10.0)
Percent mammographic density (PD) <sup>b</sup> , mean (SD)	21.4 (18.3)	21.0 (18.9)	23.7 (14.9)	20.0 (16.6)	17.1 (17.1)	23.3 (15.3)
Menopausal status, <i>n</i> (%)						
Premenopausal	9593 (33.8)	8346 (39.5)	1247 (17.3)	2621 (19.8)	1229 (22.1)	1392 (18.1)
Postmenopausal	18769 (66.2)	12795 (60.5)	5974 (82.7)	10605 (80.2)	4320 (77.9)	6285 (81.9)
BMI	25.3 (4.2)	25.3 (4.2)	25.4 (4.1)	25.5 (4.2)	25.6 (4.3)	25.4 (4.1)
Father identified, <i>n</i> (%)	24991 (88.1)	19251 (91.1)	5740 (79.5)	11172 (84.5)	5023 (90.5)	6149 (80.1)
Mother identified, <i>n</i> (%)	25961 (91.5)	19887 (94.1)	6074 (84.1)	11706 (88.5)	5211 (93.9)	6495 (84.6)
Number of full siblings, <i>n</i> (%)						
0	7725 (27.2)	5110 (24.2)	2615 (36.2)	4116 (31.1)	1395 (25.1)	2721 (35.4)
1	10158 (35.9)	7978 (37.7)	2180 (30.2)	4344 (32.8)	2024 (36.5)	2320 (30.2)
2 or more	10479 (36.9)	8053 (38.1)	2426 (33.6)	4766 (36.1)	2130 (38.4)	2636 (34.4)
Number of children, <i>n</i> (%)						
0	5994 (21.2)	4845 (22.9)	1149 (15.9)	2120 (16.0)	880 (15.9)	1240 (16.2)
1	5100 (18.0)	3728 (17.6)	1372 (19.0)	2391 (18.1)	920 (16.6)	1471 (19.2)
2 or more	17268 (60.8)	12568 (59.5)	4700 (65.1)	8715 (65.9)	3749 (67.5)	4966 (64.6)

<sup>a</sup> Age at baseline were reported for controls, whereas age at diagnosis was reported for cases.

<sup>b</sup> Mammography date was the closest date to baseline for controls, while mammography date for cases was the closest date to breast cancer diagnosis.

**Supplementary Table 2. Hazard ratio (95% CI) of cancers among relatives of index women by protein-truncating variants in index women.**

	PTV absence <sup>a</sup>	<i>CHEK2</i>	<i>BRCA2</i>	<i>ATM</i>	<i>BRCA1</i>	<i>PALB2</i>	<i>BARD1</i>	<i>RAD51C</i>	<i>RAD51D</i>
<b>Breast</b>									
Any age	Ref	<b>1.47 (1.10-1.98)</b>	<b>1.64 (1.04-2.59)</b>	1.49 (0.80-2.79)	<b>4.14 (2.61-6.58)</b>	<b>2.51 (1.13-5.57)</b>	1.87 (0.82-4.29)	2.18 (0.88-5.37)	NA
< 50 years	Ref	<b>2.07 (1.15-3.71)</b>	2.03 (0.91-4.56)	<b>2.97 (1.16-7.58)</b>	<b>9.99 (5.50-18.15)</b>	3.70 (0.79-17.38)	NA	1.47 (0.19-11.10)	NA
≥ 50 years	Ref	1.30 (0.91-1.85)	1.49 (0.85-2.61)	1.05 (0.48-2.27)	<b>2.02 (1.07-3.81)</b>	2.10 (0.92-4.80)	<b>2.46 (1.04-5.85)</b>	2.42 (0.88-6.63)	NA
<b>Prostate</b>									
Any age	Ref	1.04 (0.71-1.54)	0.75 (0.35-1.58)	0.81 (0.37-1.78)	1.57 (0.85-2.91)	1.85 (0.81-4.20)	NA	<b>2.90 (1.31-6.44)</b>	NA
< 55 years	Ref	0.94 (0.13-6.97)	NA	2.97 (0.40-21.81)	3.77 (0.51-27.76)	<b>7.77 (1.05-57.51)</b>	NA	NA	NA
≥ 55 years	Ref	1.05 (0.71-1.56)	0.78 (0.37-1.65)	0.71 (0.29-1.70)	1.47 (0.76-2.87)	1.56 (0.61-3.99)	NA	<b>3.06 (1.37-6.82)</b>	NA
<b>Melanoma</b>									
Any age	Ref	0.73 (0.33-1.64)	0.40 (0.06-2.84)	0.84 (0.22-3.27)	1.17 (0.29-4.67)	2.23 (0.63-7.95)	3.48 (0.52-23.53)	1.40 (0.21-9.48)	NA
< 40 years	Ref	2.32 (0.72-7.49)	NA	<b>4.97 (1.26-19.61)</b>	NA	NA	NA	NA	NA
≥ 40 years	Ref	0.43 (0.14-1.35)	0.49 (0.07-3.51)	NA	1.44 (0.36-5.78)	2.69 (0.75-9.62)	4.11 (0.60-27.91)	1.71 (0.26-11.50)	NA
<b>Ovarian</b>									
Any age	Ref	1.23 (0.51-2.95)	<b>9.06 (5.01-16.36)</b>	0.91 (0.13-6.57)	<b>3.75 (1.21-11.68)</b>	NA	NA	<b>8.27 (1.87-36.63)</b>	NA
< 55 years	Ref	1.47 (0.36-5.99)	<b>5.99 (1.81-19.82)</b>	NA	<b>9.60 (3.11-29.67)</b>	NA	NA	<b>7.81 (1.11-55.05)</b>	NA
≥ 55 years	Ref	1.12 (0.36-3.48)	<b>10.79 (5.41-21.50)</b>	1.36 (0.19-9.94)	NA	NA	NA	<b>8.58 (2.01-36.59)</b>	NA
<b>Pancreatic</b>									
Any age	Ref	0.58 (0.14-2.33)	1.62 (0.40-6.48)	3.03 (0.96-9.53)	1.33 (0.19-9.39)	2.87 (0.41-20.28)	NA	3.19 (0.45-22.57)	NA
< 55 years	Ref	3.99 (0.52-30.34)	NA	NA	NA	<b>34.23 (4.74-246.94)</b>	NA	<b>35.90 (4.48-287.78)</b>	NA
≥ 55 years	Ref	0.31 (0.04-2.23)	1.78 (0.44-7.11)	<b>3.25 (1.03-10.26)</b>	1.45 (0.21-10.22)	NA	NA	NA	NA
<b>Non-breast</b>									
<b>HBOC-related</b>									
Any age	Ref	0.96 (0.70-1.32)	<b>1.65 (1.10-2.46)</b>	1.05 (0.59-1.89)	<b>1.76 (1.04-2.95)</b>	1.95 (0.83-4.57)	0.71 (0.10-4.84)	<b>3.31 (1.96-5.61)</b>	NA
< 50 years	Ref	1.53 (0.68-3.43)	1.45 (0.36-5.86)	2.62 (0.86-7.93)	<b>3.10 (1.02-9.43)</b>	NA	NA	2.52 (0.36-17.48)	NA
≥ 50 years	Ref	0.90 (0.65-1.26)	<b>1.67 (1.09-2.55)</b>	0.88 (0.46-1.67)	1.59 (0.94-2.68)	2.19 (0.92-5.18)	0.79 (0.12-5.41)	<b>3.41 (2.06-5.66)</b>	NA
<b>Any HBOC-related</b>									
Any age	Ref	1.18 (0.94-1.48)	<b>1.59 (1.18-2.15)</b>	1.20 (0.77-1.88)	<b>2.68 (1.92-3.74)</b>	<b>2.11 (1.14-3.91)</b>	1.21 (0.55-2.69)	<b>2.64 (1.72-4.07)</b>	NA
< 50 years	Ref	<b>1.85 (1.11-3.07)</b>	1.87 (0.94-3.71)	<b>2.72 (1.26-5.85)</b>	<b>7.11 (4.32-11.71)</b>	2.25 (0.51-9.98)	NA	1.70 (0.42-6.85)	NA
≥ 50 years	Ref	1.06 (0.83-1.35)	<b>1.54 (1.08-2.18)</b>	0.91 (0.55-1.51)	<b>1.68 (1.10-2.56)</b>	<b>2.08 (1.03-4.20)</b>	1.44 (0.64-3.25)	<b>2.85 (1.85-4.39)</b>	NA
<b>Any non-breast cancer</b>									

Any age	Ref	0.96 (0.81-1.15)	1.22 (0.94-1.59)	1.08 (0.79-1.48)	1.16 (0.83-1.64)	1.44 (0.97-2.11)	0.77 (0.37-1.62)	<b>1.72 (1.15-2.58)</b>	2.69 (0.99-7.25)
< 50 years	Ref	1.09 (0.70-1.68)	1.22 (0.58-2.60)	1.49 (0.72-3.11)	0.88 (0.34-2.28)	1.43 (0.50-4.09)	NA	1.64 (0.42-6.41)	NA
≥ 50 years	Ref	0.94 (0.79-1.13)	1.22 (0.92-1.63)	1.01 (0.71-1.44)	1.22 (0.85-1.75)	1.44 (0.94-2.18)	0.89 (0.42-1.88)	<b>1.74 (1.20-2.52)</b>	<b>3.26 (1.17-9.11)</b>
Any cancer									
Any age	Ref	1.06 (0.90-1.24)	<b>1.29 (1.00-1.65)</b>	1.14 (0.85-1.52)	<b>1.69 (1.32-2.17)</b>	<b>1.61 (1.11-2.33)</b>	0.97 (0.56-1.71)	<b>1.76 (1.26-2.44)</b>	2.16 (0.81-5.79)
< 50 years	Ref	1.36 (0.94-1.95)	1.48 (0.84-2.62)	<b>1.86 (1.03-3.35)</b>	<b>3.36 (2.10-5.39)</b>	2.01 (0.83-4.89)	NA	1.53 (0.49-4.78)	NA
≥ 50 years	Ref	1.00 (0.85-1.19)	1.25 (0.95-1.65)	1.01 (0.73-1.39)	1.33 (0.98-1.80)	1.52 (1.00-2.33)	1.15 (0.64-2.05)	<b>1.81 (1.33-2.45)</b>	2.66 (0.96-7.43)

Abbreviation: PTV = protein-truncating variant; CI = confidence interval; NA= not available; HBOC=Hereditary Breast and Ovarian Cancer syndrome.

Hazard ratios were estimated via Cox regression, adjusted for birth years of relatives, cohort and breast cancer case-control status of index women at study entry. Hazard ratios for any age, cancer-specific early- and late-onset age are shown respectively.

Significant associations ( $P < 0.05$ ) are marked in bold.

<sup>a</sup> PTV absence of index women was defined based on the absence of PTVs of any studied risk gene which included *CHEK2*, *BRCA2*, *ATM*, *BRCA1*, *PALB2*, *BARD1*, *RAD51C* and *RAD51D*.

**Supplementary Table 3. Association (expressed as odds ratios with 95% CI) between cancer diagnoses at multiple sites within families of index women and the presence of protein-truncating variants in risk genes carried by index women.**

Cancer	<i>CHEK2</i>	<i>BRCA2</i>	<i>ATM</i>	<i>BRCA1</i>	<i>PALB2</i>	<i>BARD1</i>	<i>RAD51C</i>	Any risk gene	Non- <i>BRCA</i> risk genes	<i>BRCA1/2</i>
Breast, prostate	<b>2.80 (1.42-5.54)</b>	0.81 (0.11-5.83)	2.14 (0.52-8.83)	<b>4.75 (1.71-13.25)</b>	<b>8.91 (2.65-30.04)</b>	NA	3.44 (0.46-25.83)	<b>2.83 (1.77-4.53)</b>	<b>2.95 (1.73-5.05)</b>	2.40 (0.97-5.93)
Breast, melanoma	1.27 (0.17-9.22)	NA	4.45 (0.60-32.79)	NA	<b>11.50 (1.52-86.81)</b>	NA	NA	1.73 (0.54-5.58)	2.41 (0.75-7.78)	NA
Breast, ovarian	1.82 (0.25-13.40)	<b>15.09 (4.53-50.28)</b>	NA	NA	NA	NA	NA	<b>3.32 (1.17-9.44)</b>	1.15 (0.16-8.43)	<b>8.64 (2.61-28.54)</b>
Breast, pancreatic	NA	NA	NA	NA	<b>20.38 (2.66-156.28)</b>	NA	NA	1.02 (0.14-7.51)	1.41 (0.19-10.45)	NA
Prostate, melanoma	1.32 (0.18-9.65)	NA	4.66 (0.63-34.32)	NA	<b>12.03 (1.59-90.86)</b>	NA	NA	1.81 (0.56-5.84)	2.52 (0.78-8.15)	NA
Prostate, ovarian	2.01 (0.27-14.83)	5.41 (0.73-40.21)	NA	<b>15.38 (3.59-66.00)</b>	NA	NA	NA	<b>3.67 (1.28-10.48)</b>	1.27 (0.17-9.33)	<b>9.53 (2.87-31.66)</b>
Prostate, pancreatic	NA	NA	NA	NA	<b>37.89 (4.79-299.62)</b>	NA	NA	1.89 (0.25-14.41)	2.63 (0.34-20.04)	NA
Melanoma, pancreatic	NA	NA	NA	NA	<b>75.82 (8.98-640.03)</b>	NA	NA	3.78 (0.46-30.81)	5.26 (0.65-42.86)	NA
Breast and another HBOC-related site	<b>2.31 (1.25-4.29)</b>	2.24 (0.82-6.17)	1.43 (0.35-5.89)	<b>3.18 (1.14-8.83)</b>	<b>5.96 (1.77-20.03)</b>	NA	2.30 (0.31-17.25)	<b>2.39 (1.57-3.64)</b>	<b>2.25 (1.36-3.72)</b>	<b>2.63 (1.28-5.42)</b>
Two HBOC-related sites	<b>2.06 (1.17-3.65)</b>	2.12 (0.85-5.28)	1.07 (0.26-4.40)	<b>3.70 (1.58-8.67)</b>	<b>4.46 (1.33-14.97)</b>	NA	1.72 (0.23-12.90)	<b>2.17 (1.48-3.19)</b>	<b>1.90 (1.18-3.04)</b>	<b>2.77 (1.48-5.17)</b>
Breast and any other site	<b>1.75 (1.12-2.73)</b>	<b>2.42 (1.28-4.59)</b>	0.78 (0.24-2.50)	1.77 (0.76-4.13)	<b>3.91 (1.46-10.44)</b>	1.74 (0.40-7.50)	0.82 (0.11-6.16)	<b>1.77 (1.31-2.40)</b>	<b>1.64 (1.14-2.37)</b>	<b>2.14 (1.28-3.58)</b>
Cancer at any two sites	1.12 (0.79-1.58)	1.40 (0.83-2.37)	0.83 (0.41-1.69)	1.55 (0.85-2.83)	1.58 (0.63-3.95)	0.88 (0.26-3.01)	<b>2.69 (1.07-6.74)</b>	1.23 (0.97-1.54)	1.15 (0.88-1.51)	1.47 (0.99-2.18)

Abbreviation: CI = confidence interval; NA= not available; HBOC=Hereditary Breast and Ovarian Cancer syndrome.

Odds ratios of cancer diagnoses of at least 2 sites among relatives were estimated via crude model of logistic regression. Odds ratios were not available for analyses of ovary and pancreas, ovary and melanoma, and *RAD51D* due to no diagnoses at multiple sites among relatives of PTV carriers.

Significant associations ( $P < 0.05$ ) are marked in bold.

**Supplementary Table 4. Hazard ratio (95% CI) of breast cancer and non-breast HBOC-related cancers among relatives by genetic predisposition in index women, stratified by breast cancer case-control status of index women.**

	Breast cancer		Non-breast HBOC-related cancers <sup>d</sup>	
	Women with breast cancer	Breast cancer-free women	Women with breast cancer	Breast cancer-free women
PTV status by the related index women				
No. cancer cases among relatives	1,176	918	1,391	1,445
Non-carriers <sup>a</sup>	Ref	Ref	Ref	Ref
Any risk gene <sup>b</sup>	<b>1.69 (1.31-2.17)</b>	<b>2.31 (1.68-3.18)</b>	<b>1.34 (1.05-1.72)</b>	1.19 (0.83-1.68)
Non- <i>BRCA</i> risk genes	1.31 (0.95-1.80)	<b>2.23 (1.58-3.16)</b>	1.25 (0.91-1.70)	0.99 (0.65-1.51)
<i>BRCA1/2</i>	<b>2.54 (1.75-3.69)</b>	<b>2.91 (1.30-6.54)</b>	<b>1.52 (1.03-2.22)</b>	<b>2.54 (1.49-4.31)</b>
PRS quartiles by the related index women <sup>c</sup>				
No. cancer cases among relatives	1,188	2,709	1,415	4,481
0-25%	Ref	Ref	Ref	Ref
25-50%	1.07 (0.82-1.41)	<b>1.28 (1.13-1.46)</b>	1.05 (0.84-1.32)	0.99 (0.90-1.08)
50-75%	1.17 (0.91-1.50)	<b>1.63 (1.44-1.84)</b>	1.01 (0.81-1.26)	1.09 (1.00-1.19)
75-100%	<b>1.41 (1.12-1.79)</b>	<b>1.98 (1.76-2.23)</b>	1.01 (0.82-1.23)	1.09 (1.00-1.19)
Per SD increase	<b>1.19 (1.12-1.27)</b>	<b>1.32 (1.26-1.37)</b>	1.02 (0.96-1.08)	<b>1.04 (1.01-1.08)</b>

Abbreviation: PTV = protein-truncating variant; PRS = polygenic risk score; HBOC=Hereditary Breast and Ovarian Cancer syndrome.

Hazard ratios were estimated via Cox regression, adjusted for birth years of relatives, cohort and breast cancer case-control status of index women at study entry.

Significant associations ( $P < 0.05$ ) are marked in bold.

<sup>a</sup> Non-carrier status was defined as the absence of PTVs in any studied risk gene, including *CHEK2*, *BRCA2*, *ATM*, *BRCA1*, *PALB2*, *BARD1*, *RAD51C* and *RAD51D*.

<sup>b</sup> Carrier status of any studied risk gene.

<sup>c</sup> PRS quartiles were defined according to breast cancer-free index women at study entry.

<sup>d</sup> Non-breast HBOC-related sites were defined as prostate, skin (melanoma), ovary and pancreas.

**Supplementary Table 5. Hazard ratio (95% CI) of breast cancer and non-breast HBOC-related cancers among relatives by genetic predisposition in index women, followed from 1990.**

	Breast	Non-breast HBOC-related <sup>d</sup>
PTV status by the related index women		
No. cancer cases among relatives	1,268	1,764
Non-carriers <sup>a</sup>	Ref	Ref
Any risk gene <sup>b</sup>	<b>1.76 (1.38-2.25)</b>	1.23 (0.97-1.56)
Non- <i>BRCA</i> risk genes	<b>1.45 (1.07-1.97)</b>	1.12 (0.84-1.50)
<i>BRCA1/2</i>	<b>2.64 (1.79-3.89)</b>	<b>1.56 (1.06-2.28)</b>
PRS quartiles by the related index women <sup>c</sup>		
No. cancer cases among relatives	2,416	3,930
0-25%	Ref	Ref
25-50%	<b>1.20 (1.05-1.38)</b>	1.01 (0.92-1.11)
50-75%	<b>1.43 (1.25-1.63)</b>	<b>1.14 (1.04-1.25)</b>
75-100%	<b>1.81 (1.59-2.05)</b>	1.08 (0.99-1.19)
Per SD increase	<b>1.28 (1.23-1.33)</b>	<b>1.04 (1.01-1.07)</b>

Abbreviation: PTV = protein-truncating variant; PRS = polygenic risk score; HBOC=Hereditary Breast and Ovarian Cancer syndrome.

Hazard ratios were estimated via Cox regression, adjusted for birth years of relatives, cohort and breast cancer case-control status of index women at study entry.

Significant associations ( $P < 0.05$ ) are marked in bold.

<sup>a</sup> Non-carrier status was defined as the absence of PTVs in any studied risk gene, including *CHEK2*, *BRCA2*, *ATM*, *BRCA1*, *PALB2*, *BARD1*, *RAD51C* and *RAD51D*.

<sup>b</sup> Carrier status of any studied risk gene.

<sup>c</sup> PRS quartiles were defined according to breast cancer-free index women at study entry.

<sup>d</sup> Non-breast HBOC-related sites were defined as prostate, skin (melanoma), ovary and pancreas.

**Supplementary Table 6. Hazard ratio of breast cancer and non-breast HBOC-related cancers among cancer-free women at KARMA enrolment.**

	Breast cancer	Non-breast HBOC related cancers <sup>d</sup>
PTV status		
No. breast cancer cases	591	64
Non-carriers <sup>a</sup>	Ref	Ref
Any risk gene <sup>b</sup>	<b>3.24 (2.31-4.54)</b>	1.84 (0.45-7.51)
Non- <i>BRCA</i> risk genes	<b>2.98 (2.05-4.33)</b>	2.08 (0.51-8.50)
<i>BRCA1/2</i>	<b>4.97 (2.34-10.56)</b>	NA
PRS quartiles <sup>c</sup>		
No. breast cancer cases	1,187	201
0-25%	Ref	Ref
25-50%	<b>1.71 (1.39-2.11)</b>	1.39 (0.93-2.07)
50-75%	<b>2.20 (1.80-2.68)</b>	1.25 (0.83-1.89)
75-100%	<b>3.60 (2.99-4.34)</b>	1.36 (0.90-2.04)
Per SD increase	<b>1.59 (1.50-1.68)</b>	1.14 (0.99-1.31)

Abbreviation: PTV = protein-truncating variant; PRS = polygenic risk score.

Hazard ratios were estimated via Cox regression.

Significant associations ( $P < 0.05$ ) are marked in bold.

<sup>a</sup> Non-carrier status was defined as the absence of PTVs in any studied risk gene, including *CHEK2*, *BRCA2*, *ATM*, *BRCA1*, *PALB2*, *BARD1*, *RAD51C* and *RAD51D*.

<sup>b</sup> Carrier status of any studied risk gene.

<sup>c</sup> PRS quartiles were defined according to breast cancer-free index women at study entry.

<sup>d</sup> Non-breast HBOC-related sites were defined as skin (melanoma), ovary and pancreas.

**Supplementary Table 7. Hazard ratio (95% CI) of breast cancer and non-breast HBOC-related cancers among relatives of index women by combined effect of protein-truncating variants and pathogenic missense variants in index women.**

	Breast	Non-breast HBOC-related <sup>d</sup>
Carrier status by the related index women <sup>a</sup>		
No. cancer cases among relatives	2,094	2,836
Non-carriers <sup>b</sup>	Ref	Ref
Any risk gene <sup>c</sup>	<b>1.81 (1.48-2.22)</b>	<b>1.24 (1.01-1.52)</b>
Non- <i>BRCA</i> risk genes	<b>1.56 (1.22-1.99)</b>	1.13 (0.88-1.45)
<i>BRCA1/2</i>	<b>2.48 (1.78-3.45)</b>	<b>1.57 (1.13-2.17)</b>

Abbreviation: PTV = protein-truncating variant; CI = confidence interval; HBOC=Hereditary Breast and Ovarian Cancer syndrome.

Hazard ratios were estimated via Cox regression, adjusted for birth years of relatives, cohort and breast cancer case-control status of index women at study entry.

<sup>a</sup> Overall, 50 pathogenic missense variant carriers were identified (34 carriers in non-*BRCA* risk genes and 16 carriers in *BRCA1/2*). In comparison, 482 PTV carriers were identified (347 carriers in non-*BRCA* risk genes and 141 carriers in *BRCA1/2*)

Significant associations ( $P < 0.05$ ) are marked in bold.

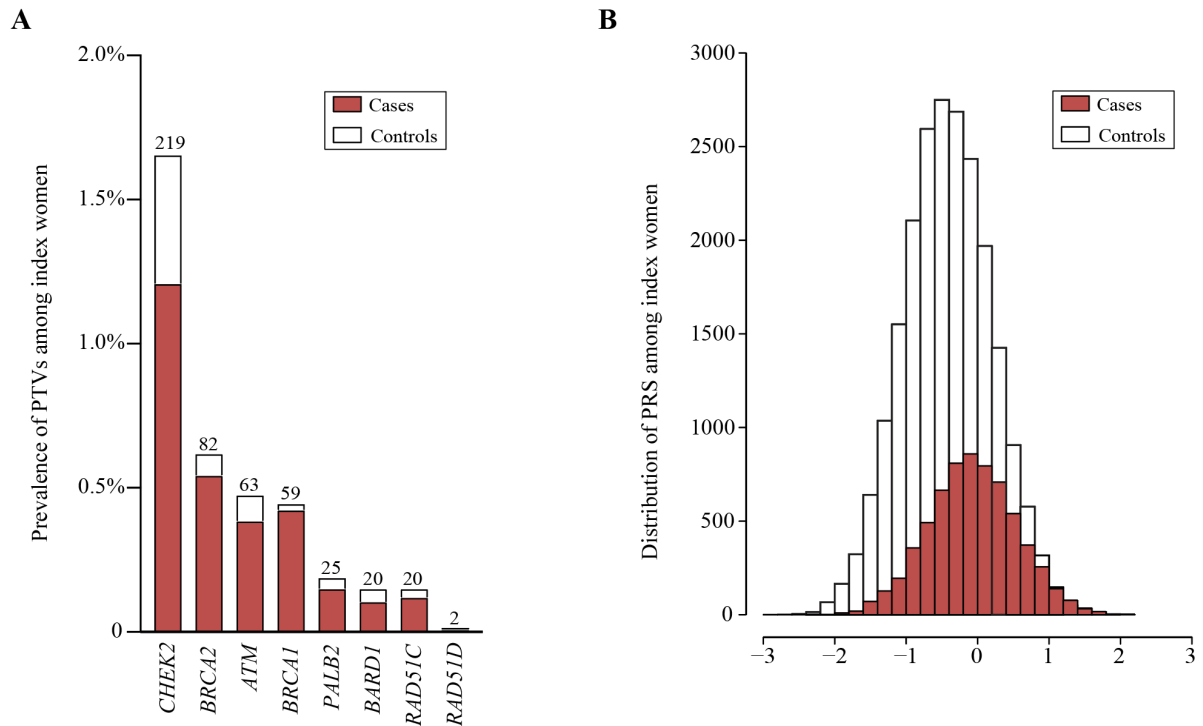
<sup>b</sup> Non-carrier status was defined as the absence of PTVs and pathogenic missense variants in any studied risk gene, including *CHEK2*, *BRCA2*, *ATM*, *BRCA1*, *PALB2*, *BARD1*, *RAD51C* and *RAD51D*.

<sup>c</sup> Carrier status of any studied risk gene.

<sup>d</sup> Non-breast HBOC-related sites were defined as prostate, skin (melanoma), ovary and pancreas.

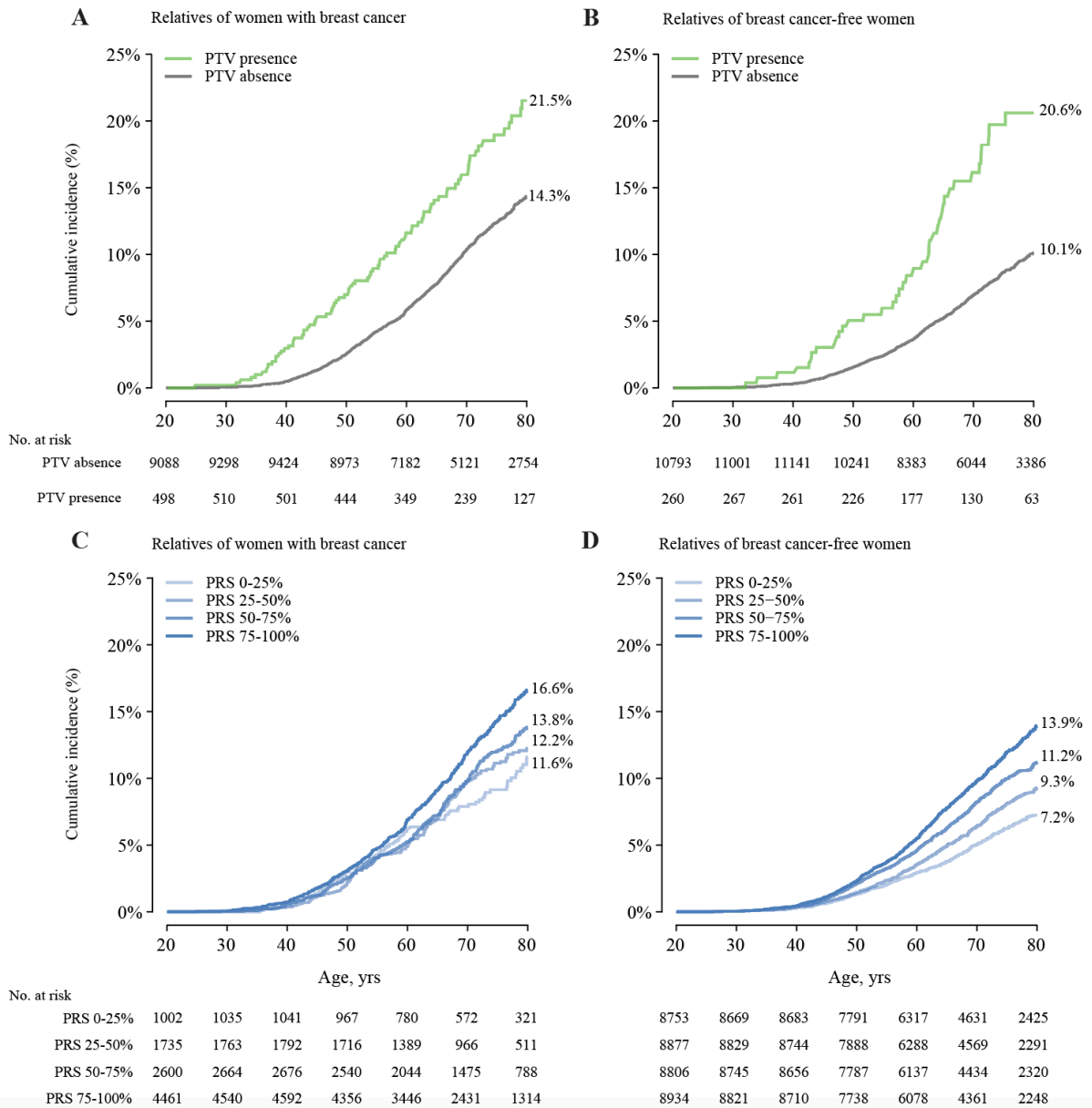


## Supplementary Figure 1



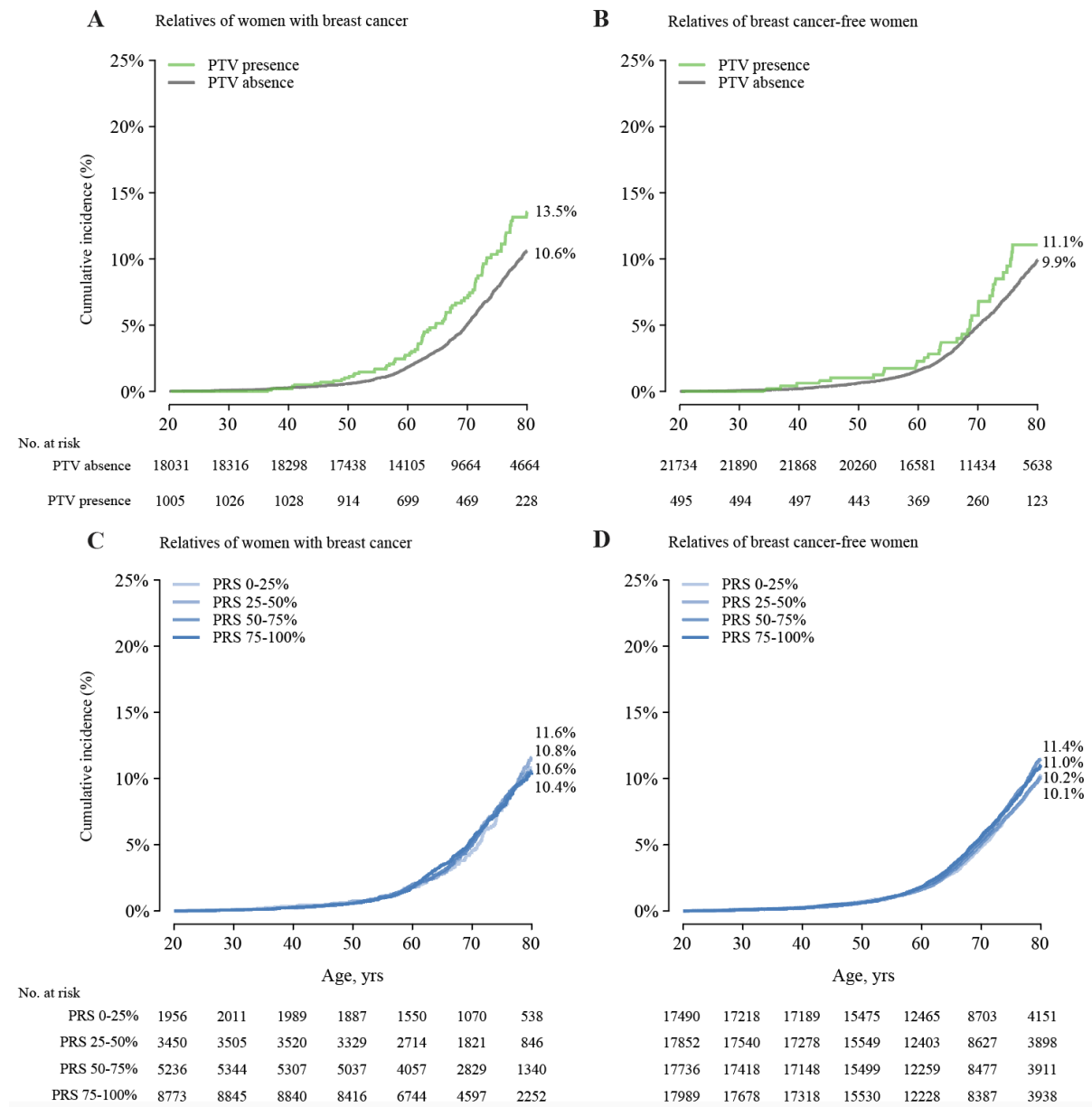
**Supplementary Figure 1. Genetic profile of index women. A** Prevalence of PTVs in index women by risk gene. *TP53* was not presented as PTV carriers were found in our study population. **B** Histogram showing the distribution of PRS of index women. The breast cancer case-control status of index women was defined as the status at study entry.

## Supplementary Figure 2



**Supplementary Figure 2. Cumulative incidence of breast cancer among female relatives stratified by breast cancer case-control status of index women.** Abbreviation: PTV = protein-truncating variant; PRS = polygenic risk score. Cumulative incidence by PTVs (A, B) and PRS (C, D) are shown. Note that number at risk might increase due to delayed study entry of relatives. PTV presence was defined based on the presence of PTVs in any studied risk gene including *CHEK2*, *BRCA2*, *ATM*, *BRCA1*, *PALB2*, *BARD1*, *RAD51C* and *RAD51D*, while PTV absence was defined absence of PTVs in these genes. The PRS quartiles were defined according to breast cancer-free index women at the study entry. The breast cancer case-control status of index women was defined as the status at study entry.

### Supplementary Figure 3



**Supplementary Figure 3. Cumulative incidence of non-breast HBOC-related cancers among relatives stratified by breast cancer case-control status of index women.** Abbreviation: PTV = protein-truncating variant; PRS = polygenic risk score. Cumulative incidence by PTVs (**A**, **B**) and PRS (**C**, **D**) are shown. Note that number at risk might increase due to delayed study entry of relatives. PTV presence was defined based on the presence of PTVs in any studied risk gene including *CHEK2*, *BRCA2*, *ATM*, *BRCA1*, *PALB2*, *BARD1*, *RAD51C* and *RAD51D*, while PTV absence was defined absence of PTVs in these genes. The PRS quartiles were defined according to breast cancer-free index women at the study entry. The breast cancer case-control status of index women was defined as the status at study entry.