JNCI: Journal of the National Cancer Institute, 2024, 116(6), 911–919
https://doi.org/10.1093/jnci/djae030
Advance Access Publication Date: February 14, 2024
Article

Cancer risks among first-degree relatives of women with a genetic predisposition to breast cancer

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Abstract

Background: Associations between germline alterations in women and cancer risks among their relatives are largely unknown.

Methods: We identified women from 2 Swedish cohorts Karolinska Mammography Project for Risk Prediction of Breast Cancer (KARMA) and prevalent KARMA (pKARMA), including 28 362 women with genotyping data and 13 226 with sequencing data. Using Swedish Multi-Generation Register, we linked these women to 133 389 first-degree relatives. Associations between protein-truncating variants in 8 risk genes and breast cancer polygenic risk score in index women and cancer risks among their relatives were modeled via Cox regression.

Results: Female relatives of index women who were protein-truncating variant carriers in any of the 8 risk genes had an increased breast cancer risk compared with those of noncarriers (hazard ratio [HR] = 1.85, 95% confidence interval [CI] = 1.52 to 2.27), with the strongest association found for protein-truncating variants in *BRCA1* and *2*. These relatives had a statistically higher risk of early onset than late-onset breast cancer ($P = .001$). Elevated breast cancer risk was also observed in female relatives of index women with higher polygenic risk score ($HR_{per\ SD} = 1.28$, 95% CI = 1.23 to 1.32). The estimated lifetime risk was 22.3% for female relatives of protein-truncating variant carriers and 14.4% for those related to women in the top polygenic risk score quartile. Moreover, relatives of index women with protein-truncating variant presence (HR = 1.30, 95% CI = 1.06 to 1.59) or higher polygenic risk score ($HR_{per\ SD}$ = 1.04, 95% CI = 1.01 to 1.07) were also at higher risk of nonbreast hereditary breast and ovary cancer syndrome-related cancers.

Conclusions: Protein-truncating variants of risk genes and higher polygenic risk score in index women are associated with an increased risk of breast and other hereditary breast and ovary syndrome–related cancers among relatives.

Female breast cancer became the most diagnosed malignancy worldwide and affected more than 2 million individuals in 2020 (1). Genetic predisposition to breast cancer has been extensively studied. Association analyses using data of more than 113 000 women revealed that protein-truncating variants of *CHEK2*, *BRCA2*, *ATM*, *BRCA1*, *PALB2*, *BARD1*, *RAD51C*, *RAD51D*, and *TP53* were statistically significantly associated with breast cancer risk with large effect sizes (2). In addition, genome-wide association studies have identified more than 200 common risk variants associated with marginally increased breast cancer risk, most of which are not within known risk genes (3). However, the cumulative effect of the common risk variants, summarized as polygenic risk score, has a substantial impact on breast cancer risk (4,5).

Genetic predisposition to breast cancer has also been shown to be associated with other cancers. For instance, *BRCA1* and *2* mutations are causative for hereditary breast and ovary cancers syndrome (6), with *BRCA2* further implicated with an increased risk of melanoma, prostate, and pancreatic cancer (7,8). Similarly, associations have been established between non-*BRCA* breast cancer risk genes and other cancers. For instance, *PALB2* has been implicated in pancreatic and prostate cancer (9,10), whereas *RAD51C* and *D* have been implicated in ovarian cancer (11,12). Similarly, *ATM* mutations are associated with an increased risk of melanoma, prostate, and pancreatic cancer (13-15). Furthermore, meta-analyses of genome-wide association studies have identified shared genetic loci between breast cancer and other types of cancers. For example, rs5013329 and rs9375701 are shared with prostate cancer, while rs200182588 and rs8037137 are shared with ovarian cancer (16).

A few studies have investigated other types of cancer risks among relatives of individuals with genetic predisposition to breast cancer (17-24). However, these studies focused on a few specific genes (mainly *BRCA1* and *2*) and did not consider other risk genes or common risk variants of breast cancer. In addition, the studies were performed using selected populations such as individuals who underwent clinical genetic testing. These limitations may restrict the applicability of these findings to the general population.

With linkage to multiple Swedish national registers, this population-based cohort study aimed to investigate whether the risk of breast cancer and other types of cancer among first-degree relatives of women was associated with a genetic

Received: September 7, 2023. Revised: January 23, 2024. Accepted: February 5, 2024

predisposition to breast cancer. Protein-truncating variants of these established risk genes, *CHEK2*, *BRCA2*, *ATM*, *BRCA1*, *PALB2*, *BARD1*, *RAD51C*, and *RAD51D*, and breast cancer polygenic risk score were considered in this study.

Methods

Study population

The index women were identified from Karolinska Mammography Project for Risk Prediction of Breast Cancer (KARMA) and prevalent KARMA (pKARMA) cohort. KARMA comprises 70 877 women who attended mammography screening or clinical mammography from 2011 to 2013 at 4 hospitals in Sweden (25). pKARMA is a cohort of 5002 invasive breast cancer patients diagnosed between 2001 and 2008 in Stockholm and 5433 breast cancer-free women from KARMA (26). KARMA and pKARMA participants donated blood samples at study enrollment. All breast cancer patients along with randomly selected breast cancer–free women from KARMA and pKARMA were genotyped. This led to a final sample size of 28 362 genotyped women, 13 226 of whom were also sequenced. All index women provided informed consent, and the research was approved by the regional ethical review board in Stockholm, Sweden.

A total of 133 723 first-degree relatives of the index women were first identified from the Swedish Multi-Generation Register (27), which included parents, full siblings, and offspring. After excluding those who died or emigrated before the start of follow-up (age 20 years for the relatives themselves, or January 1, 1958, whichever came later), 133 389 relatives were kept as the study population for further analyses (see Figure 1).

Genetic profile of index women

Blood samples of index women were genotyped using Illumina iCOGS Array or OncoArray as previously described (28,29).

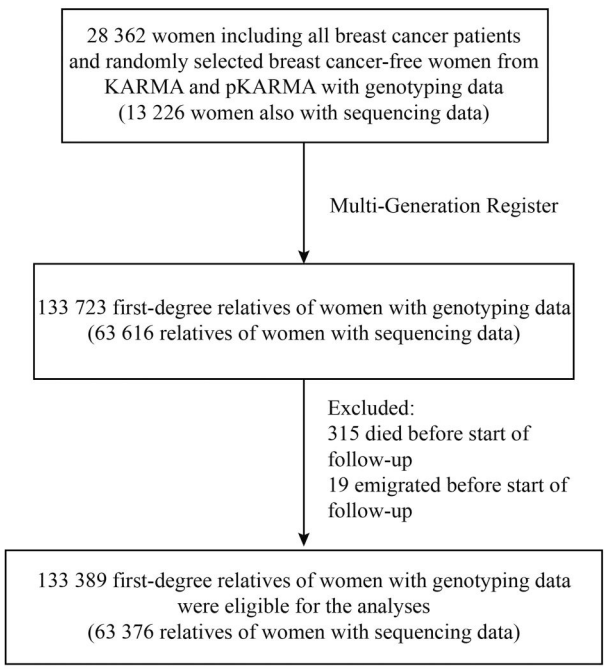

Figure 1. Flowchart of sample attrition and analytical population. First-degree relatives included parents, siblings, and children. Start of follow-up was defined as age 20 years for the relatives or January 1, 1958, whichever came later. KARMA = Karolinska Mammography Project for Risk Prediction of Breast Cancer; pKARMA = prevalent KARMA.

Quality control and imputation were performed by the Breast Cancer Association Consortium (https://bcac.ccge.medschl.cam.ac.uk/). In brief, missing genotypes were imputed using the 1000 Genomes Project phase 3 panel in Genome Reference Consortium Human Build 37 (hg19) coordinates using ShapeIt (30) and IMPUTE (31). Polygenic risk score based on the 313 single-nucleotide polymorphisms was computed using PLINK 2.0 with the weights described by Mavaddat et al. (4,32).

A total of 13 226 index women's blood samples were sequenced using a gene panel that covers coding regions and exon-intron boundaries of known or suspected breast cancer risk genes. The details of sequencing experiments, bioinformatic analyses, and protein-truncating variant definition can be found elsewhere (2,33). Briefly, variants introducing frameshifts, premature stop codons, disruption of transcriptional read frames, or affecting canonical splice sites were regarded as protein-truncating variants, except *BRCA2* stop-gain variant c.9976A > T (K3326X) and other variants located 3' thereof (34). This study focused on protein-truncating variants of the following risk genes: *CHEK2*, *BRCA2*, *ATM*, *BRCA1*, *PALB2*, *BARD1*, *RAD51C*, and *RAD51D* (2).

Missense variants were defined as pathogenic based on annotations of "pathogenic" or "likely pathogenic" in ClinVar (35). For *BRCA1* and 2, pathogenic missense variants were further defined according to the criteria established by an international panel of the Evidence-Based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) consortium (36).

Exposure definition

Carrier status for index women was defined as the presence of a protein-truncating variant in any of the 8 studied risk genes, while noncarrier status was defined as the absence of protein-truncating variants in these genes. The quartiles of polygenic risk score for all index women were determined based on breast cancer–free index women at the time of study entry.

The exposure of relatives was defined as the genetic profile of the related index women. For relatives linked to multiple index women, relatives were preferentially linked to protein-truncating variant–carrying index women to increase power, otherwise to a randomly selected linked index woman.

Outcome definitions

Information on the first cancer diagnosis was retrieved using the *International Classification of Diseases, Seventh Revision* codes from the Swedish Cancer Register. Hereditary breast and ovary syndrome–related cancers included breast cancer, ovarian cancer, prostate cancer, pancreatic cancer, and melanoma. Data on death and migration were extracted from the Swedish Cause of Death Register and the Swedish Migration Register, respectively. Each relative of index women was followed from age 20 years, or January 1, 1958 (starting date of the Swedish Cancer Register), whichever came later, until the earliest record of invasive cancer, emigration, or death, alternatively age 80 years or December 31, 2017, whichever came first.

Statistical analyses

Hazard ratios (HRs) were calculated using the Cox regression model to determine cancer risks among relatives using the R package survival (version 3.2.10). Attained age of the relatives was used as the underlying timescale, and models were adjusted for the birth years of the relatives as well as the study cohort and breast cancer case-control status of the related index women at study entry, with robust standard errors to account for

within-family correlation. To study associations with early and late-onset cancers separately, we split follow-up time into cancer-specific early and late age periods (defined according to literature) (37-41). Wald tests (simple Wald test for protein-truncating variant carrier status, joint Wald test across quartiles for polygenic risk score) were used to assess the statistical significance of differences in (log-) hazard ratios between early and late-onset cancers using the R package car (version 3.1.2). Adjusted cumulative incidence curves were shown after adjusting for breast cancer case-control status of index women using standardized Cox regression using the R package stdReg (version 3.4.1) and plotted via survminer (version 0.4.9). Associations between diagnoses of cancers at multiple sites among relatives and protein-truncating variant carriership in index women were modeled via logistic regression. All analyses were performed in R (version 4.0.5). All *P* values were 2-sided and considered statistically significant when the *P* value was less than .05.

Sensitivity analyses

To examine the robustness of our findings, sensitivity analyses were performed. First, hazard ratios of breast and nonbreast hereditary breast and ovary syndrome–related cancers among relatives by genetic predisposition in index women, stratified by breast cancer case-control status of index women, were calculated. Second, hazard ratios of breast and nonbreast hereditary breast and ovary syndrome–related cancers among relatives were calculated using follow-up during the recent decades (follow-up started from either the age of 20 years or from January 1, 1990, whichever came later). Third, hazard ratios of breast and nonbreast hereditary breast and ovary syndrome–related cancers among cancer-free women at KARMA enrollment were calculated based on these women's protein-truncating variant status and polygenic risk score. Fourth, pathogenic missense variants were included in the gene-based analyses in addition to protein-truncating variants. Carrier status was defined as the presence of a protein-truncating variant or pathogenic missense variant in any of the 8 studied risk genes, and the noncarrier status was defined as the absence of protein-truncating variants and pathogenic missense variants in these genes.

Results

Supplementary Table 1 (available online) shows baseline characteristics of index women with genetic information. Comparability was observed in age, mammographic density, menopausal status, body mass index, and family structure, regardless of the breast cancer case-control status. Table 1 and Supplementary Figure 1 (available online) present the genetic profile of the index women, as well as a summary of the distribution of cancer patients among their relatives, categorized by the index women's genetic predisposition. Of the 482 index women who were protein-truncating variant carriers of any of the 8 risk genes, 79.3% had breast cancer. The proportion of breast cancer patients among carriers ranged from 50.0% for *RAD51D* to 94.9% for *BRCA1*. Among their female relatives, 11.7% had breast cancer, and 22.2% of all first-degree relatives had any type of cancer; 28 362 women had information on polygenic risk score of whom 25.5% were breast cancer patients. In each quartile, 6073 to 8474 women were defined, with the proportion of breast cancer patients increasing from 12.3% in the bottom quartile to 38.2% in the top quartile. For index women in the bottom polygenic risk score quartile, 4% of their female relatives had breast cancer, and 17% of all first-degree relatives had any type of cancer. In contrast, for index women in the top polygenic risk score quartile, 7.7% of their female relatives had breast cancer, and 18.9% of all first-degree relatives had any type of cancer.

Table 2 presents the relative breast cancer risk of female relatives of index women with a genetic predisposition to breast cancer. Female relatives of protein-truncating variant carriers of any studied risk genes were at increased breast cancer risk (HR =

Table 1. Summary statistics of cancer distribution among relatives, stratified by index women's genetic predisposition status

	Index women		Female relatives		All relatives		
Genetic predisposition	No.	Breast cancer patients, No. (%)	No.	Breast cancer patients, No. (%)	No.	Hereditary breast and ovarian cancer syndrome–related cancer patients, No. (%)	Any cancer patients, No. (%)
Protein-truncating variants							
All	13 226	7677 (58.0)	31 754	2094 (6.6)[d]	63 376	4942 (7.8)	12 013 (19.0)
Noncarriers[a]	12 744	7295 (57.2)	30 618	1962 (6.4)	61 132	4685 (7.7)	11 517 (18.8)
Any risk gene[b]	482	382 (79.3)	1140	133 (11.7)[d]	2253	259 (11.5)	501 (22.2)
CHEK2	219	160 (73.1)	530	53 (10.0)	1040	101 (9.7)	209 (20.1)
BRCA2	82	72 (87.8)	189	21 (11.1)	370	44 (11.9)	85 (23.0)
ATM	63	51 (81.0)	149	14 (9.4)	302	28 (9.3)	64 (21.2)
BRCA1	59	56 (94.9)	132	29 (22.0)	256	46 (18.0)	68 (26.6)
PALB2	25	20 (80.0)	55	8 (14.5)	113	17 (15.0)	33 (29.2)
BARD1	20	14 (70.0)	57	7 (12.3)	102	11 (10.8)	22 (21.6)
RAD51C	20	16 (80.0)	45	6 (13.3)	99	18 (18.2)	27 (27.3)
RAD51D	2	1 (50.0)	3	0 (0.0)	8	0 (0.0)	2 (20.0)
Polygenic risk score[c]							
All	28 362	7221 (25.5)	66 288	3897 (5.9)[d]	133 389	9812 (7.4)	24 018 (18.0)
0%-25%	6073	750 (12.3)	14 398	571 (4.0)	28 978	1837 (6.3)	4914 (17.0)
25%-50%	6594	1289 (19.5)	15 662	803 (5.1)	31 554	2165 (6.9)	5653 (17.9)
50%-75%	7216	1937 (26.8)	16 941	1048 (6.2)	34 188	2600 (7.6)	6205 (18.1)
75%-100%	8474	3241 (38.2)	19 902	1528 (7.7)[d]	39 910	3336 (8.4)	7544 (18.9)

[a] Noncarrier status was defined as the absence of protein-truncating variants in any studied risk gene, including *CHEK2*, *BRCA2*, *ATM*, *BRCA1*, *PALB2*, *BARD1*, *RAD51C*, and *RAD51D*.
[b] Carrier status of any studied risk gene.
[c] Polygenic risk score quartiles were defined according to breast cancer–free index women at study entry.
[d] Of breast cancer patients in female relatives, 6.3% (133 of 2094) were linked to protein-truncating variant carriers of any of the studied risk genes, and 39.2% (1528 of 3897) were linked to index women in the top polygenic risk score quartile.

Table 2. Hazard ratio (95% CI) for breast cancer among female relatives by genetic predisposition in index women[a]

Genetic predisposition in index women and No. cancer patients among relatives	All female relatives			Mothers			Siblings and offspring		
	By age at breast cancer diagnosis among relatives			By age at breast cancer diagnosis among relatives			By age at breast cancer diagnosis among relatives		
	Any age	Younger than 50 y	50 y and older	Any age	Younger than 50 y	50 y and older	Any age	Younger than 50 y	50 y and older
Protein-truncating variant status by the related index women									
No. breast cancer patients among relatives	2094	456	1638	1173	142	1031	922	314	608
Noncarriers[b]	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
Any risk gene[c]	**1.85 (1.52 to 2.27)**	**3.00 (2.10 to 4.28)**	**1.49 (1.17 to 1.90)**	**1.99 (1.56 to 2.55)**	**3.79 (2.35 to 6.11)**	**1.68 (1.26 to 2.23)**	**1.71 (1.25 to 2.36)**	**2.56 (1.63 to 4.01)**	1.24 (0.80 to 1.92)
Non-*BRCA* risk genes	**1.59 (1.25 to 2.02)**	**2.08 (1.29 to 3.37)**	**1.44 (1.09 to 1.91)**	**1.78 (1.33 to 2.40)**	**2.56 (1.32 to 4.97)**	**1.65 (1.19 to 2.30)**	1.38 (0.92 to 2.07)	1.84 (0.98 to 3.43)	1.15 (0.68 to 1.94)
BRCA1 and 2	**2.59 (1.84 to 3.63)**	**5.05 (3.03 to 8.41)**	**1.69 (1.10 to 2.59)**	**2.62 (1.76 to 3.91)**	**6.32 (3.37 to 11.86)**	**1.88 (1.14 to 3.10)**	**2.64 (1.60 to 4.38)**	**4.28 (2.26 to 8.12)**	1.44 (0.67 to 3.11)
Polygenic risk score quartiles by the related index women[d]									
No. breast cancer patients among relatives	3897	878	3019	2467	348	2119	1430	530	900
0%-25%	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
25%-50%	**1.26 (1.12 to 1.41)**	1.02 (0.81 to 1.29)	**1.35 (1.18 to 1.54)**	**1.25 (1.08 to 1.45)**	0.90 (0.63 to 1.29)	**1.34 (1.14 to 1.57)**	**1.26 (1.05 to 1.51)**	1.10 (0.82 to 1.49)	**1.36 (1.08 to 1.72)**
50%-75%	**1.54 (1.37 to 1.72)**	**1.40 (1.13 to 1.74)**	**1.58 (1.39 to 1.80)**	**1.55 (1.35 to 1.78)**	1.35 (0.98 to 1.86)	**1.60 (1.37 to 1.86)**	**1.50 (1.26 to 1.80)**	**1.43 (1.08 to 1.90)**	**1.55 (1.24 to 1.95)**
75%-100%	**1.85 (1.66 to 2.06)**	**1.58 (1.28 to 1.95)**	**1.95 (1.73 to 2.21)**	**1.91 (1.67 to 2.18)**	**1.62 (1.18 to 2.21)**	**1.98 (1.71 to 2.29)**	**1.76 (1.48 to 2.09)**	**1.55 (1.18 to 2.03)**	**1.90 (1.53 to 2.36)**
Per SD increase	**1.28 (1.23 to 1.32)**	**1.25 (1.16 to 1.34)**	**1.29 (1.24 to 1.34)**	**1.30 (1.24 to 1.35)**	**1.26 (1.13 to 1.42)**	**1.30 (1.24 to 1.36)**	**1.25 (1.18 to 1.32)**	**1.23 (1.12 to 1.35)**	**1.26 (1.18 to 1.35)**

[a] 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 and early and late-onset age are shown respectively. Statistically significant associations ($P < .05$) are marked in bold. CI = confidence interval.
[b] Noncarrier status was defined as the absence of protein-truncating variants in any studied risk gene, including *CHEK2*, *BRCA2*, *ATM*, *BRCA1*, *PALB2*, *BARD1*, *RAD51C*, and *RAD51D*.
[c] Carrier status of any studied risk gene.
[d] Polygenic risk score quartiles were defined according to breast cancer-free index women at study entry.

1.85, 95% CI = 1.52 to 2.27). Interestingly, the risk was statistically significantly higher for those diagnosed with an early onset breast cancer (HR = 3.00, 95% CI = 2.10 to 4.28) than for those with late-onset breast cancer (HR = 1.49, 95% CI = 1.17 to 1.90; $P = .001$). The magnitude of the increased risks, diagnosed at any age, were comparable for mothers (HR = 1.99, 95% CI = 1.56 to 2.55) and siblings and offspring (HR = 1.71, 95% CI = 1.25 to 2.36). Increased risk was observed in both relatives of *BRCA1* and *2* protein-truncating variant carriers (HR = 2.59, 95% CI = 1.84 to 3.63) and protein-truncating variant carriers of non-*BRCA* risk genes (HR = 1.59, 95% CI = 1.25 to 2.02). When further stratified by individual gene, increased breast cancer risk was seen in relatives of the protein-truncating variant carriers of *CHEK2* (HR = 1.47, 95% CI = 1.10 to 1.98), *BRCA2* (HR = 1.64, 95% CI = 1.04 to 2.59), *BRCA1* (HR = 4.14, 95% CI = 2.61 to 6.58), and *PALB2* (HR = 2.51, 95% CI = 1.13 to 5.57; Supplementary Table 2, available online).

Female relatives of index women with a higher polygenic risk score were at an elevated risk for breast cancer, with a hazard ratio per standard deviation of 1.28 (95% CI = 1.23 to 1.32; Table 2). The effect sizes varied, ranging from 1.26 (95% CI = 1.12 to 1.41) for the second polygenic risk score quartile to 1.85 (95% CI = 1.66 to 2.06) for the top polygenic risk score quartile when compared with the bottom quartile (Table 2). The magnitude of these increased risks was also comparable for mothers and siblings and offspring. No statistically significant difference between risks for early and late-onset breast cancer was observed among relatives of index women in higher polygenic risk score quartiles ($P = .18$).

Table 3 presents the relative risk of different types of cancers among relatives of index women with a genetic predisposition to breast cancer. Relatives of index women with higher polygenic risk score were at a slightly increased risk of nonbreast hereditary breast and ovary syndrome–related cancers ($HR_{per\ SD} = 1.04$, 95% CI = 1.01 to 1.07). For all cancers, relatives of index women with a higher polygenic risk score had a slightly increased risk ($HR_{per\ SD} = 1.05$, 95% CI = 1.04 to 1.07), with the effect size ranging from 1.08 (95% CI = 1.03 to 1.12) for the bottom quartile to 1.13 (95% CI = 1.08 to 1.17) for the top quartile. Relatives of protein-truncating variant carriers of any studied risk genes were at increased risk of nonbreast hereditary breast and ovary syndrome–related cancers (HR = 1.30, 95% CI = 1.06 to 1.59), which may be largely attributed to the association between *BRCA1* and *2* mutation of women and ovarian cancer among women's relatives (HR = 7.05, 95% CI = 4.15 to 11.98). When further stratified by individual gene, statistically significantly higher risks of early onset cancer among relatives of protein-truncating variant carriers of these risk genes were observed: *ATM*-melanoma (HR = 4.97, 95% CI = 1.26 to 19.61), *PALB2*-prostate (HR = 7.77, 95% CI = 1.05 to 57.51), *PALB2*-pancreas (HR = 34.23, 95% CI = 4.74 to 246.94), and *RAD51C*-ovary (HR = 7.81, 95% CI = 1.11 to 55.05) (Supplementary Table 2, available online). Furthermore, we examined the association between carriers of individual genes and the occurrence of multiple types of cancers within families. Among relatives, diagnoses of prostate and pancreatic cancer (odd ratio [OR] = 37.89, 95% CI = 4.79 to 299.62), breast and pancreatic cancer (OR = 20.38, 95% CI = 2.66 to 156.28), and breast and prostate cancer (OR = 8.91, 95% CI = 2.65 to 30.04) were more likely to relate to *PALB2* protein-truncating variant carriers (Supplementary Table 3, available online).

Female relatives of protein-truncating variant carriers of any of the studied risk genes had a breast cancer risk of 22.3% (95% CI = 18.4% to 26.2%) by age 80 years in contrast with 12.0% (95% CI = 10.7% to 13.4%) for relatives of noncarriers (Figure 2, A).

Table 3. Hazard ratio (95% CI) of any cancers among relatives by genetic predisposition in index women[a]

Genetic predisposition in index women and No. cancer patients among relatives	Prostate	Melanoma	Ovarian	Pancreatic	Nonbreast HBOC–related[e]	Any HBOC–related	Any nonbreast cancer	Any cancer
Protein-truncating variant status by the related index women								
No. cancer patients among relatives	1757	539	284	255	2836	4942	9909	12 013
Noncarriers[b]	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
Any risk gene[c]	1.10 (0.85 to 1.44)	0.99 (0.57 to 1.73)	**2.75 (1.76 to 4.31)**	1.36 (0.72 to 2.55)	**1.30 (1.06 to 1.59)**	**1.51 (1.31 to 1.75)**	1.09 (0.97 to 1.23)	**1.22 (1.11 to 1.35)**
Non-*BRCA* risk genes	1.10 (0.81 to 1.49)	1.07 (0.57 to 1.99)	1.42 (0.68 to 2.97)	1.28 (0.60 to 2.71)	1.16 (0.90 to 1.49)	**1.33 (1.11 to 1.59)**	1.05 (0.92 to 1.21)	**1.15 (1.02 to 1.29)**
BRCA1 and *2*	1.06 (0.65 to 1.73)	0.71 (0.23 to 2.21)	**7.05 (4.15 to 11.98)**	1.51 (0.49 to 4.72)	**1.69 (1.23 to 2.32)**	**2.02 (1.60 to 2.54)**	1.20 (0.97 to 1.48)	**1.44 (1.21 to 1.72)**
Polygenic risk score quartiles by the related index women[d]								
No. cancer patients among relatives	3736	1122	520	517	5896	9812	20 106	24 018
0%-25%	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
25%-50%	1.02 (0.92 to 1.14)	0.90 (0.75 to 1.08)	0.92 (0.69 to 1.22)	1.21 (0.91 to 1.62)	1.00 (0.92 to 1.09)	**1.08 (1.01 to 1.16)**	**1.05 (1.00 to 1.10)**	**1.08 (1.03 to 1.12)**
50%-75%	1.11 (1.00 to 1.23)	0.90 (0.75 to 1.08)	1.00 (0.76 to 1.31)	1.29 (0.98 to 1.70)	1.08 (0.99 to 1.17)	**1.22 (1.14 to 1.30)**	1.03 (0.99 to 1.08)	**1.09 (1.05 to 1.14)**
75%-100%	1.09 (0.98 to 1.21)	0.95 (0.80 to 1.14)	1.07 (0.82 to 1.39)	1.14 (0.86 to 1.50)	1.07 (0.99 to 1.16)	**1.32 (1.24 to 1.41)**	1.02 (0.98 to 1.07)	**1.13 (1.08 to 1.17)**
Per SD increase	**1.04 (1.00 to 1.08)**	1.00 (0.93 to 1.06)	1.03 (0.94 to 1.13)	1.07 (0.97 to 1.17)	**1.04 (1.01 to 1.07)**	**1.13 (1.10 to 1.15)**	1.01 (1.00 to 1.03)	**1.05 (1.04 to 1.07)**

[a] 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. Statistically significant associations ($P < .05$) are marked in bold. CI = confidence interval; HBOC = hereditary breast and ovarian cancer syndrome.
[b] Noncarrier status was defined as the absence of protein-truncating variants in any studied risk gene, including *CHEK2*, *BRCA2*, *ATM*, *BRCA1*, *PALB2*, *BARD1*, *RAD51C*, and *RAD51D*.
[c] Carrier status of any studied risk gene.
[d] Polygenic risk score quartiles were defined according to breast cancer–free index women at study entry.
[e] Nonbreast HBOC-related sites were defined as prostate, skin (melanoma), ovary, and pancreas.

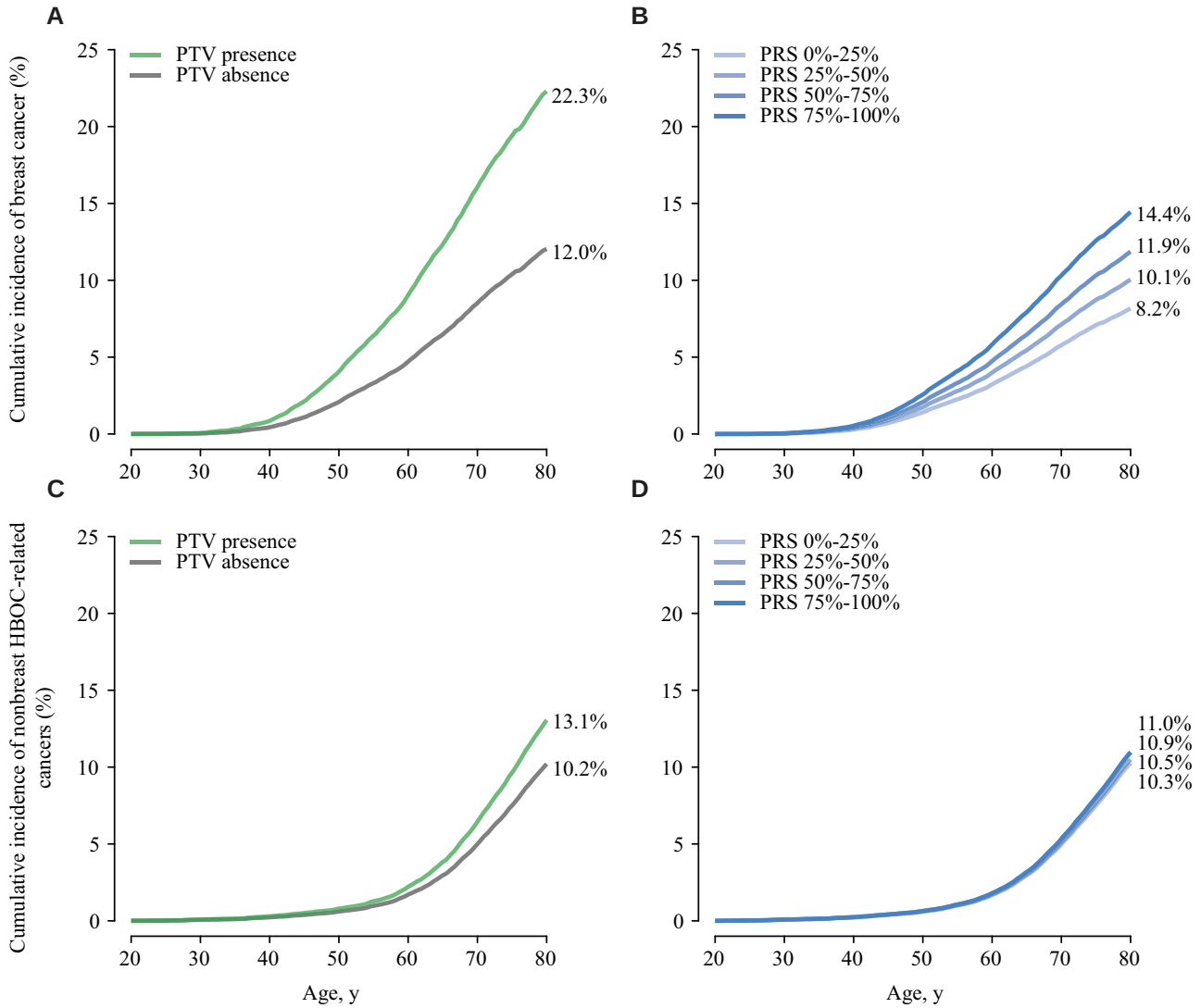

Figure 2. Adjusted cumulative incidence of breast **(A, B)** and nonbreast HBOC-related cancers **(C, D)** among relatives stratified by the germline genetic profile of index women. The adjusted cumulative incidence was estimated using standardized Cox regression, adjusting for the breast cancer case-control status of index women at study entry. PTV presence was defined based on the presence of PTVs in any of the studied risk genes including *CHEK2*, *BRCA2*, *ATM*, *BRCA1*, *PALB2*, *BARD1*, *RAD51C*, and *RAD51D*, while PTV absence was defined as absence of PTVs in these genes. The PRS quartiles were defined according to index women without breast cancer at study entry. HBOC = hereditary breast and ovarian cancer syndrome; PRS = polygenic risk score; PTV = protein-truncating variant.

Similarly, female relatives of index women in higher polygenic risk score quartiles were at an increased risk of breast cancer. Specifically, relatives of index women in the top polygenic risk score quartile had the lifetime risk of 14.4% (95% CI = 10.9% to 18.0%), which was higher than 8.2% (95% CI = 5.6% to 10.8%) for relatives of index women in the bottom polygenic risk score quartile (Figure 2, B). For nonbreast hereditary breast and ovary syndrome–related cancers, relatives of protein-truncating variant carriers of any of the studied risk genes had a risk of 13.1% (95% CI = 10.5% to 15.7%) by age 80 years compared with 10.2% (95% CI = 8.9% to 11.6%) among relatives of noncarriers (Figure 2, C). However, relatives from different polygenic risk score groups had similar risks of hereditary breast and ovary syndrome–related cancers by age 80 years, ranging from 10.3% (95% CI = 7.2% to 13.3%) for the bottom quartile to 11.0% (95% CI = 8.2% to 13.7%) for the top quartile (Figure 2, D).

In the sensitivity analyses, an increased breast cancer risk was seen in relatives of protein-truncating variant carriers in both analyses among relatives of women with breast cancer (HR = 1.69, 95% CI = 1.31 to 2.17) and breast cancer–free women (HR = 2.31, 95% CI = 1.68 to 3.18) (Supplementary Table 4, available online). Among relatives of protein-truncating variant carriers, relatives of women with breast cancer had a lifetime risk of 21.5% in contrast to 20.6% for relatives of breast cancer–free women (Supplementary Figure 2, A and B, available online). An increased breast cancer risk was also observed in relatives of women with a higher polygenic risk score in both analyses among relatives of women with breast cancer (HR = 1.19, 95% CI = 1.12 to 1.27) and of breast cancer–free women (HR = 1.32, 95% CI = 1.26 to 1.37). When stratified by breast cancer case-control status of index women, relatives of women with breast cancer had a lifetime breast cancer risk ranging from 11.6% to 16.6% across polygenic risk score quartiles in contrast to 7.2% to 13.9% for relatives of breast cancer–free women (Supplementary Figure 2, C and D, available online). In contrast, less pronounced increased risks of nonbreast hereditary breast and ovary syndrome–related cancers were observed among relatives of index women with a genetic predisposition, regardless of breast cancer

case-control status (Supplementary Table 4; Supplementary Figure 3, available online).

In the sensitivity analyses of cancer risks in recent decades (relatives were followed from 1990) (Supplementary Table 5, available online), a similarly increased breast cancer risk was observed among female relatives of both protein-truncating variant carriers (HR = 1.76, 95% CI = 1.38 to 2.25) and women with a higher polygenic risk score ($HR_{per\ SD}$ = 1.28, 95% CI = 1.23 to 1.33) in comparison with those reported in Table 2.

In the sensitivity analyses among cancer-free women at KARMA enrollment, an increased breast cancer risk was observed among women carrying protein-truncating variants (HR = 3.24, 95% CI = 2.31 to 4.54) and women with a higher polygenic risk score ($HR_{per\ SD}$ = 1.59, 95% CI = 1.50 to 1.68) (Supplementary Table 6, available online), substantially higher than those reported among relatives in Table 2.

In the sensitivity analyses including pathogenic missense variants, similar risk estimates were observed for breast cancer (HR = 1.81, 95% CI = 1.48 to 2.22) and nonbreast hereditary breast and ovary syndrome–related cancers (HR = 1.24, 95% CI = 1.01 to 1.52) among relatives of risk gene variant carriers (Supplementary Table 7, available online) as compared with those reported in Tables 2 and 3.

Discussion

In this population-based cohort study, leveraging data from 133 389 first-degree relatives of 28 362 index women, we found female relatives of index women who had protein-truncating variants in any of the risk genes or a higher polygenic risk score were at increased breast cancer risk. Additionally, we found that relatives of protein-truncating variant carriers of any of the risk genes were at a modestly increased risk of nonbreast hereditary breast and ovary syndrome–related cancers, whereas relatives of index women with a higher polygenic risk score were at a slightly increased risk of nonhereditary breast and ovary syndrome–related cancers. The increased cancer risk in the relatives of KARMA women with germline alterations was substantially lower than the risk among KARMA women, which reflects that first-degree relatives share on average 50% genetics.

For the protein-truncating variant analyses, we focused on risk genes whose protein-truncating variants were statistically significantly associated with breast cancer risk among carriers, as determined by a study using data from more than 113 000 women (2). As expected, breast cancer risk was highest among female relatives of *BRCA1* and 2 protein-truncating variant carriers. We also observed a notably increased risk among relatives of protein-truncating variant carriers of other risk genes, which aligns with the effect sizes reported in carriers (2). The association of *BRCA1* and 2 protein-truncating variants was statistically more significant in the analysis for early onset breast cancer and weaker, but still significant, in the analysis for late-onset breast cancer. This finding suggests that the age-specific effects of protein-truncating variants on breast cancer risk observed in index women also apply to their female relatives (2). When studying the protein-truncating variant of *BRCA1* and *BRCA2* separately, we found that presence of *BRCA1* protein-truncating variant in index women was statistically significantly associated with early and late-onset breast cancer risks among relatives. No statistically significant associations with early or late-onset breast cancer risks were found for protein-truncating variants of *BRCA2*, which agrees with the observed larger impact of *BRCA1* mutations on breast cancer risk (2,42). Moreover, we also found that female relatives of protein-truncating variant carriers of other risk genes were at a higher breast cancer risk, a finding that, to our knowledge, has not been revealed previously.

In addition, this study is the first to investigate the lifetime risk of breast and other cancers among the relatives of women with breast cancer polygenic risk score. Our results demonstrated that polygenic risk score of index women was positively associated with increased breast cancer risk among female relatives, without any evidence of a statistically significant age-specific effect.

We also provided breast cancer risk estimates for relatives based on the protein-truncating variant status and polygenic risk score quartile of index women. Female relatives of protein-truncating variant carriers of any of the studied genes had a cumulative breast cancer incidence of 22.3% by age 80 years. In addition, relatives of index women in the top polygenic risk score quartiles had a cumulative breast cancer incidence of 14.4%. Both estimates are higher than the 10.1% reported for the general Swedish population (43). In addition, given that 39.2% of breast cancer patients in female relatives were related to index women in the top polygenic risk score quartile, while only 6.3% were related to protein-truncating variant carriers, our results suggest that considering the polygenic risk score of index women may be more effective for identifying relatives at increased risk for breast cancer than considering only variants of risk genes in a population setting.

Germline mutations in *BRCA1* and 2 predispose carriers to hereditary breast and ovary syndrome–related cancers, including melanoma, pancreatic, ovarian, and prostate cancer among high-risk groups (7,44,45). In our population-based study, relatives of *BRCA1* and 2 protein-truncating variant carriers were at an increased risk of ovarian cancer. This finding aligns with those previously reported among pedigrees of *BRCA1* and 2 mutation carriers (18). In contrast, we did not find an elevated risk of prostate cancer among male relatives of *BRCA2* protein-truncating variant carriers, despite *BRCA2* having been implicated in prostate cancer (7). This discrepancy might be attributed to the protein-truncating variants located within the ovarian cancer cluster region of *BRCA2* covered by our sequencing regions, which confers a limited increased risk of prostate cancer among carriers (46). In addition, we found several statistically significant associations between protein-truncating variants and early onset cancer risks among relatives, such as *ATM*-melanoma, *PALB2*-pancreas, and *PALB2*-prostate, corroborating gene-cancer associations previously reported in case-control or family-based studies (47-49).

When we examined the association of protein-truncating variant carriers and cancer aggregation within families (multiple types of cancers in 1 family), we found that carriership of *PALB2* protein-truncating variant in index women was associated with multiple diagnoses of hereditary breast and ovary syndrome–related cancers. These results were consistent with previous studies identifying *PALB2* as a breast and pancreatic cancer susceptibility gene (2,9,49). Taken together, *PALB2* might be another key gene that facilitates the clustering of these cancers within families and warrants further research.

The major strength of this study lies in the large number of women for whom we had genotype and sequence data, as well as the linkage to multiple Swedish national registers. Through this linkage, we were able to identify first-degree relatives with a long and virtually complete follow-up, which represents a substantial advantage over family-based studies. Our findings are generalizable to countries where the populations have a similar genetic

background to the Swedish population and where similar mammographic screening programs are in place. The main limitation is the restricted statistical power for protein-truncating variant analyses of individual gene as well as the pathogenic missense variant analyses due to the low frequency of protein-truncating variant carriers, particularly for less common cancers like melanoma and pancreatic cancer.

In summary, our study demonstrated that relatives of women with protein-truncating variants in any of the 8 studied risk genes, or those with a higher breast cancer polygenic risk score, are at elevated risk for both breast and other hereditary breast and ovary syndrome–related cancers at the population level. Our results suggest that rare genetic predispositions to breast cancer, beyond *BRCA1* and 2—such as *PALB2*—have the potential to be informative for cancer aggregation in families. Moreover, our findings indicate that relatives of women who either carry these rare mutations or have a high breast cancer polygenic risk score could benefit from increased awareness because of their elevated cancer risk.

Data availability

Access to phenotypes, biospecimens, and genotypes from the KARMA study can be requested from https://karmastudy.org/data-access/. Access to the pKARMA phenotypes and genotypes is restricted because of institutional review board requirements, but data can be shared upon reasonable request to the principal investigator of pKARMA (Kamila Czene).

Author contributions

Qingyang Xiao, PhD (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Visualization; Writing—original draft; Writing—review & editing), Xinhe Mao, MD, MSc (Data curation; Investigation; Methodology; Writing—review & editing), Alexander Ploner, PhD (Investigation; Methodology; Software; Visualization; Writing—review & editing), Felix Grassmann, PhD (Data curation; Investigation; Software; Writing—review & editing), Juan Rodriguez, PhD (Data curation; Investigation; Writing—review & editing), Mikael Eriksson, PhD (Investigation; Writing—review & editing), Per Hall, MD, PhD (Funding acquisition; Investigation; Project administration; Resources; Writing—review & editing), and Kamila Czene, PhD (Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Writing—review & editing).

Funding

This work was supported by the Swedish Research Council (Grant 2022-00584), the Swedish Cancer Society (Grants 22 2207 and 19 0267), and the Stockholm County Council (Grant 20200102). XM was supported by the China Scholarship Council (grant number: 201806210002).

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgement

The funding sources had no role in study design; data collection, analysis, or interpretation; or the decision to approve publication of the finished manuscript.

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JNCI: Journal of the National Cancer Institute, 2024, 116, 911–919
https://doi.org/10.1093/jnci/djae030
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