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Research article

Breast cancer risk associated with *BRCA1* and *BRCA2* pathogenic variants in the Eastern Chinese population

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HIGHLIGHTS

- The study investigated breast cancer gene 1/2 *(BRCA1/2)* mutation penetrance in the Eastern Chinese population.
- Of the 2216 breast cancer probands, 109 (4.90%) carried *BRCA1/2* mutations.
- Penetrance of breast cancer was 22.50% and 18.20% in *BRCA1* and *BRCA2* carriers, respectively.
- The results suggest prophylactic mastectomy may not be necessary for *BRCA1/2* carriers.
- The findings provide new insights for breast cancer prevention in Chinese patients who are *BRCA1/2* mutation carriers.

GRAPHICAL ABSTRACT

Breast cancer risk associated with *BRCA1* and *BRCA2* pathogenic variants in the Eastern Chinese population. Lower penetrance of breast cancer in Chinese individuals carrying these mutations was observed compared to that in Western populations. *BRCA:* Breast cancer gene

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ABSTRACT

Background: Population-based penetrance studies of breast cancer gene 1/2 (*BRCA1/2*) pathogenic or likely pathogenic (P/LP) variants in the Eastern Chinese population are currently lacking; thus, we aimed to investigate the penetrance of breast cancer and other malignant tumors among BRCA1/2 P/LP variant carriers using a population-based breast cancer cohort from communities in Eastern China.

Methods: Between July 2019 and March 2021, we tested 2216 breast cancer probands from Chinese communities for *BRCA1/2* mutations and collected detailed information on the age, survival status, and malignancy history of first-degree relatives. The kin-cohort method was used to calculate the penetrance of breast cancer and other malignant tumors.

Results: Of the 2216 breast cancer probands, 109 (4.90%) carried *BRCA1/2* P/LP variants, 49 in the *BRCA1* gene and 60 in the *BRCA2* gene. The penetrance of female breast cancer by 85 years of age was 22.50% and 18.20% in *BRCA1* and *BRCA2* P/LP variant carriers, respectively. The penetrance of ovarian cancer by 85 years of age was 26.00% in *BRCA1* P/LP variant carriers. The penetrance of other malignancies did not reach statistical significance owing to the small number of events.

Conclusions: Our findings showed that breast cancer penetrance among *BRCA1* and *BRCA2* P/LP variant carriers was 22.50% and 18.20%, respectively, which suggests that prophylactic mastectomy may not be necessary for such Chinese individuals.

Trial registration: ClinicalTrials.gov; https://clinicaltrials.gov/ct2/show/NCT04265937.

Introduction

Germline pathogenic or likely pathogenic (P/LP) variants of the tumor suppressor genes *BRCA1* and *BRCA2* have been recognized as genetic susceptibility factors for breast cancer.[1] These genes play vital roles in DNA repair and maintenance of genomic stability, and the presence of P/LP variants in *BRCA1/2* significantly increases the lifetime risk of developing breast cancer.[2–5] Therefore, an accurate estimation of breast cancer penetrance in individuals carrying *BRCA1/2* P/LP variants is essential for guiding preventive measures and clinical interventions.[6]

Previous studies conducted in Western populations have shown that the cumulative risk of breast cancer by the age of 70 years in breast cancer gene 1/2 (*BRCA1/2)* P/LP variant carriers ranges from 40 to 65%.[2–5] However, risk estimates can vary across studies owing to differences in study populations, sampling schemes, and statistical methods.[7] The high cumulative lifetime risk of breast cancer in individuals carrying *BRCA1/2* P/LP variants has prompted aggressive approaches to breast cancer prevention, including bilateral prophylactic mastectomy, highlighting the importance of accurate penetrance estimation.[6]

Despite a comparatively lower burden of breast cancer in China than in developed nations, there has been a notable increase in both the incidence and mortality rates of the disease over the past decade.[8] Large-scale studies focusing on *BRCA1/2* P/LP variants have been conducted in the Chinese populations [9–12] but only two studies have investigated the penetrance of these variants.[13,14] Both studies used the kin-cohort statistical method and included participants from hereditary breast cancer family registries or consecutive patients with breast cancer in hospitals. The cumulative lifetime breast cancer risk among carriers of *BRCA1/2* P/LP variants in the Chinese population ranged from 36.5 to 53.7%.[13,14]

Owing to the typically more severe condition of patients, hospital-based studies show biases that result in overestimated disease prevalence, severity, and treatment effects, leading to a higher observed penetrance than that in community-based studies.[15] Population-based penetrance studies of *BRCA1/2* P/LP variants in China are currently lacking. The Screening of Genetic Susceptibility Genes for Breast Cancer Patients and Establishment of High-Risk Populations in Chinese Communities, also known as the SIGHT study, aims to recruit population-based breast cancer survivors in Jiangsu, Zhejiang, and Shanghai in Eastern China to estimate the penetrance of breast cancer and other malignant tumors in carriers of *BRCA1/2* P/LP variants.[16] Hence, this study aimed to investigate the penetrance of breast cancer and other malignant tumors among *BRCA1/2* P/LP variant carriers using a population-based breast cancer cohort from communities in Eastern China.

Methods

Study cohort

The SIGHT study aimed to recruit female breast cancer survivors residing in the Jiangsu Province, Zhejiang Province, and Shanghai Municipality. To identify and inform eligible participants, the study team utilized various sources, including the local Center for Disease Control and Prevention (CDC), community health service centers, and patient anticancer clubs. All female breast cancer survivors in the communities were contacted via phone and letters. On the day of sampling, the study team collected clinical data, genetic information, family history, and blood samples. The information of first-degree relatives was recorded in detail, and a detailed pedigree was drawn for those with a family history of malignancy. In cases in which two or more participants belonged to the same family and shared a blood relationship, only the first participant was included [Figure 1]. The detailed study protocol is found in our published article.[16]

A total of 3520 female breast cancer survivors were notified during the study period, of which 2251 patients agreed to participate and had their clinical data and blood samples collected. Four participants were excluded because of incomplete data collection, and an additional 31 patients were excluded because of their blood relationships with the enrolled proband. A total of 2216 probands were included in the final data analysis, resulting in an overall participation rate of 63.0% compared with the total number of breast cancer survivors in the communities, as reported by the local CDC. Table 1 provides detailed information on the comparison of the enrolled patients with breast cancer in this study with all patients in the communities.

BRCA1 and BRCA2 analysis

Sample preparation and next-generation sequencing were conducted at the Shanghai AITA Biomedical Research Institute following a previously published protocol.[16]

Statistical analysis

Statistical analyses were conducted to estimate the penetrance of breast cancer and other common malignant tumors in individuals carrying *BRCA1/2* P/LP variants. The kin-cohort method, based on Mendelian inheritance patterns, regardless of genetic testing results, was used to estimate the cumulative risk of disease in carrier and non-carrier kin. Age at onset served as the time variable, and time was censored at the age

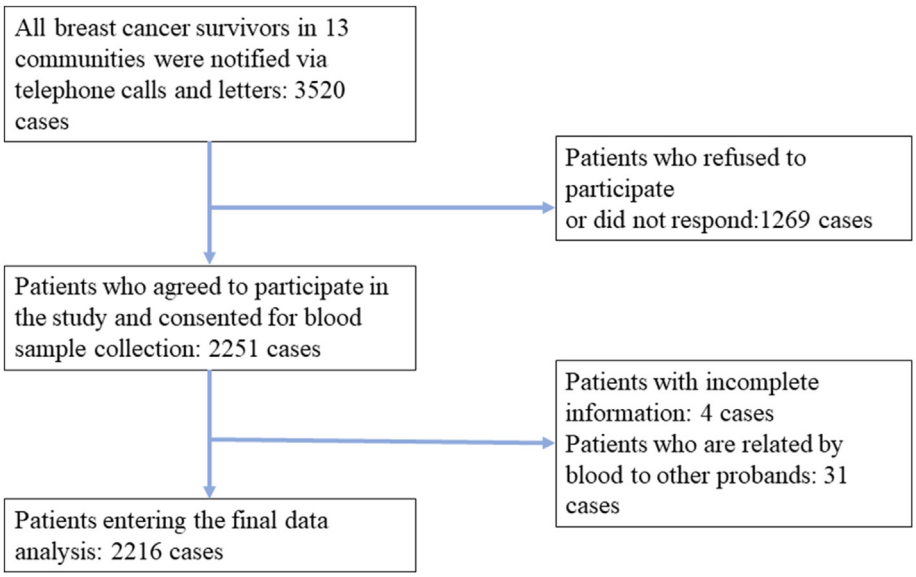

Figure 1. Flowchart illustrating the recruitment of patients with breast cancer.

of last contact or death for disease-free individuals. Participants with missing data were excluded from the analysis. Bootstrap methods were used to calculate 95% confidence intervals (CIs) through 1000 random samplings of the data, with the family as the unit of analysis. The cumulative risk ratio was used to compare the penetrance of *BRCA1/2* P/LP variant carriers and non-carriers of different ages. Age knots were set at 20 years, with intervals of 5 years, up to 85 years. A statistically significant 95% CI of the cumulative risk ratio was calculated, excluding a null value of one. The statistical analysis was performed using the R software and t and the previously established kin-cohort package (version 0.7-2015).[17,18]

Results

This study was conducted in the Eastern Chinese population and included 2216 breast cancer probands, with 109 *BRCA1/2* P/LP variants identified (4.90%). Of the total, 49 and 60 probands had *BRCA1* and *BRCA2* variants, respectively [Table 2]. The mean age at onset for the probands without *BRCA1/2* P/LP variants was 52 years. For probands with *BRCA1* mutations, the mean age at onset was 45 years, whereas probands with *BRCA2* mutations exhibited a mean age at onset of 48 years [Figure 2]. The study also included 13,957 first-degree relatives, including 7138 males and 6819 females. Of these, 280 first-degree relatives were identified as *BRCA1* P/LP variant carriers, including 146 males and 134 females, while 354 first-degree relatives were identified as *BRCA2* P/LP variant carriers, including 189 males and 165 females.

Among first-degree relatives, 160 female breast cancer cases were observed. Specifically, there were nine cases in *BRCA1* families, 11 cases in *BRCA2* families, and 140 cases in non-carrier families. Additionally, there were 24 cases of ovarian cancer in first-degree relatives, with seven cases in *BRCA1* families, one case in *BRCA2* families, and 16 cases in non-carrier families [Table 3].

Using the kin-cohort method, we estimated that the penetrance of female breast cancer by the age of 85 years was 22.50% (cumulative risk ratio: 4.02, 95% CI: 1.56–7.56) for *BRCA1* P/LP variant carriers and 18.20% (cumulative risk ratio: 3.21, 95% CI: 1.35–5.72) for *BRCA2* P/LP variant carriers. For *BRCA1* P/LP variant carriers, the penetrance of ovarian cancer by the age of 85 years was 26.00% (cumulative risk ratio: 44.65, 95% CI: 9.98–202.49), but the penetrance of ovarian cancer in *BRCA2* P/LP variant carriers did not reach statistical significance because of the small number of events. For noncarriers, the penetrance of breast and ovarian cancer was 5.70% and 0.50%, respectively. These rates were similar to the cumulative incidence of breast and ovarian cancers among Shanghai residents aged 85 years in 2016 (breast cancer, 4.60%; ovarian cancer, 0.70%) [Table 3].[19]

Owing to the limited number of events, statistical significance could not be determined for the penetrance of the other nine common malignancies in *BRCA1/2* P/LP variant carriers. However, the penetrance rates of these nine common malignancies in non-carriers were relatively close to the cumulative incidence in Shanghai residents aged 85 years in 2016 [Table 3].[19]

Table 4 displays the changes in breast cancer penetrance among *BRCA1/2* P/LP variant carriers by age. For *BRCA1* P/LP variant carriers, breast cancer penetrance increased from 1.90% at 35 years to 22.50% at 85 years, while for *BRCA2* P/LP variant carriers, it increased from 1.60% at 35 years to 18.20% at 85 years. Compared to non-carriers, the most

Table 1
The comparison between the data of breast cancer survivors recruited from this study and the data of all breast cancer survivors in the communities provided by local CDC.

Patient's area (municipality/province)	Breast cancer survivors in this study[a]			Breast cancer survivors registered by local CDC[b]			Participation rate in this study, %
	No. of case	Proportion of patients by age of on set, %		No. of case	Proportion of patients by age of on set, %		
		<50 years	≥50 years		<50 years	≥50 years	
Shanghai	689	33.2	66.8	1085	38.8	61.2	63.5
Jiangsu	470	52.6	47.4	846	37.1	62.9	55.6
Zhejiang	1057	47.9	52.1	1589	36.2	63.8	66.5
Total	2216	44.2	55.8	3520	37.1	62.9	63.0

[a] The time of recruitment is from July 2019 to March 2021; [b] The time cut-off point for breast cancer survivors data provided by local CDC is June 2021. CDC: Center for Disease Control and Prevention.

Table 2
The P/LP variants of *BRCA1/2* gene found in this study.

BRCA1			*BRCA2*		
Age of onset (years)	Mutation	Origin of patient	Age of onset (years)	Mutation	Origin of patient
41	*BRCA1 c.894delT*	Shanghai Municipality	39	*BRCA2 c.37G>T*	Jiangsu Province
51	*BRCA1 c.894delT*	Shanghai Municipality	54	*BRCA2 c.37G>T*	Jiangsu Province
36	*BRCA1 c.869delT*	Zhejiang Province	62	*BRCA2 c.262–263delCT*	Shanghai Municipality
36	*BRCA1 c.981–982delAT*	Zhejiang Province	39	*BRCA2 c.433dupG*	Zhejiang Province
27	*BRCA1 c.1132delA*	Zhejiang Province	51	*BRCA2 c.439C>T*	Jiangsu Province
43	*BRCA1 c.1132delA*	Zhejiang Province	68	*BRCA2 c.470–474delAGTCA*	Jiangsu Province
43	*BRCA1 c.1132delA*	Zhejiang Province	56	*BRCA2 c.470–474delAGTCA*	Jiangsu Province
47	*BRCA1 c.1252G>T*	Jiangsu Province	46	*BRCA2 c.470–474delAGTCA*	Jiangsu Province
59	*BRCA1 c.1252G>T*	Jiangsu Province	42	*BRCA2 c.771–775delTCAAA*	Jiangsu Province
50	*BRCA1 c.1252G>T*	Jiangsu Province	42	*BRCA2 c.1055dupA*	Zhejiang Province
47	*BRCA1 c.1252G>T*	Jiangsu Province	42	*BRCA2 c.1465–1471delTCTGGAA*	Zhejiang Province
41	*BRCA1 c.1608delT*	Jiangsu Province	51	*BRCA2 c.2471T>G*	Shanghai Municipality
51	*BRCA1 c.1608delT*	Jiangsu Province	51	*BRCA2 c.2514dupA*	Zhejiang Province
44	*BRCA1 c.1953–1956delGAAA*	Zhejiang Province	73	*BRCA2 c.2657dupA*	Shanghai Municipality
43	*BRCA1 c.1961dupA*	Jiangsu Province	50	*BRCA2 c.2845delT*	Shanghai Municipality
53	*BRCA1 c.2090–2091delTC*	Jiangsu Province	56	*BRCA2 c.2845delT*	Shanghai Municipality
33	*BRCA1 c.2110–2111delAA*	Zhejiang Province	42	*BRCA2 c.2845delT*	Shanghai Municipality
38	*BRCA1 c.2110–2111delAA*	Zhejiang Province	51	*BRCA2 c.2845delT*	Shanghai Municipality
42	*BRCA1 c.2217dupA*	Zhejiang Province	48	*BRCA2 c.3109C>T*	Jiangsu Province
38	*BRCA1 c.2740G>T*	Jiangsu Province	54	*BRCA2 c.3109C>T*	Jiangsu Province
49	*BRCA1 c.2866–2870delTCTCA*	Zhejiang Province	35	*BRCA2 c.3109C>T*	Jiangsu Province
46	*BRCA1 c.3329delA*	Zhejiang Province	62	*BRCA2 c.3189–3192delGTCA*	Zhejiang Province
58	*BRCA1 c.3329dupA*	Shanghai Municipality	34	*BRCA2 c.3189–3192delGTCA*	Zhejiang Province
54	*BRCA1 c.3359–3363delTTAAT*	Zhejiang Province	50	*BRCA2 c.3256dupA*	Shanghai Municipality
40	*BRCA1 c.3607C>T*	Zhejiang Province	53	*BRCA2 c.3256dupA*	Shanghai Municipality
45	*BRCA1 c.3607C>T*	Jiangsu Province	43	*BRCA2 c.3365delG*	Shanghai Municipality
38	*BRCA1 c.3607C>T*	Jiangsu Province	39	*BRCA2 c.3365delG*	Shanghai Municipality
44	*BRCA1 c.3770–3771delAG*	Zhejiang Province	49	*BRCA2 c.3599–3600delGT*	Jiangsu Province
40	*BRCA1 c.3959delC*	Zhejiang Province	46	*BRCA2 c.3865–3868delAAAT*	Zhejiang Province
54	*BRCA1 c.4065–4068delTCAA*	Zhejiang Province	33	*BRCA2 c.5351dupA*	Jiangsu Province
40	*BRCA1 c.4228delG*	Zhejiang Province	56	*BRCA2 c.5576–5579delTTAA*	Shanghai Municipality
35	*BRCA1 c.4293delC*	Jiangsu Province	55	*BRCA2 c.5682C>G*	Shanghai Municipality
44	*BRCA1 c.4362–4386del25*	Zhejiang Province	43	*BRCA2 c.5682C>G*	Zhejiang Province
49	*BRCA1 c.4819G>T*	Jiangsu Province	38	*BRCA2 c.5682C>G*	Zhejiang Province
46	*BRCA1 c.5138-1G>T*	Shanghai Municipality	664	*BRCA2 c.5682C>G*	Zhejiang Province
38	*BRCA1 c.5154G>A*	Jiangsu Province	52	*BRCA2 c.5682C>G*	Zhejiang Province
49	*BRCA1 c.5154G>A*	Jiangsu Province	53	*BRCA2 c.6205–6206delTT*	Shanghai Municipality
42	*BRCA1 c.5154G>A*	Jiangsu Province	45	*BRCA2 c.6302dupA*	Jiangsu Province
63	*BRCA1 c.5215+2dupT*	Shanghai Municipality	44	*BRCA2 c.6405–6409delCTTAA*	Jiangsu Province
44	*BRCA1 c.5215+2dupT*	Shanghai Municipality	37	*BRCA2 c.6547delG*	Jiangsu Province
51	*BRCA1 c.5216-2delA*	Shanghai Municipality	38	*BRCA2 c.6547delG*	Jiangsu Province
35	*BRCA1 c.5470–5477delATTGGGCA*	Jiangsu Province	59	*BRCA2 c.6486–6489delACAA*	Shanghai Municipality
49	*BRCA1 c.5470–5477delATTGGGCA*	Jiangsu Province	58	*BRCA2 c.6486–6489delACAA*	Shanghai Municipality
48	*BRCA1 c.5533–5540delATTGGGCA*	Shanghai Municipality	56	*BRCA2 c.7090G>T*	Shanghai Municipality
63	*BRCA1 c.5533–5540delATTGGGCA*	Shanghai Municipality	27	*BRCA2 c.7142delC*	Shanghai Municipality
55	*BRCA1 c.5533–5540delATTGGGCA*	Zhejiang Province	59	*BRCA2 c.7409dupT*	Zhejiang Province
37	*BRCA1 c.5533–5540delATTGGGCA*	Zhejiang Province	46	*BRCA2 c.7409dupT*	Zhejiang Province
53	*BRCA1 c.5533–5540delATTGGGCA*	Shanghai Municipality	38	*BRCA2 c.7409dupT*	Zhejiang Province
37	*BRCA1 c.5566C>T*	Shanghai Municipality	49	*BRCA2 c.7409dupT*	Zhejiang Province
			47	*BRCA2 c.7409dupT*	Zhejiang Province
			40	*BRCA2 c.7409dupT*	Zhejiang Province
			36	*BRCA2 c.7409dupT*	Jiangsu Province
			57	*BRCA2 c.7409dupT*	Jiangsu Province
			55	*BRCA2 c.7673–7674delAG*	Shanghai Municipality
			60	*BRCA2 c.8234dupT*	Shanghai Municipality
			53	*BRCA2 c.8377G>T*	Zhejiang Province
			49	*BRCA2 c.8377G>T*	Zhejiang Province
			57	*BRCA2 c.8584dupC*	Shanghai Municipality
			50	*BRCA2 c.8687–8690delGTGC*	Shanghai Municipality
			43	*BRCA2 c.10150C>T*	Shanghai Municipality

BRCA: Breast cancer gene; P/LP: Pathogenic or likely pathogenic.

rapid increase in breast cancer penetrance among *BRCA1* P/LP variant carriers occurred around the age of 35 years, with a cumulative risk ratio of 29.85, which then leveled off and reached a cumulative risk ratio of 4.02 at 85 years. For *BRCA2* P/LP variant carriers, the rapid increase in breast cancer penetrance started around 35 years and continued until 45 years, with a cumulative risk ratio of 32.90, before slowing down to a cumulative risk ratio of 3.21 at 85 years. The cumulative risk of breast cancer did not change significantly from 65 to 85 years of age for both *BRCA1* and *BRCA2* P/LP variant carriers.

Discussion

To the best of our knowledge, this study is the first population-based investigation of the penetrance of *BRCA1/2* P/LP variants in a Chinese population comprising patients with breast cancer from community sources. The findings demonstrated that by the age of 85 years, the penetrance of breast cancer among Chinese individuals carrying *BRCA1/2* P/LP variants was 22.50% and 18.20%, respectively. These rates are notably lower than those reported in Caucasian populations and previous studies

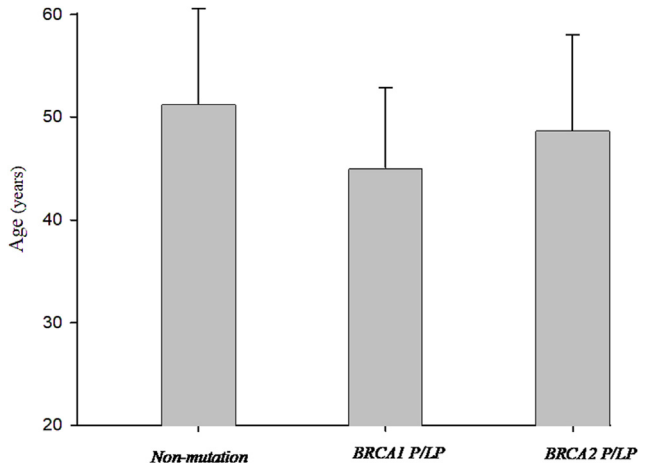

Figure 2. The average age of the probands. There was no statistically significant difference among the groups. *BRCA:* Breast cancer gene; P/LP: Pathogenic or likely pathogenic.

conducted in Chinese populations. The observed differences may be attributed to variations in the study samples and research methodologies.

Family history of the proband is crucial for calculating the penetrance of mutation carriers. However, it is important to note that this method assumes an equal risk of breast cancer among family members of carriers, regardless of whether they have been diagnosed with breast cancer during the study.[15] Therefore, sample selection is essential to ensure that the selected samples accurately represent the entire population. Otherwise, there may be inaccuracies in the penetrance results owing to sampling errors.

Previous studies on the penetrance of *BRCA1/2* P/LP variant carriers in the Chinese population primarily focused on hospital-based patients. Among these studies, two employed the kin-cohort method.[13,14] Zhang et al. mined a total of 1635 breast–ovarian cancer families registered in the Hong Kong Hereditary Breast Cancer Family Registry (China) and reported a breast cancer penetrance of 53.7% and 48.3% for *BRCA1* and *BRCA2* P/LP variant carriers, respectively, by the age of 70. However, the breast cancer penetrance of non-carriers in this study was as high as 16.1% by the age of 70 years. Considering that the lifetime risk of breast cancer in Hong Kong (China) women was 7.1% in 2019,[20] the sample used in this study may not accurately represent the general population of Hong Kong, China, potentially leading to an overestimation of the penetrance of *BRCA1* and *BRCA2* P/LP variant carriers. Yao et al.[14] investigated 1821 patients with breast cancer from the Breast Center at Peking University Cancer Hospital and reported breast cancer penetrance of 37.9% and 36.5% for *BRCA1* and *BRCA2* P/LP variant carriers, respectively, by the age of 70 years. However, this study did not explicitly provide information on the penetrance in noncarriers, as calculated using the kin-cohort method. Government reports indicated a breast cancer risk of 3.6% among women aged 70 years in the general population of Beijing in 2013.[21] Consequently, it is not feasible to directly compare the breast cancer incidence in the general population of Beijing with the penetrance among non-carriers in this study to determine the presence of any sampling bias that may have affected the accuracy of calculating the penetrance of P/LP variant carriers.

Our study was conducted in the economically developed areas of Eastern China, specifically in the Jiangsu Province, Zhejiang Province,

Table 3
Penetrance and cumulative risk ratio of cancer to age 85 years, by mutation status and cancer site in this study and cumulative incidence of cancer among Shanghai residents aged 85 years in 2016 by cancer site.

Cancer site	*BRCA1*			*BRCA2*			No mutation		Cumulative incidence in Shanghai 2016, %[16]
	No. of relatives with cancer	Cumulative incidence, % (95% CI)	Cumulative risk ratio (95% CI)	No. of relatives with cancer	Cumulative incidence, % (95% CI)	Cumulative risk ratio (95% CI)	No. of relatives with cancer	Cumulative incidence, % (95% CI)	
Female Breast[a]	9	22.50 (9.50–37.40)	4.02 (1.56–7.56)	11	18.20 (8.20–29.00)	3.21 (1.35–5.72)	140	5.70 (4.40–6.90)	4.60
Ovary[a]	7	26.00 (5.60–35.90)	44.65 (9.98–202.49)	1	5.20 (0.001–12.30)	8.29 (0.0014–24.87)	16	0.50 (0.09–0.90)	0.70
Prostate[b]	1	9.50 (0–34.20)	3.72 (0–19.23)	2	9.70 (0–18.80)	3.84 (0–9.70)	21	2.60 (1.10–4.20)	4.40
Pancreas[c]	2	11.00 (0–22.80)	6.09 (0–14.96)	4	31.10 (0.002–56.60)	26.95 (0.0015–60.39)	43	1.80 (1.20–2.80)	1.80
Lung[c]	8	12.10 (3.80–22.60)	1.45 (0.47–2.82)	8	35.70 (5.20–74.30)	4.52 (0.64–10.58)	221	8.60 (7.10–9.80)	8.50
Liver, gallbladder, bile duct[c]	3	6.50 (0–18.22)	1.36 (0.00002–4.15)	6	15.80 (3.60–37.60)	3.44 (0.74–9.27)	162	4.80 (3.80–6.50)	3.10
Colorectum[c]	7	29.40 (2.40–82.70)	8.68 (0.55–29.96)	5	8.90 (1.70–21.10)	2.27 (0.39–6.17)	109	3.40 (2.50–4.70)	5.00
Stomach[c]	3	10.20 (0.002–25.5)	1.82 (0–5.10)	10	15.10 (4.30–29.90)	2.72 (0.72–6.24)	204	5.60 (4.60–6.70)	3.60
Esophagus[c]	3	1.60 (0–3.80)	1.02 (0–2.92)	3	6.40 (0–16.80)	4.49 (0–13.95)	64	1.60 (1.10–2.20)	0.90
Kidney, bladder[c]	2	5.70 (0–13.90)	4.61 (0–15.04)	2	2.90 (0–6.70)	2.26 (0.00006–6.51)	27	1.30 (0.60–2.00)	1.80
Leukemias, lymphomas[c]	5	10.60 (1.0–17.90)	8.60 (0.57–19.46)	0	0	–	36	1.20 (0.60–2.10)	1.40

[a] Only female first-degree relatives were analyzed; [b] Only male first-degree relatives were analyzed; [c] All first-degree relatives were analyzed. *BRCA*: Breast cancer gene.

Table 4
Penetrance and cumulative risk ratio of breast cancer by age and mutation status.

Age (years)	*BRCA1*		*BRCA2*		Breast cancer risk of non-carriers, % (95% CI)
	Breast cancer risk, % (95% CI)	Cumulative risk ratio	Breast cancer risk, % (95% CI)	Cumulative risk ratio	
By age 35	1.90 (0–4.00)	29.85	1.60 (0–3.90)	22.93	0.08 (0–0.20)
By age 45	1.90 (0–4.00)	4.11	11.50 (9.90–37.50)	32.90	0.60 (0.40–0.80)
By age 55	11.30 (2.10–22.70)	6.95	14.40 (5.20–21.40)	9.18	1.80 (1.30–2.30)
By age 65	22.50 (9.50–37.40)	6.95	18.20 (8.20–29.00)	5.48	3.40 (2.60–4.20)
By age 75	22.50 (9.50–37.40)	5.58	18.20 (8.20–29.00)	4.42	4.20 (3.30–5.10)
By age 85	22.50 (9.50–37.40)	4.02	18.20 (8.20–29.00)	3.21	5.70 (4.40–6.90)

BRCA: Breast cancer gene.

and Shanghai Municipality. These three areas are geographically adjacent, share the same nationality and culture, and exhibit consistent levels of economic development. To facilitate patient recruitment, breast cancer survivors from these regions were selected as the study population. The participation rate in our study was high, with 63.00% of eligible individuals participating in the study. The cumulative incidence of 11 different types of malignant tumors, including breast cancer, in non-carriers in our study was highly similar to that in Shanghai residents in 2016.[19] This indicates that patients with breast cancer from specific geographic areas within the communities selected in our study accurately represent the general population.

In our study, the cumulative risk ratios of breast cancer at 85 years were 4.02 and 3.21 for *BRCA1* and *BRCA2*, respectively. Similar results were reported in studies conducted by Yao et al.[14] in Beijing (odds ratios, 3.77 and 4.42 for *BRCA1* and *BRCA2* P/LP variants in breast cancer, respectively) and by Zhang et al.[13] in Hong Kong, China (breast cancer risk ratio, 3.31 for *BRCA1/2* P/LP variants). These findings are consistent with the results of the present study. Hu et al.[22] reported slightly higher odds ratios for *BRCA1* and *BRCA2* in a large-scale case-control study conducted in a United States (US) population (7.62 and 5.23, respectively) compared to those in a Chinese population, but the relative risks were still similar. These results suggest that the relative risk of breast cancer associated with *BRCA1/2* P/LP variants may remain constant in the population, which could explain why the penetrance of these variants is lower in the Chinese population than in the US population. In the US, the lifetime risk of breast cancer in the general population is approximately 10–12%, whereas for *BRCA1/2* P/LP variant carriers, it is approximately 50%.[22] In 2016, the cumulative risk of breast cancer among Shanghai residents aged 85 years was 4.6%.[19] Assuming a similar relative risk, the lifetime risk of breast cancer in *BRCA1/2* P/LP variant carriers in our study was 22.50% and 18.20%, respectively. Several other studies have reported similar findings. Tryggvadottir et al.[23] observed an increase in the cumulative incidence of breast cancer before the age of 70 years in *BRCA2* P/LP variant carriers in Iceland, from 18.6% in 1920 to 71.9% in 2002, compared to an increase from 2.6% to 10.7% in non-carriers and from 1.8% to 7.5% in the general population. The risk of disease increased four-fold during this period. However, it should be noted that breast cancer is likely influenced by complex interactions between genetic and environmental factors, and it is not yet conclusive that the relative risk of genetic factors remains constant. Further studies are required to confirm these findings.

We observed that the incidence of ovarian cancer among carriers of *BRCA1* P/LP variants was 26.00%, which was considerably lower than that the rates reported in Western populations.[24] However, the number of ovarian cancer cases among the carriers of *BRCA2* P/LP variants was insufficient to draw statistically significant conclusions. Wu et al.[25] reported the detection of *BRCA1/2* germline P/LP variants in 28.50% of Chinese patients with ovarian cancer, with the detection rate of *BRCA2* P/LP variants being only 7.60%, accounting for only 26.7% of all P/LP variants. In contrast, studies in Western patients with ovarian cancer have found that *BRCA2* P/LP variants account for approximately 40% of all P/LP variants.[26,27] This inconsistency may explain the lower number of ovarian cancer cases carrying *BRCA2* P/LP variants in our study. Increasing the sample size could help address this issue.

Recent studies have also shown that *BRCA1/2* P/LP variants are linked with an elevated risk of pancreatic and gastric cancers and *BRCA2* P/LP variants with prostate cancer.[28] However, we did not observe any statistically significant patterns in our study, possibly due to the limited sample size. Further investigation is necessary to gather more data on these associations.

In our study, breast cancer penetrance among carriers of *BRCA1* and *BRCA2* P/LP variants was 22.50% and 18.20%, respectively. These rates are close to or even below the high-risk threshold of absolute breast cancer risk at the age of 80 years, as defined by the guidelines of the National Institute for Health and Care Excellence in the United Kingdom.[29] However, it is important to note that breast cancer incidence in China is still on the rise. As indicated by Tryggvadottir et al.,[23] with an increasing risk of breast cancer in the general population, the risk of breast cancer among carriers of *BRCA1/2* P/LP variants is expected to increase. Therefore, it is imperative to continually monitor data in the Chinese population and adjust breast cancer prevention strategies accordingly.

The study has some limitations. First, the patients selected for this study only represent Jiangsu, Zhejiang, and Shanghai in Eastern China but not other regions. The vast majority of residents in Eastern China are of Han nationality. As a multiethnic country, the diversity of genetic backgrounds in China is beyond the scope of this study. Second, family history information in this study was obtained through interviews with the probands and was not supported by medical records. Some studies have confirmed that the sensitivity of family history reports differs for various cancers[30,31]; however, the accuracy of family histories of first-degree relatives is significantly higher than that of second-degree relatives.[30] This study only used family history information from first-degree relatives, which was expected to be more accurate. Moreover, the similarity between the penetrance of non-carriers of *BRCA1/2* P/LP variants in our study and the breast cancer incidence among Shanghai residents in 2016[19] provides additional support for the trustworthiness of our family history data. Finally, the *BRCA1/2* P/LP variants analyzed in this study were obtained from patients with breast cancer. The presence of breast cancer cluster regions (BCCRs) and ovarian cancer cluster regions (OCCRs) within the *BRCA1/2* gene[32] may affect the accuracy of the results when gene mutations obtained from patients with breast cancer are used to calculate the penetrance of other malignant tumors, such as ovarian cancer. Risch et al.[26] reported a similar phenomenon. Hence, increasing the sample size may have reduced these effects.

In conclusion, in this population-based study, we found a notably lower incidence of breast cancer in Chinese *BRCA1/2* P/LP variant carriers than in the Western population or hospital-based Chinese studies. This discovery suggests the need for re-evaluation of preventive measures, such as aggressive prophylactic mastectomy, for breast cancer prevention in these individuals.

Authors contribution

Conception and design: Zhen Hu and Yun Liu; administrative support: Zhen Hu; collection and assembly of data: all authors; data analysis and interpretation: Sanjian Yu, Zezhou Wang, Jialong Xiao, Liqin Chen, Xiaofang Lu, Tingting Su, Qianqian Yu, Honglian Wang, Ying Zheng, Yun Liu, and Zhen Hu; manuscript writing: Sanjian Yu, Zezhou Wang, Honglian Wang, Ying Zheng, Yun Liu, and Zhen Hu. All the authors critically revised and approved the final version of the manuscript.

Ethics statement

Following the *Declaration of Helsinki* and Good Clinical Practice guidelines, the study protocol was approved by the Institutional Review Board of Fudan University Shanghai Cancer Center (registration number: 1905202-3). All participants provided written informed consent prior to enrollment.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors declare that generative artificial intelligence (AI) and AI assisted technologies were not used in the writing process or any other process during the preparation of this manuscript.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability statement

The data generated in this study are available within the article and it will be available from the corresponding author upon request.

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