Impact of *BRCA* Mutation on the Survival and Risk of Contralateral Breast Cancer in Asian Breast Cancer Patients

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Abstract

Purpose

Breast cancer is increasing around the globe, including Asia. We aimed to examine the survival and risk of contralateral breast cancer (CBC) in Asian breast cancer patients with *BRCA* mutations.

Methods

A total of 128 breast cancer patients with germline *BRCA* mutations and 4,754 control breast cancer patients were enrolled. Data on clinical pathologic characteristics, survival and CBC were collected from the medical record. The rates of survival and CBC were estimated by Kaplan-Meier method.

Results

The mean age of onset in *BRCA* mutation carriers was significantly younger than control patients (*BRCA* vs. Non-*BRCA*: 43.9 vs. 53.2 years-old). *BRCA* mutation carriers had a higher proportion of triple-negative breast cancer (TNBC) (52%) than control patients (12%, $p<0.001$). The risk of CBC was significantly higher in *BRCA* mutation patients than in control cases (hazard ratio (HR) = 3.95, 95% CI 2.71-5.75); when stratified by genotype, the HRs (95%CI) were 4.84 (3.00-7.82) for *BRCA1* and 3.13 (1.78-5.49) for *BRCA2* carriers, respectively. Moreover, *BRCA1* mutation patients with triple-negative breast cancer (TNBC) as their first breast cancer had the highest risk of CBC (HR = 5.55, 95% CI 3.29-9.34). However, we did not observe any differences in relapse-free survival and overall survival between mutation carriers and control patients.

Conclusion

Our study suggest that *BRCA* patients had a significantly higher risk of developing CBC, particularly for *BRCA1* mutation carriers with TNBC as the first breast cancer.

Introduction

Breast cancer, the most common type of malignancy, is the leading cause of cancer-related death of women in Taiwan and worldwide [1]. One phenomenon of Asian breast cancer patients is that they have a relatively younger onset age than Western patients [2, 3], which suggests that a proportion of Asian breast cancer patients is being affected by the genetic mutation of inherited genes such as *BRCA1* and *BRCA2* [2, 3].

Women with germline *BRCA* mutations have extremely high lifetime risks of developing breast and ovarian cancers [4–7]. Previous studies have shown that the cumulative incidence of breast cancer for *BRCA1* and *BRCA2*-mutation carriers by 80 years old was about 72% [confidence interval (CI) 65% – 79%] and 69% (61% – 77%), respectively [7]. More specifically, reports from Asian *BRCA* studies revealed that *BRCA1* and *BRCA2* mutation carriers have a 49–54% and 35–48% chance of developing breast cancer,

respectively [6, 7]. The risk of recurrent or contralateral breast cancer (CBC) also significantly increases in *BRCA* mutation carriers compared to non-*BRCA* carrier patients [4, 8–10]. The prognostic impact of germline *BRCA* mutations in breast cancer patients is controversial. A prospective study revealed similar prognoses in patients with and without *BRCA* mutations [11]. In contrast, another large cohort and meta-analysis studies suggested that *BRCA* mutations were associated with worse overall survival [12, 13].

However, the majority of studies to date focused on the clinical manifestation of *BRCA* mutations are from European, North American, African or African–American populations. Although the number of reports from Asian populations have been increasing, most are focused on the prevalence and epidemiology of *BRCA* [2, 3, 14–18]. The clinical characteristics, pathologic features, prognosis, and risk of CBC remain uncertain in Asian patients with *BRCA* mutated breast cancer. To estimate the survival and risk of CBC, we used information from a total of 4,882 Taiwanese (ethnic Han Chinese) breast cancer patients. Among them, one-hundred and twenty-eight cases were carriers of germline *BRCA1* or *BRCA2* mutations.

Patients And Method

1. Patient

We collected 128 breast cancer patients who carried germline *BRCA1* or *BRCA2* mutations during the period 1995–2019 from previous academic studies and hospital-based gene diagnoses [2, 3]. The criteria used to select patients for genetic studies or to recommend them for genetic diagnosis was based mainly on NCCN guidelines, which consider factors such as young-onset age, significant familial history and whether age at TNBC diagnosis is less than 60 years old [19]. Ninety patients were diagnosed in National Taiwan University Hospital (NTUH); the remaining were diagnosed at other Taiwanese hospitals.

The control group came from NTUH breast cancer patients. In NTUH's cancer registry database, we found a total of 6,948 patients during the period 1995–2019. First, we excluded 1,470 patients who had incomprehensive data, which means that some fields, such as tumor size or lymph node status, may have been lacking. Second, we excluded patients with *BRCA* mutations and patients who had family history of breast cancer and/or ovarian cancer in their first/second relatives. This strategy eliminates *BRCA* mutations in control patients as much as possible. A final total of 4,754 breast cancer patients were enrolled as the control patient group.

All clinical, pathologic data and survival information were recorded from medical charts. The presence of estrogen receptors (ER), progesterone receptors (PR), and Her2 were determined by immunohistochemical staining. The presence of ER or PR was considered negative when less than 1% of the tumor cells showed positive staining. Positive expression of hormone receptors was classified as luminal type breast cancer, which can be further divided into luminal A and B classifications. We classified breast tumors with PR expression less than 20%, Ki67 more than 20% and/or histologic grade III as Luminal B type[20, 21]. For Her2 staining, a score of 0 or 1 + was considered negative; specimens with a score of 2 + were confirmed

by fluorescence in situ hybridization analysis. The tumor histological grade was defined using the Nottingham combined histological grading system.

Statistics

We used the chi-squared test and Fisher's exact test to calculate the significance of variances between each group. We calculated and compared the survival by different groups using Kaplan-Meier analysis. Followup (in years) was considered as the time interval between the date of breast cancer diagnosis and the date of these endpoints: date of CBC diagnosis, date of death, latest date of follow up, or end of followup (December 31, 2019), whichever came first. Cox proportional hazards regression analysis was used to estimate the hazards ratios of survival and second breast cancer and corresponding 95% confidence interval (CI) for various factors, including tumor size, lymph node status, molecular types and genotype of BRCA. Statistical analyses were performed using SPSS software (version 17.0) and all *p* values are two-sided, and *p*-values less than 0.05 are considered statistically significant.

Results

1. Clinical characteristics

Clinical and pathologic characteristics are shown in Table 1. Sixty-eight patients had *BRCA1* mutations while 60 patients had *BRCA2* mutations. Patients with *BRCA* mutations had a significantly younger age of onset than that of control patients (*BRCA* vs. control: 43.9 vs. 52.5 years-old, $p < 0.001$). Additionally, molecular types between *BRCA* and non-*BRCA* patients were significantly different ($p < 0.001$); a higher proportion of *BRCA* mutation patients than non-*BRCA* patients had TNBC (*BRCA* vs. control: 52.3% vs. 12.0%), followed by the ER(+) Her2(-) patients (41.4% vs. 61.3%). A small proportion of *BRCA* patients had ER(+) Her2(+) breast cancer (5.5% vs. 11.1%), and none of them had pure Her2 type cancer (0 vs. 10.4%). When stratified by genotype, 76% (n = 56) of *BRCA1* patients had TNBC whereas 66.7% (n = 40) of *BRCA2* patients had ER(+) Her2(-) breast cancer.

Table 1
Patient and tumor characteristics according to germline *BRCA* status.

Characteristics	***BRCA* mutated (n = 128)**	***BRCA1* mutated (n = 68)**	***BRCA2* mutated (n = 60)**	***BRCA* non-mutated (n = 4754)**	***BRCA* vs. non-*BRCA*** ***p* value**
Age (years, mean ± SD)	43.9 ± 10.1	42.4 ± 10.2	45.6 ± 9.8	53.2 ± 11.6	< 0.001
Molecular type					< 0.001
ER(+)Her2(-)^{LuminalA}	37	8	29	1813	
ER(+)Her2(-)^{LuminalB}	16	5	11	793	
ER(+)Her2(+)	7	3	4	470	
Her2(+)	0	0	0	456	
TNBC	67	52	15	514	
unknown	1	0	1	704	
Disease status of diagnosis					
(de novo) stage IV	4	3	1	250	0.185
Stage 0-III					
T classification					0.713
T0	2	1	1	154	
T1	58	33	25	1919	
T2	51	27	24	2029	
T3-4	10	3	7	402	
unknown	4	2	2	0	
N classification (post)					0.814
N0	75	43	32	2767	
N1	25	13	12	1078	
N2	12	4	8	408	
N3	7	3	4	210	
unknown	6	3	3	0	

Characteristics	*BRCA* mutated (n = 128)	*BRCA1* mutated (n = 68)	*BRCA2* mutated (n = 60)	*BRCA* non-mutated (n = 4754)	*BRCA* vs. non-*BRCA* *p* value
Second malignancies (not Breast cancer)					< 0.001
Positive	20	10	10	238	< 0.001
Ovarian cancer	17	9	8	8	< 0.001
Other cancers	3	2	1	230	< 0.001

There were no difference in the distributions of tumor size and LN status between *BRCA* and non-*BRCA* mutation patients. *BRCA* mutation patients had a significantly higher risk of developing second non-breast cancer ($p < 0.001$). The main second malignancy was ovarian cancer, whose incidence was similar between *BRCA1* and *BRCA2* patients. For the 17 patients with ovarian cancer, twelve (70.6%) of them developed ovarian cancer after breast cancer and 5 cases had ovarian cancer before breast cancer. The types of the second malignancy for the control cases were significantly different from that of *BRCA* patients; the most common cancer of the control patients was lung cancer ($p < 0.001$).

2. Relapse-free And Overall Survival

The median follow time was 4.67 (range 0.1 to 22.9) years. Kaplan-Meier analysis revealed that relapse-free survival (RFS) for patients with stage 0 to III breast cancer was similar between *BRCA* and control patients (Fig. 1A, $p = 0.967$). The RFS for *BRCA* patients was 85.2% (95% confidence interval (CI) 92.2% – 78.1%) at five years and 78.5 % (95% CI 87.5% – 69.5 %)at 10 years. On the other hand, the RFS for control patients was 86.2% (95% CI 87.4%-85.0%) and 79.0% (95% CI 80.8% – 77.2%) at 5 and 10 years, respectively. When stratified by *BRCA1* and *BRCA2* genotyping, the 10-year RFS for *BRCA1* patients was 82.6% (95% CI 71.2% – 93.9%) whereas the RFS for *BRCA2* patients was 74.4% (95 CI 60.1% – 88.3%). There was no significant difference in RFS between *BRCA1*, *BRCA2* and control patients (Fig. 1B).

The prognostic factors for RFS in both *BRCA* and control patients were the tumor size and LN classification (Figs. 1C – 1F). Large tumor sizes and advanced LN classification resulted in poor RFS. When stratified by molecular types, the control patients with ER(+) Her2(-)$^{\text{LuminalA}}$ breast cancer had the best RFS out of all other types of breast cancer. Patients with ER(-)Her2(+) breast cancer had the worst RFS (Fig. 1G). For *BRCA* mutation carriers, patients with TNBC had a better RFS trend than those with other types of breast cancer (Fig. 1H), probably because most TNBC patients had stage I breast cancer.

Among the entire cohort, tumor size, LN classification and molecular types were independent risk factors for RFS (Table 2). Thus, we analyzed the impact of *BRCA* after adjusting for these major prognostic factors in a multivariable model; the results showed no difference in RFS between *BRCA* and control

patients (HR = 1.071, 95% CI 0.689–1.664, Table 2). In contrast, large tumor size, advanced LN status, ER(+) Her2(-)^{LuminalB}, ER(-) Her2(+) and TNBC remained the independent prognostic factors for RFS. Similarly, there was no difference in the overall survival (OS) between *BRCA* and control patients (HR = 0.721, 95% CI = 0.396–1.314). The tumor size, LN classification and molecular types were the independent risk factors of OS. Compared to patients with ER(+) Her2(-)^{LuminalA}, patients with ER(+) Her2(-)^{LuminalB}, ER(-)Her2(+) or TNBC had a significantly inferior OS (Table 3).

Table 2
Univariate and multivariate analysis of relapse-free survival

Clinical	**Univariate**				**Multivariate**			
Characteristics	HR	lower	upper	P	HR	lower	upper	P
Tumor size								
T0-1	reference				reference			
T2	2.653	2.180	3.228	< 0.001	1.864	1.516	2.291	< 0.001
T3-4	5.594	4.370	7.160	< 0.001	3.387	2.590	4.428	< 0.001
LN								
N0	reference				reference			
N1	2.124	1.748	2.582	< 0.001	2.131	1.732	2.622	< 0.001
N2	4.234	3.426	5.231	< 0.001	3.732	2.966	4.695	< 0.001
N3	6.976	5.474	8.891	< 0.001	4.914	3.747	6.445	< 0.001
Molecular type								
ER(+)Her2(-)^{LuminalA}	reference				reference			
ER(+)Her2(-)^{LuminalB}	1.399	1.138	1.720	0.001	1.302	1.053	1.610	0.015
ERHer2(+)	1.380	1.060	1.798	0.017	1.017	.770	1.345	0.903
Her2(+)	1.885	1.478	2.405	< 0.001	1.573	1.218	2.032	0.001
TNBC	1.276	.990	1.643	0.060	1.304	1.001	1.699	0.049
Genotyping								
non-*BRCA*	reference				reference			
BRCA	0.991	0.647	1.517	0.967	1.071	0.689	1.664	0.761

Table 3
Multivariate analysis of overall survival

Clinical	**Multivariate**			
Characteristics	HR	lower	upper	P
Tumor size				
T0-1	reference			
T2	1.686	1.318	2.157	< 0.001
T3-4	2.503	1.753	3.576	< 0.001
LN				
N0	reference			
N1	1.859	1.440	2.400	< 0.001
N2	3.170	2.390	4.204	< 0.001
N3	3.996	2.818	5.665	< 0.001
Molecular type				
ER(+)Her2(-)^{LuminalA}	reference			
ER(+)Her2(-)^{LuminalB}	1.729	1.338	2.235	< 0.001
ER(+)Her2(+)	1.107	0.759	1.615	0.598
ER(-)Her2(+)	1.537	1.084	2.180	0.016
TNBC	1.681	1.203	2.348	0.002
Genotyping				
non-*BRCA*	reference			
BRCA	0.721	0.396	1.314	0.286
Multivariate model include tumor size, LN, molecular type and genotyping				

3. Risk Of Contralateral Breast Cancer

The risk of contralateral breast cancer (CBC) was significantly higher in *BRCA* mutation patients than in control cases (HR = 3.950, 95% CI 2.712–5.752, p < 0.001.. The CBC risk was 26.0% (95% CI 16.0% – 36.0%) at 10 years and 44.0% (95% CI 27.1% – 60.8%) at 15 years in BRCA mutation patients, compared to 6.6% (95% CI 5.6% – 7.6%) at 10 years and 10.4% (95% CI 8.2% – 12.6%) at 15 years in control patients (Fig. 2A). When stratified y *BRCA1* and *BRCA2* genotyping, both patient groups had a significantly increased risk of CBC in comparison to control patients (*BRCA1*: HR = 4.844, 95% CI 3.001–7.820, p <

0.001; *BRCA2*: HR = 3.130, 95% CI 1.782–5.498, p < 0.001). We then classified patients by molecular types; both ER(+) and TNBC *BRCA* mutation patients had a significantly higher risk of getting CBC than control patients with ER(+) breast cancer and TNBC, respectively (Figs. 2C and 2D).

Unlike RFS, tumor size, LN classification and molecular type did not affect the risk of CBC. *BRCA* mutation was the only independent risk factor of developing CBC in the analysis of the overall patients.

4. Characteristics of CBC risk in *BRCA* mutation carriers

Previous studies reported that patients younger than 40 years old had a higher risk of having CBC [9], so we divided patients into two groups: people at or younger than 40 years-old and people older than 40 years-old. However, the CBC risk was similar between *BRCA* patients younger and older than 40 years old (Fig. 3A). We found that there was a higher trend of CBC risk in *BRCA1* mutation patients (HR = 1.814, 95% CI 0.865–3.805, p = 0.115) compared to that of *BRCA2* mutation carriers. Similarly, TNBC patients had a higher trend of developing CBC than ER(+) *BRCA* patients (HR = 1.657, 95% CI 0.778–3.530, p = 0.185, Fig. 3B). When genotype and molecular types were integrated, *BRCA1* patients with TNBC had the highest risk of CBC compared to other *BRCA* mutation patients (Fig. 3C and 3D). The CBC risk of *BRCA1* patients with TNBC was 39.3% (95% CI 19.9% – 58.7%) and 63.6% (95% CI 39.0% – 88.1%) at 10 and 15 years, respectively. In comparison to the control patients, *BRCA1* patients with TNBC had a greater than five-fold risk of developing CBC (HR = 5.550, 95% CI 3.295–9.349, p < 0.001).

Figure 3 Cumulative incidence of CBC in patients among *BRCA* mutation. The x-axis is followup time (years) and y-axis is cumulative incidence of CBC. (A) Risk of CBC by age onset of the first breast cancer (Less or equal to 40 year-old vs. more than 40 year-old. (B) Risk of CBC by ER(+) vs. TNBC (C) Risk of CBC by between different genotype and molecular type. (D) Risk of CBC by *BRCA1* with TNBC vs. others.</fig>

5. Relationship Between Survival And Cbc

For the entire cohort, patients with and without CBC had a similar RFS (HR = 0.760, 95% CI 0.540–1.070) and OS (HR = 0.864, 95% CI 0.597–1.251). For the 128 *BRCA* mutation patients, 22 patients relapsed; 2 patients relapsed before CBC and 20 patients relapsed after CBC. For all patients with CBC, the 5-year RFS after CBC was 86.9% (95% CI 82.0% – 91.8%).

Discussion

This is, to the best of our knowledge, the first study to investigate the clinical-pathologic characteristics, survival and risk of CBC in Asian *BRCA*-mutated breast cancer patients. The characteristics of early-onset and molecular type of breast cancer in our patients are compatible with results in Western ethnic patients [4, 22]. We observed similar survival between *BRCA* mutated and non-mutated breast cancer patients.

However, a significantly elevated risk of CBC was noted in *BRCA*-mutated breast cancer patients, especially *BRCA1* patients with TNBC.

The risk of CBC was about four- times higher in *BRCA* mutation carriers than noncarriers. The cumulative 10-year risk of CBC was about 26.0%. Prior studies estimated the 10-year risk of CBC to be about 21% – 30%. When the observation period lengthened to 20 years, the risk of CBC could increase up to about 40% [9, 23]. Many studies have investigated CBC risk factors. Graeser MK *et al.* and van den Broek AJ *et al.* reported that a younger onset age of the first breast cancer was associated with a significantly elevated risk of CBC in patients with *BRCA* mutations [9, 24]. However, we did not find an elevated risk of CBC in *BRCA* patients younger than 40 years old in our present cohort, which may be due to ethnic differences or limited followup time. Additionally, the small number of young-onset patients in our cohort may be another reason why our results showed no difference in CBC risk between patients younger and older than 40 years old. In our cohort, only 39% of patients were younger than 40 years old when they had their first breast cancer; the median onset age of the first breast cancer in *BRCA1* and *BRCA2* patients were 42.2 and 45.6 years old, respectively. We are continuing enrolling early onset of Taiwanese breast cancer patients to better understand the epidemiology as well as risk factors of CBC in Asian breast cancer patients.

However, in concordance with previous studies [9], our data revealed that *BRCA1* patients had a higher trend of developing CBC than *BRCA2* patients. When classified by genotype and molecular types, *BRCA1* patients with TNBC had the highest risk of getting CBC; the CBC risk of these patients was up to 63.6% (95% CI 39.0% – 88.1%) at 15 years, about a five-fold increase in comparison to control patients. *BRCA1* patients with ER(+) breast cancer had similar risk of developing CBC compared to whole *BRCA2* patients (Fig. 3C).

The ASCO consensus and NCCN guidelines suggest that risk-reducing mastectomy and contralateral prophylactic mastectomy (CPM) should be considered for *BRCA* mutation carriers [19, 25]. CPM can reduce the risk of CBC. Some studies even reported that CPM can reduce mortality for *BRCA* mutation patients in the long-term follow-up [26–28]. However, the CPM rate was relative lower in Asian countries[29]. In our study, only two *BRCA* mutation patients received CPM; this is one of the reasons of the high CBC risk in our cohort. Therefore, CPM will be considered for our patients to reduce the risk of CBC, especially for *BRCA1* patients with TNBC.

The impact of germline *BRCA* mutations on the survival of breast cancer patients is controversial. A prospective study revealed that patients with young-onset breast cancer who carry a *BRCA* mutation have similar survival as non-carriers[11]. Another large cohort study showed that *BRCA1* mutation carriers, independent of clinical-pathological and therapy characteristics, had a worse overall survival (OS) than noncarriers[13]. Subsequent ovarian cancer in *BRCA1* breast cancer survivors may contribute to the lower OS. The breast cancer mortality rate was not significantly superior in *BRCA* mutation patients[13]. Our study demonstrated that *BRCA* breast cancer patients had a similar RFS in comparison to that of control patients. However, the risk of non-breast second malignancies, especially ovarian cancer, was

significantly higher than that of control patients. Besides from ovarian cancer, we also saw two cases of endometrial cancer. One patient's endometrial cancer received multi-gene sequencing and the result showed loss-of-heterozygosity of the *BRCA1* gene, indicating that *BRCA1* mutation was involved in tumorigenesis. Furthermore, several recent studies found an increased risk of uterine cancer in *BRCA* mutation carriers [30, 31]. These facts suggested that the prevention of second malignancies is an important issue in *BRCA* breast cancer survivors.

Asians comprise of 60% of the world's population and this number is still increasing. A prior review study revealed that Asian *BRCA* patients had a similar epidemiology and mutation spectrum compared to Western countries [15]; that fact implies that most *BRCA* mutation carriers are Asian. In this study, we provided evidence that our *BRCA* patients had an increased risk of CBC and second malignancies. The phenomena resemble the cancer risks of other ethnic groups, suggesting that Asian *BRCA* carriers are a high-risk population susceptible to breast cancer, CBC and second malignancies. In particular, we found that *BRCA1* patients with TNBC as their first cancer had a greater than five-fold risk of developing CBC. Thus, genetic counseling and management of Asian *BRCA* mutation carriers needs to improve in the future.

Declarations

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Data availability

The datasets used during the current study are available from the corresponding author on reasonable request.

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Ethics declarations

Conflict of interest

All the authors declare that they have no conflict of interest.

Ethics approval

BRCA mutation patients were collected from two studies, which were approved by the Medical Ethics Committee of the National Taiwan University Hospital (201308077RINA and 201706090RINA). Ninety patients received gene diagnosis at National Taiwan University Hospital. Although other patients were diagnosed at other hospitals, most of the *BRCA* mutation carriers were refereed to genetic clinic of the National Taiwan University Hospital for genetic counseling so we could collect their data.

Informed consent

In this study, all procedures were performed in accordance with the Declaration of Helsinki.

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Figures

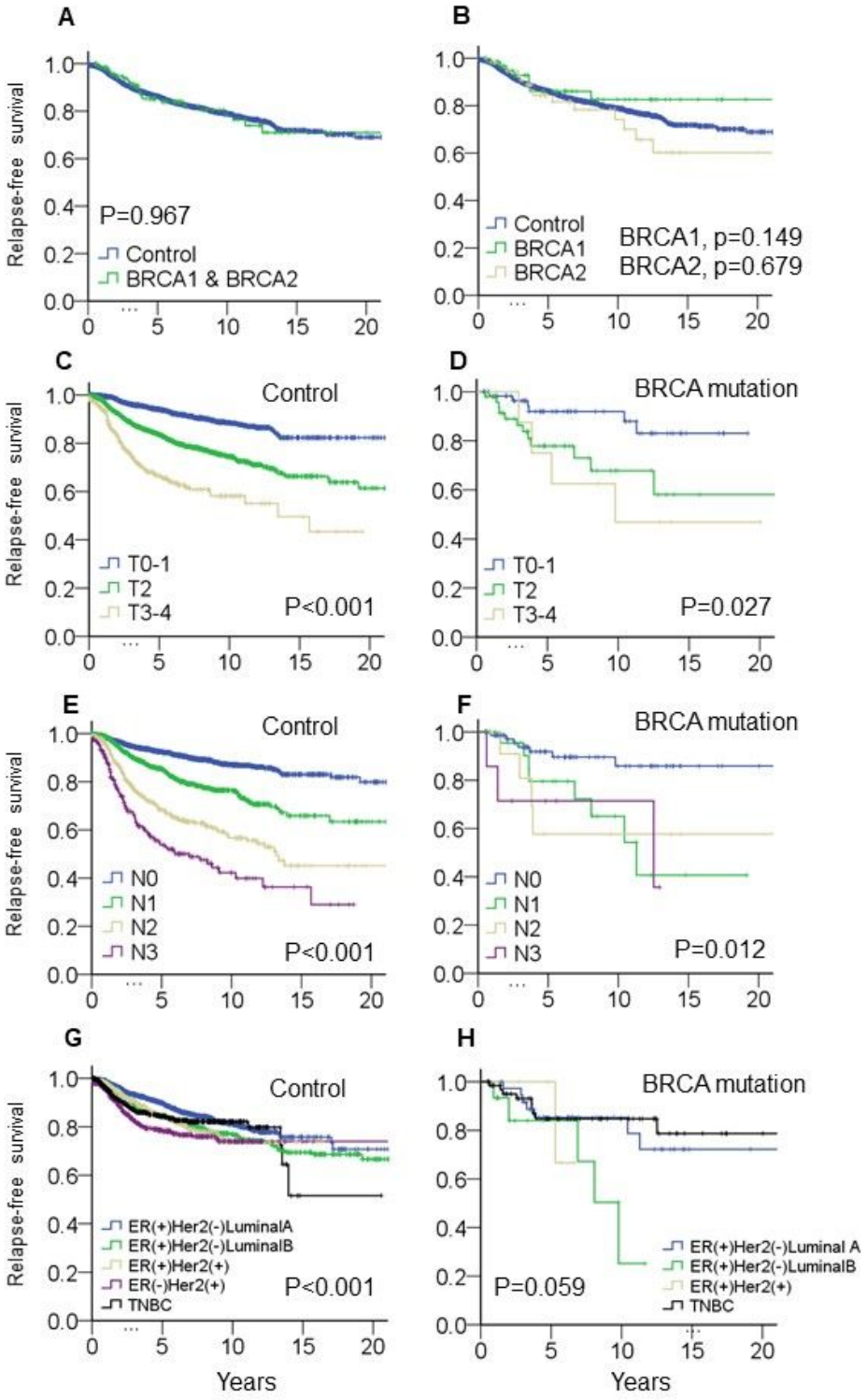

Figure 1

Relapse-free survival analysis by different characteristics. The x-axis is followup time (years) and y-axis is cumulative relapse-free survival. (A) Kaplan-Meier analysis of relapse-free survival by BRCA mutation (Control patients versus (vs.) patients with BRCA1 &2 mutation). (B) Kaplan-Meier analysis of relapse-free survival by different BRCA mutation groups (Control patients vs. patients with BRCA1 and Control patients vs BRCA2 mutation). (C) Kaplan-Meier analysis of relapse-free survival by T classification

among control patients. (D) Kaplan-Meier analysis of relapse-free survival by T classification among patients with BRCA1 &2 mutation. (E) Kaplan-Meier analysis of relapse-free survival by N classification among control patients. (F) Kaplan-Meier analysis of relapse-free survival by N classification among patients with BRCA1 &2 mutation. (G) Kaplan-Meier analysis of relapse-free survival by molecular type among control patients. (H) Kaplan-Meier analysis of relapse-free survival by molecular type among patients with BRCA1 &2 mutation.

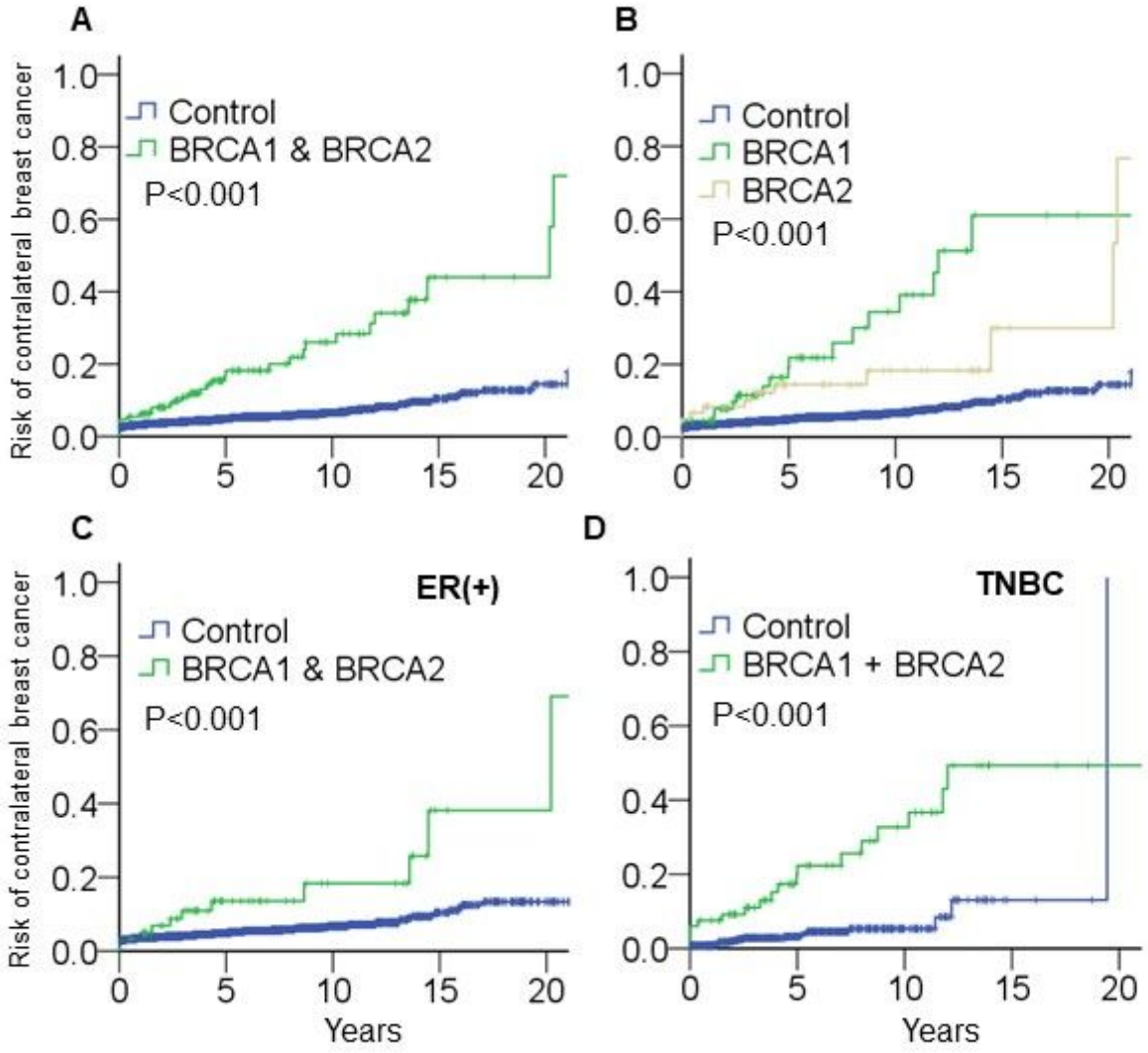

Figure 2

Cumulative incidence of contralateral breast cancer (CBC). The x-axis is followup time (years) and y-axis is cumulative incidence of CBC. (A) Risk of CBC by BRCA mutation (Control patients versus (vs.) patients with BRCA1 &2 mutation). (B) Risk of CBC by different BRCA mutation groups (Control patients vs. patients with BRCA1 and Control patients vs BRCA2 mutation). (C) Risk of CBC among ER (+) by BRCA mutation (Control patients versus (vs.) patients with BRCA1 &2 mutation). (D) Risk of CBC among TBNC patients by BRCA mutation (Control patients versus (vs.) patients with BRCA1 &2 mutation).

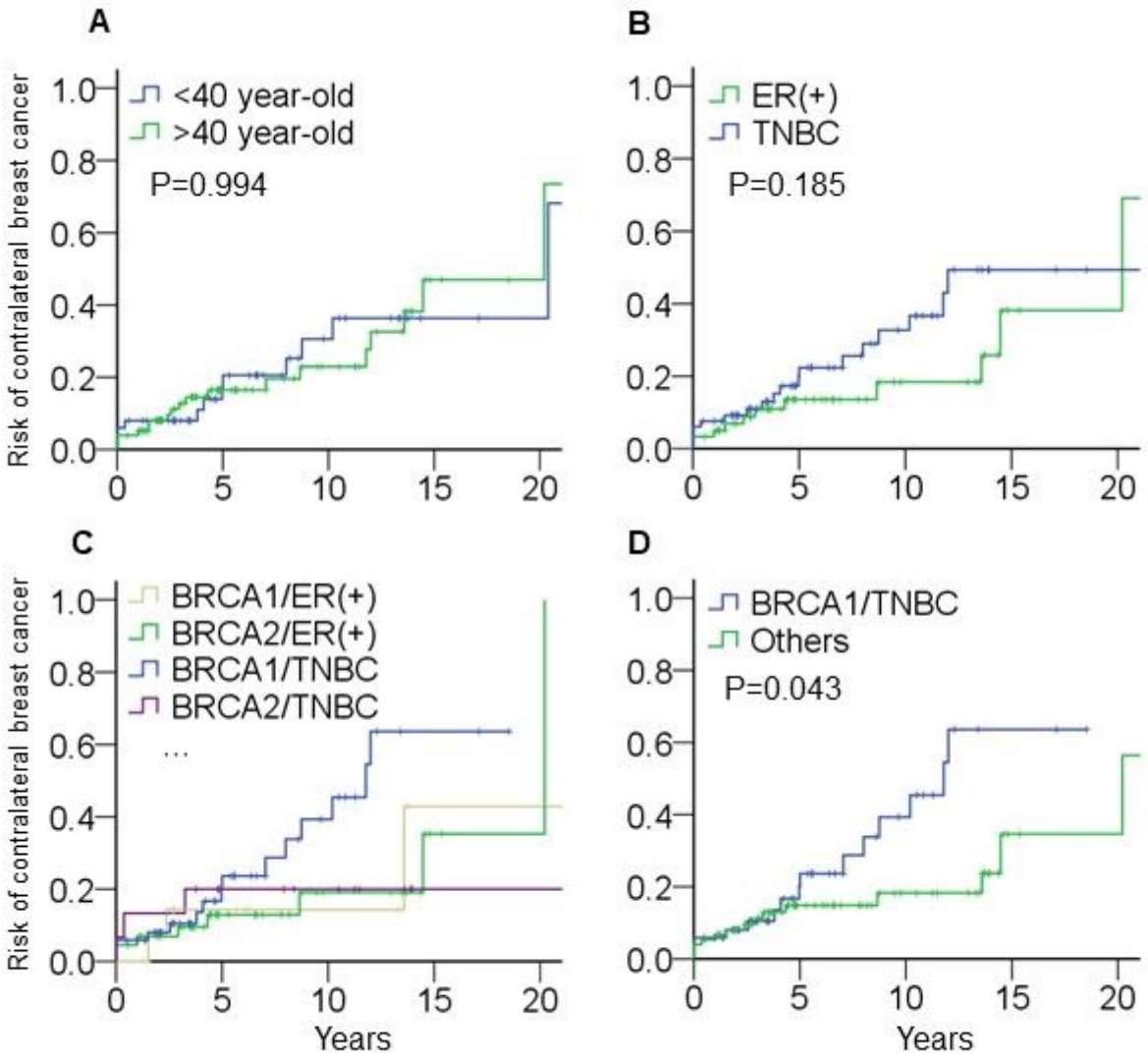

Figure 3

Cumulative incidence of CBC in patients among BRCA mutation. The x-axis is followup time (years) and y-axis is cumulative incidence of CBC. (A) Risk of CBC by age onset of the first breast cancer (Less or equal to 40 year-old vs. more than 40 year-old. (B) Risk of CBC by ER(+) vs. TNBC (C) Risk of CBC by between different genotype and molecular type. (D) Risk of CBC by BRCA1 with TNBC vs. others.