Clinics in Oncology

Research Article
Published: 20 Oct, 2021

Contralateral Prophylactic Mastectomy Improves Survival Only Marginally in Patients with Unilateral Triple-Negative Breast Cancer: A Cohort Study Based on SEER Database

*Pengcheng Yang, Yuxin Chu, Qian Li, Tianyu Lei, Jia Song, Tingting Ning and Qinyong Hu**

Cancer Center, Renmin Hospital of Wuhan University, China

Abstract

Background: The effect of Contralateral Prophylactic Mastectomy (CPM) on the survival rate of Triple-Negative Breast Cancer (TNBC) patients is still controversial. The purpose of this study was to confirm whether unilateral TNBC patients benefit from CPM.

Methods: 10,006 patients with unilateral TNBC in the Surveillance, Epidemiology and End Results (SEER) database were enrolled in this study; Propensity Score Matching (PSM) was applied to balance patient assignments. After PSM, 3,039 pairs of patients were divided into a CPM group and no-CPM group, respectively. All the patients have undergone total mastectomy or radical mastectomy. Cox proportional hazards regression models were used to evaluate Overall Survival (OS) and Breast Cancer-Specific Survival (BCSS) of the two groups. Subgroup analysis was introduced to exclude the effect of confounding factors. To identify potential variables for prognosis, Kaplan-Meier survival analysis and Cox regression analysis were used and were presented by Kaplan-Meier curve and forest plot separately.

Results: With a median follow-up time of 34.5 months (IQR 1 to 83 months), the estimated 5-year BCSS rates for patients in the CPM group and the no-CPM group were 81.96% and 78.71%, the 5-year OS rates were 80.10% and 75.05%, respectively. CPM improved the BCSS (hazard ratio [HR] =0.79; 95% confidence interval [CI] =0.69-0.90, p=0.001) and OS (HR=0.74; 95% CI=0.66-0.84, p<0.001) of unilateral TNBC patients. Univariate subgroup analyses revealed that there was no significant difference in survival time for patients in stage N3 who underwent CPM or not (p>0.05).

Conclusion: CPM only limitedly improved BCSS and OS in patients with unilateral TNBC undergoing total mastectomy or radical mastectomy and was not recommended for stage N3 patients.

Keywords: Breast neoplasms; Prophylactic mastectomy; Survival analysis; Triple negative breast neoplasms

OPEN ACCESS

Correspondence:

Qinyong Hu, Cancer Center, Renmin Hospital of Wuhan University, No. 99, Zhangzhidong Road, Wuchang District, Wuhan, China, Tel: +8613986123799; E-mail: rm001223@whu.edu.cn

Received Date: *15 Sep 2021*

Accepted Date: *06 Oct 2021*

Published Date: *20 Oct 2021*

Citation:

Yang P, Chu Y, Li Q, Lei T, Song J, Ning T, et al. Contralateral Prophylactic Mastectomy Improves Survival Only Marginally in Patients with Unilateral Triple-Negative Breast Cancer: A Cohort Study Based on SEER Database. Clin Oncol. 2021; 6: 1868.

ISSN: 2474-1663

Copyright *© 2021 Qinyong Hu. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.*

Abbreviations

CPM: Contralateral Prophylactic Mastectomy; TNBC: Triple-Negative Breast Cancer; SEER: Surveillance, Epidemiology and End Results; OS: Overall Survival; BCSS: Breast Cancer-Specific Survival; HR: Hazard Ratio; CI: Confidence Interval; PSM: Propensity Score Matching; BCT: Breast-Conserving Therapy

Introduction

Triple-Negative Breast Cancer (TNBC) refers to a heterogeneous collection of breast cancer that lacks the expression of Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal growth factor Receptor 2 (HER2), accounting for 12% to 17% of all breast cancers [1,2]. According to WHO statistics in 2018, the incidence rate of breast cancer today is nearly the same as that of lung cancer (11.6% of the total cases) in both sexes combined, accounting for almost 1 in 4 cancer cases among women [3]. TNBC tends to be biologically aggressive and with a lack of commonly utilized targeting agents, which is often associated with a worse prognosis and tends to relapse earlier compared with other subtypes of breast cancer [1,4-6]. About 1% to 4% of patients with unilateral breast cancer developed Contralateral Breast Cancer (CBC) within 5 to 12 years and the risk increases by 0.5% to 0.75% per year, in triple-negative disease cases, the risk of CBC was increased steadily over time [7-9].

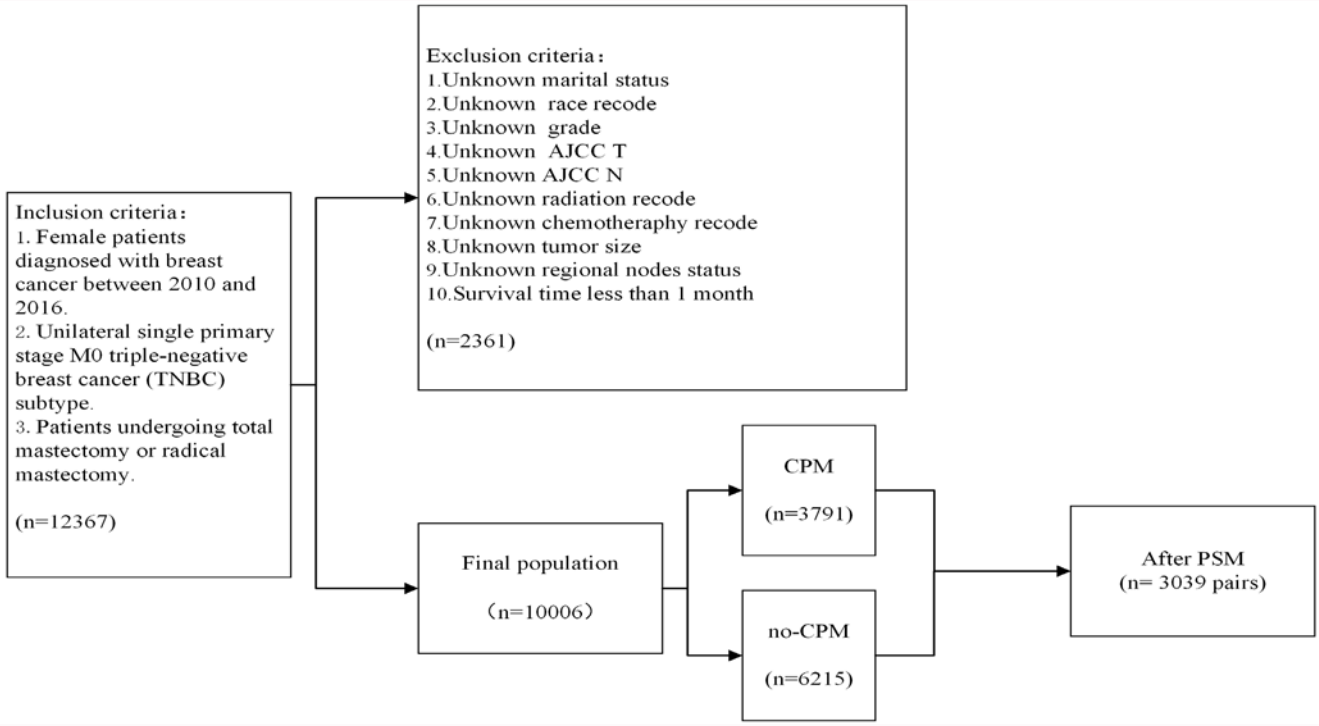

Figure 1: The flowchart of patients' selection from the SEER database.

The risk of death for bilateral breast cancer was approximately 2.50 times higher than unilateral breast cancer [10]. Therefore, reducing the incidence of contralateral breast cancer will be helpful to reduce the mortality of breast cancer patients.

Plenty of studies have demonstrated that breast cancer patients could obtain a survival advantage and decrease cancer-related anxiety from Contralateral Prophylactic Mastectomy (CPM) [11-17]. However, CPM is usually more applicable to breast cancer patients with BRCA mutations because they have a higher risk of developing Contralateral Breast Cancer (CBC), this risk was higher in BRCA1 compared to BRCA2 carriers [18]. A retrospective study demonstrated that among patients with BRCA mutations, 57.1% have the clinical TNBC subtype [19]. Despite the use of CPM has been increased in breast cancer patients these years, only a limited number of studies focused on CPM in TNBC [20,21].

In this study, we used the Surveillance, Epidemiology, and End Results (SEER) database to evaluate the impact of CPM on the clinical outcome of unilateral TNBC patients undergoing total mastectomy or radical mastectomy.

Patients and Methods

Patient selection

All data used in the current study were obtained from Surveillance, Epidemiology, and End Results (SEER) 18 registries Custom Data (with additional treatment fields) of the National Cancer Institute in the United States. We used SEER*Stat version 8.3.6 to download data files directly. No informed consent or institutional review board approval was required in the present study due to the public-available data of SEER. The inclusion criteria were: (a) Female patients diagnosed with breast cancer between 2010 and 2016. (b) Unilateral single primary stage M0 Triple-Negative Breast Cancer (TNBC) subtype. (c) Patients undergoing total mastectomy or radical mastectomy. Patients missing any of the following information were excluded: Marital status, race recode, age at diagnosis, AJCC TNM stage, tumor size, the status of regional nodes, radiation recode, vital status recodes, and follow-up. Patients before 2010 or after 2016 were excluded because these patients were not recorded in SEER 18 registries Custom Data. People with postoperative survival time of less than one month were also excluded. The selection process was shown in Figure 1.

Data collection

The following variables were collected from all patients: Age at diagnosis, marital status, race recode, laterality, grade, AJCC TNM stage, tumor size, regional nodes status, surgery type, radiation recode, chemotherapy recode, survival months, and vital status recode. In the study, Breast Cancer-Specific Survival (BCSS) was used as the primary study outcome and was calculated from the date of diagnosis to the date of death caused by breast cancer. The secondary endpoint was Overall Survival (OS) (time from diagnosis to death from any cause).

Statistical analysis

The main demographic data include age at diagnosis, marital status, race recode. Age was divided into three subgroups (<40, 40-59 and ≥ 60 years). Marital status comprised married and not married (divorced, widowed, single, and separated). Race categories included white, black, and other (American Indian/AK Native, Asian/Pacific Islander). Tumor features included TNM stage, tumor size, and regional nodes status. Treatment methods were classified into surgery (radical mastectomy and total mastectomy), chemotherapy, and radiotherapy. Propensity Score Matching (PSM) was applied to balance patient assignments to properly assess the effects of CPM. The Chi-square test was used to evaluate the differences between the variables. OS and BCSS were estimated by the Kaplan-Meier method, and differences between groups were assessed using the log-rank test.

Table 1: Baseline characteristics of TNBC patients included in this study (n=10006 and n=6078 after PSM).

Variables	Before PSM			p	After PSM			p
	Total, n (%)	No-CPM, n (%)	CPM, n (%)		Total, n (%)	No-CPM, n (%)	CPM, n (%)	
	n=10006	n=6215 (62.1)	n=3791 (37.9)		n=6078	n=3039	n=3039	
Age				**<0.001**				**0.484**
<40	1382 (13.80)	490 (7.90)	892 (23.50)		928 (15.30)	459 (15.10)	469 (15.40)	
40-59	5892 (58.90)	3364 (54.10)	2528 (66.70)		4377 (72.00)	2178 (71.70)	2199 (72.40)	
≥ 60	2732 (27.30)	2361 (38.00)	371 (9.80)		773 (12.70)	402 (13.20)	371 (12.20)	
Race				**<0.001**				**0.734**
White	7261 (72.60)	4222 (67.90)	3039 (80.20)		4673 (76.90)	2341 (77.00)	2332 (76.70)	
Black	1885 (18.80)	1343 (21.60)	542 (14.30)		1008 (16.60)	507 (16.70)	501 (16.50)	
Other	860 (8.60)	650 (10.50)	210 (5.50)		397 (6.50)	191 (6.30)	206 (6.80)	
Marital status				**<0.001**				**0.091**
Married	5728 (57.20)	3256 (52.40)	2472 (65.20)		3766 (62.00)	1915 (63.00)	1851 (60.90)	
Not Married	4278 (42.80)	2959 (47.60)	1319 (34.80)		2312 (38.00)	1124 (37.00)	1188 (39.10)	
Laterality				**0.451**				**0.739**
Left	5050 (50.50)	3155 (50.80)	1895 (50.00)		3037 (50.00)	1525 (50.20)	1512 (49.80)	
Right	4956 (49.50)	3060 (49.20)	1896 (50.00)		3041 (50.00)	1514 (49.80)	1527 (50.20)	
Grade				**0.003**				**0.713**
I	142 (1.40)	96 (1.50)	46 (1.20)		79 (1.30)	36 (1.20)	43 (1.40)	
II	1543 (15.40)	1018 (16.40)	525 (13.80)		891 (14.70)	435 (14.30)	456 (15.00)	
III	8236 (82.30)	5050 (81.30)	3186 (84.00)		5054 (83.20)	2542 (83.60)	2512 (82.70)	
IV	85 (0.80)	51 (0.80)	34 (0.90)		54 (0.90)	26 (0.90)	28 (0.90)	
Stage T				**<0.001**				**0.583**
1	3059 (30.60)	1722 (27.70)	1337 (35.30)		2037 (33.50)	996 (32.80)	1041 (34.30)	
2	4900 (49.00)	3019 (48.60)	1881 (49.60)		2988 (49.20)	1520 (50.00)	1468 (48.30)	
3	1395 (13.90)	969 (15.60)	426 (11.20)		772 (12.70)	383 (12.60)	389 (12.80)	
4	652 (6.50)	505 (8.10)	147 (3.90)		281 (4.60)	140 (4.60)	141 (4.60)	
Stage N				**<0.001**				**0.002**
0	3059 (30.60)	1722 (27.70)	1337 (35.30)		3307 (54.40)	1716 (56.50)	1591 (52.40)	
1	4900 (49.00)	3019 (48.60)	1881 (49.60)		1702 (28.00)	787 (25.90)	915 (30.10)	
2	1395 (13.90)	969 (15.60)	426 (11.20)		701 (11.50)	349 (11.50)	352 (11.60)	
3	652 (6.50)	505 (8.10)	147 (3.90)		368 (6.10)	187 (6.20)	181 (6.00)	
Tumor size (mm)				**<0.001**				**0.234**
<20	2765 (27.60)	1549 (24.90)	1216 (32.10)		1843 (30.30)	894 (29.40)	949 (31.20)	
20-50	5490 (54.90)	3414 (54.90)	2076 (54.80)		3321 (54.60)	1692 (55.70)	1629 (53.60)	
>50	1751 (17.50)	1252 (20.10)	499 (13.20)		914 (15.00)	453 (14.90)	461 (15.20)	
Regional nodes positive				**<0.001**				**0.551**
0	6050 (60.50)	3532 (56.80)	2518 (66.40)		3782 (62.20)	1911 (62.90)	1871 (61.60)	
1-3	2467 (24.70)	1592 (25.60)	875 (23.10)		1549 (25.50)	758 (24.90)	791 (26.00)	
≥ 4	1489 (14.90)	1091 (17.60)	398 (10.50)		747 (12.30)	370 (12.20)	377 (12.40)	
Surgery type				**<0.001**				**0.979**
Radical mastectomy	4475 (44.70)	3147 (50.60)	1328 (35.00)		2499 (41.10)	1249 (41.10)	1250 (41.10)	
Total mastectomy	5531 (55.30)	3068 (49.40)	2463 (65.00)		3579 (58.90)	1790 (58.90)	1789 (58.90)	
Chemotherapy				**<0.001**				**0.273**
No/unknown	2121 (21.20)	1673 (26.90)	448 (11.80)		807 (13.30)	389 (12.80)	418 (13.80)	
Yes	7885 (78.80)	4542 (73.10)	3343 (88.20)		5271 (86.70)	2650 (87.20)	2621 (86.20)	
Radiotherapy				**0.053**				**0.828**
No/unknown	6869 (68.60)	4223 (67.90)	2646 (69.80)		4040 (66.50)	2024 (66.60)	2016 (66.30)	
Yes	3137 (31.40)	1992 (32.10)	1145 (30.20)		2038 (33.50)	1015 (33.40)	1023 (33.70)	

Table 2: Cox proportional hazard regression model of breast cancer-specific survival (n=6078).

Variables	Univariate Cox		Multivariate Cox	
	HR (95% CI)	P value	HR (95% CI)	P value
CPM				
No	Ref.		Ref.	
Yes	0.83 (0.72-0.95)	0.006	0.79 (0.69-0.90)	0.001
Age				
<40	Ref.		Ref.	
40-59	0.69 (0.58-0.81)	<0.001	0.81 (0.68-0.97)	0.021
≥ 60	0.74 (0.58-0.95)	0.017	0.95 (0.73-1.22)	0.669
Race				
White	Ref.		Ref.	
Black	1.19 (1.00-1.41)	0.044	1.13 (0.95-1.35)	0.156
Other	0.63 (0.45-0.89)	0.009	0.73 (0.52-1.04)	0.082
Marital status				
Married	Ref.		Ref.	
Not Married	1.26 (1.10-1.44)	0.001	1.14 (0.99-1.31)	0.062
Laterality				
Left	Ref.			
Right	1.02 (0.89-1.17)	0.774		
Grade				
I	Ref.		Ref.	
II	1.64 (0.72-3.75)	0.238	1.63 (0.71-3.72)	0.247
III	2.27 (1.01-5.06)	0.046	2.00 (0.89-4.49)	0.093
IV	3.96 (1.52-10.31)	0.005	3.42 (1.31-8.95)	0.012
Stage T				
1	Ref.		Ref.	
2	2.20 (1.82-2.66)	<0.001	1.37 (0.93-2.01)	0.111
3	5.28 (4.27-6.52)	<0.001	1.97 (1.18-3.31)	0.01
4	7.29 (5.65-9.42)	<0.001	2.84 (1.82-4.42)	<0.001
Stage N				
0	Ref.		Ref.	
1	2.69 (2.27-3.18)	<0.001	0.98 (0.67-1.43)	0.911
2	5.47 (4.49-6.66)	<0.001	1.09 (0.71-1.67)	0.706
3	9.29 (7.56-11.42)	<0.001	1.79 (1.16-2.75)	0.009
Tumor size (mm)				
<20	Ref.		Ref.	
20-50	2.23 (1.84-2.71)	<0.001	1.30 (0.87-1.93)	0.195
>50	5.84 (4.74-7.19)	<0.001	1.87 (1.13-3.10)	0.015
Regional nodes positive				
0	Ref.		Ref.	
1-3	2.62 (2.22-3.10)	<0.001	2.35 (1.64-3.37)	<0.001
≥ 4	7.10 (6.03-8.36)	<0.001	4.43 (3.00-6.54)	<0.001
Surgery type				
Radical mastectomy	Ref.		Ref.	
Total mastectomy	0.46 (0.40-0.53)	<0.001	0.97 (0.83-1.13)	0.683
Chemotherapy				
No	Ref.		Ref.	
Yes	1.44 (1.15-1.79)	0.001	0.70 (0.55-0.89)	0.004
Radiotherapy				
No	Ref.		Ref.	
Yes	2.34 (2.05-2.68)	<0.001	1.01 (0.87-1.18)	0.863

Univariate and multivariate Cox proportional hazards regression models were performed to identify the independent factors with a significant impact on patient survival. Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) were calculated for each prognostic factor. All the statistical analyses were performed using SPSS statistical software, version 26.0 (SPSS, Chicago, IL, USA). A two-tailed P<0.05 was considered statistically significant.

Results

Patient characteristics

Based on the inclusion and exclusion criteria, 10,006 patients were included in our study, of which 3,791 (37.9%) patients underwent CPM while 6,215 (62.1%) patients did not undergo Contralateral Prophylactic Mastectomy (no-CPM). Most variables showed a significant difference between the two groups (p<0.05), except for laterality and radiotherapy (p>0.05). Compared with those patients who did not receive CPM, patients in the CPM group were more <60 years old (90.2% *vs.* 62.0%), more white race (80.2% *vs.* 67.9%), more married (65.2% *vs.* 52.4%), and more patients underwent total mastectomy (65.0% *vs.* 49.4%). There was little difference in proportion distribution among other variables. After PSM, a total of 3,039 pairs of cases were matched. We analyzed the baseline data of each subgroup and found that there was no significant statistical difference between these two groups besides the N stage. Table 1 summarizes the demographic and clinical characteristics of the patients in both groups before and after PSM.

Survival analysis of all population

The median follow-up time was 34.5 months (IQR 1 to 83 months). 860 (14.1%) patients died from breast cancer specifically, 378 (12.4%) in the CPM group and 482 (15.8%) in the no-CPM group. The estimated 5-year Breast Cancer-Specific Survival (BCSS) rates for patients in the CPM group and no-CPM group were 81.96% and 78.71%, the 5-year Overall Survival (OS) rates were 80.10% and

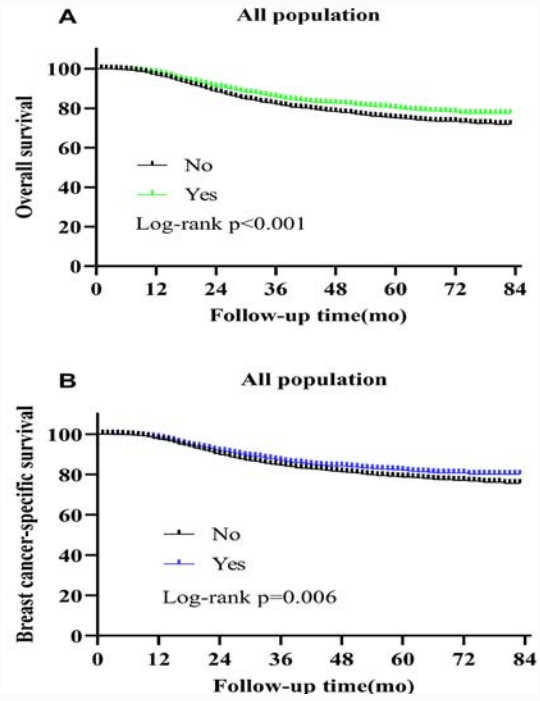

Figure 2: Survival curves with the log-rank tests of (A) overall survival (p<0.001) and (B) breast cancer-specific survival (p<0.001).

Table 3: Cox proportional hazard regression model of overall survival (n=6078).

	Univariate Cox		Multivariate Cox	
Variables	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
CPM				
No	Ref.		Ref.	
Yes	0.78 (0.69-0.88)	<0.001	0.74 (0.66-0.84)	<0.001
Age				
<40	Ref.		Ref.	
40-59	0.71 (0.60-0.84)	<0.001	0.83 (0.70-0.98)	0.032
≥ 60	0.96 (0.78-1.20)	0.74	1.17 (0.93-1.47)	0.172
Race				
White	Ref.		Ref.	
Black	1.18 (1.00-1.38)	0.045	1.13 (0.96-1.33)	0.132
Other	0.60 (0.44-0.84)	0.002	0.71 (0.51-0.99)	0.045
Marital status				
Married	Ref.		Ref.	
Not Married	1.31 (1.15-1.48)	<0.001	1.18 (1.04-1.35)	0.01
Laterality				
Left	Ref.			
Right	1.00 (0.88-1.13)	0.959		
Grade				
I	Ref.		Ref.	
II	1.33 (0.67-2.61)	0.416	1.34 (0.68-2.65)	0.397
III	1.73 (0.90-3.34)	0.101	1.61 (0.83-3.11)	0.161
IV	3.38 (1.52-7.53)	0.003	3.06 (1.36-6.85)	0.007
Stage T				
1	Ref.		Ref.	
2	2.03 (1.71-2.41)	<0.001	1.23 (0.88-1.74)	0.23
3	4.57 (3.77-5.55)	<0.001	1.89 (1.18-3.05)	0.009
4	6.38 (5.04-8.08)	<0.001	2.60 (1.73-3.90)	<0.001
Stage N				
0	Ref.		Ref.	
1	2.44 (2.09-2.85)	<0.001	0.96 (0.67-1.38)	0.836
2	4.80 (4.00-5.76)	<0.001	1.04 (0.70-1.57)	0.836
3	8.00 (6.60-9.70)	<0.001	1.70 (1.13-2.57)	0.011
Tumor size (mm)				
<20	Ref.		Ref.	
20-50	2.11 (1.77-2.51)	<0.001	1.43 (1.00-2.03)	0.048
>50	5.10 (4.21-6.17)	<0.001	1.88 (1.18-2.99)	0.008
Regional nodes positive				
0	Ref.		Ref.	
1-3	2.42 (2.07-2.82)	<0.001	2.31 (1.64-3.24)	<0.001
≥ 4	6.31 (5.43-7.34)	<0.001	4.31 (2.98-6.23)	<0.001
Surgery type				
Radical mastectomy	Ref.		Ref.	
Total mastectomy	0.49 (0.43-0.56)	<0.001	0.97 (0.84-1.12)	0.706
Chemotherapy				
No	Ref.		Ref.	
Yes	1.17 (0.97-1.41)	0.111	0.62 (0.51-0.76)	<0.001
Radiotherapy				
No	Ref.		Ref.	
Yes	2.08 (1.83-2.35)	<0.001	0.96 (0.83-1.11)	0.607

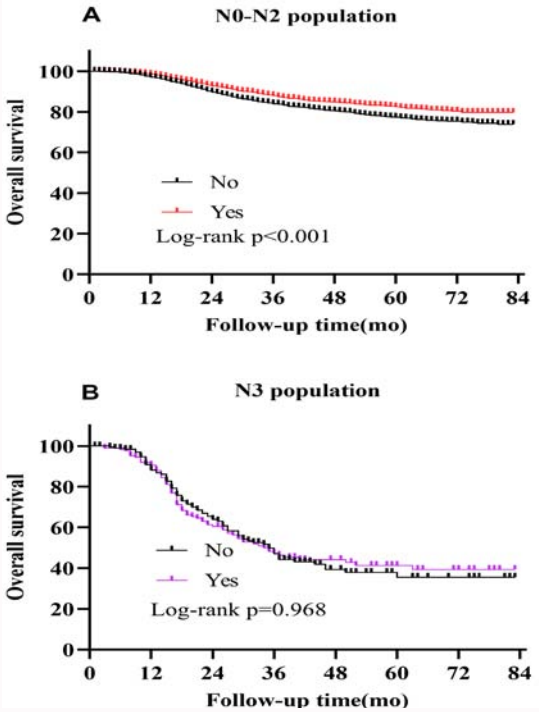

Figure 3: Survival curves with the log-rank tests of breast cancer-specific survival for N0-N2 population (A), N3 population (B).

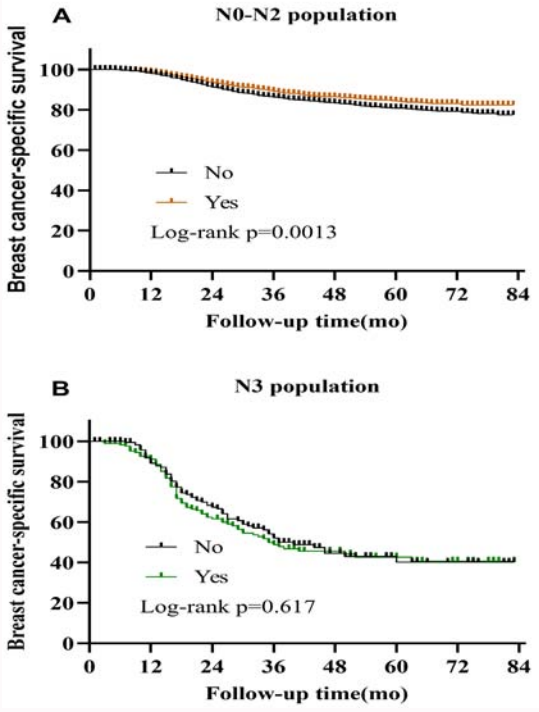

Figure 4: Survival curves with the log-rank tests of overall survival for N0-N2 population (A), N3 population (B).

75.05%, respectively. The Kaplan Meier analysis revealed that patients who underwent CPM had better survival than the patients in the no-CPM group in both BCSS and OS (both log-rank p<0.005, Figure 2). Univariate and multivariate Cox proportional hazard models were estimated to investigate the effect of risk factors on BCSS and OS.

In the univariate analysis of BCSS, all factors were associated

Variables	Total,n(%)	No-CPM, n(%)	CPM, n (%)	HR (95% CI)	P
CPM					
No	3039(50)			Ref.	
Yes	3039(50)			0.74(0.66-0.84)	<0.001
Age					
<40	928(15.30)	459(15.10)	469(15.40)	Ref.	
40-59	4377(72.00)	2178(71.70)	2199(72.40)	0.83(0.70-0.98)	0.032
≥60	773(12.70)	402(13.20)	371(12.20)	1.17(0.93-1.47)	0.172
Race					
White	4673(76.90)	2341(77.00)	2332(76.70)	Ref.	
Black	1008(16.60)	507(16.70)	501(16.50)	1.13(0.96-1.33)	0.132
Other	397(6.50)	191(6.30)	206(6.80)	0.71(0.51-0.99)	0.045
Marital status					
Married	3766(62.00)	1915(63.00)	1851(60.90)	Ref.	
Not Married	2312(38.00)	1124(37.00)	1188(39.10)	1.18(1.04-1.35)	0.01
Grade					
I	79(1.30)	36(1.20)	43(1.40)	Ref.	
II	891(14.70)	435(14.30)	456(15.00)	1.34(0.68-2.65)	0.397
III	5054(83.20)	2542(83.60)	2512(82.70)	1.61(0.83-3.11)	0.161
IV	54(0.90)	26(0.90)	28(0.90)	3.06(1.36-6.85)	0.007
Stage T					
T1	2037(33.50)	996(32.80)	1041(34.30)	Ref.	
T2	2988(49.20)	1520(50.00)	1468(48.30)	1.23(0.88-1.74)	0.23
T3	772(12.70)	383(12.60)	389(12.80)	1.89(1.18-3.05)	0.009
T4	281(4.60)	140(4.60)	141(4.60)	2.60(1.73-3.90)	<0.001
Stage N					
N0	3307(54.40)	1716(56.50)	1591(52.40)	Ref.	
N1	1702(28.00)	787(25.90)	915(30.10)	0.96(0.67-1.38)	0.836
N2	701(11.50)	349(11.50)	352(11.60)	1.04(0.70-1.57)	0.836
N3	368(6.10)	187(6.20)	181(6.00)	1.70(1.13-2.57)	0.011
Tumor size(mm)					
＜20	1843(30.30)	894(29.40)	949(31.20)	Ref.	
20-50	3321(54.60)	1692(55.70)	1629(53.60)	1.43(1.00-2.03)	0.048
＞50	914(15.00)	453(14.90)	461(15.20)	1.88(1.18-2.99)	0.008
Regional nodes positive					
0	3782(62.20)	1911(62.90)	1871(61.60)	Ref.	
1-3	1549(25.50)	758(24.90)	791(26.00)	2.31(1.64-3.24)	<0.001
≥4	747(12.30)	370(12.20)	377(12.40)	4.31(2.98-6.23)	<0.001
Surgery type					
Radical mastectomy	2499(41.10)	1249(41.10)	1250(41.10)	Ref.	
Total mastectomy	3579(58.90)	1790(58.90)	1789(58.90)	0.97(0.84-1.12)	0.706
Chemotherapy					
No	807(13.30)	389(12.80)	418(13.80)	Ref.	
Yes	5271(86.70)	2650(87.20)	2621(86.20)	0.62(0.51-0.76)	<0.001
Radiotherapy					
No	4040(66.50)	2024(66.60)	2016(66.30)	Ref.	
Yes	2038(33.50)	1015(33.40)	1023(33.70)	0.96(0.83-1.11)	0.607

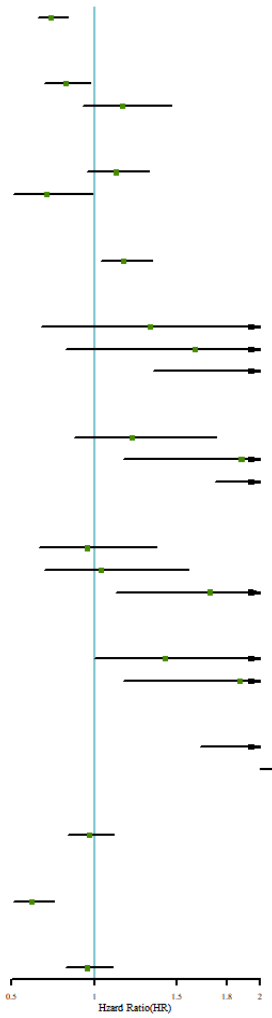

Figure 5: Forest plot of Hazard Ratios (HRs) of OS for Contralateral Prophylactic Mastectomy (CPM) group versus non-Contralateral Prophylactic Mastectomy (no-CPM) group in the subgroup analysis.

with BCSS in TNBC patients compared with each reference group, with the exclusion of laterality (P>0.05). All relevant factors were integrated into the multivariate Cox regression analysis of BCSS. The multivariate analysis demonstrated that patients of grade IV, more advanced T stage (T3-T4), stage N3, tumor size >50 mm and more regional nodes positive resulted in an adverse survival outcome of TNBC (HR>1, P<0.05). CPM, other races, chemotherapy, and midlife (40 to 59 years old) were protective factors for women with TNBC (HR<1, P<0.05). The results of the multivariate analysis were shown in Table 2.

The univariate Cox regression analysis of Overall Survival (OS) indicated laterality and radiotherapy were not significantly associated with OS. According to previous clinical experience, radiotherapy was one of the conventional treatment protocols for TNBC, so radiotherapy was also included in the multivariate Cox proportional hazards model. Results showed that unmarried, grade IV, more advanced T stage (T3-T4), stage N3, larger tumors, and more regional nodes positive were proved to be positively associated with breast cancer-specific mortality (HR>1, P<0.05). Patients in CPM, chemotherapy, midlife (40 to 59 years old), and the other race (American Indian/AK Native, Asian/Pacific Islander) group experience better survival (HR<1, P<0.05). CPM was shown to be the factor associated with improved cancer outcomes in both univariate and multivariate analysis of OS (univariate analysis: HR=0.78, CI=0.69-0.88, P<0.001, and multivariate analysis: HR=0.74, CI= 0.66-0.84, P<0.001), detailed in Table 3.

In conclusion, these analysts suggested that TNBC patients undergoing radical mastectomy or total mastectomy could benefit from CPM and chemotherapy. K-M survival curve for BCSS and OS was shown in Figure 2.

Subgroup analysis

The baseline of stage N remained unbalanced after propensity score matching (Table 1); therefore stage N may be a potential confounder and was included in the subgroup analysis. According to the results of BCSS and OS multivariate Cox survival analysis, the N stage was divided into N0-N2 group and N3 group because there was no significant difference between N1-N2 patients and N0 patients (log-rank P>0.05). K-M survival curves showed that stage N0-N2 patients in the CPM group had superior BCSS and OS than

Variables	Total,n(%)	No-CPM, n(%)	CPM, n (%)	HR (95% CI)	P
CPM					
No	3039(50)			Ref.	
Yes	3039(50)			0.79(0.69-0.90)	0.001
Age					
<40	928(15.30)	459(15.10)	469(15.40)	Ref.	
40-59	4377(72.00)	2178(71.70)	2199(72.40)	0.81(0.68-0.97)	0.021
≥60	773(12.70)	402(13.20)	371(12.20)	0.95(0.73-1.22)	0.669
Race					
White	4673(76.90)	2341(77.00)	2332(76.70)	Ref.	
Black	1008(16.60)	507(16.70)	501(16.50)	1.13(0.95-1.35)	0.156
Other	397(6.50)	191(6.30)	206(6.80)	0.73(0.52-1.04)	0.082
Marital status					
Married	3766(62.00)	1915(63.00)	1851(60.90)	Ref.	
Not Married	2312(38.00)	1124(37.00)	1188(39.10)	1.14(0.99-1.31)	0.062
Grade					
I	79(1.30)	36(1.20)	43(1.40)	Ref.	
II	891(14.70)	435(14.30)	456(15.00)	1.63(0.71-3.72)	0.247
III	5054(83.20)	2542(83.60)	2512(82.70)	2.00(0.89-4.49)	0.093
IV	54(0.90)	26(0.90)	28(0.90)	3.42(1.31-8.95)	0.012
Stage T					
T1	2037(33.50)	996(32.80)	1041(34.30)	Ref.	
T2	2988(49.20)	1520(50.00)	1468(48.30)	1.37(0.93-2.01)	0.111
T3	772(12.70)	383(12.60)	389(12.80)	1.97(1.18-3.31)	0.01
T4	281(4.60)	140(4.60)	141(4.60)	2.84(1.82-4.42)	<0.001
Stage N					
N0	3307(54.40)	1716(56.50)	1591(52.40)	Ref.	
N1	1702(28.00)	787(25.90)	915(30.10)	0.98(0.67-1.43)	0.911
N2	701(11.50)	349(11.50)	352(11.60)	1.09(0.71-1.67)	0.706
N3	368(6.10)	187(6.20)	181(6.00)	1.79(1.16-2.75)	0.009
Tumor size(mm)					
<20	1843(30.30)	894(29.40)	949(31.20)	Ref.	
20-50	3321(54.60)	1692(55.70)	1629(53.60)	1.30(0.87-1.93)	0.195
>50	914(15.00)	453(14.90)	461(15.20)	1.87(1.13-3.10)	0.015
Regional nodes positive					
0	3782(62.20)	1911(62.90)	1871(61.60)	Ref.	
1-3	1549(25.50)	758(24.90)	791(26.00)	2.35(1.64-3.37)	<0.001
≥4	747(12.30)	370(12.20)	377(12.40)	4.43(3.00-6.54)	<0.001
Surgery type					
Radical mastectomy	2499(41.10)	1249(41.10)	1250(41.10)	Ref.	
Total mastectomy	3579(58.90)	1790(58.90)	1789(58.90)	0.97(0.83-1.13)	0.683
Chemotherapy					
No	807(13.30)	389(12.80)	418(13.80)	Ref.	
Yes	5271(86.70)	2650(87.20)	2621(86.20)	0.70(0.55-0.89)	0.004
Radiotherapy					
No	4040(66.50)	2024(66.60)	2016(66.30)	Ref.	
Yes	2038(33.50)	1015(33.40)	1023(33.70)	1.01(0.87-1.18)	0.863

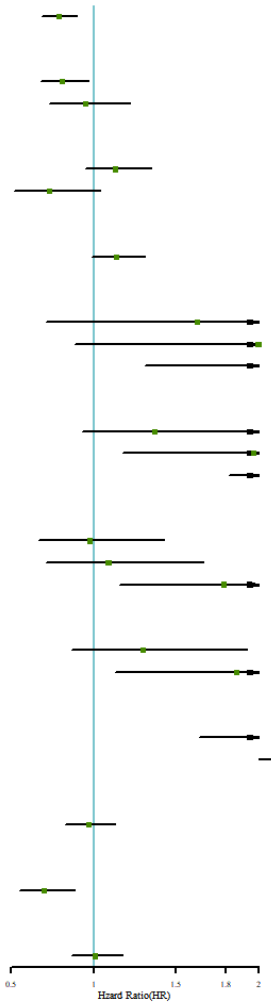

Figure 6: Forest plot of Hazard Ratios (HRs) of BCSS for Contralateral Prophylactic Mastectomy (CPM) group versus non-Contralateral Prophylactic Mastectomy (no-CPM) group in the subgroup analysis.

those in the no-CPM group (log-rank P<0.05) (Figure 3, 4), while stage N3 patients in both groups did not derive survival benefit from CPM (log-rank P>0.05).

The subgroup analyses were illustrated by forest plots of HRs, which revealed that factors positively associated with the prognosis of TNBC patients included CPM, chemotherapy, and middle age (40 to 59 years old). These two forest plots also more visualize that higher tumor stage (stage T3-T4 and N3), larger tumor tissue (tumor size >50 mm), and more regional positive lymph nodes were risk factors for TNBC patients (Figure 5, 6).

Discussion

It is still controversial that whether patients with TNBC can get survival benefits from the contralateral prophylactic mastectomy. In this study, the clinical characteristics of patients with TNBC and the effect of CPM on the prognosis of TNBC patients were analyzed retrospectively, which was based on a large population from the SEER database. Our results suggest that patients with unilateral TNBC undergoing total mastectomy or radical mastectomy may obtain survival benefits from CPM.

In a previous cohort study of 1325 TNBC patients; Adkins et al. [22] investigated the effect of surgical approaches on the prognosis in TNBC patients. This study reported the 5-year Overall Survival rate (OS) of patients undergoing Breast-Conserving Therapy (BCT) and mastectomy was 74% and 63%, respectively. Our study showed that patients undergoing CPM have a higher 5-year Overall Survival rate (OS) of 80.10%, and we took a more rigorous manner to eliminate the possible effect of confounders.

Reducing recurrence is one of the ways to reduce the risk of death in this special population. Several studies have shown that female TNBC patients are at a higher risk of relapse and have an associated poorer prognosis compared with those with other subtypes of breast cancer [1,23], an early peak of recurrences at 3 years after diagnosis which was responsible for the poor prognosis of triple-negative breast cancer [24]. CPM could prolong the BCSS of TNBC patients by decreasing the risk of subsequent contralateral breast cancer.

In addition, TNBC complicated with occult cancer may be another reason for poor prognosis. The overall rate of occult cancer in breast cancer was about 7.1%, simple total mastectomy or radical

mastectomy cannot completely remove occult cancer that may coexist [25]. Therefore, recurrence or progression will occur. King et al. [26] reported a part of occult breast cancer was detected in contralateral prophylactic mastectomy specimens. Prophylactic resection of the contralateral breast could minimize the risk of this occult cancer. Although our study could not directly prove that CPM could increase the resection rate of occult cancer, it also indirectly showed that the expanded resection could reduce the risk of death, and we speculated that this risk might be caused by occult cancer, so further histopathological examination to verify the existence of occult cancer in the contralateral breast is necessary.

Although studies by Bedrosian et al. [14] and Brewster et al. [27] suggested that ER-negative or hormone receptor-negative breast cancer patients were more likely to receive benefit from CPM, their studies were not specific to the triple-negative subtype and therefore may underestimate the effect of CPM on receptor-positive patients.

In our observation, we found that not all unilateral TNBC patients could obtain a better prognosis from CPM. Unlike N0-N2 patients, there was no significant difference in survival of stage N3 patients with or without CPM (Figure 3, 4). Identifying subgroups more likely to achieve better treatment outcomes from CPM may be of great significance in choosing a more personalized approach for patients.

There are several limitations to this study, including those inherent to a retrospective observational study design. First, the study may be affected by selection bias. Second, the demographic information provided by the SEER database does not include complications and other detailed factors. The contribution of these factors to survival benefits cannot be evaluated. Third, the interval between surgery and radiotherapy and chemotherapy and the data of chemotherapy regimens may also have an impact on survival outcomes and provide important implications for clinical practice. Fourth, some studies have shown that BRCA1/2 mutation carriers with breast cancer have a high risk of contralateral disease, carriers of the BRCA1 gene mutation are more likely to develop triple-negative breast cancer, and these women usually choose to undergo contralateral mastectomy, to reduce the likelihood of recurrence [28,29]. However, the SEER database does not provide data on the status of BRCA1/2 mutation. Lack of availability of this information in the database limits us to evaluate the influence of these factors. Despite certain limitations, our study is a population-based study that includes a large number of unilateral TNBC patients, and the results are convincing.

Conclusion

In conclusion, our study demonstrates that CPM does improve survival in patients with unilateral triple-negative breast cancer, excluding those with stage N3, but this improvement is very limited. Therefore, clinicians should be extra cautious when choosing whether to apply CPM. Further prospective clinical trials are still needed to validate our findings.

References

1. Newman LA, Reis-Filho JS, Morrow M, Carey LA, King TA. The 2014 Society of Surgical Oncology Susan G. Komen for the Cure Symposium: Triple-negative breast cancer. Ann Surg Oncol. 2015;22(3):874-82.
2. De Santis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Sauer GA, et al. Breast cancer statistics, 2019. CA Cancer J Clin. 2019;69(6):438-51.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
4. Li X, Yang J, Peng L, Sahin AA, Huo L, Ward KC, et al. Triple-negative breast cancer has worse overall survival and cause-specific survival than non-triple-negative breast cancer. Breast Cancer Res Treat. 2017;161(2):279-87.
5. Bianchini G, Balko JM, Mayer IA, Sanders ME, Gianni L. Triple-negative breast cancer: Challenges and opportunities of a heterogeneous disease. Nature Rev Clin Oncol. 2016;13(11):674-90.
6. Dawood S. Triple-negative breast cancer: Epidemiology and management options. Drugs. 2010;70(17):2247-58.
7. Yoon TI, Kwak BS, Yi OV, Kim S, Um E, Yun KW, et al. Age-related risk factors associated with primary contralateral breast cancer among younger women versus older women. Breast Cancer Res Treat. 2019;173(3):657-65.
8. Montgomery LL, Tran KN, Heelan MC, Van Zee KJ, Massie MJ, Payne DK, et al. Issues of regret in women with contralateral prophylactic mastectomies. Ann Surg Oncol. 1999;6(6):546-52.
9. Mose S, Adamietz IA, Thilmann C, Saran F, Pahnke R, Bottcher HD. [The prognosis of bilateral breast carcinoma compared to unilateral breast tumor. 5- and 10-year follow-ups]. Strahlenther Onkol. 1995;171(4):207-13.
10. Kuo WH, Yen AM, Lee PH, Chen KM, Wang J, Chang KJ, et al. Cumulative survival in early-onset unilateral and bilateral breast cancer: An analysis of 1907 Taiwanese women. Br J Cancer. 2009;100(4):563-70.
11. Peralta EA, Ellenhorn JD, Wagman LD, Dagis A, Andersen JS, Chu DZ. Contralateral prophylactic mastectomy improves the outcome of selected patients undergoing mastectomy for breast cancer. Am J Surg. 2000;180(6):439-45.
12. Goldflam K, Hunt KK, Gershenwald JE, Singletary SE, Mirza N, Kuerer HM, et al. Contralateral prophylactic mastectomy. Predictors of significant histologic findings. Cancer. 2004;101(9):1977-86.
13. Tuttle TM, Habermann EB, Grund EH, Morris TJ, Virnig BA. Increasing use of contralateral prophylactic mastectomy for breast cancer patients: A trend toward more aggressive surgical treatment. J Clin Oncol. 2007;25(33):5203-9.
14. Bedrosian I, Hu CY, Chang GJ. Population-based study of contralateral prophylactic mastectomy and survival outcomes of breast cancer patients. J Natl Cancer Inst. 2010;102(6):401-9.
15. Wong-Brown MW, Meldrum CJ, Carpenter JE, Clarke CL, Narod SA, Jakubowska A, et al. Prevalence of BRCA1 and BRCA2 germline mutations in patients with triple-negative breast cancer. Breast Cancer Res Treat. 2015;150(1):71-80.
16. Lostumbo L, Carbine NE, Wallace J. Prophylactic mastectomy for the prevention of breast cancer. Cochrane Database Syst Rev. 2010(11):CD002748.
17. Hatcher MB, Fallowfield L, Hern R. The psychosocial impact of bilateral prophylactic mastectomy: Prospective study using questionnaires and semistructured interviews. BMJ. 2001;322(7278):76.
18. Valachis A, Nearchou AD, Lind P. Surgical management of breast cancer in BRCA-mutation carriers: A systematic review and meta-analysis. Breast Cancer Res Treat. 2014;144(3):443-55.
19. Atchley DP, Albarracin CT, Lopez A, Valero V, Amos CI, Gonzalez-Angulo AM, et al. Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. J Clin Oncol. 2008;26(26):4282-8.
20. Stucky CC, Gray RJ, Wasif N, Dueck AC, Pockaj BA. Increase in contralateral prophylactic mastectomy: Echoes of a bygone era? Surgical trends for unilateral breast cancer. Ann Surg Oncol. 2010;17(Suppl 3):330-7.

21. Lizarraga I, Schroeder MC, Weigel RJ, Thomas A. Surgical management of breast cancer in 2010-2011 SEER registries by hormone and HER2 receptor status. Ann Surg Oncol. 2015;22(Suppl 3):S566-72.

22. Adkins FC, Gonzalez-Angulo AM, Lei X, Hernandez-Aya LF, Mittendorf EA, Litton JK, et al. Triple-negative breast cancer is not a contraindication for breast conservation. Ann Surg Oncol. 2011;18(11):3164-73.

23. Anders CK, Carey LA. Biology, metastatic patterns, and treatment of patients with triple-negative breast cancer. Clin Breast Cancer. 2009;9(Suppl 2):S73-81.

24. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, et al. Triple-negative breast cancer: Clinical features and patterns of recurrence. Clin Cancer Res. 2007;13(15 Pt 1):4429-34.

25. Arai M, Yokoyama S, Watanabe C, Yoshida R, Kita M, Okawa M, et al. Genetic and clinical characteristics in Japanese hereditary breast and ovarian cancer: first report after establishment of HBOC registration system in Japan. J Hum Genet. 2018;63(4):447-57.

26. King TA, Pilewskie M, Muhsen S, Patil S, Mautner SK, Park A, et al. Lobular carcinoma in situ: A 29-year longitudinal experience evaluating clinicopathologic features and breast cancer risk. J Clin Oncol. 2015;33(33):3945-52.

27. Brewster AM, Bedrosian I, Parker PA, Dong W, Peterson SK, Cantor SB, et al. Association between contralateral prophylactic mastectomy and breast cancer outcomes by hormone receptor status. Cancer. 2012;118(22):5637-43.

28. Evans DG, Ingham SL, Baildam A, Ross GL, Lalloo F, Buchan I, et al. Contralateral mastectomy improves survival in women with BRCA1/2-associated breast cancer. Breast Cancer Res Treat. 2013;140(1):135-42.

29. Lakhani SR, Van De Vijver MJ, Jacquemier J, Anderson TJ, Osin PP, Mc Guffog L, et al. The pathology of familial breast cancer: Predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. J Clin Oncol. 2002;20(9):2310-8.