Original Article

Factors influencing post-mastectomy reconstruction in breast cancer patients aged 40 years and younger

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Background: Young women (age ≤40 years) with breast cancer are more likely to undergo post-mastectomy reconstruction compared to women >40 years. While White race, lower co-morbidity, and treatment at academic centers are associated with reconstruction in older patients, such factors have not been established in patients ≤40 years.

Methods: Female patients aged ≤40 years with stage I–III unilateral invasive breast cancer undergoing mastectomy from 2010–2018 were identified using the National Cancer Database (NCDB), and divided into groups: mastectomy alone (MA) and mastectomy with reconstruction (MR). Multivariable logistic regression and Cox proportional hazards models identified factors associated with MR, contralateral prophylactic mastectomy (CPM), and overall survival (OS).

Results: Of 43,065 patients, 66% underwent MR and 34% had MA. MR patients were more often non-Hispanic White, privately insured, and had more favorable disease (all P<0.001). CPM was performed in over half of all patients (61% MR, 51% MA). Private insurance, higher income, and CPM were positively associated with MR. MR patients had superior 5-year OS (92% *vs.* 85% MA, P<0.001). In patients who received neoadjuvant chemotherapy, the MR group had higher overall pathologic complete response (pCR) rates, and pCR was associated with MR.

Conclusions: In patients ≤40 years, demographic factors predicted MR while more advanced disease was associated with MA and poorer OS. The OS benefit of MR and CPM and universally high rates of CPM may be due to selection bias towards additional surgery in young patients with favorable prognosis, or to genetic factors not available in the NCDB.

Keywords: Post-mastectomy reconstruction; young women; breast cancer; age ≤40 years; contralateral prophylactic mastectomy (CPM)

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Introduction

Approximately 1 in 8 women will be diagnosed with breast cancer during their lifetime. Young women make up a small but important portion of this group. Approximately 6% of breast cancers in the United States occur in women <40 years old, a significant finding considering screening mammography is recommended to begin at age 40 years for an average risk woman (1). Breast cancer patients age ≤40 years are more often diagnosed with advanced disease and aggressive subtypes such as triple negative breast cancer (TNBC), human epidermal growth factor receptor 2 positive ($HER2^+$) breast cancer, and inflammatory breast cancer (2-5). Young age at breast cancer diagnosis is associated with poorer outcomes such as disease recurrence and mortality, and breast cancer is the leading cause of cancer-related deaths in women ≤40 years (2,3,6-9).

Previous studies have established that young women with breast cancer are more likely to undergo mastectomy and mastectomy with reconstruction (MR) compared to women >40 years (6,7,10,11), with reconstruction rates reaching 89% in the multicenter Young Women's Breast Cancer Study (12). Rates of contralateral prophylactic mastectomy (CPM) are also higher in breast cancer patients ≤40 years, and have increased over time, mirroring increasing use of MR (6,11,13). These trends persist despite an increasing body of compelling evidence demonstrating that women—and particularly young women—who undergo breast conserving therapy (BCT) have superior survival outcomes (14-17), and despite well-established literature showing lack of survival benefit for CPM in average-risk women with unilateral breast cancer (18).

Many factors influence whether patients undergo MR, including demographic and disease characteristics as well as use of adjuvant therapy, particularly radiation (19-22). Prior research has identified persistent socioeconomic and geographic disparities in the receipt of MR, with non-White race, public insurance, and receiving care in the South or West regions of the United States all associated with lower rates of MR (20,21). However, in these studies without age stratification, young women are likely not adequately represented due to the relatively low incidence of breast cancer in this population. Several retrospective cohort studies specifically examining patients >65 years have shown that younger age, White race, lower co-morbidity score, and treatment at academic centers are positively associated with MR (19,22,23). However, there is a paucity of high-quality population-level research focusing on these questions in women age ≤40 years with newly diagnosed breast cancer (12,24).

Utilizing the National Cancer Database (NCDB), we aimed to identify factors influencing MR in female patients aged ≤40 years with unilateral invasive breast cancer. In addition, we examined whether the factors associated with MR were predictors of CPM, and which patient, tumor, and treatment variables were associated with autologous *vs.* implant-based reconstruction. Finally, we determined the relationship of MR and CPM with overall survival (OS). It is our hope that our findings will help breast oncology providers and patients better understand the complexities of surgical decision-making in young women with breast cancer and address disparities in post-mastectomy care in this unique population. We present this article in accordance with the STROBE reporting checklist (https://abs.amegroups.com/article/view/10.21037/abs-23-48/rc).

Highlight box

Key findings

- Contralateral prophylactic mastectomy (CPM) is performed in over half of women ≤40 years regardless of whether they undergo reconstruction.
- Private insurance, higher income, and CPM are all positively associated with post-mastectomy reconstruction.
- Pathologic complete response to neoadjuvant chemotherapy was associated with increased rates of post-mastectomy reconstruction.

What is known and what is new?

- Young women with breast cancer are more likely to undergo post-mastectomy reconstruction than women >40 years.
- Post-mastectomy reconstruction is predicted by similar demographic factors in young women and women >40 years.
- In young women, more advanced disease was associated with decreased rates of post-mastectomy reconstruction.
- CPM remains common in young women despite a lack of evidence for improved survival.

What is the implication, and what should change now?

- Breast surgeons should ensure that all women are appropriately counselled on their reconstruction options and associated risks and benefits.

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). After Institutional Review Board exemption due to the deidentified data source, a retrospective cohort study using the NCDB was performed. Jointly sponsored by the American College of Surgeons

and the American Cancer Society, the NCDB is a clinical oncology database sourced from hospital registry data that represents >70% of newly diagnosed cancer cases nationwide, and 1,500 Commission on Cancer (CoC)-accredited facilities. Definitions of the database variables are available from the dictionary of NCDB Participant Use Data File (http://ncdbpuf.facs.org). The CoC's NCDB and the hospitals participating in the CoC NCDB are the sources of the de-identified data used herein: they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

Female patients aged ≤40 years with American Joint Committee on Cancer (AJCC) clinical stage I–III unilateral invasive breast cancer treated with mastectomy {subcutaneous [nipple-sparing (NSM)], simple (total), modified radical} from 2010–2018 were included (*Figure 1*). Simple mastectomy in the NCDB includes skin-sparing mastectomy for patients who underwent reconstruction. Patients who did not have surgery, underwent partial mastectomy or radical mastectomy, or had AJCC clinical stage IV disease were excluded. Bilateral disease was excluded to ensure all included bilateral mastectomies were also CPM. Invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), and other primary breast malignancies were included (histology codes 8500, 8521, 8523, 8525, 8541, 8543, 8520, 8524, 8522, 8502, 8575, 8343, 8260, 8453, 8510, 8512, 8513) (http://ncdbpuf.facs.org).

Patients were stratified by receipt of reconstruction: mastectomy alone (MA) and MR. Reconstruction was further categorized as autologous, implant-based, or combined-type (implant and autologous). The NCDB codes reconstruction as part of the first course of treatment regardless of whether performed at the time of mastectomy (immediate) or delayed. Patient characteristics (age, race, Charlson-Deyo comorbidity score, insurance status, household income, education level, distance to facility), facility information (type, community designation), tumor factors (AJCC 7th edition clinical stage and pathologic stage, histologic grade, hormone receptor status), and treatment information (breast and axillary surgery, reconstruction, chemotherapy, endocrine therapy, radiation therapy, sequence of treatment, length of stay, 30-day readmission rates) were collected. Patients were considered hormone receptor positive (HR^+) if either or both of the estrogen or progesterone receptors were positive. Facility type and location were unavailable because the NCDB suppresses this data for patients <40 due to low case counts. The 2012 definitions of "Scope of Regional Lymph Node Surgery", "Percent No High School Degree Quartiles" and "Median Income Quartiles" were applied to the dataset, resulting in exclusion of these variables for patients from 2010–2011. The two lowest (<$40,227 and $40,227–$50,353) and two highest ($50,354–$63,332, ≥$63,333) median income quartiles were combined for simplicity of analysis. Axillary lymph node dissection (ALND) is considered removal of greater than three lymph nodes based on coding for the "Scope of Regional Lymph Node Surgery" variable.

Chi-squared analyses evaluated differences among the cohorts for patient, tumor, and treatment characteristics. Multivariable logistic regression identified factors associated with MR, reconstruction type, and CPM. Patients designated in the NCDB as receiving combined-type reconstruction were included in the autologous group for this analysis. Kaplan-Meier survival estimates compared 5-year OS, and multivariable Cox proportional hazards regression identified factors associated with OS. A subset analysis of patients who underwent neoadjuvant chemotherapy (NAC) was performed to determine if treatment response was associated with MR or CPM. Those who received NAC or both neoadjuvant and adjuvant chemotherapy were included in this analysis. Downstage, defined by pathologic stage less than clinical stage for both tumor (T) and nodal (N) response; and upstage, classified as pathologic stage greater than clinical stage, were compared between groups. Pathologic complete response (pCR) was considered pT0N0 and those with cN0 disease were excluded from calculations for N response. All statistical analysis was performed using STATA SE Version 17.0.

Results

Demographics and clinical characteristics

Of the 43,065 patients who met inclusion criteria, 28,508 (66%) underwent MR and 14,557 (34%) underwent MA. Mean age was not different between groups (35.3 years MR *vs.* 35.4 years MA). Non-Hispanic Black and Hispanic patients comprised a greater proportion of the MA group (*Table 1*). Significantly more patients in the MR group had private insurance (83.8% MR *vs.* 68.5% MA, P<0.001), higher annual income (≥$50,354, 71.5% MR *vs.* 57.1% MA, P<0.001), and higher levels of education. More MR patients had cT1 tumors (42.6% MR *vs.* 29.5% MA, P<0.001) and over two-thirds were clinically node-negative (67.8% MR *vs.* 51.1% MA, P<0.001). Poorly differentiated tumors (51.1% MR *vs.* 56.6% MA, P<0.001) and TNBC (18.6% MR *vs.* 22.1% MA, P<0.001) were more common in the MA group.

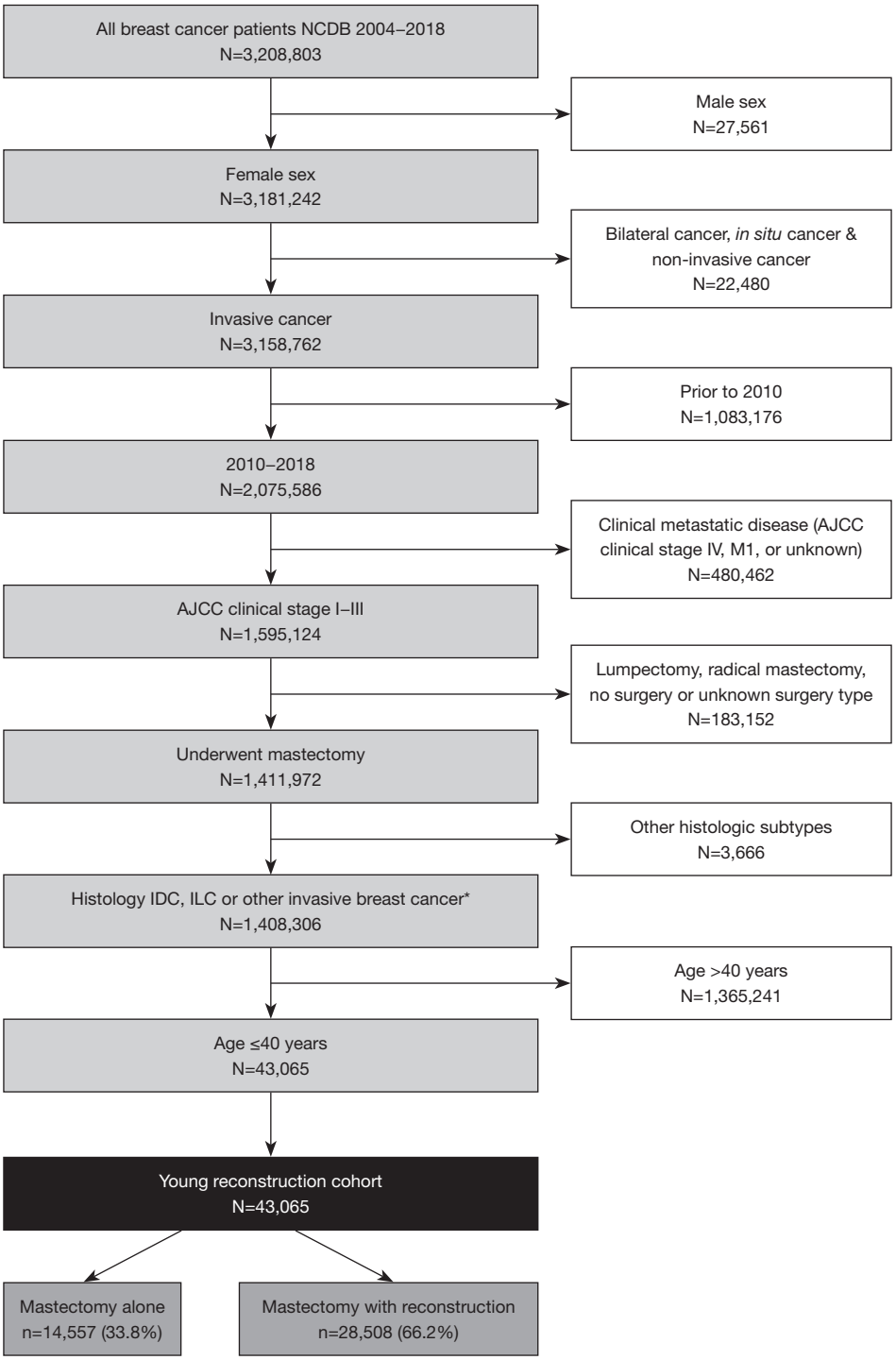

Figure 1 Study inclusion and exclusion criteria. *, included histology codes: 8500, 8521, 8523, 8525, 8541, 8543, 8520, 8524, 8522, 8502, 8575, 8343, 8260, 8453, 8510, 8512, 8513. NCDB, National Cancer Database; AJCC, American Joint Committee on Cancer; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

Table 1 Demographics and clinical characteristics for female patients ≤40 years with unilateral breast cancer undergoing mastectomy, NCDB 2010–2018

Characteristics	MA (n=14,557)	MR (n=28,508)	P value
Age, years, mean (± standard deviation)	35.4 (±4.03)	35.3 (±4.12)	0.657
Race			<0.001
Non-Hispanic White	8,811 (60.5)	19,934 (69.9)	
Non-Hispanic Black	2,382 (16.4)	3,463 (12.2)	
Hispanic	1,862 (12.8)	2,541 (8.9)	
Other	1,502 (10.3)	2,570 (9.0)	
Charlson-Deyo co-morbidity score			<0.001
0	13,569 (93.2)	26,649 (93.5)	
1	868 (6.0)	1,713 (6.0)	
≥2	120 (0.8)	146 (0.5)	
Insurance status			<0.001
None	923 (6.4)	577 (2.1)	
Private	9,850 (68.5)	23,654 (83.8)	
Public (Medicare/Medicaid)	3,608 (25.1)	3,982 (14.1)	
Income[†]			<0.001
≤$50,353	5,486 (42.9)	7,004 (28.5)	
≥$50,354	7,289 (57.1)	17,556 (71.5)	
Education level[‡]			<0.001
≥13%	6,037 (46.8)	8,535 (34.5)	
<13%	6,855 (53.2)	16,178 (65.5)	
Community			<0.001
Metro	11,980 (84.3)	24,799 (89.8)	
Urban	1,999 (14.1)	2,555 (9.3)	
Rural	231 (1.6)	249 (0.9)	
Distance to facility			<0.001
≤10 miles	6,201 (42.6)	11,662 (40.9)	
11–50 miles	5,516 (37.9)	10,732 (37.6)	
>50 miles	2,840 (19.5)	6,114 (21.5)	
Tumor histology			0.001
IDC	13,334 (91.6)	26,102 (91.6)	
ILC	531 (3.6)	1,010 (3.5)	
IDC and ILC	518 (3.6)	1,147 (4.0)	
Other	174 (1.2)	249 (0.9)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	MA (n=14,557)	MR (n=28,508)	P value
HR status			<0.001
$HR^+/HER2^-$	7,035 (48.4)	15,093 (52.9)	
$HR^+/HER2^+$	2,550 (17.5)	5,131 (18.0)	
$HR^-/HER2^+$	1,120 (7.7)	1,855 (6.5)	
$HR^-/HER2^-$	3,220 (22.1)	5,292 (18.6)	
Unknown	628 (4.3)	1,135 (4.0)	
Grade			<0.001
I: well differentiated	863 (5.9)	2,234 (7.8)	
II: moderately differentiated	4,585 (31.5)	10,210 (35.8)	
III: poorly differentiated	8,233 (56.6)	14,575 (51.1)	
IV: undifferentiated	53 (0.4)	54 (0.2)	
Unknown	820 (5.6)	1,434 (5.0)	
Clinical T stage			<0.001
1	4,283 (29.5)	12,111 (42.6)	
2	6,403 (44.1)	12,390 (43.6)	
3	2,733 (18.8)	3,325 (11.7)	
4	1,045 (7.2)	527 (1.8)	
Unknown	51 (0.4)	66 (0.2)	
Clinical N stage			<0.001
0	7,407 (51.1)	19,269 (67.8)	
1	5,370 (37.0)	7,569 (26.7)	
2	919 (6.3)	876 (3.1)	
3	703 (4.9)	556 (1.9)	
Unknown	104 (0.7)	136 (0.5)	
AJCC clinical stage			<0.001
I	3,354 (23.0)	10,532 (36.9)	
II	7,381 (50.7)	14,341 (50.3)	
III	3,822 (26.3)	3,635 (12.8)	
Pathologic T stage			<0.001
0	1,863 (13.1)	4,100 (14.7)	
1	5,180 (36.5)	13,412 (48.0)	
2	4,811 (33.9)	8,175 (29.2)	
3	1,580 (11.1)	1,538 (5.5)	
4	305 (2.2)	115 (0.4)	
Unknown	450 (3.2)	605 (2.2)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	MA (n=14,557)	MR (n=28,508)	P value
Pathologic N stage			<0.001
0	6,665 (46.9)	17,167 (61.4)	
1	4,562 (32.1)	7,733 (27.6)	
2	1,803 (12.7)	2,093 (7.5)	
3	883 (6.2)	651 (2.3)	
Unknown	289 (2.0)	339 (1.2)	
Pathologic M stage			<0.001
0	3,862 (98.2)	8,872 (99.2)	
1	72 (1.8)	71 (0.8)	
Unknown	0 (0.0)	1 (0.0)	
AJCC pathologic stage			<0.001
0	509 (3.6)	1,053 (3.8)	
I	3,181 (22.3)	9,874 (35.2)	
II	5,337 (37.5)	10,123 (26.0)	
III	3,268 (23.0)	3,317 (11.8)	
IV	75 (0.5)	69 (0.2)	
Unknown	1,869 (13.1)	3,645 (13.0)	

Data are shown as n (%) unless otherwise stated. †, median income quartiles—matches patient zip code with median income in the zip code, excludes patients before 2012; ‡, percent no high school degree 2012—matches patient zip code against the proportion of adults in the zip code that did not graduate high school, excludes patients before 2012. NCDB, National Cancer Database; MA, mastectomy alone; MR, mastectomy with reconstruction; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; AJCC, American Joint Committee on Cancer.

AJCC pathologic stage was also higher in the MA group compared to MR (stage III 11.8% MR *vs.* 23.0% MA).

Treatment characteristics

MR patients less frequently received chemotherapy (82.9% MR *vs.* 90.1% MA, P<0.001), including NAC (*Table 2*). Receipt of endocrine therapy was higher in the MR group, mirroring HR status. ALND was more commonly performed in the MA group (61.8% MA *vs.* 44.6% MR, P<0.001). The majority of patients in both groups underwent CPM (60.6% MR *vs.* 50.9% MA, P<0.001). Nearly a quarter of patients in the MA group received modified radical mastectomy compared with a small number of cases in the MR group (24.3% MA *vs.* 7.4% MR, P<0.001). Rates of hospital readmission within 30 days of surgery were low and similar between groups (*Table 2*). Radiation was administered to half of patients in the MA group compared with only one-third in the MR group (54.3% MA *vs.* 37.4% MR, P<0.001).

Factors associated with post-mastectomy reconstruction

More recent treatment year (OR 1.06), higher income (OR 1.54), higher cT stage (OR 1.60), and CPM (OR 1.27, all P<0.001) (*Table 3*) were all positively associated with MR. Patients with TNBC, high grade tumors, and cN+ disease were each significantly less likely to undergo MR. Post-mastectomy radiation was associated with 25% reduced likelihood of MR (OR 0.75, P<0.001), and patients treated with adjuvant chemotherapy were also less likely to have MR (OR 0.87, P=0.009).

Post-mastectomy reconstruction type

In the MR group, implant-based reconstruction was most

Table 2 Treatment characteristics for female patients ≤40 years with unilateral breast cancer undergoing mastectomy, NCDB 2010–2018

Characteristics	MA (n=14,557)	MR (n=28,508)	P value
Chemotherapy sequence			<0.001
None	1,433 (9.9)	4,836 (17.1)	
Neoadjuvant†	5,681 (39.2)	8,999 (31.7)	
Adjuvant	5,871 (40.5)	11,115 (39.2)	
Unknown sequence	1,504 (10.4)	3,393 (12.0)	
Endocrine therapy			<0.001
None	5,472 (37.6)	9,241 (32.4)	
Endocrine therapy	8,786 (60.4)	18,755 (65.8)	
Unknown	299 (2.0)	512 (1.8)	
Immunotherapy			<0.001
None	12,198 (83.8)	23,414 (82.1)	
Immunotherapy	2326 (16.0)	5,031 (17.7)	
Unknown	33 (0.2)	62 (0.2)	
Receipt of radiation			<0.001
None	6,260 (43.1)	17,091 (60.0)	
Radiation	7,888 (54.3)	10,667 (37.4)	
Unknown	385 (2.6)	726 (2.6)	
Breast surgery			<0.001
Simple mastectomy	3,608 (24.8)	5,666 (19.9)	
Nipple sparing mastectomy	0 (0)	3,450 (12.1)	
Modified radical mastectomy	3,537 (24.3)	2,100 (7.4)	
Contralateral prophylactic mastectomy	7,412 (50.9)	17,292 (60.6)	
Axillary surgery			<0.001
None	154 (1.4)	268 (1.1)	
Sentinel lymph node biopsy	3,964 (36.4)	12,505 (54.0)	
Axillary lymph node dissection	6,738 (61.8)	10,343 (44.6)	
Unknown	43 (0.4)	64 (0.3)	
Length of hospital stay, days			<0.001
0	3,153 (21.7)	4,632 (16.3)	
1	6,237 (42.8)	10,353 (36.3)	
2	2,076 (14.3)	6,894 (24.2)	
3	503 (3.5)	2,004 (7.0)	
4	177 (1.2)	1,033 (3.6)	
≥5	2,411 (16.5)	3,592 (12.6)	
Readmission within 30 days of surgery			0.265
No readmission	13,787 (96.5)	27,010 (96.3)	
Readmitted	500 (3.5)	1,042 (3.7)	

Data are shown as n (%). †, those undergoing neoadjuvant chemotherapy and adjuvant chemotherapy were included in the neoadjuvant chemotherapy group. NCDB, National Cancer Database; MA, mastectomy alone; MR, mastectomy with reconstruction.

Table 3 Multivariable logistic regression analyzing factors associated with post-mastectomy reconstruction, contralateral prophylactic mastectomy and type of reconstruction for female patients ≤40 years with unilateral breast cancer undergoing mastectomy, NCDB 2010–2018

Effects	Post-mastectomy reconstruction			Implant-based reconstruction			Autologous reconstruction[†]			Contralateral prophylactic mastectomy		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Age, increasing age	0.99	0.98, 0.99	0.002	1	0.99, 1.01	0.806	1.02	1.01, 1.03	<0.001	0.99	0.98, 0.99	0.004
Year, more recent year	1.06	1.04, 1.09	<0.001	0.99	0.95, 1.02	0.446	0.9	0.87, 0.93	<0.001	0.97	0.95, 0.99	0.003
Race												
Non-Hispanic White		Reference			Reference			Reference			Reference	
Non-Hispanic Black	0.9	0.80, 1.00	0.06	0.81	0.71, 0.93	0.003	1.33	1.16, 1.51	<0.001	0.65	0.60, 0.71	<0.001
Hispanic	0.88	0.77, 1.02	0.085	1	0.87, 1.15	1	0.97	0.82, 1.15	0.716	0.61	0.55, 0.68	<0.001
Other	0.79	0.69, 0.91	0.001	0.98	0.82, 1.17	0.834	1.01	0.86, 1.19	0.866	0.54	0.48, 0.61	<0.001
Charlson-Deyo co-morbidity score												
0		Reference			Reference			Reference			Reference	
≥1	1	0.87, 1.15	0.987	1.01	0.86, 1.17	0.927	1.16	1.00, 1.34	0.052	1.17	1.04, 1.33	0.007
Insurance												
Private		Reference			Reference			Reference			Reference	
Uninsured	0.35	0.28, 0.44	<0.001	0.99	0.75, 1.33	0.987	1.09	0.81, 1.48	0.565	0.66	0.54, 0.81	<0.001
Public	0.55	0.50, 0.61	<0.001	0.98	0.88, 1.10	0.733	1.01	0.89, 1.14	0.91	0.83	0.77, 0.90	<0.001
Income												
≤$50,353		Reference			Reference			Reference			Reference	
≥$50,354	1.54	1.38, 1.71	<0.001	0.97	0.84, 1.10	0.608	1.03	0.90, 1.18	0.626	0.9	0.83, 0.98	0.017
Education level												
Low		Reference			Reference			Reference			Reference	
High	1.07	0.98, 1.17	0.145	1.16	1.04, 1.29	0.007	0.84	0.76, 0.94	0.002	1.13	1.05, 1.23	0.003
Distance from facility												
<10 miles		Reference			Reference			Reference			Reference	
11–50 miles	0.93	0.85, 1.01	0.076	1.06	0.98, 1.16	0.14	0.98	0.89, 1.08	0.641	1.13	1.06, 1.21	<0.001
>50 miles	1.01	0.84, 1.21	0.917	0.96	0.79, 1.17	0.678	1.01	0.83, 1.24	0.918	0.93	0.83, 1.05	0.245
HR status												
$HR^+/HER2^-$		Reference			Reference			Reference			Reference	
$HR^+/HER2^+$	0.86	0.76, 0.97	0.017	0.95	0.83, 1.09	0.465	1.07	0.92, 1.24	0.37	1.08	0.97, 1.21	0.148
$HR^-/HER2^+$	0.9	0.80, 1.02	0.094	0.96	0.83, 1.10	0.566	1.07	0.93, 1.24	0.341	0.97	0.87, 1.09	0.676
$HR^-/HER2^-$	0.79	0.72, 0.87	<0.001	0.94	0.85, 1.04	0.221	1.07	0.97, 1.19	0.178	1.26	1.16, 1.38	<0.001

Table 3 (*continued*)

Table 3 (*continued*)

Effects	Post-mastectomy reconstruction			Implant-based reconstruction			Autologous reconstruction[†]			Contralateral prophylactic mastectomy		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Grade												
I–II		Reference			Reference			Reference			Reference	
III–IV	0.88	0.82, 0.95	0.001	1	0.92, 1.09	0.951	0.96	0.87 1.05	0.361	1.04	0.97, 1.11	0.256
Clinical T stage												
1–2		Reference			Reference			Reference			Reference	
3–4	1.6	1.47, 1.74	<0.001	1.06	0.95, 1.19	0.27	1.04	0.91, 1.20	0.524	0.78	0.72, 0.84	<0.001
Clinical N stage												
0		Reference			Reference			Reference			Reference	
1–3	0.75	0.69, 0.82	<0.001	1.03	0.93, 1.14	0.515	1.02	0.91, 1.15	0.692	0.99	0.92, 1.06	0.797
Receipt of chemotherapy												
None		Reference			Reference			Reference			Reference	
Neoadjuvant chemotherapy	1.04	0.91, 1.18	0.597	0.93	0.82, 1.62	0.297	1.04	0.91, 1.19	0.542	1.34	1.21, 1.50	<0.001
Adjuvant chemotherapy	0.87	0.78, 0.96	0.009	1.01	0.89, 1.14	0.905	1.05	0.93, 1.18	0.441	1.17	1.07, 1.28	0.001
Receipt of radiation												
None		Reference			Reference			Reference			Reference	
Radiation	0.75	0.69, 0.82	<0.001	0.98	0.89, 1.08	0.783	1.03	0.93, 1.14	0.579	0.9	0.84, 0.97	0.005
Axillary surgery												
Sentinel lymph node biopsy		Reference			Reference			Reference			Reference	
No surgery	0.61	0.47, 0.79	<0.001	0.7	0.49, 1.00	0.051	1.19	0.74, 1.59	0.67	0.99	0.75, 1.29	0.925
Axillary lymph node dissection	0.68	0.63, 0.74	<0.001	1.03	0.94, 1.13	0.5	1.16	1.05, 1.27	0.002	0.91	0.84, 0.98	0.013
Mastectomy type												
Unilateral mastectomy		Reference			N/A			N/A			N/A	
Contralateral prophylactic mastectomy	1.27	1.16, 1.39	<0.001									
Receipt of reconstruction												
No		N/A			N/A			N/A			Reference	
Yes										1.27	1.16, 1.40	<0.001

[†], patients with "autologous and implant" reconstruction were included in the autologous group. NCDB, National Cancer Database; OR, odds ratio; CI, confidence interval; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; N/A, not available.

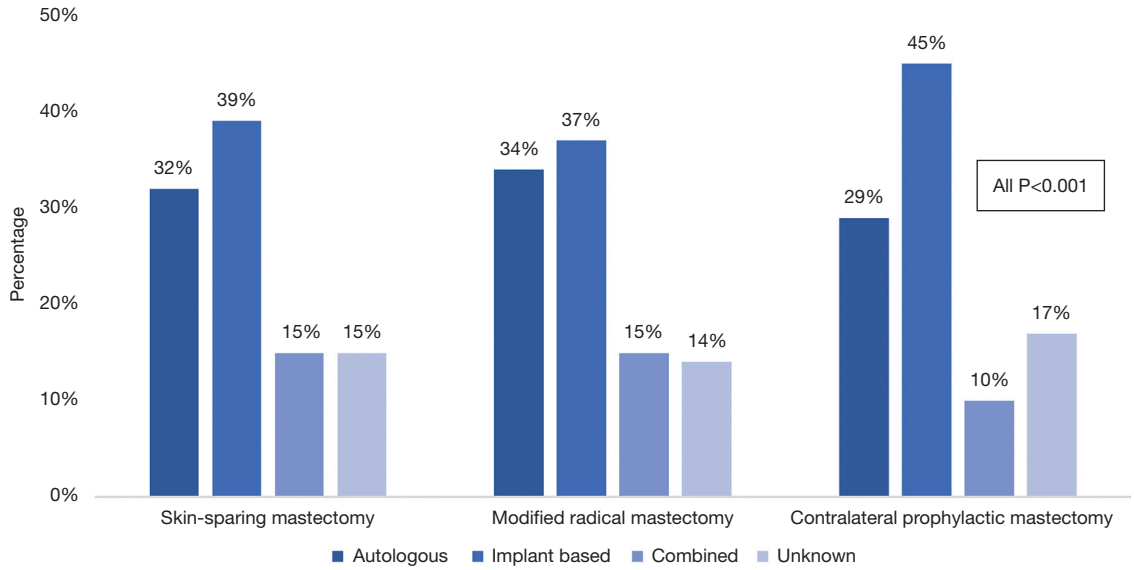

Figure 2 Post-mastectomy reconstruction type for female patients ≤40 years with unilateral breast cancer, NCDB 2010–2018. All patients who underwent nipple sparing mastectomy are coded in the NCDB as having an "unknown" type of reconstruction. NCDB, National Cancer Database.

common (37.3%), followed by autologous (26.1%), and combined-type reconstruction (10.1%). When stratified by surgery type, implant-based reconstruction was most common after all mastectomy types and made up nearly half of the reconstruction cases for patients who underwent CPM (44.5%) (*Figure 2*). Autologous reconstruction was the second most common type of reconstruction across groups. Since patients who completed NSM are coded in the NCDB as having "unknown" type of reconstruction, the "unknown" group accounts for NSM as well as a small number in whom reconstruction type is truly unaccounted for.

Factors associated with post-mastectomy reconstruction type

After controlling for patient (age, year, race, Charlson-Deyo score, insurance, income, education), facility (distance), tumor (HR status, grade, clinical T and N stage), and treatment characteristics (radiation, chemotherapy, axillary surgery, and mastectomy type), the only factor positively associated with implant-based reconstruction was higher level of education (OR 1.16, P=0.007) (*Table 3*). Factors positively associated with autologous reconstruction included increasing age (OR 1.02, P<0.001), non-Hispanic Black race (OR 1.33, P<0.001), and ALND (1.16, P=0.002). Patients treated in more recent years (OR 0.90, P<0.001) and those with higher education (OR 0.84, P=0.002) were less likely to undergo autologous reconstruction.

Factors associated with CPM

Patients with TNBC were nearly 30% more likely to undergo CPM (OR 1.26, P<0.001) than those with HR^+/$HER2^-$ disease; MR patients were also 30% more likely to have CPM (OR 1.27 P<0.001) (*Table 3*). Compared to patients not treated with chemotherapy, those who received NAC or adjuvant chemotherapy were more likely to undergo CPM (OR 1.34, OR 1.17, respectively, both P≤0.001). Patients of non-White race and those with no insurance or public insurance were less likely to undergo CPM. More advanced cT stage (OR 0.78, P<0.001) and ALND (OR 0.91, P=0.013) were negatively associated with CPM (*Table 3*).

Factors associated with OS

On Kaplan-Meier analysis, 5-year OS was superior in the MR group (92% MR *vs.* 85% MA, P<0.001) (*Figure 3A*). When stratified by receipt of reconstruction and CPM, CPM did not confer a significant survival benefit in either MR or MA (*Figure 3B*). On multivariable Cox regression for all patients in the cohort, increasing age (hazard ratio 0.97, P<0.001) and Hispanic race (hazard ratio 0.80, P=0.011)

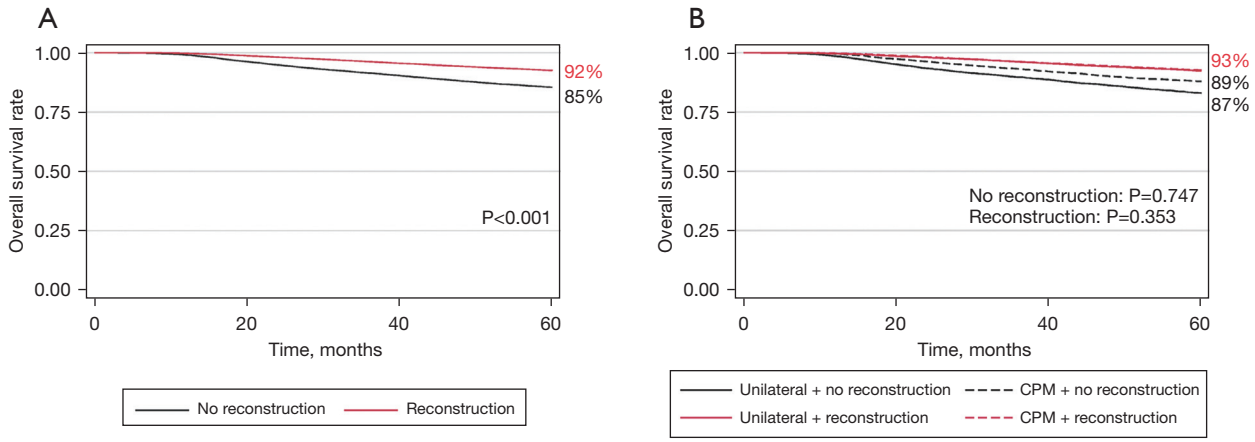

Figure 3 Kaplan-Meier 5-year overall survival estimates for female patients with unilateral breast cancer undergoing mastectomy, NCDB 2010–2018. (A) Comparing patients by receipt of reconstruction. (B) Comparing patients by receipt of reconstruction and/or CPM. NCDB, National Cancer Database; CPM, contralateral prophylactic mastectomy.

were associated with superior OS (*Table 4*). Non-Hispanic Black race was associated with poorer OS as compared to non-Hispanic White race (hazard ratio 1.16, P=0.045), as was public insurance compared to private (hazard ratio 1.39, P<0.001). Compared to $HR^+/HER2^-$ tumors, $HR^+/HER2^+$ and $HR^-/HER2^+$ tumors were associated with improved OS, but OS was not significantly worse in TNBC. More advanced T and N stage at diagnosis and higher tumor grade were associated with poorer OS, as were receipt of NAC (hazard ratio 1.47, P=0.003) and radiation (hazard ratio 1.13, P=0.044). Patients who received reconstruction (hazard ratio 0.76, P<0.001) and those who underwent CPM had improved survival (hazard ratio 0.80, P<0.001) compared to those who did not.

Therapy response in patients treated with NAC

Significantly more patients in the MR group achieved in-breast pCR (35.1% *vs.* 26.7% MA, P<0.001) (Figure S1). Similarly, axillary pCR (45.1% *vs.* 37.9%, P<0.001) and overall pCR (25.9% *vs.* 21.3%, P<0.001) were more common in MR than MA. On multivariable logistic regression, overall pCR (OR 1.20, P=0.021) and in-breast pCR (OR 1.30, P=0.003) were associated with MR, but not with CPM (Table S1). On multivariable Cox regression, those who achieved overall pCR, in-breast pCR, and axillary pCR (hazard ratio 0.20, 0.41, 0.34, all P<0.001) had superior OS (Table S2).

Discussion

Our study identifies factors associated with post-mastectomy reconstruction in a large, contemporary, nationally representative sample of young women with unilateral invasive breast cancer. We found that reconstruction was performed less often in minority groups and those with lower socioeconomic advantage, as well as for patients with more advanced disease and less favorable prognosis. Interestingly, in this cohort of patients age ≤40 years, CPM rates were universally high regardless of receipt of reconstruction, though CPM was independently associated with greater likelihood of reconstruction. Additionally, our data shows a survival benefit associated with both reconstruction and CPM—a finding which may be due to inherent selection bias and requires further investigation.

In our cohort, patients who received reconstruction were more often White, privately insured, and reported higher income levels compared to patients who did not undergo reconstruction. This is similar to findings from a 2000–2014 SEER database study of 321,206 women showing that MR was less likely in patients aged ≤40 years who were non-White (OR 0.68, 95% CI: 0.62–0.75), not married (0.83, 95% CI: 0.75–0.92), and located in the South or West regions of the United States (21). In studies not stratified by age, persistent disparities in race, income, education and insurance status affect receipt of reconstruction (20,25,26), as do geographic location, facility type, and access to plastic

Table 4 Multivariable Cox proportional hazards analyzing factors associated with overall survival for female patients ≤40 years with unilateral breast cancer undergoing mastectomy, NCDB 2010–2018

Effects	Hazard ratio	95% CI	P value
Age, increasing age	0.97	0.96, 0.98	<0.001
Year, more recent year	0.99	0.95, 1.02	0.395
Race			
Non-Hispanic White		Reference	
Non-Hispanic Black	1.16	1.01, 1.34	0.045
Hispanic	0.8	0.67, 0.95	0.011
Other	0.76	0.63, 0.92	0.004
Charlson-Deyo co-morbidity score			
0		Reference	
≥1	1.11	0.92, 1.34	0.264
Insurance			
Private		Reference	
Uninsured	1.16	0.89, 1.52	0.259
Public	1.39	1.23, 1.57	<0.001
Income			
≤$50,353		Reference	
≥$50,354	0.95	0.85, 1.08	0.472
Education level			
Low		Reference	
High	1.01	0.89, 1.14	0.846
Distance to facility			
<10 miles		Reference	
11–50 miles	1.08	0.98, 1.20	0.129
>50 miles	1.14	0.95, 1.36	0.156
HR status			
$HR^+/HER2^-$		Reference	
$HR^+/HER2^+$	0.54	0.43, 0.68	<0.001
$HR^-/HER2^+$	0.45	0.36, 0.56	<0.001
$HR^-/HER2^-$	1.18	0.98, 1.42	0.078
Grade			
I–II		Reference	
III–IV	1.78	1.56, 2.03	<0.001
Clinical T stage			
1–2		Reference	
3–4	0.58	0.52, 0.64	<0.001
Clinical N stage			
0		Reference	
1–3	1.63	1.42, 1.85	<0.001
Receipt of chemotherapy			
No chemotherapy		Reference	
Neoadjuvant chemotherapy	1.47	1.14, 1.90	0.003
Adjuvant chemotherapy	1.09	0.85, 1.39	0.498
Receipt of endocrine therapy			
No		Reference	
Yes	0.54	0.45, 0.64	<0.001
Receipt of radiation			
No radiation		Reference	
Radiation	1.13	1.00, 1.28	0.044
Breast surgery			
Unilateral mastectomy		Reference	
Contralateral prophylactic mastectomy	0.8	0.73, 0.88	<0.001
Axillary lymph node surgery			
Sentinel lymph node biopsy		Reference	
No axillary surgery	1.03	0.68, 1.55	0.888
Axillary lymph node dissection	0.56	0.49, 0.63	<0.001
Receipt of reconstruction			
No		Reference	
Yes	0.76	0.68, 0.84	<0.001

NCDB, National Cancer Database; CI, confidence interval; HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

surgeons (26,27). In a 2004–2015 NCDB analysis of breast cancer patients ≥70 years old undergoing mastectomy, Cortina *et al.* demonstrated that patients who were White, had private insurance, and treated in the Northeast and in metropolitan areas were more likely to undergo reconstruction (22).

In our study, less favorable disease features and more comprehensive multimodal therapy were negatively associated with MR. Patients with TNBC (OR 0.79, P<0.001) and those with cN+ disease (OR 0.75, P<0.001)

were less likely to undergo reconstruction. Others have also shown that higher AJCC stage, nodal positivity, larger tumor size, higher grade, and HR^- disease decrease the likelihood of MR (19,20,22,25,28,29). In our cohort, patients with cT3–4 tumors were 60% more likely to undergo reconstruction than those with cT1–2 disease, but this may be due to the use of NAC and subsequent therapy response. In fact, while NAC was not independently associated with MR, those who achieved overall or breast pCR were 20% and 30% more likely to undergo reconstruction, respectively. Conversely, adjuvant chemotherapy was associated with a modest decrease in likelihood of MR (OR 0.87, P=0.009). This may be due to factors such as genomic testing results or more advanced disease at surgical pathology prompting adjuvant chemotherapy and radiation recommendations, patients being less inclined to undergo additional surgery unrelated to oncologic outcome, and desire to avoid delays in adjuvant treatment due to recovery time and potential complications associated with reconstruction (30). We also hypothesize that patients who receive NAC and have a favorable response may be more likely to elect reconstruction due to provider willingness to offer this procedure and time available for plastic surgery consultation and decision-making.

As expected, and consistent with others, our study found receipt of radiation was associated with a lower likelihood of MR (OR 0.75, P<0.001) (29,31). This may be related to radiation oncology preference for no reconstruction at the time of post-mastectomy radiation delivery and the increased incidence of complications and inferior cosmesis when radiation follows reconstruction (32-34).

In our contemporary cohort of young women, similar to earlier studies not stratified by age, implant-based reconstruction was the most common type (11,35,36), and in our study, this rate was particularly high in patients that underwent CPM. Unfortunately, the NCDB codes all reconstruction following NSM as "unknown", thus our analysis cannot draw conclusions on reconstruction type for these patients. However, the desire for nipple preservation may be partially motivating high rates of reconstruction and CPM, as "unknown" accounts for over 12% of our MR cohort and 17% of the CPM group.

The majority of all patients in our study underwent CPM regardless of receipt of reconstruction (60.6% MR and 50.9% MA). While CPM rates are higher in younger women, and reach 35% in other series (37-39), our data may reflect more current trends since our cohort spanned 2010–2018. CPM was 30% more likely in patients who received NAC and 20% more likely in those treated with adjuvant chemotherapy, potentially reflecting patients' desire for "peace of mind" after receiving a cancer diagnosis and treatment (12,40,41). Mirroring factors associated with reconstruction, ours and prior research demonstrates that patients are more likely to undergo CPM if they are younger, White, have private insurance, or less advanced disease (13,22,35,37,41). Additionally, we found a strong relationship between CPM and MR; each procedure was independently associated with a 30% increased likelihood of the other (both OR 1.27, P<0.001). Other studies have also shown a close association between reconstruction and bilateral mastectomy, particularly in younger women (11,26,35-37).

While information not available in the NCDB, such as genetic and family risk factors, likely contribute to the high rate of CPM in women ≤40 years, psychosocial factors and misunderstanding of breast cancer prognosis and contralateral breast cancer (CBC) risk also play an important role (11,13,42). In one retrospective study of 100 CPM patients at a single institution, 58% did not have a medical indication (i.e., pathogenic variant carrier) for the procedure (43). Instead, patients may be choosing CPM due to misplaced anxiety about breast cancer recurrence, preference to avoid future imaging surveillance, as well as concern about aesthetic outcomes and breast symmetry. This was evidenced in a mixed-methods study evaluating patients' decisions for CPM and reconstruction, in which 82.4% of patients who chose CPM reported improved quality of life characterized by relief from worry about future cancer; CPM also yielded higher mean scores for satisfaction with breast (82.4% *vs.* 70.6%) and with outcome (98.9% *vs.* 75.2%) (44). Further, in a survey study of 3,631 women with newly diagnosed unilateral stage 0–II breast cancer, 37.3% of patients who received CPM believed it improved survival for all women with breast cancer (41). These findings suggest that new methods for patient education about the likelihood of CBC, potential risks of CPM, and lack of survival benefit are needed to help address these misconceptions. In addition, recent evidence suggesting a survival benefit with BCT compared to mastectomy, particularly for younger women (14-17) should be shared with patients who are appropriate candidates for either procedure from an oncologic and genetic standpoint, and might discourage the decision for unilateral mastectomy, which itself often prompts CPM.

Somewhat surprisingly, both receipt of CPM and MR were associated with an OS benefit on multivariable Cox

regression in our study. This is in contrast to established research that consistently demonstrates no survival advantage for MR or CPM in patients without an increased risk of CBC (45-49). However, other retrospective analyses have shown contradictory results (50,51), including a survival benefit with CPM particularly in younger women with HR^- breast cancer (52). Our findings likely reflect inherent cofounders in our analysis, or a selection bias towards performing CPM and MR in patients with a favorable prognosis. Since the NCDB does not include personal risk factors such as family history and genetic testing information, these variables are not accounted for in our study. Our OS benefit could also be explained by potential disparate populations of young breast cancer patients: one group undergoing early screening due to family history or pathogenic variants in whom breast cancers are detected at early stage, and another group who present with palpable breast tumors or clinically positive axilla. The treatment recommended to each group would differ, as would their oncologic outcomes, and perhaps MR and CPM are prioritized differently by both patients and providers in each group.

Like other studies based on large retrospective datasets, ours has limitations. Local-regional recurrence and disease-specific survival are not included in the NCDB, limiting our outcomes to OS, an imperfect measure especially in a cohort of young women. The NCDB does not collect data on smoking status or body mass index (BMI), which are important potential contraindications to immediate reconstruction, and/or additional surgery such as CPM. Facility type and location variables are suppressed for patients <40 years due to low sample size, preventing comparison to other studies examining these variables. Since the NCDB does not provide information on timing of reconstruction, there is no way to determine whether it was truly immediate, delayed, or intermediate/delayed (i.e., immediate tissue expander placement, delayed autologous reconstruction), all of which are quite different in clinical practice. The inability to differentiate which patients received immediate *vs.* delayed reconstruction could have biased our OS results, assuming that delayed reconstruction was necessary due to advanced disease requiring adjuvant chemotherapy and/or radiation and that this group had inferior prognosis compared with patients who received immediate reconstruction. However, there are likely fewer differences between the two groups who received reconstruction (immediate *vs.* delayed) than the groups that received any reconstruction *vs.* no reconstruction since non-oncologic surgery is generally only offered when disease is limited or has responded well to systemic therapy and/or radiation, prognosis is sufficiently favorable, and the patient's overall health is amenable to additional procedures and recovery. Additionally, there are no data in the NCDB on surgical decision-making factors such as aesthetic concerns and genetic or family risk of breast cancer, which likely contribute to the high CPM rates in young women. We selected the 2010–2018 cohort to ensure complete prognostic marker data since HER2 status was collected beginning in 2010, and to contribute a modern study to the literature on post-mastectomy reconstruction and CPM. While using this more contemporary cohort limited our sample size, our analysis is one of the largest and most nationally representative to address these questions in the unique group of young breast cancer patients.

Conclusions

In summary, our study shows persistent disparities amongst women age ≤40 years with unilateral invasive breast cancer in receipt of MR and CPM. Despite the Women's Health and Cancer Rights Act of 1998's provision of financial protection to women who choose to undergo mastectomy and reconstruction, our data reflecting cancer care 20 years later suggest that lack of private insurance and lower income may still be potential barriers (53). While more advanced disease and receipt of multimodal treatment may discourage patients from pursuing non-essential procedures such as reconstruction and CPM, breast surgeons should ensure access and equitable care are available to all women with all types of breast cancer. We must also ensure our patients are adequately educated about the true risks and benefits of post-mastectomy reconstruction and CPM to empower them to make well-informed decisions.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://abs.amegroups.com/article/view/10.21037/abs-23-48/coif). A.S. receives honoraria as a speaker for Endomag. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional Review Board exemption was obtained as the data source is deidentified and this was a retrospective cohort study. Inform consent was not required.

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Supplementary

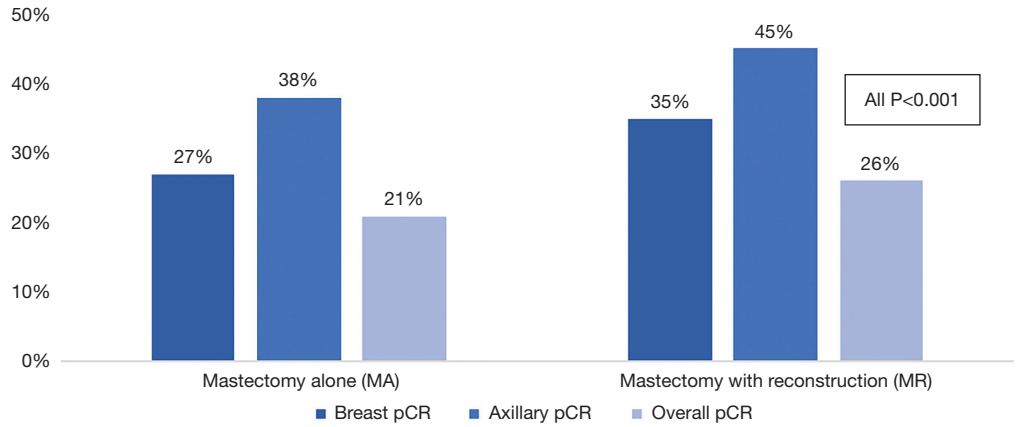

Figure S1 Pathologic response to neoadjuvant chemotherapy for female patients ≤40 years with unilateral breast cancer undergoing mastectomy, NCDB 2010–2018. pCR, pathologic complete response; NCDB, National Cancer Database.

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Table S1 Multivariable logistic regression analyzing factors associated with post-mastectomy reconstruction and contralateral prophylactic mastectomy for female patients ≤40 years with unilateral breast cancer undergoing mastectomy after neoadjuvant chemotherapy, NCDB 2010–2018

Effects	Factors	Reconstruction						Contralateral prophylactic mastectomy					
		Including breast pCR & axillary pCR			Including overall pCR			Including breast pCR & axillary pCR			Including overall pCR		
		OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Age	Increasing age	0.99	0.97, 1.00	0.083	0.98	0.97, 1.00	0.086	0.99	0.97, 1.00	0.163	0.99	0.97, 1.00	0.159
Year	More recent year	1.07	1.03, 1.11	0.001	1.07	1.03, 1.11	0.001	0.99	0.96, 1.03	0.893	0.99	0.96, 1.03	0.867
Race	Non-Hispanic White		Reference			Reference			Reference			Reference	
	Non-Hispanic Black	0.85	0.71, 1.02	0.088	0.85	0.70, 1.02	0.079	0.63	0.53, 0.75	<0.001	0.63	0.53, 0.75	<0.001
	Hispanic	0.83	0.67, 1.05	0.116	0.83	0.66, 1.04	0.106	0.67	0.56, 0.82	<0.001	0.67	0.56, 0.82	<0.001
	Other	0.872	0.68, 1.12	0.288	0.88	0.68, 1.13	0.300	0.55	0.45, 0.67	<0.001	0.55	0.45, 0.68	<0.001
Charlson-Deyo co-morbidity score	0		Reference			Reference			Reference			Reference	
	≥1	0.79	0.61, 1.03	0.078	0.79	0.61, 1.03	0.081	1.48	1.13, 1.92	0.004	1.48	1.14, 1.92	0.004
Insurance	Private		Reference			Reference			Reference			Reference	
	Uninsured	0.35	0.23, 0.51	<0.001	0.35	0.25, 0.51	<0.001	0.71	0.52, 0.97	0.032	0.72	0.52, 0.98	0.036
	Public	0.63	0.53, 0.74	<0.001	0.62	0.53, 0.74	<0.001	0.85	0.73, 0.99	0.045	0.86	0.73, 0.99	0.044
Income	≤$50,353		Reference			Reference			Reference			Reference	
	≥$50,354	1.69	1.43, 2.01	<0.001	1.69	1.43, 2.01	<0.001	0.92	0.78, 1.08	0.293	0.92	0.78, 1.07	0.288
Education level	Low		Reference			Reference			Reference			Reference	
	High	0.95	0.81, 1.13	0.592	0.95	0.81, 1.13	0.588	1.25	1.08, 1.45	0.003	1.26	1.08, 1.45	0.002
Distance from facility	<10 miles		Reference			Reference			Reference			Reference	
	11–50 miles	0.82	0.71, 0.96	0.014	0.82	0.71, 0.96	0.013	1.10	0.96, 1.25	0.158	1.10	0.96, 1.25	0.162
	>50 miles	0.75	0.57, 0.99	0.042	0.75	0.57, 0.99	0.588	0.84	0.68, 1.03	0.101	0.84	0.68, 1.03	0.094
HR status	$HR^+/HER2^-$		Reference			Reference,			Reference			Reference	
	$HR^+/HER2^+$	0.70	0.54, 0.90	0.006	0.724	0.56, 0.93	0.014	1.30	1.01, 1.68	0.041	1.34	1.04, 1.73	0.022
	$HR^-/HER2^+$	0.85	0.67, 1.06	0.145	0.90	0.72, 1.12	0.349	0.83	0.67, 1.02	0.073	0.86	0.71, 1.07	0.180
	$HR^-/HER2^-$	0.715	0.61, 0.84	<0.001	0.74	0.63, 0.87	<0.001	1.25	1.07, 1.47	0.006	1.29	1.10, 1.50	0.001
Grade	I–II		Reference			Reference			Reference			Reference	
	III–IV	0.88	0.76, 1.02	0.093	0.90	0.78, 1.04	0.148	1.01	0.88, 1.17	0.846	1.03	0.89, 1.19	0.682
Receipt of radiation	None		Reference			Reference			Reference			Reference	
	Radiation	0.79	0.67, 0.95	0.010	0.79	0.66, 0.93	0.006	1.01	0.86, 1.17	0.948	0.99	0.85, 1.15	0.871
Axillary surgery	Sentinel lymph node biopsy		Reference			Reference			Reference			Reference	
	No surgery	0.26	0.11, 0.62	0.002	0.27	0.12, 0.63	0.002	0.92	0.44, 1.92	0.830	0.93	0.44, 1.95	0.842
	Axillary lymph node dissection	0.58	0.49, 0.69	<0.001	0.57	0.48, 0.67	<0.001	1.01	0.86, 1.18	0.905	0.97	0.84, 1.13	0.713
Mastectomy type	Unilateral mastectomy		Reference			Reference			N/A			N/A	
	Contralateral prophylactic mastectomy	1.50	1.28, 1.75	<0.001	1.51	1.29, 1.76	<0.001						
Receipt of reconstruction	No		N/A			N/A			Reference			Reference	
	Yes							1.50	1.29, 1.75	<0.001	1.51	1.29, 1.76	<0.001
Overall pCR	No		N/A			Reference			N/A			Reference	
	Yes				1.20	1.03, 1.40	0.021				1.11	0.96, 1.30	0.168
Breast pCR	No		Reference			N/A			Reference			N/A	
	Yes	1.30	1.09, 1.54	0.003				1.09	0.93, 1.29	0.271			
Axillary pCR	No		Reference						Reference				
	Yes	1.07	0.91, 1.25	0.435				1.16	0.99, 1.35	0.064			

NCDB, National Cancer Database; pCR, pathologic complete response; OR, odds ratio; CI, confidence interval; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; N/A, not applicable.

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Table S2 Multivariable Cox regression for female patients ≤40 years with unilateral breast cancer undergoing mastectomy after neoadjuvant chemotherapy, NCDB 2010–2018

Effects	Factors	Including breast pCR & axillary pCR			Including overall pCR		
		Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Age	Increasing age	0.97	0.95, 0.99	0.001	0.97	0.95, 0.99	0.001
Year	Increasing year	0.96	0.91, 1.01	0.101	0.97	0.92, 1.02	0.213
Race	Non-Hispanic White		Reference			Reference	
	Non-Hispanic Black	1.16	0.96, 1.39	0.119	1.16	0.97, 1.40	0.105
	Hispanic	0.91	0.72, 1.14	0.421	0.90	0.71, 1.14	0.383
	Other	0.72	0.54, 0.96	0.026	0.68	0.50, 0.91	0.010
Charlson-Deyo co-morbidity score	0		Reference			Reference	
	≥1	0.98	0.72, 1.33	0.898	1.00	0.73, 1.36	0.979
Insurance	Private		Reference			Reference	
	Uninsured	1.38	0.98, 1.94	0.065	1.34	0.94, 1.92	0.104
	Public	1.36	1.15, 1.63	<0.001	1.36	1.15, 1.62	<0.001
Income	≤$50,353		Reference			Reference	
	≥$50,354	1.14	0.93, 1.39	0.205	1.15	0.95, 1.40	0.152
Education	Low		Reference			Reference	
	High	0.98	0.81, 1.20	0.887	0.97	0.80, 1.17	0.741
Distance from facility	<10 miles		Reference			Reference	
	11–50 miles	0.95	0.81, 1.10	0.475	0.96	0.83, 1.12	0.623
	>50 miles	1.20	0.94, 1.53	0.149	1.28	1.01, 1.64	0.045
HR status	$HR^+/HER2^-$		Reference			Reference	
	$HR^+/HER2^+$	0.53	0.35, 0.79	0.002	0.48	0.32, 0.72	<0.001
	$HR^-/HER2^+$	0.58	0.40, 0.83	0.003	0.53	0.36, 0.76	0.001
	$HR^-/HER2^-$	1.46	1.05, 2.04	0.025	1.31	0.95, 1.82	0.100
Grade	I-II		Reference			Reference	
	III-IV	1.64	1.35, 2.00	<0.001	1.51	1.24, 1.84	<0.001
Endocrine therapy	No		Reference			Reference	
	Yes	0.44	0.32, 0.60	<0.001	0.46	0.34, 0.63	<0.001
Receipt of Radiation	No radiation		Reference			Reference	
	Radiation	0.86	0.71, 1.04	0.133	0.94	0.77, 1.14	0.531
Mastectomy type	Unilateral mastectomy		Reference			Reference	
	Contralateral prophylactic mastectomy	0.80	0.69, 0.93	0.003	0.77	0.67, 0.89	<0.001
Axillary surgery	Sentinel lymph node biopsy		Reference			Reference	
	No axillary surgery	0.67	0.18, 2.49	0.555	0.49	0.13, 1.83	0.288
	Axillary lymph node dissection	0.84	0.68, 1.04	0.111	0.66	0.54, 0.82	<0.001
Receipt of Reconstruction	No						
	Yes	0.86	0.73, 1.00	0.054	0.82	0.70, 0.96	0.015
Overall pCR	No		N/A			Reference	
	Yes				0.20	0.15, 0.27	<0.001
Breast pCR	No		Reference			N/A	
	Yes	0.41	0.32, 0.52	<0.001			
Axillary pCR	No		Reference				
	Yes	0.34	0.28, 0.42	<0.001			

NCDB, National Cancer Database; pCR, pathologic complete response; CI, confidence interval; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; N/A, not applicable.

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