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Distance to a Plastic Surgeon and Type of Insurance Plan Are Independently Predictive of Postmastectomy Breast Reconstruction

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Abstract

Background—The psychosocial benefits of postmastectomy breast reconstruction are well established; however, health care barriers persist. The authors evaluated statewide patient population to further identify obstacles to reconstruction.

Methods—A linked data set combining the North Carolina Central Cancer Registry with administrative claims from Medicare, Medicaid, and private insurance plans identified women diagnosed with breast cancer from 2003 to 2006. For inclusion in the study, women must have had a mastectomy within 6 months of diagnosis and had continuous insurance enrollment at least 2 years postoperatively ($n = 5381$). Multivariable logistic regression was used to model odds of reconstruction.

Results—Approximately 20 percent underwent reconstruction ($n = 1130$). Distance to a plastic surgeon—10 to 20 miles (OR, 0.78) and greater than 20 miles (OR, 0.73; $p < 0.05$)—was significantly predictive of no reconstruction, independent of other well-known disparities, including age, race, rural location, and lower household income. Women with government-funded health care, such as Medicare (OR, 0.58) and Medicaid (OR, 0.24; $p < 0.001$), were also significantly less likely to undergo reconstruction. Consistent with previous study, advanced cancer stage and receipt of radiation therapy decreased the likelihood of reconstruction. Furthermore, when the authors compared immediate to delayed reconstruction, rural location, chemotherapy, and radiation therapy were significantly predictive of delay.

Conclusions—This is the first population-based study to demonstrate distance to care and insurance plan as significant predictors of receipt of reconstruction. Additional research is needed to understand health care barriers and to determine whether distance to a plastic surgeon can be ameliorated by outreach programs.

CLINICAL QUESTION/LEVEL OF EVIDENCE—Risk, III.

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The psychosocial benefits of postmastectomy breast reconstruction, including improvements in self-esteem, sexuality, and body image, are well documented.[1–3] They hold true for reconstruction performed at the time of mastectomy (immediate) and that performed in a separate setting (delayed).[4] Despite undisputed benefits, access to breast reconstruction, regardless of timing, remains limited by socioeconomic and demographic factors. Previously published data confirm age, race, level of education, income level, and geographic location as barriers to reconstruction.[5,6] Density of plastic surgeons per state of residence[6] and type of health insurance[7] have also been recently identified as additional barriers to breast reconstruction. We evaluated our state-based patient population to further investigate these and further obstacles to reconstruction. Specifically, we queried whether geographic distance to a plastic surgeon would affect a woman's likelihood of having the procedure. We compared barriers to reconstruction across public and private health insurance. Finally, we assessed whether timing of reconstruction, either immediate or delayed, affected these variables. We hypothesized that greater distance from a plastic surgeon would lower the likelihood of receipt of reconstruction and that this effect might be mitigated with the inclusion of the delayed cohort.

PATIENTS AND METHODS

Data

The Integrated Cancer Information and Surveillance System is a state-based data set that represents the linkage of the North Carolina Central Cancer Registry to beneficiaries in Medicare, Medicaid, and private insurance plans across the state. The linked Integrated Cancer Information and Surveillance System data represent approximately 80 percent of the North Carolina population with cancer through 2010. Cancer registry data were available for all incident breast cancer cases diagnosed from 2003 to 2006; the insurance administrative data include monthly enrollment data and inpatient, outpatient, and professional claims.

Study Sample

We included all breast cancer cases other than those with inflammatory disease or diagnosed at death or autopsy between 2003 and 2006 (n = 27,638) (Fig. 1). Patients were excluded if they had distant metastatic disease (n = 1058), multiple breast cancers (n = 747) or more than one primary cancer within 3 years before or 1 year after diagnosis (n = 550). Women were also excluded if they did not undergo a mastectomy (n = 17,766) or mastectomy was performed more than 6 months after diagnosis (n = 733). To be certain that we captured all potential health care use related to reconstruction, we required continuous insurance enrollment for 2 years following the date of undergoing mastectomy (excluding n = 1377). Lastly, we excluded 26 patients who were simultaneously enrolled in Medicare, Medicaid, and private insurance. The final cohort included 5381 patients who met all study inclusion and exclusion criteria.

Exposure and Outcome Measurement

We stratified the sample by insurance payer to calculate distances to the nearest possible surgeon who performs breast reconstruction. Geographic coordinates for the surgeon were identified based on the zip code centroid reported on all possible claims for breast

reconstruction within each payer. This provided the coordinates to all possible surgeons performing reconstruction within that payer. Straight-line distances were then calculated between the nearest possible surgeon (within their payer) and the patient's address at diagnosis. Actual distance to reconstruction was also calculated for those women who underwent reconstruction and was based on the zip code reported on the first claim for reconstruction. Based on thresholds observed in previous literature,[8,9] we then categorized distance to provider into three groups, less than 10 miles, 10 to 20 miles, and greater than or equal to 20 miles.

To examine outcomes, we dichotomized the cohort into women who received breast reconstruction within 2 years from the date of mastectomy compared with women with no evidence of breast reconstruction. We further stratified the women who received reconstruction by the timing of their reconstruction. In keeping with previously published Surveillance, Epidemiology, and End Results data, women were classified as receiving "immediate" reconstruction if it was performed less than 4 months after mastectomy; any reconstruction initiated 4 or more months after mastectomy was considered "delayed" reconstruction.

Covariates

Patient demographic and tumor characteristics were defined using data from the cancer registry. These included the following covariates measured at the time of the patient's diagnosis: patient age, race, year of diagnosis, cancer stage, and estrogen receptor and progesterone receptor status. Patient comorbidities measured by the Charlson index were defined using the insurance claims data. Claims data also provided relevant breast cancer treatment information, including receipt of chemotherapy, radiation therapy, and the type of breast reconstruction. Socioeconomic covariates included an indicator of rurality using rural-urban commuting area codes and census tract level of median household income for 2005 to 2009 from the American Community Survey.

Analytic Strategy

Crude analyses were performed to examine the associations between each covariate and breast reconstruction. In the entire cohort ($n = 5381$), logistic regression was used to estimate the odds of receiving postmastectomy breast reconstruction (versus not). We were specifically interested in the effect of distance defined as the straight-line distance from the patient's home to the closest surgeon reimbursed for reconstruction by that patient's insurance. In the subset of women who underwent reconstruction ($n = 1130$), logistic models were also used to estimate the odds of receiving delayed reconstruction (versus immediate) while controlling for covariates. Among these women who underwent reconstruction, distance was measured as the actual distance to the surgeon who was reported on that patient's claim. All logistical models were adjusted for covariates, including age, race, year of diagnosis, stage, estrogen/progesterone receptor status, comorbidity index, receipt of chemotherapy and radiation therapy, type of insurance, rural/urban,[10] census tract measure of income, and type of reconstruction. Sensitivity analyses were conducted excluding individuals with missing distance information. SAS 9.4 (SAS Institute, Inc., Cary, N.C.) analytic software was used.

RESULTS

Approximately 20 percent of patients underwent postmastectomy breast reconstruction (n = 1130) (Table 1).

Distance to a breast reconstructive surgeon was significantly associated with receipt of reconstruction. This effect was independent of other well-known predictors of health disparities, including age, race, rurality, and lower household income. Women living 10 to 20 miles from the nearest surgeon had approximately 22 percent lower odds of undergoing breast reconstruction (OR, 0.78; 95 percent CI, 0.63 to 0.96), and women living 20 miles or more from the nearest surgeon had 27 percent lower odds (OR, 0.73; 95 percent CI, 0.57 to 0.93) compared with women who lived within 10 miles (Fig. 2).

Women with federally funded health care [i.e., Medicaid (OR, 0.24; 95 percent CI, 0.19 to 0.32) and Medicare (OR, 0.58; 95 percent CI, 0.45 to 0.74)] had significantly lower odds of undergoing reconstruction compared with women with private insurance. Minority women had 50 percent lower odds of receiving reconstruction compared to non-Hispanic whites (OR, 0.48; 95 percent CI, 0.37 to 0.61) (Table 2). Consistent with previous studies,[5,6] increasing age at diagnosis, advanced cancer stage, and receipt of radiation therapy also decreased the odds of reconstruction. Effect sizes were of similar magnitude and precision in the sensitivity analyses, excluding observations with missing distance information.

Among women who received reconstruction (n = 1130), distance to the actual performing surgeon was not associated with whether or not a woman received immediate versus delayed reconstruction (Table 3). However, delayed reconstruction was associated with rural county of residence, chemotherapy, and radiation therapy. Women living in rural counties were 63 percent more likely to receive delayed reconstruction after controlling for other covariates (OR, 1.63; 95 percent CI, 1.11 to 2.38) (Table 4).

DISCUSSION

Breast reconstruction has repeatedly been shown to be of psychosocial benefit for breast cancer patients.[1,3] Nevertheless, only 21 percent of our patients underwent postmastectomy reconstruction, and this is consistent with other reports in the literature.[11] Because breast reconstruction has well-documented psychosocial benefits, it remains concerning that such a small proportion of women receive treatment.[1–3] We believe immediate breast reconstruction, when possible, is the preferred approach; however, only 16 percent of our patients underwent immediate postmastectomy reconstruction. When queried, nearly half of women who underwent delayed breast reconstruction would have preferred to have it performed in an immediate setting.[12] The aesthetic results of immediate versus delayed reconstruction are arguably superior[11,13] and, more importantly, patients report lower psychological health disturbance scores when they undergo reconstruction at the time of mastectomy.[14] Although the American College of Surgeons National Accreditation Program for Breast Centers guidelines require that patients are offered a preoperative referral to a reconstructive/plastic surgeon,[15] this is far from universal. In fact, the study in 2008 by Alderman et al. revealed that only 33 percent of patients report their general surgeon even

discussed breast reconstruction with them. This was irrespective of tumor behavior (ductal carcinoma in situ versus invasive) and comorbidities. The likelihood of this discussion, however, was increased in younger patients with higher levels of education.[16] Faced with relatively low use rates of breast reconstruction, we are left to question what barriers remain between patients facing mastectomy and surgeons who can reconstruct their breast(s).

This is the first population-based study to demonstrate distance to care and insurance carrier as significant predictors of receipt of breast reconstruction. Our data also suggest that this particular barrier to care (distance) may be ameliorated when breast reconstruction occurs in a delayed fashion. Clinically, this is not an unexpected finding. The local oncologic team (i.e., breast surgeon, medical oncologist, radiation oncologist, and radiographer) may not routinely include a plastic surgeon or one who accepts the patient's health insurance. It is also possible that the referring surgeons are consciously or unconsciously aware of patients' geographic and insurance barriers and that this too affects their decision-making. Age, previously identified as a bias affecting discussion of breast reconstruction, is also a proxy variable for those more likely to have private insurance, as women who were younger, white, and residing in urban areas were more likely to have private insurance.

In the delayed setting, the immediate needs of the cancer patient (i.e., excision and adjuvant therapies) have been addressed and the patient is free to pursue other goals, which may include breast reconstruction. Some limitations, such as travel distance to a reconstructive surgeon, may be addressed by the elective timing of delayed reconstruction (e.g., financial savings or leave from work).

Strengths of our study include access to a unique cancer registry–linked claims database, which includes women from multiple payers. Our study includes claims from federally funded insurance and from private payers. We were also uniquely able to capture both immediate and delayed breast reconstruction claims (i.e., claims >4 months from mastectomy). Furthermore, we have the ability to assess World Health Organization files claims for breast reconstruction by analyzing provider specialty codes. Using specialty information provided in the claims, approximately 95 percent of procedures were performed by plastic surgeons. These patterns of specialty care concurred with the American Society of Plastic Surgeons roster describing active surgeons across the state and, when compared, suggests that nearly all providers of plastic surgery are board certified and self-report as plastic surgeons for billing purposes.

Limitations of our study include unmeasured confounders such as individual income levels, patient choice, and decision-making, which may be more significant in breast reconstruction than in reconstruction of defects caused by other cancers. Distance was measured by a Euclidean (straight-line) method. However, road networks or traffic conditions may also be a consideration when seeking surgery. We also located providers within zip code centroids, which are less sensitive than actual practice address. This study focused on the state of North Carolina, and findings may not be generalizable to other populations. However, North Carolina is the ninth largest state and is racially and geographically diverse (35 percent racial/ethnic minority; 40 percent rural).[17]

Relocation of patients or surgeons is not a practical solution to address distance as a barrier to reconstruction. Perhaps, however, a significant impact on breast reconstruction use may be made through novel outreach options. We, and others, have initiated options such as early staged reconstruction techniques and telemedicine. For example, we allow patients to continue all other cancer care in the community (e.g., chemotherapy, physical therapy, radiation therapy) and travel only for breast reconstruction. If the reconstruction is performed early (e.g., within 14 days of locally performed mastectomy), it can achieve similar or even improved aesthetic results compared with immediate breast reconstruction.[18] Furthermore, we offer plastic surgery teleconsultation for patients who are unable to travel to our center. Although eventually they will have to arrange transportation for surgery and follow-up, they are educated as to their options without the financial and logistical difficulties of travel upfront. We remain optimistic about the potential for outreach. We need more data and additional research into these novel approaches to compare outcomes of staged reconstruction and telemedicine.

Acknowledgments

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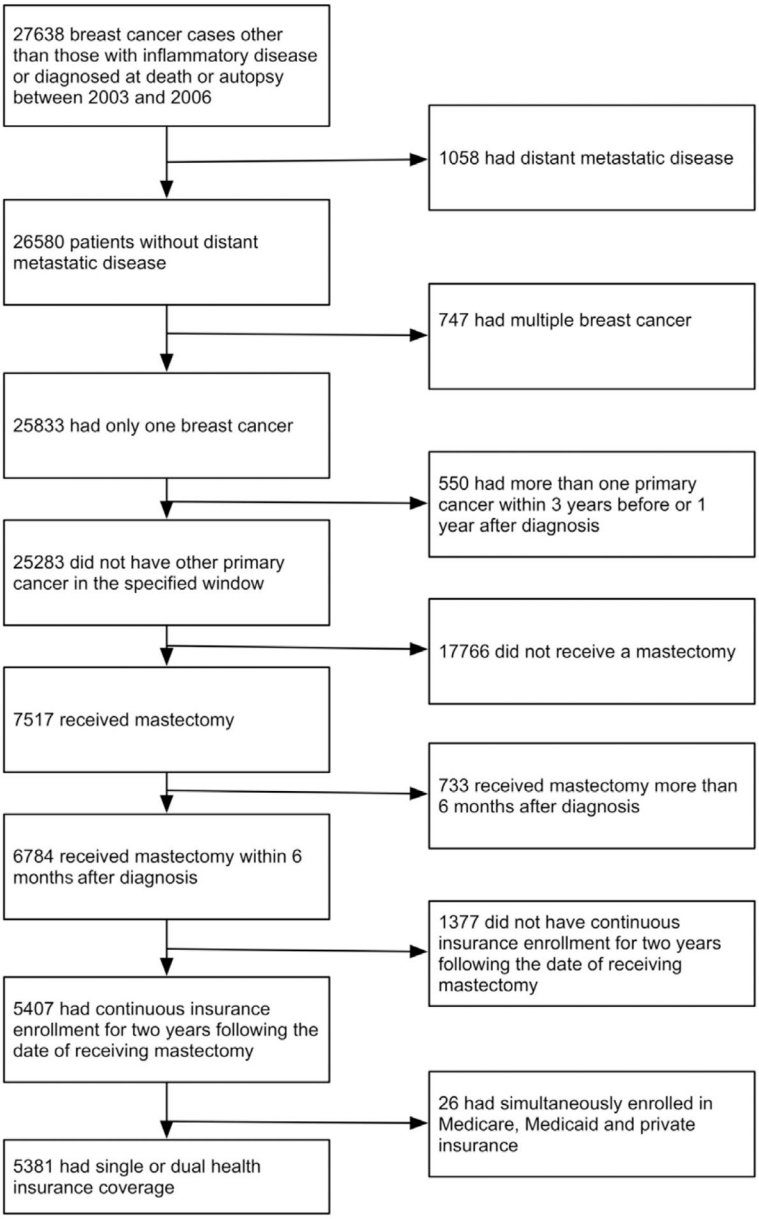

Fig. 1.
Cohort creation.

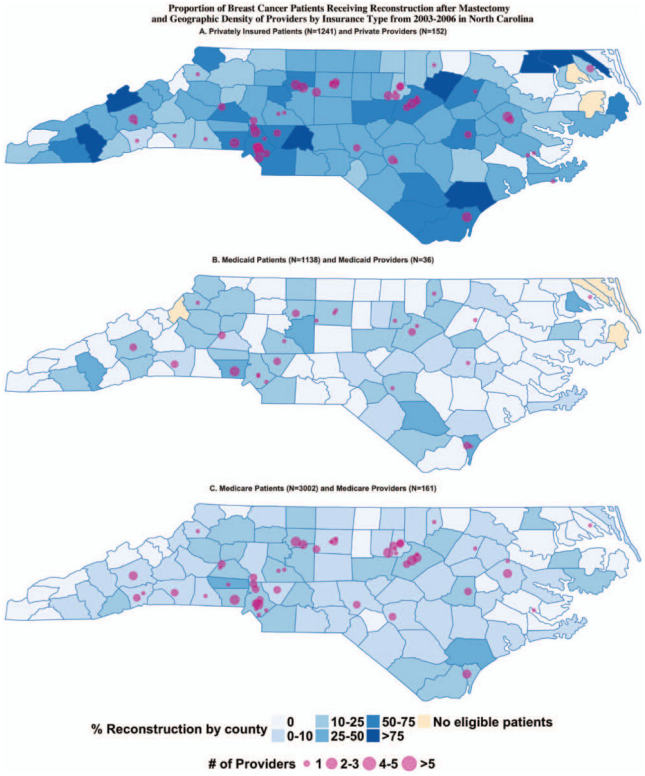

Fig. 2.

Proportion of breast cancer patients undergoing reconstruction after mastectomy and geographic density of providers by insurance type from 2003 to 2006 in North Carolina.

Table 1

Cohort Creation

Selection Criteria	No. of Included Patients (%)	No. of Excluded Patients (%)
Female breast cancer (exclusion of inflammatory breast cancer) diagnosed between 2003 and 2006, not diagnosed by death certificate or autopsy	27,638	
Excluded distant metastatic patients for 2-yr cohort	26,580 (96)	1058 (4)
Include only one breast cancer diagnosis patients	25,833 (97)	747 (3)
Exclude other origin cancer diagnosed within 3 yr before and 1 yr after breast cancer diagnosis	25,283 (98)	550 (2)
Received mastectomy	7517 (30)	17,766 (70)
Received mastectomy within 6 mo after diagnosis	6784 (90)	733 (10)
Continuous coverage through 2 yr after mastectomy	5407 (80)	1377 (20)
Excluded patients enrolled in Medicare, Medicaid, and private	5381 (100)	26 (0)

Table 2

Cohort Summary

Categories	Total (%)	Breast Reconstruction*†			p
		No Reconstruction	Immediate	Delayed	
No. of patients	5381	4251 (79%)	863 (16%)	267 (5%)	
Age at diagnosis					<0.0001
Mean ± SD	66 ± 13.2	69.3 ± 11.7	54.9 ± 11.3	50.3 ± 11.2	
Range	22–98	30–98	22–93	23–79	
Age group at diagnosis, yr					<0.0001
<50	735 (14)	297 (7, 40)	299 (35, 41)	139 (52, 19)	
50–59	883 (16)	541 (13, 61)	270 (31, 31)	72 (27, 8)	
60–69	1312 (24)	1070 (25, 82)	199 (23, 15)	43 (16, 3)	
≥70	2451 (46)	2343 (55, 96)	95 (11, 4)	13 (5, 1)	
Distance between home address and the nearest surgeon performing breast reconstruction					<0.0001
<10 miles	2934 (55)	2246 (53, 77)	533 (62, 18)	155 (58, 5)	
10–20 miles	1289 (24)	1028 (24, 80)	200 (23.16)	61 (23, 5)	
≥20 miles	1149 (21)	970 (23, 84)	128 (15, 11)	51 (19, 4)	
Missing	<11	<11	<11	0 (0, 0)	
Distance between home address and the actual performing surgeon					<0.0001
<10 miles	410 (8)	0 (0, 0)	320 (37, 78)	90 (34, 22)	
10–20 miles	283 (5)	0 (0, 0)	224 (26, 79)	59 (22, 21)	
≥20 miles	406 (8)	0 (0, 0)	299 (35.74)	107 (40.26)	
Missing	31 (1)	0 (0, 0)	20 (2, 65)	<11	
Not applicable	4251 (79)	4251 (100, 100)	0 (0, 0)	0 (0, 0)	
Race					<0.0001
Non-Hispanic white	4405 (82)	3422 (80, 78)	751 (87, 17)	232 (87, 5)	
Others	976 (18)	829 (20, 85)	112 (13, 11)	35 (13, 4)	
Rural (county)					<0.0001
No	3333 (62)	2499 (59, 75)	658 (76, 20)	176 (66, 5)	
Yes	2048 (38)	1752 (41, 86)	205 (24, 10)	91 (34, 4)	
Median household income quartile 2005–2009 (census tract)					<0.0001

Categories	Breast Reconstruction*†				p
	Total (%)	No Reconstruction	Immediate	Delayed	
First	1268 (24)	1089 (26, 86)	133 (15,10)	46 (17, 4)	
Second	1258 (23)	1040 (24, 83)	156 (18,12)	62 (23, 5)	.
Third	1267 (24)	976 (23, 77)	219 (25,17)	72 (27, 6)	.
Fourth	1258 (23)	864 (20, 69)	318 (37, 25)	76 (28, 6)	
Not available	330 (6)	282 (7, 85)	37 (4, 11)	Less than 11	
Cancer stage					<0.0001
0/I	3096 (58)	2370 (56, 77)	609 (71, 20)	117 (44, 4)	
II/III	2238 (42)	1840 (43, 82)	249 (29, 11)	149 (56, 7)	
Unknown	47 (1)	41 (1, 87)	<11	<11	
Insurance type					<0.0001
Private only	1241 (23)	543 (13, 44)	515 (60, 41)	183 (69, 15)	
Medicare or Medicare with private	3002 (56)	2691 (63, 90)	266 (31, 9)	45 (17, 1)	
Any Medicaid	1138 (21)	1017 (24, 89)	82 (10, 7)	39 (15, 3)	
Radiation therapy					<0.0001
No	4262 (79)	3337 (78, 78)	749 (87, 18)	176 (66, 4)	
Yes	1119 (21)	914 (22, 82)	114 (13, 10)	91 (34, 8)	
Chemotherapy					<0.0001
No	3491 (65)	2884 (68, 83)	528 (61, 15)	79 (30, 2)	
Yes	1890 (35)	1367 (32, 72)	335 (39, 18)	188 (70, 10)	
Year of diagnosis					0.2413
2003	1368 (25)	1084 (25, 79)	225 (26, 16)	59 (22, 4)	
2004	1376 (26)	1080 (25, 78)	221 (26, 16)	75 (28, 5)	
2005	1280 (24)	1032 (24, 81)	180 (21, 14)	68 (25, 5)	
2006	1357 (25)	1055 (25, 78)	237 (27, 17)	65 (24, 5)	
Charlson score					<0.0001
0	2043 (38)	1622 (38, 79)	306 (35, 15)	115 (43, 6)	
1+	1068 (20)	974 (23, 91)	72 (8, 7)	22 (8, 2)	
Unable to assess	2270 (42)	1655 (39, 73)	485 (56, 21)	130 (49, 6)	
First or only cancer diagnosis					
No	921 (17)	780 (18, 85)	117 (14, 13)	24 (9, 3)	<0.0001

Categories	Breast Reconstruction*†				p
	Total (%)	No Reconstruction	Immediate	Delayed	
Yes	4460 (83)	3471 (82, 78)	746 (86, 17)	243 (91, 5)	
Type of reconstruction					<0.0001
None	4251 (79)	4251 (100, 100)	0 (0, 0)	0 (0, 0)	
Implant-based	744 (14)	0 (0, 0)	608 (70, 82)	136 (51, 18)	
Autologous with tissue expander or implant	119 (2)	0 (0, 0)	84 (10, 71)	35 (13, 29)	
Autologous alone	252 (5)	0 (0, 0)	162 (19, 64)	90 (34, 36)	
Not otherwise specified	15 (0)	0 (0, 0)	<11	<11	
ER and PR status					0.0290
ER- or PR-positive	2204 (41)	1742 (41, 79)	358 (41, 16)	104 (39, 5)	
ER- and PR-negative	622 (12)	485 (11, 78)	90 (10, 14)	47 (18, 8)	
Borderline/undetermined/unknown	2555 (47)	2024 (48, 79)	415 (48, 16)	116 (43, 5)	

ER, estrogen receptor; PR, progesterone receptor.

*There are no missing observations in breast reconstruction.

†Two numbers in parenthesis means (column %, row %).

Table 3

Model for Receipt of Any Postmastectomy Breast Reconstruction

Variables	OR (95% CI)
Age at diagnosis	0.90 (0.89–0.91)[§]
Cancer stage	
0/I	Referent
II/III	0.75 (0.61–0.93)[†]
Unknown	1.11 (0.42–2.91)
Charlson score	
0	Referent
1+	0.88 (0.67–1.17)
Unable to assess	1.75 (1.41–2.17)[§]
Chemotherapy	
No	Referent
Yes	1.10 (0.89–1.37)
Distance between home address and the nearest surgeon performing breast reconstruction within each payer cohort	
<10 miles	Referent
10–20 miles	0.78 (0.63–0.96)[†]
≥20 miles	0.73 (0.57–0.93)[†]
Missing	0.57 (0.08–3.93)
ER and PR status	
ER- or PR-positive	Referent
ER- and PR-negative	0.99 (0.76–1.30)
Borderline/undetermined/unknown	0.82 (0.64–1.05)
First or only cancer diagnosis	
No	0.89 (0.71–1.13)
Yes	Referent
Insurance type	
Private only	Referent
Medicare or Medicare with Private	0.58 (0.45–0.74)[§]
Any Medicaid	0.24 (0.19–0.32)[§]
Median household income quartile 2005–2009 (census tract)	
First	0.68 (0.52–0.89)[‡]
Second	0.73 (0.57–0.94)[†]
Third	0.86 (0.68–1.07)
Fourth	Referent
Not available	0.56 (0.37–0.84)[‡]
Race	
Non-Hispanic white	Referent
Others	0.48 (0.37–0.61)[§]

Variables	OR (95% CI)
Radiation therapy	
No	Referent
Yes	0.43 (0.34–0.54)§
Rural (county)	
No	Referent
Yes	0.65 (0.54–0.79)§
Year of diagnosis	
2003	Referent
2004	1.47 (1.12–1.92)‡
2005	1.25 (0.91–1.73)
2006	1.42 (1.03–1.96)†

*Logistic regression result (reconstruction = 1 vs. not = 0) OR < 1: less likely to undergo reconstruction (use continuous age variable). Total no. of observations, 5381; total no. of observations used, 5381; model fit Akaike information criterion = 3803.092.

†$p < 0.05$.

‡$p < 0.01$.

§$p < 0.001$.

Table 4

Model for Receipt of Delayed Reconstruction *

Variables	OR (95% CI)
Age at diagnosis	0.98 (0.96–1.00) †
Cancer stage	
0/I	Referent
II/III	1.36 (0.90–2.05)
Unknown	1.56 (0.16–15.17)
Charlson score	
0	Referent
1+	1.13 (0.63–2.05)
Unable to assess	1.11 (0.76–1.62)
Chemotherapy	
No	Referent
Yes	2.42 (1.62–3.63) ‡
Distance between home address and the actual performing surgeon	
<10 miles	Referent
10–20 miles	0.81 (0.54–1.22)
≥20 miles	0.88 (0.59–1.31)
Missing	1.44 (0.51–4.06)
ER and PR status	
ER- or PR-positive	Referent
ER- and PR-negative	1.45 (0.92–2.29)
Borderline/undetermined/unknown	1.22 (0.76–1.98)
First or only cancer diagnosis	
No	0.82 (0.50–1.36)
Yes	Referent
Insurance type	
Private only	Referent
Medicare or Medicare with private	0.93 (0.56–1.54)
Any Medicaid	1.24 (0.76–2.04)
Median household income quartile 2005–2009 (census tract)	
First	1.14 (0.69–1.89)
Second	1.42 (0.91–2.20)
Third	1.33 (0.89–1.98)
Fourth	Referent
Not available	0.95 (0.42–2.11)
Race	
Non-Hispanic white	Referent
Others	0.76 (0.48–1.21)
Radiation therapy	
No	Referent

Variables	OR (95% CI)
Yes	1.55 (1.03–2.34)†
Rural (county)	
No	Referent
Yes	1.63 (1.11–2.38)†
Type of reconstruction	
Implant-based	Referent
Autologous with tissue expander or implant	1.37 (0.85–2.22)
Autologous alone	2.24 (1.55–3.22)‡
Not otherwise specified	1.78 (0.44–7.26)
Year of diagnosis	
2003	Referent
2004	1.52 (0.92–2.50)
2005	1.40 (0.75–2.61)
2006	1.24 (0.66–2.33)

* Logistic regression result (immediate = 0 vs. delay = 1) OR < 1: less likely to undergo delayed reconstruction (use continuous age variable); 1130 read, 1130 used. Model fit Akaike information criterion = 1131.078.

† $p < 0.05$.

‡ $p < 0.001$.