Immediate Postmastectomy Breast Reconstruction Showed Limited Advantage in Patient Survival after Stratifying by Family Income

Yi-Zhou Jiang*, Yi-Rong Liu, Ke-Da Yu, Wen-Jia Zuo, Zhi-Ming Shao*

Department of Breast Surgery, Cancer Center and Cancer Institute, Shanghai Medical College, Fudan University, Shanghai, P.R. China

Abstract

Background: Postmastectomy breast reconstruction is widely used in breast cancer patients for its aesthetic effect. Although several studies have casted suspicion upon the oncological safety of immediate breast reconstruction after mastectomy, the potential impact of different reconstruction methods on patient survival remains unclear.

Patients and Methods: We identified 35,126 female patients diagnosed with breast cancer from January 1, 1998 to December 31, 2002 in the Surveillance, Epidemiology, and End Results database. Breast cancer-specific survival (BCSS) and overall survival (OS) were compared among patients who underwent mastectomy with or without immediate breast reconstruction (autologous reconstruction or implant reconstruction) using Cox proportional hazard regression models.

Results: In multivariate analysis unadjusted for family income, patients undergoing immediate postmastectomy reconstruction exhibited improved BCSS [pooled reconstruction (any types of reconstruction): hazard ratio (HR) = 0.87, 95% confidence interval (CI) 0.80–0.95, P = 0.001] and OS (pooled reconstruction: HR = 0.70, 95% CI 0.65–0.75, P<0.001) compared to patients who underwent mastectomy alone. However, after stratifying by family income, patients receiving reconstruction showed limited advantage in BCSS and OS compared with those undergoing mastectomy alone. When comparing between the two reconstruction methods, no significant differences were observed in either BCSS (implant versus autologous reconstruction: HR = 1.11, 95%CI 0.90–1.35, P = 0.330) or OS (implant versus autologous reconstruction: HR = 1.07, 95% 0.90–1.28, P = 0.424).

Conclusions: Compared to mastectomy alone, immediate postmastectomy reconstruction had limited advantage in survival after adjusting for confounding factor of family income. Our findings, if validated in other large databases, may help to illustrate the actual effect of immediate postmastectomy reconstruction on patient survival.

Introduction

Breast cancer is the most common female malignancy in both the developing and developed countries, with over 1.3 million cases diagnosed annually and almost 0.5 million deaths [1,2]. As a major treatment protocol, mastectomy is used to treat nearly 60,000 patients diagnosed with breast cancer in the United States (US) annually [3,4]. While this procedure may have a profound impact on the patient’s physical well-being, the surgical result of this procedure will impair a patient’s body image. Such drawbacks can be effectively remedied by breast reconstruction, especially when performed immediately after mastectomy [5–7]. Although several studies suggest the oncological safety of breast reconstruction by demonstrating that immediate breast reconstruction neither impedes the local recurrence [8,9] nor delays adjuvant therapies [10,11], the underlying interactions between grafts and residual breast tissues are ambiguous.

Recently, adipocytes have been suggested to play an important role in the origin and development of breast cancer. Yasushi Manabe and his colleagues [12] found that mature adipose cells promoted the growth of breast cancer cells in collagen gel matrix culture through their growth-promoting effect on estrogen receptor (ER)-positive tumor cells. Puneeth Iyengar’s group [13] revealed that adipocytes contributed significantly to tumor growth at early stages through secretion and processing of collagen VI. Obviously, autologous breast reconstruction would increase the number of adipocytes in the surgical region, but it remains elusive whether this lipofilling effect will impair the oncological safety of reconstruction.

In the present study, we used the US National Cancer Institute’s (NCI) Surveillance, Epidemiology, and End Results (SEER)
Table 1. Demographic and tumor characteristics of the study sample.

| Variable            | Mastectomy only | Reconstruction Type | All | Autologous Only | Implant Only | P_1  | P_2  |
|---------------------|-----------------|---------------------|-----|-----------------|--------------|------|------|
|                     | NO. (%)         | NO. (%)             | NO. (%) | NO. (%) | NO. (%) |      |      |
| Age, y              | 29003           | 6123                | 2649 | 1412           |              |      |      |
| <45                 | 4460 (15.4)     | 2059 (33.6)         | 908 (34.3) | 493 (34.9) | <0.001 | 0.106 |
| 45–64               | 12900 (44.5)    | 3559 (58.1)         | 1545 (58.3) | 790 (55.9) |        |      |
| >64                 | 11643 (40.1)    | 505 (8.2)           | 196 (7.4) | 129 (9.1) | <0.001 | <0.001 |
| Race                |                 |                     |      |                 |              |      |      |
| White               | 22988 (79.6)    | 5273 (86.3)         | 2208 (83.5) | 1248 (88.6) |        |      |
| Black               | 2758 (9.5)      | 523 (8.6)           | 303 (11.5) | 82 (5.8)   |        |      |
| Other               | 3147 (10.9)     | 314 (5.1)           | 134 (5.1) | 78 (5.5)   |        |      |
| Marital status      |                 |                     |      |                 |              |      |      |
| Married             | 16121 (55.6)    | 4183 (68.3)         | 1815 (68.5) | 961 (68.1) | <0.001 | 0.904 |
| Not married         | 11660 (40.2)    | 1763 (28.8)         | 761 (28.7) | 409 (29.0) |        |      |
| Unknown             | 1222 (4.2)      | 177 (2.9)           | 73 (2.8)  | 42 (3.0)   |        |      |
| Family income       |                 |                     |      |                 |              |      |      |
| <$4645              | 6168 (21.3)     | 795 (13.0)          | 366 (13.8) | 177 (12.5) | <0.001 | 0.122 |
| $4645–$5116         | 9002 (31.0)     | 1394 (22.8)         | 592 (22.3) | 362 (25.6) |        |      |
| $5117–$6281         | 6808 (23.3)     | 1697 (27.7)         | 787 (29.7) | 366 (25.9) |        |      |
| >$6281              | 7024 (24.2)     | 2237 (36.5)         | 904 (34.1) | 507 (35.9) |        |      |
| Year of diagnosis   |                 |                     |      |                 |              | 0.035| 0.130|
| 1998–2000           | 14996 (51.7)    | 3079 (50.3)         | 1353 (51.1) | 686 (48.6) |        |      |
| 2001–2002           | 14007 (48.3)    | 3044 (49.7)         | 1296 (48.9) | 726 (51.4) |        |      |
| County type         |                 |                     |      |                 |              |      |      |
| Metropolitan        | 24042 (82.9)    | 5610 (91.6)         | 2430 (91.7) | 1285 (91.0) | <0.001 | 0.429 |
| Nonmetropolitan     | 4961 (17.1)     | 513 (8.4)           | 219 (8.3)  | 127 (9.0)  |        |      |
| County education    |                 |                     |      |                 |              |      |      |
| High                | 14203 (49.0)    | 3364 (54.9)         | 1338 (50.5) | 805 (57.0) | <0.001 | <0.001 |
| Low                 | 14799 (51.0)    | 2759 (45.1)         | 1311 (49.5) | 607 (43.0) |        |      |
| Laterality          |                 |                     |      |                 |              | 0.485| 0.141|
| Right               | 14292 (49.3)    | 2995 (48.9)         | 1323 (49.9) | 671 (47.5) |        |      |
| Left                | 14708 (50.7)    | 3127 (51.1)         | 1326 (50.1) | 741 (52.5) |        |      |
| Tumor size          |                 |                     |      |                 |              |      |      |
| <2 cm               | 12742 (44.6)    | 3193 (52.5)         | 1304 (49.7) | 802 (57.0) | <0.001 | <0.001 |
| 2–5 cm              | 13337 (46.7)    | 2502 (41.2)         | 1119 (42.7) | 534 (38.0) |        |      |
| >5 cm               | 2487 (8.7)      | 382 (6.3)           | 200 (7.6)  | 71 (5.0)   |        |      |
| Grade               |                 |                     |      |                 |              | 0.016| 0.001|
| I                   | 3611 (12.5)     | 732 (12.0)          | 283 (10.7)  | 196 (13.9) |        |      |
| II                  | 11274 (38.9)    | 2405 (39.3)         | 1015 (38.3) | 565 (40.0) |        |      |
| III                 | 13033 (44.9)    | 2735 (44.7)         | 1248 (47.1) | 596 (42.2) |        |      |
| Unknown             | 1085 (3.7)      | 251 (4.1)           | 103 (3.9)  | 55 (3.9)   |        |      |
| Node status         |                 |                     |      |                 |              |      |      |
| Negative            | 14842 (51.2)    | 3323 (54.3)         | 1375 (51.9) | 809 (57.3) | <0.001 | <0.001 |
| 1–3 positive        | 7735 (26.7)     | 1778 (29.0)         | 766 (28.9)  | 405 (28.7) |        |      |
| >3 positive         | 5443 (18.6)     | 862 (14.1)          | 429 (16.2)  | 165 (11.7) |        |      |
| Unknown             | 983 (3.4)       | 160 (2.6)           | 79 (3.0)   | 33 (2.3)   |        |      |
| ER                  |                 |                     |      |                 |              | 0.122| 0.029|
| Positive            | 17574 (60.7)    | 3815 (62.5)         | 1594 (60.4) | 910 (64.6) |        |      |
Inclusion and exclusion criteria

Ethics statement

Data management and statistical analysis

Materials and Methods

Inclusion and exclusion criteria

Materials and Methods

Ethics statement

Our study was approved by the independent ethical committee/ institutional review board of Fudan University Shanghai Cancer Center (Shanghai Cancer Center Ethical Committee). The data released through the SEER database does not require informed patient consent because cancer is a reportable disease in every state in the US.

Demographic statistics included age at diagnosis, race, marital status, family income, year of diagnosis, county metropolitan status and county education level (Table 1). Age was categorized into <45, 45–64, >64 years groups. Race and ethnicity were coded as white, black, and other (American Indian/AK Native, Asian/Pacific Islander). Marital status was coded as married and not married including divorced, widowed, single (never married) and separated. Annual family income were divided into four groups (4645, 4645–5116, 5117–6281, >6281) by the quartiles income of all studied cases. According to the median percent of individuals having over a 12th grade education level, county education was divided as high or low. Tumor characteristics included laterality, tumor size, histological grade, lymph nodes status, ER status, progesterone receptor (PR) status, and radiotherapy. For histological grade IV (SEER program code: undifferentiated or anaplastic) or missing data regarding reconstruction status were also excluded.

Demographic statistics included age at diagnosis, race, marital status, family income, year of diagnosis, county metropolitan status and county education level (Table 1). Age was categorized into <45, 45–64, >64 years groups. Race and ethnicity were coded as white, black, and other (American Indian/AK Native, Asian/Pacific Islander). Marital status was coded as married and not married including divorced, widowed, single (never married) and separated. Annual family income were divided into four groups (<4645, 4645–5116, 5117–6281, >6281) by the quartiles income of all studied cases. According to the median percent of individuals having over a 12th grade education level, county education was divided as high or low. Tumor characteristics included laterality, tumor size, histological grade, lymph nodes status, ER status, progesterone receptor (PR) status, and radiotherapy. For histological grade IV (SEER program code: undifferentiated or anaplastic) or missing data regarding reconstruction status were also excluded.

Data management and statistical analysis

Demographic and tumor characteristics were generated for patients who underwent mastectomy alone and those who underwent different methods of immediate postmastectomy reconstruction.

Materials and Methods

Ethics statement

Our study was approved by the independent ethical committee/ institutional review board of Fudan University Shanghai Cancer Center (Shanghai Cancer Center Ethical Committee). The data released through the SEER database does not require informed patient consent because cancer is a reportable disease in every state in the US.

Inclusion and exclusion criteria

Data were obtained from the current SEER database consisting of 18 population-based cancer registries. We selected female patients diagnosed with unilateral breast cancer from January 1, 1998, through December 31, 2002. Patients diagnosed with breast cancer before 1998 were excluded because SEER did not record reconstruction data until 1998 [14]; Patients diagnosed with breast cancer after 2002 were excluded to ensure adequate follow-up time.

We included 35,126 patients in this study according to the following criteria: female, age of diagnosis between 18 and 84 years, breast cancer as the primary and only cancer diagnosis, unilateral breast cancer, pathologically confirmed infiltrating ductal carcinoma (IDC, ICD-O-3 8500/3), AJCC stages I to III, undergoing following types of mastectomy including total mastectomy, modified radical mastectomy, radical mastectomy, extended radical mastectomy, or mastectomy otherwise unspecified (surgery of primary site code: 40–80). Patients treated with partial or subcutaneous mastectomy were excluded. Patients with histological grade IV (SEER program code: undifferentiated or anaplastic) or missing data regarding reconstruction status were also excluded.

Data management and statistical analysis

Demographic and tumor characteristics were generated for patients who underwent mastectomy alone and those who underwent the first course of reconstruction immediately at the time of their mastectomy. The latter group of patients were further categorized into implant only and autologous only (including reconstruction with rectus abdominis flap, latissimus dorsi flap, and flap not otherwise specified) subgroups. Patients who received other types of reconstruction or received combination of autologous and implant techniques were not included in either the implant or the autologous groups.

Demographic statistics included age at diagnosis, race, marital status, family income, year of diagnosis, county metropolitan status and county education level (Table 1). Age was categorized into <45, 45–64, >64 years groups. Race and ethnicity were coded as white, black, and other (American Indian/AK Native, Asian/Pacific Islander). Marital status was coded as married and not married including divorced, widowed, single (never married) and separated. Annual family income were divided into four groups (<4645, 4645–5116, 5117–6281, >6281) by the quartiles income of all studied cases. According to the median percent of individuals having over a 12th grade education level, county education was divided as high or low. Tumor characteristics included laterality, tumor size, histological grade, lymph nodes status, ER status, progesterone receptor (PR) status, and radiotherapy. For histological grade IV (SEER program code: undifferentiated or anaplastic) or missing data regarding reconstruction status were also excluded.

Data management and statistical analysis

Demographic and tumor characteristics were generated for patients who underwent mastectomy alone and those who underwent the first course of reconstruction immediately at the time of their mastectomy. The latter group of patients were further categorized into implant only and autologous only (including reconstruction with rectus abdominis flap, latissimus dorsi flap, and flap not otherwise specified) subgroups. Patients who received other types of reconstruction or received combination of autologous and implant techniques were not included in either the implant or the autologous groups.

Demographic statistics included age at diagnosis, race, marital status, family income, year of diagnosis, county metropolitan status and county education level (Table 1). Age was categorized into <45, 45–64, >64 years groups. Race and ethnicity were coded as white, black, and other (American Indian/AK Native, Asian/Pacific Islander). Marital status was coded as married and not married including divorced, widowed, single (never married) and separated. Annual family income were divided into four groups (<4645, 4645–5116, 5117–6281, >6281) by the quartiles income of all studied cases. According to the median percent of individuals having over a 12th grade education level, county education was divided as high or low. Tumor characteristics included laterality, tumor size, histological grade, lymph nodes status, ER status, progesterone receptor (PR) status, and radiotherapy. For histological grade IV (SEER program code: undifferentiated or anaplastic) or missing data regarding reconstruction status were also excluded.

Chi-square tests were used to evaluate the differences between mastectomy and different reconstruction types. Kaplan-Meier plots and log-rank tests were performed to compare unadjusted BCSS and OS among different treatment groups. Adjusted hazard ratios (HRs)
with 95% confidence intervals (CIs) were estimated using Cox proportional hazard regression models. All the statistical analyses were performed with SPSS statistics, version 20 (SPSS, Chicago, IL, USA). A two-sided \( P < 0.05 \) was deemed to be statistically significant.

**Results**

**Demographic and tumor characteristics**

A total of 35,126 patients were included in this study according to the inclusion and exclusion criteria stated above, of which 29,003 patients underwent mastectomy alone while 6,123 patients underwent immediate breast reconstruction after mastectomy. Furthermore, in the reconstruction group, 2,649 females received autologous reconstruction and 1,412 patients received implant reconstruction. The remaining 2062 females received other types of reconstruction, including reconstruction not otherwise specified (unknown if flap), abdominus recti flap plus implant, latissimus dorsi flap plus implant and flap not otherwise specified plus implant, were unsuitable to be classified into either the implant or the autologous groups. All demographic and tumor characteristics are shown in Table 1.

Patients with younger age (percentage of patients who underwent mastectomy alone versus pooled reconstruction: 15.4% vs. 33.6% for \(<45\) y, \( P < 0.001 \), white race (79.6% vs. 86.3%, \( P < 0.001 \)), higher family income (47.7% vs. 64.2%, for \( >$5117 \), \( P < 0.001 \)), higher education level (49.0% vs. 54.9%, \( P < 0.001 \)) were more likely to undergo reconstruction. Also, women who were married at diagnosis (55.6% vs. 68.3%, \( P < 0.001 \)) and lived in metropolis (82.9% vs. 91.6%, \( P < 0.001 \)) were more likely to receive immediate reconstruction. As to tumor characteristics, the reconstruction group was associated with smaller tumor size (44.6% vs. 52.5% for \( \leq 2 \) cm, \( P < 0.001 \)), fewer positive lymph nodes (51.2% vs. 54.3% for node negative, \( P < 0.001 \); 26.7% vs. 29.0% for 1–3 positive nodes, \( P < 0.001 \)) and less application of radiotherapy (22.0% vs. 18.2%, \( P < 0.001 \)). Laterality (\( P = 0.485 \)) was well balanced between the mastectomy and reconstruction groups. All demographic and tumor characteristics showed similarity between different reconstruction types (autologous only and implant only, Table 1) except race, tumor size, country education level, tumor grade and node status.

**Comparison of survival between the mastectomy group and the pooled reconstruction group**

We analyzed the unadjusted BCSS and OS via Kaplan-Meier plots. The median follow-up time was 107 months. Compared with patients undergoing mastectomy alone, women receiving
Table 2. Cox proportional hazard regression model of Breast Cancer-Specific Survival.

| Variablea | Univariate | Multivariate |
|-----------|------------|--------------|
|           | HR (95%CI) | P            | HR (95%CI) | P          |
| Reconstruction type |           |              |            |            |
| Mastectomy only | 1.00       | 1.00         | -          | -          |
| Pooled reconstruction | 0.74 (0.68–0.80) | <0.001 | 0.87 (0.80–0.95) | 0.001 |
| Autologous only | 0.83 (0.74–0.93) | 0.001 | 0.90 (0.80–1.01) | 0.065 |
| Implant only | 0.61 (0.51–0.72) | <0.001 | 0.80 (0.68–0.96) | 0.014 |
| Age, y |            |              |            |            |
| <45 | 1.39 (1.30–1.49) | <0.001 | 1.16 (1.08–1.25) | <0.001 |
| 45–64 | 1.00       | 1.00         | -          | -          |
| >64 | 1.16 (1.08–1.24) | <0.001 | 1.41 (1.32–1.52) | <0.001 |
| Race |            |              |            |            |
| White | 1.00       | 1.00         | -          | -          |
| Black | 1.95 (1.80–2.12) | <0.001 | 1.39 (1.28–1.51) | <0.001 |
| Otherb | 0.85 (0.77–0.95) | 0.003 | 0.88 (0.79–0.97) | 0.014 |
| Marital status |              |            |            |            |
| Married | 1.00       | 1.00         | -          | -          |
| Not marriedc | 1.31 (1.24–1.39) | <0.001 | 1.17 (1.10–1.24) | <0.001 |
| Year of diagnosis |            |              |            |            |
| 1998–2000 | 1.00       | 1.00         | -          | -          |
| 2001–2002 | 0.95 (0.90–1.01) | 0.016 | 0.92 (0.87–0.97) | 0.003 |
| County type |            |              |            |            |
| Metropolitan | 1.00       | 1.00         | -          | -          |
| Nonmetropolitan | 0.98 (0.90–1.06) | 0.630 | 1.07 (0.98–1.16) | 0.132 |
| County educationd |            |              |            |            |
| High | 1.00       | 1.00         | -          | -          |
| Low | 1.18 (1.12–1.25) | <0.001 | 1.02 (0.96–1.08) | 0.579 |
| Laterality |            |              |            |            |
| Right | 1.00       | 1.00         | -          | -          |
| Left | 1.02 (0.97–1.08) | 0.454 | 1.02 (0.96–1.08) | 0.507 |
| Tumor size |            |              |            |            |
| <2 cm | 1.00       | 1.00         | -          | -          |
| 2–5 cm | 3.25 (3.03–3.49) | <0.001 | 1.93 (1.79–2.08) | <0.001 |
| >5 cm | 6.49 (5.94–7.71) | <0.001 | 2.72 (2.47–3.00) | <0.001 |
| Gradee |            |              |            |            |
| I | 1.00       | 1.00         | -          | -          |
| II | 3.40 (2.86–4.04) | <0.001 | 2.28 (1.91–2.71) | <0.001 |
| III | 7.42 (6.27–8.77) | <0.001 | 3.25 (2.73–3.86) | <0.001 |
| Node status |            |              |            |            |
| Negative | 1.00       | 1.00         | -          | -          |
| 1–3 positive nodes | 2.45 (2.28–2.64) | <0.001 | 2.08 (1.93–2.25) | <0.001 |
| >3 positive nodes | 5.86 (5.46–6.29) | <0.001 | 4.10 (3.78–4.44) | <0.001 |
| ERf |            |              |            |            |
| Positive | 1.00       | 1.00         | -          | -          |
| Negative | 2.29 (2.16–2.42) | <0.001 | 1.41 (1.30–1.53) | <0.001 |
| PRf |            |              |            |            |
| Positive | 1.00       | 1.00         | -          | -          |
| Negative | 2.12 (2.00–2.24) | <0.001 | 1.38 (1.28–1.49) | <0.001 |

Table 2. Cont.

| Variablea | Univariate | Multivariate |
|-----------|------------|--------------|
|           | HR (95%CI) | P            | HR (95%CI) | P          |
| Yes | 1.00       | 1.00         | -          | -          |
| No | 0.45 (0.43–0.48) | <0.001 | 1.06 (0.99–1.13) | 0.073 |

*Adjusted by Cox proportional hazards models including all factors, as categorized in Table 2.
*Including American Indian/AK Native, Asian/Pacific Islander.
*Including divorced, widowed, single (never married), separated.
*High indicates a county with greater than 78.0% of individuals having over a 12th grade education level. Low indicates a county with less than 78.0% (including 78.0%) of individuals having over a 12th grade education level. (78.0% is the median of all county education data studied).
*Grade are coded as followings: Well differentiated; Grade I; Moderately differentiated; Grade II; Poorly differentiated; Grade III; Unknown.
*ER: Estrogen Receptor; PR: Progesterone Receptor.

doi:10.1371/journal.pone.0082807.t002

Comparison of survival stratified by family income

We hypothesize that there might be confounding factors which would affect the relationship between reconstruction and clinical outcomes. Therefore, we further performed multivariate analysis stratifying by the potential characteristics, such as age, ER status, node status and tumor size (data not shown) and found only family income to be a confounding factor. After stratifying by family income (Table 4), only patients with income more than $6281 demonstrated slightly improved BCSS in both the pooled reconstruction group (HR = 0.85, 95% CI 0.73–0.99, P = 0.034) and the implant group (HR = 0.66, 95% CI 0.47–0.91, P = 0.010), but not in the autologous group (HR = 0.94, 95% CI 0.77–1.15, P = 0.553). Also patients with income between $4,645 and $5,116 in the pooled reconstruction group experienced limited advantage in BCSS (HR = 0.83, 95% CI 0.70–0.99, P = 0.040). No difference in survival was observed between the remaining groups. Thus, immediate postmastectomy breast reconstruction showed limited advantage in patient survival after stratifying by family income.
Table 3. Cox proportional hazard regression model of Overall Survival.

| Variablea | Univariate | Multivariate |
|-----------|------------|--------------|
| HR (95%CI) | P | HR (95%CI) | P |
| Reconstruction type | | | |
| Mastectomy only | 1.00 | - | 1.00 | - |
| Pooled reconstruction | 0.49 (0.45–0.52) | <0.001 | 0.70 (0.65–0.75) | <0.001 |
| Autologous only | 0.54 (0.49–0.60) | <0.001 | 0.73 (0.66–0.81) | <0.001 |
| Implant only | 0.44 (0.38–0.50) | <0.001 | 0.67 (0.58–0.78) | <0.001 |
| Age, y | | | |
| <45 | 1.17 (1.10–1.25) | <0.001 | 1.07 (1.00–1.14) | 0.040 |
| 45–64 | 1.00 | - | 1.00 | - |
| >64 | 2.52 (2.40–2.64) | <0.001 | 2.57 (2.44–2.70) | <0.001 |
| Race | | | |
| White | 1.00 | - | 1.00 | - |
| Black | 1.64 (1.54–1.75) | <0.001 | 1.33 (1.24–1.43) | <0.001 |
| Otherb | 0.74 (0.69–0.81) | <0.001 | 0.80 (0.74–0.87) | <0.001 |
| Marital status | | | |
| Married | 1.00 | - | 1.00 | - |
| Not married2 | 1.72 (1.65–1.80) | <0.001 | 1.34 (1.29–1.40) | <0.001 |
| Year of diagnosis | | | |
| 1998–2000 | 1.00 | - | 1.00 | - |
| 2001–2002 | 0.95 (0.90–0.99) | 0.012 | 0.94 (0.90–0.98) | 0.003 |
| County type | | | |
| Metropolitan | 1.00 | - | 1.00 | - |
| Nonmetropolitan | 1.10 (1.04–1.17) | 0.002 | 1.04 (0.98–1.11) | 0.205 |
| County educationd | | | |
| High | 1.00 | - | 1.00 | - |
| Low | 1.21 (1.16–1.26) | <0.001 | 1.04 (0.98–1.11) | 0.096 |
| Laterality | | | |
| Right | 1.00 | - | 1.00 | - |
| Left | 0.99 (0.95–1.03) | 0.659 | 0.99 (0.95–1.03) | 0.650 |
| Tumor size | | | |
| <2 cm | 1.00 | - | 1.00 | - |
| 2–5 cm | 1.98 (1.89–2.07) | <0.001 | 1.51 (1.44–1.60) | <0.001 |
| >5 cm | 3.15 (2.94–3.38) | <0.001 | 2.07 (1.91–2.23) | <0.001 |
| Grade3 | | | |
| I | 1.00 | - | 1.00 | - |
| II | 1.51 (1.39–1.65) | <0.001 | 1.27 (1.17–1.39) | <0.001 |
| III | 2.24 (2.07–2.43) | <0.001 | 1.54 (1.42–1.68) | <0.001 |
| Node status | | | |
| Negative | 1.00 | - | 1.00 | - |
| 1–3 positive nodes | 1.53 (1.45–1.61) | <0.001 | 1.53 (1.45–1.61) | <0.001 |
| >3 positive nodes | 2.91 (2.77–3.07) | <0.001 | 2.69 (2.53–2.86) | <0.001 |
| ERf | | | |
| Positive | 1.00 | - | 1.00 | - |
| Negative | 1.57 (1.50–1.64) | <0.001 | 1.24 (1.16–1.32) | <0.001 |
| PRf | | | |
| Positive | 1.00 | - | 1.00 | - |
| Negative | 1.57 (1.51–1.64) | <0.001 | 1.25 (1.18–1.33) | <0.001 |

Table 3. Cont.

| Variablea | Univariate | Multivariate |
|-----------|------------|--------------|
| HR (95%CI) | P | HR (95%CI) | P |
| Yes | 1.00 | - | 1.00 | - |
| No | 0.72 (0.69–0.76) | <0.001 | 1.18 (1.11–1.24) | <0.001 |

Comparison of survival between the subgroups of reconstruction

To further explore the impact of different reconstruction methods on patient outcome, Cox proportional hazard regression models were performed with implant reconstruction group as reference (Table 5). In univariate analysis, autologous reconstruction was associated with poorer BCSS (HR = 1.36, 95% CI 1.11–1.67, P = 0.003) and OS (HR = 1.24, 95% CI 1.04–1.47, P = 0.018). However, this association did not present in multivariate analysis in either BCSS (HR = 1.11, 95% CI 0.90–1.35, P = 0.330) or OS (HR = 1.07, 95% CI 0.90–1.28, P = 0.424).

Discussion

By using data from the SEER database and dividing patients into subgroups according to demographic and tumor characteristics, we were able to analyze the impact of different breast reconstruction methods on survival in a wide range of patients. Our findings suggest that immediate postmastectomy breast reconstruction shows limited advantages in BCSS in breast cancer patients after stratifying by family income. Furthermore, no statistical difference in either BCSS or OS was observed between the autologous reconstruction group and the implant reconstruction group.

Several previous studies have demonstrated that immediate postmastectomy reconstruction was correlated with better survival in breast cancer patients. A study using data from the Danish Breast Cancer Cooperative Group, included 580 implant reconstructed breast cancer patients and 1,158 individually matched controls, discovered significantly improved disease-free survival (HR = 0.78, 95% CI 0.6–0.95) in reconstructed patients [15]. Bezuhl et al. [5] also revealed improved BCSS among breast cancer patients undergoing immediate reconstruction in their analysis of the SEER database. Jayant Agarwal and his colleagues [7] found that patients who underwent reconstruction after mastectomy had a higher BCSS than those undergoing mastectomy alone, when controlling for demographic and oncologic covariates. However, none of these studies examined the influence of patients’ socioeconomic factors on survival. In the present study, women received reconstruction showed better BCSS and OS in multivariate analysis after adjusting for demographic and clinicopathological variables. Further stratifying patients by family income, however, we observed slightly improved BCSS only in patients with higher income. Combined with previous studies, our
results demonstrated that the improved survival outcomes were largely attributable to patients' family income. A possible explanation was that with higher family income, patients were more likely to undergo reconstruction [5–7] (Table 1) and have access to better medical service (e.g. neoadjuvant or adjuvant chemotherapy, adjuvant hormonal therapy, molecularly targeted therapy), which had profound effects on survival [16–18].

Recent studies suggested that adipocytes had positive roles in the origin and development of breast cancer. Yasushi Manabe et al. [12] found that mature adipose cells can promote the growth of breast carcinoma cells in collagen gel matrix culture. Petit et al. [19] designed a matched-cohort study including 59 lipofilled patients and 118 matched controls using the European Institute of Oncology database, and a higher risk of local event was observed in patients undergoing lipofilling. In our present study, we found that autologous reconstruction was associated with decreased BCSS and OS in univariate analysis. Thus we hypothesized that the autologous reconstruction group may demonstrate worse outcome than the implant group because of the increased number of adipocytes in the surgical region. After adjusting for demographic and tumor characteristics, we failed to observe any significant differences in either BCSS or OS between the autologous group and the implant group. A reasonable explanation is that additional adipocytes brought to the site by autologous reconstruction could promote local recurrence, but this does not significantly impair patient survival. However, we could not examine local recurrence in different reconstruction groups since the SEER database lacked this information, and a longer follow-up period would be required to demonstrate the difference in rate of local recurrence amongst the two reconstruction methods.

Compared with the prior SEER based studies [5–7], our study differs in several critical aspects. First, our study has an adequate follow-up time with median follow-up time of 107 months, ensuring more reliable results. Second, we adjusted the impact of socioeconomic factors (including county type, county education level) on survival and stratified patients by annual family income, revealing that family income was an important confounder for survival outcome. Furthermore, we compared survival between different reconstruction methods, revealing that there was no statistical difference in survival amongst the two methods.

In conclusion, our findings reveal that immediate postmastectomy reconstruction has limited advantage in patient survival after mastectomy reconstruction has limited advantage in patient survival after mastectomy alone stratified by family income.

Table 4. Cox proportional hazard regression model of Breast Cancer-Specific Survival comparing reconstruction method to mastectomy alone stratified by family income.

| Variablea | Pooled Reconstruction | Autologous Only | Implant Only |
|-----------|-----------------------|----------------|-------------|
| Family income | HR (95%CI) | P | HR (95%CI) | P | HR (95%CI) | P |
| $<4645 | 0.85 (0.67–1.08) | 0.178 | 0.72 (0.50–1.03) | 0.070 | 0.91 (0.56–1.46) | 0.684 |
| $4645–$5116 | 0.83 (0.70–0.99) | 0.040 | 0.79 (0.61–1.02) | 0.067 | 0.85 (0.62–1.17) | 0.326 |
| $5117–$6281 | 0.91 (0.78–1.07) | 0.243 | 0.95 (0.78–1.16) | 0.636 | 0.89 (0.64–1.24) | 0.497 |
| $>6281 | 0.85 (0.73–0.99) | 0.034 | 0.94 (0.77–1.15) | 0.553 | 0.66 (0.47–0.91) | 0.010 |

*aAdjusted by Cox proportional hazards models including all factors, as categorized in Table 2.

doi:10.1371/journal.pone.0082807.t004

Table 5. Cox proportional hazard regression model comparing reconstruction method to implant only.

| Variablea | Breast Cancer-Specific Survival | Overall Survival |
|-----------|--------------------------------|----------------|
| | Univariate | Multivariate | Univariate | Multivariate |
| Reconstruction type | HR (95%CI) | P | HR (95%CI) | P | HR (95%CI) | P | HR (95%CI) | P |
| Pooled reconstruction | 1.21 (1.01–1.46) | 0.041 | 1.08 (0.89–1.30) | 0.438 | 1.12 (0.95–1.31) | 0.173 | 1.03 (0.88–1.21) | 0.689 |
| Autologous only | 1.36 (1.11–1.67) | 0.003 | 1.11 (0.90–1.35) | 0.330 | 1.24 (1.04–1.47) | 0.018 | 1.07 (0.90–1.28) | 0.424 |
| Implant only | 1.00 | - | 1.00 | - | 1.00 | - | 1.00 | - |

*aAdjusted by Cox proportional hazards models including all factors, as categorized in Table 2, and family income.

doi:10.1371/journal.pone.0082807.t005
stratifying by the factor of family income. Autologous reconstruction does not impair the survival outcome. Further pre-clinical and clinical study should attempt to confirm these conclusions and clarify the underlying mechanism of the interaction between reconstruction, especially autologous reconstruction, and survival.

Acknowledgments
The authors are grateful to Jiong Wu, Jin-Song Lu, Guang-Yu Liu, Gen-Hong Di and Zhen-Zhou Shen for their excellent data handling.

References
1. WHO Fact sheet no. 297 (January 2013). WHO website. Available at www.who.int/mediacentre/factsheets/fs297/en/. Accessed 2013 Nov 8.
2. American Cancer Society (2011) Global Cancer Facts & Figures 2nd Edition. Atlanta: American Cancer Society, 2011.
3. Cordeiro PG (2008) Breast reconstruction after surgery for breast cancer. N Engl J Med 359: 1590–1601.
4. Siegel R, Naishadham D and Jemal A (2013) Cancer statistics, 2013. CA Cancer J Clin 63: 11–30.
5. Bezahly M, Temple C, Sigurdson LJ, Davis RB, Flowerdew G, et al. (2009) Immediate postmastectomy reconstruction is associated with improved breast cancer-specific survival: evidence and new challenges from the Surveillance, Epidemiology, and End Results database. Cancer 115: 4648–4654.
6. Agarwal S, Liu JH, Ciriaco CA, Buys S, Agarwal JP (2010) Survival in breast cancer patients undergoing immediate breast reconstruction. Breast J 16: 503–509.
7. Agarwal S, Agarwal S, Pappas L, Neumayer L (2012) A population-based study of breast cancer-specific survival following mastectomy and immediate or early-delayed breast reconstruction. Breast J 18: 226–232.
8. Sandellin K, Wickman M, Billgren AM (2004) Oncological outcome after immediate breast reconstruction for invasive breast cancer: a long-term study. Breast 13: 210–218.
9. Medina-Franco H, Vasconez LO, Fix RJ, Heslin MJ, Beenken SW, et al. (2002) Factors associated with local recurrence after skin-sparing mastectomy and immediate breast reconstruction for invasive breast cancer. Ann Surg 235: 814–819.
10. Downes KJ, Glatt BS, Ratchwala SK, Mick R, Fraker DL, et al. (2005) Skin-sparing mastectomy and immediate reconstruction is an acceptable treatment option for patients with high-risk breast carcinoma. Cancer 103: 906–913.
11. Gouy S, Rouzier R, Missana MC, Attalib D, Youssf O, et al. (2005) Immediate reconstruction after neoadjuvant chemotherapy: effect on adjuvant treatment starting and survival. Ann Surg Oncol 12: 161–166.
12. Manabe Y, Toda S, Miyazaki K, Sugihara H (2003) Mature adipocytes, but not preadipocytes, promote the growth of breast carcinoma cells in collagen gel matrix culture through cancer-stromal cell interactions. J Pathol 201: 221–228.
13. Iyengar P, Espina V, Williams TW, Lin Y, Berry D, et al. (2005) Adipocyte-derived collagen VI affects early mammary tumor progression in vivo, demonstrating a critical interaction in the tumor/stroma microenvironment. J Clin Invest 115: 1163–1176.
14. Shambbaugh EM WM, Axelell LM (1998) Summary staging guide for the cancer Surveillance, Epidemiology, and End Results reporting program. In: Fritz A, Ries L, eds. SEER Program Code Manual. 3rd ed. Bethesda, MD: National Cancer Institute. SEER website. Available at: http://seer.cancer.gov/manuals/AppendC.pdf. Accessed Nov 8.
15. Holmich LR, Dering M, Henriksen TF, Krag C, Tange UB, et al. (2005) Delayed breast reconstruction with implants after invasive breast cancer does not impair prognosis. Ann Plast Surg 61: 11–18.
16. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, et al. (2005) Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years’ adjuvant treatment for breast cancer. Lancet 365: 60–62.
17. Coombes RC, Hall E, Gibson LJ, Paridaens R, Jassam J, et al. (2004) A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. New England Journal of Medicine 350: 1081–1092.
18. Thurlimann B, Keshaviah A, Coates AS, Mouridsen H, Mauriac L, et al. (2005) A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. New England Journal of Medicine 353: 2747–2757.
19. Petit JY, Rietjens M, Bottero E, Rotmensz N, Berndini F, et al. (2013) Evaluation of fat grafting safety in patients with intra epithelial neoplasia: a matched-cohort study. Ann Oncol 24: 1479–1484.

Author Contributions
Conceived and designed the experiments: YZJ KDY ZMS. Performed the experiments: YZJ YRL KDY. Analyzed the data: YZJ YRL KDY WJZ. Contributed reagents/materials/analysis tools: YZJ KDY YRL WJZ. Wrote the paper: YZJ KDY YRL WJZ ZMS.