Lipofilling of the Breast Does Not Increase the Risk of Recurrence of Breast Cancer: A Matched Controlled Study

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Background: Although many plastic surgeons perform autologous fat grafting (lipofilling) for breast reconstruction after oncologic surgery, it has not been established whether postoncologic lipofilling increases the risk of breast cancer recurrence. The authors assessed the risk of locoregional and systemic recurrence in patients who underwent lipofilling for breast reconstruction.
Methods: The authors identified all patients who underwent segmental or total mastectomy for breast cancer (719 breasts) (i.e., cases) or breast cancer risk reduction or benign disease (305 cancer-free breasts) followed by breast reconstruction with lipofilling as an adjunct or primary procedure between June of 1981 and February of 2014. They also then identified matched patients with breast cancer treated with segmental or total mastectomy followed by reconstruction without lipofilling (670 breasts) (i.e., controls). The probability of locoregional recurrence was estimated by the Kaplan-Meier method.
Results: Mean follow-up times after mastectomy were 60 months for cases, 44 months for controls, and 73 months for cancer-free breasts. Locoregional recurrence was observed in 1.3 percent of cases (nine of 719 breasts) and 2.4 percent of controls (16 of 670 breasts). Breast cancer did not develop in any cancer-free breast. The cumulative 5-year locoregional recurrence rates were 1.6 percent and 4.1 percent for cases and controls, respectively. Systemic recurrence occurred in 2.4 percent of cases and 3.6 percent of controls ($p = 0.514$). There was no primary breast cancer in healthy breasts reconstructed with lipofilling.
Conclusions: The study results showed no increase in locoregional recurrence, systemic recurrence, or second breast cancer. These findings support the oncologic safety of lipofilling in breast reconstruction. (*Plast. Reconstr. Surg.* 137: 385, 2016.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Risk, II.

A survey of the American Society of Plastic Surgeons in 2010 regarding the safety of autologous fat grafting (lipofilling) of the breast found that 49 percent of respondents considered the lack of evidence supporting the oncologic safety of lipofilling to be a significant obstacle to its use for breast reconstruction or cosmetic augmentation.[1] A concern is that adult adipose tissue–derived stem cells transferred with the lipoaspirate may reactivate dormant tumor cells within the breast or activate primary breast cancer.

Clinical and animal studies have shown conflicting results[2–5] as to whether lipofilling confers a higher risk for recurrence of breast cancer. Furthermore, it remains unknown which groups of patients might be more susceptible to any lipofilling-induced increase in the risk of recurrence. Although lipofilling of the breast is performed worldwide in thousands of patients per year, including as an alternative to implant placement for breast augmentation in some patients, there has been no study published with a control group regarding the oncologic safety of lipofilling in general or lipofilling of the breast. This lack of

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evidence has made many surgeons reluctant to offer lipofilling to patients, and surgeons who do perform lipofilling may have some concern that lipofilling may increase the risk for breast cancer recurrence.

The primary objective of this study was to determine whether lipofilling as an adjunct or primary breast reconstruction procedure increases the rate of locoregional recurrence of breast cancer. The secondary objective was to determine whether patients without breast cancer who underwent lipofilling after risk-reducing mastectomy had an increased risk of primary breast cancer.

PATIENTS AND METHODS

Patient Identification

The Institutional Review Board of The University of Texas M. D. Anderson Cancer Center approved this retrospective analysis. The patients for analysis were identified in two stages. First, the database of prospectively collected data maintained by the M. D. Anderson Department of Plastic Surgery was searched for all patients who underwent segmental or total mastectomy for breast cancer or breast cancer risk reduction followed by breast reconstruction with lipofilling as an adjunct or primary procedure. For the patients identified as a result of this search, the dates of segmental or total mastectomy ranged from June of 1981 through April of 2013, and the dates of lipofilling ranged from January of 2001 through February of 2014. The patients identified from this initial search were divided into two groups: patients who underwent mastectomy for breast cancer treatment (i.e., cases) and patients who underwent mastectomy for reduction of breast cancer risk (i.e., cancer-free breasts), of which *BRCA* mutation information was available for 233 patients. Thirty-three patients were *BRCA1/BRCA2* mutation carriers.

In the second stage of patient identification, the database of prospectively collected data maintained by the M. D. Anderson Department of Breast Medical Oncology was searched to identify patients with breast cancer who underwent mastectomy and breast reconstruction during the period from June of 1981 through April of 2013 but did not undergo lipofilling (i.e., controls).

Study Design

To assess the effect of lipofilling on the risk of locoregional recurrence of breast cancer, we compared outcomes in the breasts reconstructed with (i.e., cases) and without (i.e., controls) lipofilling after mastectomy for breast cancer. Breasts reconstructed with lipofilling after mastectomy for breast cancer risk reduction or benign disease were analyzed to achieve our secondary objective of determining whether patients who underwent lipofilling after risk-reducing mastectomy had an increased risk of primary breast cancer.

Statistical Analysis

Descriptive statistics, such as means and standard deviations, were used to summarize age and follow-up time. Frequencies and proportions were used to summarize the categorical characteristics. Demographic and clinical information was compared by using Fisher's exact test and the Wilcoxon rank sum test. The recurrence-free survival time was defined as the interval from the date of mastectomy to the date of first locoregional recurrence or the date of last follow-up if no locoregional recurrence was observed. Patients without locoregional recurrence were censored in the analyses. The probability of locoregional recurrence was estimated by the Kaplan-Meier product-limit method. Because lipofilling was often performed at various time intervals after the oncologic surgery, we used time-dependent Cox proportional hazards regression models to assess the effect of lipofilling on locoregional recurrence. We also used the multivariable Cox proportional hazards regression models to adjust the potential confounding factors. All the tests were two-sided. The p value was calculated by comparing breast cancer patients who received lipofilling to breast cancer patients who did not receive lipofilling. A value of $p < 0.05$ was considered significant. The analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, N.C.) and R (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Our initial search of the plastic surgery database identified 1024 consecutive breasts reconstructed with lipofilling, 719 of them cancerous breasts (cases) and 305 of them cancer-free breasts (removed for breast cancer risk reduction). Of the 305 cancer-free breasts, *BRCA* status was available for 233 patients, of which 33 patients were carriers of the *BRCA1/BRCA2* mutation. For the *BRCA* carriers, the mean follow-up time after mastectomy was 33.6 months and the mean time to lipofilling was 18.4 months. Through our search of the breast medical oncology database, we matched with the cases 670 cancerous breasts reconstructed without lipofilling (controls). The

last patient follow-up was in November of 2014. Table 1 summarizes the patient and tumor characteristics. The mean follow-up time after mastectomy was significantly longer in cases (lipofilling) than in controls (no lipofilling) (59.6 months and 44.0 months, respectively; $p < 0.001$). The cases were older than the controls (mean age, 47.7 years and 46.5 years, respectively; $p = 0.039$). Cases and controls also differed with respect to pathologic stage, with cases more likely to have stage 0 or 1 cancer ($p < 0.001$). Tumor location and hormonal status (estrogen and progesterone receptor) were balanced between cases and controls. Controls were more likely to have *HER2/neu*-positive tumors (11.6 percent and 6.4 percent, respectively; $p = 0.001$) and more likely to receive chemotherapy ($p < 0.001$). Cases were more likely to receive hormonal therapy ($p = 0.043$).

Table 2 summarizes the characteristics of lipofilling (number of sessions and total volume injected) between cancer and benign cases. The two groups were similar with respect to the number of sessions. Total volume was greater in cases ($p = 0.007$).

Table 3 summarizes the differences in the risk of locoregional recurrence between lipofilling and no lipofilling in several subgroups. Overall, locoregional recurrence occurred in 1.3 percent of the cases (nine of 719 breasts) and 2.4 percent of the controls (16 of 670 breasts) ($p = 0.455$). We found that lipofilling did not affect the risk of locoregional recurrence in subgroups defined on the basis of pathologic stage, breast quadrant where the tumor was located, mastectomy, hormone receptor status, or use of chemotherapy or radiation therapy. We also used the multivariate Cox proportional hazards model in which we compared locoregional recurrence between cases and controls by adjusting for chemotherapy, radiation therapy, hormonal therapy, and clinical stage ($p = 0.348$). The only subgroup examined in which lipofilling was associated with an increased risk of locoregional recurrence was the subgroup treated with hormonal therapy, 1.4 percent and 0.5 percent for lipofilling and no lipofilling, respectively ($p = 0.038$). When a multivariate Cox proportional hazards model was performed only for hormonal therapy patients (adjusted for factors such as chemotherapy, radiation therapy, and clinical stage), lipofilling was still a significant factor with an increased risk of locoregional recurrence ($p = 0.031$).

Table 4 summarizes the differences in the risk of systemic recurrence between lipofilling and no lipofilling in several subgroups. Overall, systemic recurrence occurred in 2.4 percent of the cases (17 of 719 breasts) and 3.6 percent of the controls (24 of 670 breasts) ($p = 0.514$). There was no significant difference in the rates of systemic tumor recurrence between the breasts reconstructed with and without lipofilling overall or in any of the subgroups examined.

As shown in Figure 1, the cumulative 3-year and 5-year locoregional recurrence rates were 0.3 percent and 1.6 percent, respectively, for the cases (lipofilling) and 1.3 percent and 4.1 percent, respectively, for the controls (no lipofilling). The incidence of locoregional recurrence was 0.25 cases per 100 person-years for the cases and 0.65 cases per 100 person-years for the controls ($p = 0.455$). In the 305 healthy breasts reconstructed with lipofilling after risk-reducing mastectomy, no cases of breast cancer were observed during the follow-up period.

DISCUSSION

In contrast to previous studies that have evaluated the incidence of breast cancer recurrence in breast cancer patients who have undergone lipofilling for breast reconstruction after mastectomy, our study included a control group. In addition, our study included more patients than did previous studies. In our study, we found no significant differences in the rates of locoregional recurrence or systemic recurrence between breasts reconstructed with lipofilling and breasts reconstructed without lipofilling. We also compared rates of locoregional recurrence in breasts reconstructed with and without lipofilling within several subgroups defined on the basis of clinical, pathologic, and lipofilling procedure characteristics, and we found that the only subgroup in which the locoregional recurrence rate was higher for lipofilling was the subgroup treated with hormonal therapy. We also did not find any instances of primary breast cancer development in healthy breasts reconstructed with lipofilling, inclusive of 33 patients who were carriers for the *BRCA1/BRCA2* mutation.

The increasing popularity of fat grafting is evidenced by the significant increase in articles being published on the subject. We could find only two articles on fat grafting for breast reconstruction published in 1993, but in 2013, more than 120 articles on this topic were published. Many of the previously reported studies focused on the technical aspects of serial fat grafting, including the number of fat grafting sessions required and the total volume usually used for breast reconstruction.

Table 1. Patient and Tumor Characteristics by Subgroup

Variable	All (%)	Lipofilling			Control	*p*†
		All Lipofilling (%)	Lipofilling* (No Cancer) (%)	Lipofilling (Cancer) (%)	No Lipofilling (Cancer) (%)	
No. of breasts	1694	1024	305	719	670	
Mean follow-up time after mastectomy ± SD, mo	52.9 ± 49.3	60.7 ± 47.1	73.5 ± 56.8	59.6 ± 46.1	43.8 ± 66.7	<0.001
Mean time from mastectomy to lipofilling ± SD, mo	—	—	44.9 ± 55.3	31.5 ± 41.3	—	
Mean age ± SD, yr	46.9 ± 9.9	47.1 ± 9.6	45.8 ± 9.7	47.7 ± 9.6	46.5 ± 10.5	0.039
Race						
Caucasian	1238 (73.1)	776 (75.8)	237 (77.7)	539 (75)	462 (69)	
African American	114 (6.7)	57 (5.6)	16 (5.2)	41 (5.7)	57 (8.5)	
Hispanic	262 (15.5)	149 (14.6)	40 (13.1)	109 (15.2)	113 (16.9)	
Asian	60 (3.5)	31 (3)	9 (3)	22 (3.1)	29 (4.3)	
Native American	6 (0.4)	3 (0.3)	1 (0.3)	2 (0.3)	3 (0.4)	
Other	14 (0.8)	8 (0.8)	2 (0.7)	6 (0.8)	6 (0.9)	0.142
Type of mastectomy						
Segmental	168 (9.9)	95 (9.3)	16 (5.2)‡	79 (11)	73 (11)	
Total	1275 (75.3)	684 (66.8)	45 (14.8)	639 (88.9)	591 (88.2)	0.999
Pathologic stage						
0	305 (18)	190 (18.6)	16 (5.2)	174 (24.2)	115 (17.2)	
I	488 (28.8)	280 (27.3)	14 (4.6)	266 (37)	208 (30.9)	
II	467 (27.6)	222 (21.7)	23 (7.5)	199 (27.7)	245 (36.6)	
III	163 (9.6)	71 (6.9)	6 (2)	65 (9)	92 (13.7)	
IV	4 (0.2)	4 (0.4)	0 (0)	4 (0.6)	0 (0)	<0.001
Histologic type						
Invasive						
Overall	1144 (67.5)	596 (58.2)	44 (14.4)	552 (76.7)	548 (81.8)	
Invasive ductal	1009 (59.6)	523 (51.1)	34 (11.1)	489 (68)	486 (72.5)	
Invasive lobular	135 (8.0)	73 (7.1)	10 (3.3)	63 (8.8)	62 (9.3)	0.467
In situ						
Overall	178 (10.5)	117 (11.4)	9 (2.9)	108 (2.5)	61 (9.1)	
DCIS	167 (9.9)	111 (10.8)	8 (2.6)	103 (14.3)	56 (8.4)	
LCIS	11 (0.6)	6 (0.6)	1 (0.3)	5 (0.7)	5 (0.7)	0.309
Breast tumor quadrant						
Upper outer	412 (24.3)	228 (22.3)	49 (16.1)	179 (24.9)	184 (27.5)	
Upper inner	148 (8.7)	92 (9)	11 (3.6)	81 (11.3)	56 (8.4)	
Lower outer	67 (4.0)	36 (3.5)	8 (2.6)	28 (3.9)	31 (4.6)	
Lower inner	68 (4.0)	42 (4.1)	11 (3.6)	31 (4.3)	26 (3.9)	0.237
Centricity						
Multifocal	84 (5.0)	44 (4.3)	5 (1.6)	39 (5.4)	40 (6)	
Multicentric	174 (10.3)	100 (9.8)	19 (6.2)	81 (11.3)	74 (11)	0.679
Hormone receptor status						
ER+	1063 (62.8)	570 (55.7)	43 (14.1)	527 (73.3)	493 (73.6)	0.952
PR+	856 (50.5)	459 (44.8)	33 (10.8)	426 (59.2)	397 (59.3)	0.999
HER2/neu+§	126 (7.4)	48 (4.7)	2 (0.7)	46 (6.4)	78 (11.6)	0.001
Ki67+‖	378 (22.3)	189 (18.5)	16 (5.2)	173 (24.1)	189 (28.2)	0.087
Chemotherapy						
Any	960 (56.7)	489 (47.8)	49 (16.1)	440 (61.2)	471 (70.3)	<0.001
Neoadjuvant	501 (29.6)	249 (24.3)	27 (8.9)	222 (30.9)	252 (37.6)	0.009
Adjuvant	538 (31.8)	284 (27.7)	25 (8.2)	259 (36)	254 (37.9)	0.470
Radiation therapy¶						
Any	633 (37.4)	337 (32.9)	60 (19.7)	277 (38.5)	296 (44.2)	0.855
Neoadjuvant	2 (0.1)	1 (0.1)	0 (0)	1 (0.1)	1 (0.1)	0.999
Adjuvant	631 (37.3)	336 (32.8)	60 (19.7)	276 (38.4)	295 (44)	0.855
Hormonal therapy#						
Any	845 (49.9)	474 (46.3)	40 (13.1)	434 (60.4)	371 (55.4)	0.043
Tamoxifen	554 (32.7)	305 (29.8)	30 (9.8)	275 (38.2)	249 (37.2)	
Raloxifene	3 (0.2)	2 (0.2)	0 (0)	2 (0.3)	1 (0.1)	
Goserelin	15 (0.9)	9 (0.9)	0 (0)	9 (1.3)	6 (0.9)	
Letrozole	97 (5.7)	66 (6.4)	7 (2.3)	59 (8.2)	31 (4.6)	
Fluoxymesterone	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Exemestane	40 (2.4)	27 (2.6)	3 (1)	24 (3.3)	13 (1.9)	
Anastrozole	300 (17.7)	178 (17.4)	20 (6.6)	158 (22)	122 (18.2)	
Leuprolide	6 (0.4)	2 (0.2)	0 (0)	2 (0.3)	4 (0.6)	
Toremifene	4 (0.2)	3 (0.3)	1 (0.3)	2 (0.3)	1 (0.1)	

DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor; +, positive.
*Of the 305 patients, *BRCA* mutation information was available for 228 patients, of which 33 patients had the *BRCA1/BRCA2* mutation (mean follow-up time after mastectomy, 33.6 mo; mean follow-up time to lipofilling, 18.4 mo).
†The *p* values were calculated by time-dependent Cox proportional hazards regression models.
‡These patients had segmental mastectomy for benign breast disease.
§Greater than or equal to 2 by immunohistochemistry; confirmed by fluorescence in situ hybridization.
‖Expression >17 percent.
¶Radiation delivery was performed the same for both groups.
#The mean duration of hormonal therapy use was 28.3 months.

Table 2. Characteristics of Lipofilling Procedures

Variables	Lipofilling			*p*†
	All Patients (%)	Patients with Cancer (%)	Patients with No Cancer (%)*	
No. of breasts	1024	719	305	
No. of sessions				
1	761 (74.3)	527 (73.3)	234 (76.7)	
2	181 (7.7)	121 (16.8)	60 (19.7)	
≥3	36 (3.5)	26 (3.6)	10 (3.3)	0.772
Total volume injected				
1–100 cc	688 (70.3)	449 (62.4)	239 (78.4)	
101–200 cc	210 (21.5)	162 (22.5)	48 (15.7)	
201–300 cc	55 (5.6)	42 (5.8)	13 (4.3)	
301–400 cc	18 (1.8)	15 (2.1)	3 (1)	
401–500 cc	2 (0.2)	2 (0.3)	0 (0)	
>500 cc	5 (0.3)	4 (0.6)	1 (0.3)	0.007

*Of the 305 patients, *BRCA* mutation information was available in 228 patients, of which 33 patients had the *BRCA1/BRCA2* mutation.
†Calculated by Fisher's exact test.

Table 3. Risks of Locoregional Breast Cancer Recurrence for Lipofilling versus No Lipofilling in Various Subgroups

Variable	Lipofilling		Control	*p*†
	Lipofilling* (No Cancer) (%)	Lipofilling (Cancer) (%)	No Lipofilling (Cancer) (%)	
No. of breasts	305	719	670	
LRR	0 (0)	9 (1.3)	16 (2.4)	0.455
Mean time from mastectomy to LRR ± ± SD, mo	—	80.7 ± 70	51.4 ± 64	0.417‡
Mean time from lipofilling to LRR ± SD, mo	—	19.3 ± 25	—	—
Race				
Caucasian		8 (1.5)	12 (2.6)	0.438
African American		1 (2.4)	2 (3.5)	0.934
Hispanic		0 (0)	2 (1.8)	0.998
Asian		0 (0)	0 (0)	—
Native American		0 (0)	0 (0)	—
Type of mastectomy				
Total		8 (1.3)	11 (1.9)	0.607
Segmental		1 (1.3)	4 (5.5)	0.972
Histologic type				
Invasive				
Ductal		6 (1.2)	9 (1.9)	0.299
Lobular		1 (1.6)	1 (1.6)	0.774
In situ				
DCIS		0 (0)	3 (5.4)	0.997
LCIS		0 (0)	0 (0)	—
Pathologic stage				
0		1 (0.6)	4 (3.5)	0.541
I		2 (0.8)	6 (2.9)	0.658
II		4 (2)	4 (1.6)	0.271
III		2 (3.1)	1 (1.1)	0.996
IV		0 (0)	0 (0)	—
Breast tumor quadrant				
Upper outer		2 (1.1)	5 (2.7)	0.963
Upper inner		0 (0)	0 (0)	—
Lower outer		1 (3.6)	0 (0)	0.998
Lower inner		0 (0)	2 (7.7)	0.998
Centricity				
Multifocal		1 (2.6)	1 (2.5)	0.997
Multicentric		2 (2.5)	1 (1.4)	0.997
Hormonal receptor status				
ER+		6 (1.1)	6 (1.2)	0.330
PR+		2 (0.5)	5 (1.3)	0.633
HER2-neu+§		1 (2.2)	0 (0)	0.998
Ki67+‖		2 (1.2)	2 (1.1)	0.162
Chemotherapy				

(*Continued*)

Table 3. (*Continued*)

Variable	Lipofilling		Control	
	Lipofilling* (No Cancer) (%)	Lipofilling (Cancer) (%)	No Lipofilling (Cancer) (%)	*p*†
Any		8 (1.8)	9 (1.9)	0.099
Neoadjuvant		5 (2.3)	2 (0.8)	0.053
Adjuvant		6 (2.3)	8 (3.1)	0.317
Radiotherapy¶				
Any		5 (1.7)	4 (1.4)	0.760
Adjuvant		5 (1.7)	4 (1.4)	0.760
Hormonal therapy#				
Any		9 (1.4)	2 (0.5)	0.038
Tamoxifen		4 (1.5)	2 (0.8)	0.151
Raloxifene		0 (0)	0 (0)	—
Goserelin		0 (0)	0 (0)	—
Letrozole		2 (3.4)	0 (0)	—
Fluoxymesterone		0 (0)	0 (0)	—
Exemestane		0 (0)	0 (0)	—
Anastrozole		3 (1.9)	0 (0)	—
Leuprolide		0 (0)	0 (0)	—
Toremifene		0 (0)	0 (0)	—
No. of sessions of lipofilling				
1		7 (1.3)	0 (0)	—
2		1 (0.8)	0 (0)	—
≥3		0 (0)	0 (0)	—
Total volume injected				
1–100 cc		7 (1.6)	0 (0)	—
101–200 cc		1 (0.6)	0 (0)	—
201–300 cc		0 (0)	0 (0)	—
301–400 cc		0 (0)	0 (0)	—
401–500 cc		0 (0)	0 (0)	—
>500 cc		0 (0)	0 (0)	—

LRR, locoregional recurrence; ER, estrogen receptor; PR, progesterone receptor; +, positive; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ.
*Of the 305 patients, *BRCA* mutation information was available in 228 patients, of which 33 patients had the *BRCA1/BRCA2* mutation (mean follow-up time after mastectomy, 33.6 mo; mean follow-up time to lipofilling, 18.4 mo).
†The *p* values were calculated by time-dependent Cox proportional hazards regression models.
‡The difference in the time from mastectomy to LRR was tested by the Wilcoxon rank sum test.
§Greater than or equal to 2 by immunohistochemistry; confirmed by fluorescence in situ hybridization.
‖Expression >17 percent.
¶Radiation delivery was performed the same for both groups.
#The mean duration of hormonal therapy use was 28.3 months.

One study examined the trends in fat grafting through a national survey of members of the American Society of Plastic Surgeons (456 respondents of 2584 members sent the survey).[1] In that study, 62 percent of respondents reported currently using fat grafting for reconstructive breast surgery. Twenty-eight percent of respondents reported currently using fat grafting for aesthetic breast surgery, and 59 percent of respondents had not performed fat grafting for aesthetic breast surgery and had no plans to do so in the future. When asked about potential obstacles to incorporation of fat grafting into clinical practice, 49 percent of respondents strongly agreed or agreed that the lack of evidence concerning the impact of fat grafting to the breast on breast cancer development or recurrence was an obstacle.

To overcome this obstacle so that 100 percent of surgeons can confidently incorporate fat grafting into their clinical practice, we first need to know what occurs physiologically when we inject fat grafts into patients' breasts. Rigotti et al. in 2007 elucidated how lipoaspirate heals irradiated tissue through a process mediated by adipose-derived adult stem cells.[6] Ultrastructural analysis of the lipoaspirate revealed a well-preserved stromal vascular component. However, well-preserved adipocytes were virtually absent. Cytologic characterization of the lipoaspirate by in vitro expansion showed that the mesenchymal stem cells corresponded to bone marrow–derived mesenchymal stem cells. Four to 6 months after injection of the lipoaspirate into the patient, adipocytes were normal, and the microvasculature exhibited normal ultrastructure. One year or more after treatment, the picture was substantially unchanged apart from a tendency toward shrinking extracellular spaces, with normal adipocytes and a well-formed microcirculation. Certainly, this information should guide clinicians to perform serial fat

Table 4. Systemic Recurrence

Variable	Lipofilling	Control	
	Lipofilling (Cancer) (%)	No Lipofilling (Cancer) (%)	*p**
No. of breasts	719	670	
Systemic recurrence	17 (2.4)	24 (3.6)	0.514
Type of mastectomy			
Total	16 (2.5)	20 (2.9)	0.507
Segmental	1 (1.3)	3 (4.1)	0.995
Histologic type			
Invasive			
Ductal	13 (2.7)	20 (4.1)	0.462
Lobular	3 (4.8)	1 (1.6)	0.248
In situ			
Ductal carcinoma in situ	0 (0.0)	0 (0.0)	—
Lobular carcinoma in situ	0 (0.0)	0 (0.0)	—
Pathologic stage			
0	0 (0)	3 (2.6)	0.996
I	3 (1.1)	7 (3.4)	0.522
II	7 (3.5)	8 (3.3)	0.132
III	5 (7.7)	5 (5.4)	0.174
IV	0 (0.0)	0 (0.0)	—
HER2-neu†	0 (0.0)	5 (3.8)	0.996
Chemotherapy			
Overall	14 (3.2)	20 (4.3)	0.123
Neoadjuvant chemotherapy	11 (4.9)	14 (5.6)	0.122
Adjuvant chemotherapy	5 (1.9)	8 (3.1)	0.523
Radiation therapy			
Overall	10 (3.6)	15 (5.1)	0.298
Adjuvant radiation therapy	10 (3.6)	15 (5.1)	0.298
Hormonal therapy	6 (1.4)	13 (3.5)	0.522

*Calculated by time-dependent Cox proportional hazards regression models.
†Positive (≥2 by immunohistochemistry, confirmed by fluorescent in situ hybridization).

grafting procedures 4 to 6 months apart. In addition, our current study found that the median time from lipofilling to detection of locoregional recurrence (19 months) was not directly related to completion of the maturation process of the vasculature and extracellular space.

Another piece of information we need to confirm the safety of fat grafting is information regarding the interaction between the fat graft and the tumor bed. Hypothetically, the transfer of adipose tissue–derived stem cells or adipose tissue–derived mesenchymal stem cells could induce dormant tumor cells to reproduce and thereby predispose the patient to locoregional recurrence. In vitro and animal studies have produced conflicting findings regarding the impact of stem cells, with some showing positive and others showing negative associations with breast cancer cell proliferation. Petit and colleagues published a retrospective European multi-institutional study of 646 cases of lipofilling of the breast and found, to the concern of many surgeons, that the risk of breast cancer recurrence was higher in patients with in situ carcinoma than in patients with invasive breast cancer .[7] In a follow-up retrospective study (59 patients), Petit et al. focused only on patients with in situ carcinoma of the breast and found that patients who underwent lipofilling had an 18 percent cumulative 5-year risk of locoregional recurrence, compared with a 3 percent cumulative 5-year risk in patients who did not undergo lipofilling.[8] An important factor to consider in both studies by Petit et al. was that a large percentage of patients undergoing breast conserving therapy received only intraoperative radiation therapy.

In contrast to the findings of Petit and colleagues,[7,8] we observed only 25 local regional recurrences (1.5 percent) and total locoregional recurrence incidence rates of 1.3 percent for lipofilling cancer patients and 2.4 percent for no-lipofilling cancer patients. In addition, we found no significant differences in 5-year cumulative locoregional recurrence rate between breast cancer patients with lipofilling (1.6 percent, 0.25 cases per 100 person-years) and breast cancer patients without lipofilling (4.1 percent, 0.65 cases per 100 person-years). Our findings were similar to those in a recent prospective study by Brenelli et al. of 59 patients[9] that found that only three patients (4 percent incidence) had a recurrence of breast cancer, with an estimated annual rate of recurrence of 1.3 percent per year.

Theoretically, segmental mastectomy should be associated with the highest risk of locoregional recurrence after lipofilling because much of the breast tissue is not resected; however, in the previously mentioned prospective study of 59 patients,[9] all three patients with a recurrence of breast cancer had invasive primary tumors and invasive recurrences. In contrast to the studies by Petit et al.[7,8] and in agreement with the 59-patient prospective study,[9] we found no significant differences in the risk of locoregional recurrence between breasts reconstructed with lipofilling and breasts reconstructed without lipofilling in either the invasive breast cancer or intraductal breast cancer subgroups. We found no significant differences in the risk of breast cancer recurrence between breasts treated with segmental mastectomy and breasts treated with total mastectomy along with lipofilling. We also found no significant differences in the incidence of recurrence when segmental and total mastectomy with lipofilling were individually compared to the control group.

The only variable that significantly increased the risk of breast cancer recurrence with lipofilling was receipt of hormonal therapy. Although

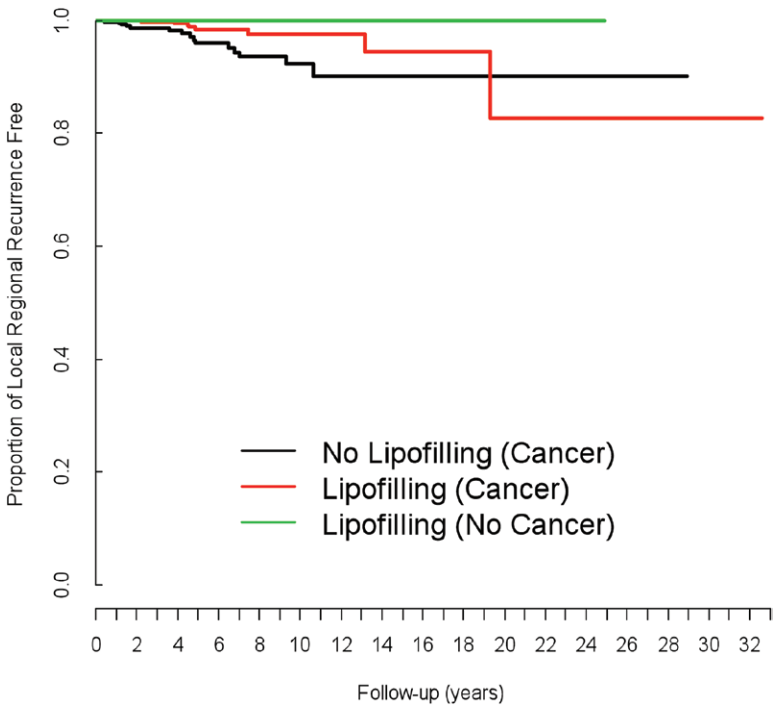

Fig. 1. Kaplan-Meier curves for locoregional recurrence–free survival for cases (cancer and lipofilling), controls (cancer and no lipofilling), and cancer-free breasts with lipofilling.

the cases were more likely to receive hormonal therapy, the cases and controls had similar hormonal receptor status. Eight of 805 patients with hormonal therapy had locoregional recurrence. Among them, the locoregional recurrence rate in the cases was approximately three times that of the controls. A hypothetical potential role of hormonal therapy in enhancing a tumorigenic microenvironment or impacting crosstalk between adipose-derived mesenchymal stem cells and breast cancer cells is unknown based on current scientific knowledge. Although lipoaspirate is a known reservoir for adipose-derived mesenchymal stem cells, adipose-derived mesenchymal stem cells are not tumorigenic per se, as they are not able to induce neoplastic transformation of normal mammary cells. However, it is not known whether adipose-derived mesenchymal stem cells can exacerbate tumorigenic behavior in breast cancer cells, theoretically creating an inflammatory microenvironment that sustains tumor growth and angiogenesis.[10] Interestingly, we also found that neither the total volume of fat injected nor the number of fat grafting sessions performed impacted locoregional recurrence. However, we found that larger grafts were required for the breasts with cancer than for the healthy breasts.

In assessment of our study, the degree to which the cases and controls were similar is an important consideration. Although there were some differences between cases and controls, including longer follow-up time, slightly older age, more stage 0 and I breast cancers, and more receipt of hormonal therapy among the cases, the cases and controls had similar hormonal receptor status, and the clinicopathologic differences tended to even the groups with respect to expected risk of locoregional recurrence. For instance, the higher stages of disease (higher risk of recurrence) and more chemotherapy (more aggressive therapy) administered in the control group were balanced against the longer follow-up time (higher risk of detecting recurrence) and more hormonal therapy (less aggressive therapy) in the case group.

SUMMARY

The results of this study showed no increase in rates of locoregional recurrence, systemic recurrence, or second breast cancer and support the oncologic safety of fat grafting in breast reconstruction. Although receipt of hormonal therapy did significantly increase the risk of locoregional recurrence of breast cancer in patients who received lipofilling compared with patients who did not receive lipofilling, the recurrence rates

were low. Before withholding lipofilling as a reconstructive option for breast cancer patients receiving hormonal therapy, a randomized trial would most be appropriate to determine the true clinical significance.

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