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Cancer Recurrence After Fat Transfer (CRAFT)- A Multicenter Case-Cohort Study

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Abstract

Background—Fat transfer is an increasingly popular method for refining post-mastectomy breast reconstructions. However, concern persists that fat transfer may promote disease recurrence. Adipocytes are derived from adipose-derived stem cells and express adipocytokines that can facilitate active breast cancer cells in laboratory models. We sough to evaluate the association

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DISCLOSURES

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between fat transfer to the reconstructed breast and cancer recurrence in patients diagnosed with local or regional invasive breast cancers.

Methods—A multi-center, case-cohort study was performed. Eligible patients from four centers (Memorial Sloan Kettering, MD Anderson, Alvin J. Siteman, and the University of Chicago) were identified by each site's institutional tumor registry or cancer data warehouse. Eligibility criteria were: mastectomy with immediate breast reconstruction between 2006 and 2011, age above 21, female sex, and incident diagnosis of invasive ductal carcinoma, stage I, II or III. Cases consisted of all recurrences during the study period, and controls consisted of a 30% random sample of the study population. Cox proportional hazards regression was used to evaluate for association between fat transfer and time to recurrence in bivariate and multivariate models.

Results—The time to disease recurrence unadjusted hazard ratio for fat transfer was 0.99 (95% CI: 0.56, 1.7). After adjustment for age, body mass index, stage, HER2/Neu receptor status, and estrogen receptor status, the hazard ratio was was 0.97 (95% CI: 0.54, 1.8).

Conclusion—In this population of breast cancer patients who had mastectomy with immediate reconstruction, fat transfer was not associated with a higher risk of cancer recurrence.

INTRODUCTION

Fat transfer has gained widespread acceptance as a surgical technique for volume restoration and contour correction in breast reconstruction.(1) Members of the American Society of Plastic Surgeons (ASPS) report performing 25,456 fat transfer procedures in 2014,(2) and 62% of surveyed members use this technique for breast reconstruction.(3) Despite its utility in improving aesthetic outcomes and optimization of symmetry following mastectomy with reconstruction, concerns regarding its oncologic safety persist.(4–9) These concerns are based on laboratory studies demonstrating that adipose derived stem cells (ASCs) and adipose derived growth factors can modulate the behavior of breast tumors *in vitro* and in animal models.(10–18) Also, laboratory studies have shown that ASCs modulate desmoplasia by elaborating extracellular matrix proteins, attenuate the antitumor immune response, and promote angiogenesis.(4, 5, 19, 20) A few retrospective clinical studies have suggested that fat transfer may increase the risk of locoregional recurrence after mastectomy for ductal carcinoma *in situ* (DCIS) or following partial mastectomy.(6–8, 21) Aside from a recent matched controlled study that shows fat transfer to be oncologically safe,(22) most clinical studies have been limited by inadequate power to detect small effects.

Recent guiding principles published by ASPS acknowledge that a limited body of evidence shows fat transfer following post-mastectomy breast reconstruction to be oncologically safe. (23) These guiding principles, however, also acknowledge the need for additional high quality studies. As such, the ASPS clinical trials committee sought to establish whether adjunctive fat transfer is associated with a higher risk of recurrence in patients who have undergone mastectomy with reconstruction for invasive breast cancer. Our experimental design took into consideration the relatively low baseline rate of cancer recurrence, and the fact that while fat transfer is very popular currently, it gained prominence as a technique relatively recently. Moreover, we recognized the immediate need for information examining the impact of fat transfer on cancer recurrence given its popularity – something that a

prospective trial could not provide. The design of this study improves upon previous work with more representative selection of controls, adjustment for duration of follow-up, and sufficient power to detect a doubling of breast cancer recurrence risk.

METHODS

Study design

A case-cohort design was used. The case-cohort approach allows for greater precision in the circumstance of a rare outcome and adjustment for different durations of follow-up.

Study population

Patients were identified through the tumor registry or data warehouse of four sites: University of Chicago, MD Anderson Cancer Center, Memorial Sloan Kettering Cancer Center (MSKCC), and the Siteman Cancer Center at Washington University (St. Louis). Institutional Review Board approval was obtained at each site. Eligible patients consisted of all women 21 years and older with incident invasive ductal carcinoma, Stages I-III, who were diagnosed between January 1, 2006 and December 31, 2011 and treated with mastectomy and immediate breast reconstruction. We excluded men, women younger than 21, women with prior breast cancer, women with Stage IV or inflammatory breast cancer. We also excluded women who had delayed breast reconstruction to minimize heterogeneity in time intervals between diagnosis, treatment, and fat transfer. Only patients with invasive ductal carcinoma were included, so patients with DCIS only, lobular carcinoma *in situ* (LCIS) only, sarcoma, invasive lobular carcinoma, or no cancer were excluded.

Identification of cases and controls

Cases consisted of all eligible patients who had experienced a recurrence (local, regional, or distant) during the study period (January 1, 2006 to December 31, 2011) as reported by each site's tumor registry or cancer data warehouse. The cohort was a 30% random sample of the control population, defined as patients who did not have a recurrence during the study period. Exposure to fat grafting was measured using medical record review in three sites and a prospectively maintained plastic surgery clinical database (at MSKCC). The approach of Cai and Zeng was used for power and sample size considerations.(24)

Statistical analyses

Fisher's exact tests were used to evaluate general association for categorical data. The Wilcoxon rank-sum test (using Van der Waerden or normal scores) was used for two-group comparisons of continuous covariates. Cox proportional hazards regression modeling was used to explore the association of covariates of interest with time to recurrence. Time to recurrence was defined as the time from the date of diagnosis to the date of a local, regional, or distant cancer recurrence. Patients who reached the end of the study period, were lost to follow-up, or died, without documented disease recurrence were considered censored. The covariates of interest were: fat transfer (yes/no), age, tumor stage (I-III), smoking status (yes/no), body mass index (BMI), estrogen receptor (ER) status (+/−), progesterone receptor (PR) status (+/−), HER2/Neu amplification status (+/−), receipt of adjuvant chemotherapy

(yes/no), receipt of neo-adjuvant chemotherapy (yes/no), receipt of adjuvant radiation therapy (yes/no), and receipt of adjuvant endocrine therapy (yes/no).

We report both bivariate and multivariate estimated hazard ratios (HR) with 95% confidence intervals (CI). The final multivariate models did not include PR status because it was highly correlated with ER status. They did not include adjuvant therapies because they were highly correlated with stage. Statistical analyses were performed using SAS (Version 9.3, SAS Institute, Inc., Cary, NC) and R.(25)

RESULTS

We identified 3,271 eligible patients across the four institutions. The study sample (n=1197) consisted of all recurrences during the study period (n=225) and a 30% random sample of the study population (n=972) (Table 1). Based on this sample size, power was calculated to be 76% against a relative risk of 2 and 86% against a relative risk of 2.22, when using a one-sided test with type-I error of 5%.

The median age was 47 (standard deviation (SD) 10.1). The median BMI was - 26.5 (SD 5.6). Detailed in Table 1, almost half of the patients in the study sample had stage I disease, and most had ER+ and PR+ tumors. More than half received adjuvant chemotherapy while approximately one quarter received radiation, endocrine, or neo-adjuvant chemotherapy. While 80% of patients were reconstructed with breast implants, the remainder were reconstructed with autologous flaps, or a combination of flap and implant. Fat transfer was performed in 64 patients (5%), including 28 at MD Anderson, 26 at Memorial Sloan Kettering, 7 at Washington University, and 3 at the University of Chicago.

Two hundred and twenty-five patients or 6.9% of the entire study population, had a recurrence of breast cancer. Of these, 124 recurrences were distant (55%), 24 were regional (11%), and 77 were local (34%). Forty-eight (4%) patients died during the study period. In bivariate analyses of associations between individual covariates of interest and time to recurrence (Table 2), patients who underwent fat transfer had an equivalent risk of cancer recurrence, relative to those who did not (HR=0.99, 95% CI 0.56, 1.7). Patients with HER2/Neu+ tumors had a lower hazard of cancer recurrence than patients with HER2/Neu− tumors (HR=0.62, 95% CI 0.42, 0.91). Patients with ER+ tumors had 51% of the risk of patients with ER− tumors ($p<0.0001$). Stage II patients had a greater hazard of cancer recurrence than Stage I patients (HR=1.5, 95% CI 1.1, 2.1) and Stage III patients had a greater hazard of cancer recurrence than Stage II patients (HR=2.0, 95% CI 1.4, 2.8). In the multivariable model, adjusting for age, stage, BMI, HER2/Neu+ and ER+, patients who had fat transfer had similar risk of recurrence as those who did not have fat transfer (risk = 97%, $p=0.93$, see Table 3).

DISCUSSION

Fat transfer was not associated with an increased probability of breast cancer recurrence in this multi-center case-cohort study. While fat transfer to the breast has also been used in the context of reconstruction for partial mastectomy,(26) or as the sole technique of breast reconstruction following mastectomy,(27) we investigated fat transfer as an adjunctive

technique to prosthetic or flap-based reconstruction. Our findings are primarily applicable for patients with Stage I-III invasive ductal carcinomas treated with mastectomy and immediate breast reconstruction.

While several epidemiological studies report a link between obesity in post-menopausal women and breast cancer,(28–31) and translational research studies report that mesenchymal cells or ASCs support the progression of existing tumors,(10, 15, 16, 32–35) none show that adipocytes form tumors *de novo*.(5) As an endocrine organ, white adipose tissue may promote breast cancer through the secretion of adipokines like leptin,(36, 37) or insulin-like growth factor.(38) Further, reduced levels of adiponectin in obese patients fosters a permissive environment for the pro-oncogenic properties of leptin.(37, 39)

ASCs offer another mechanism by which white adipose tissue can simulate breast cancer cells. The progression of breast cancer is impacted by stromal cells of mesenchymal and hematopoetic origin.(5) Under defined conditions, adipocytes(40) and their progenitors promote tumorigenesis in both *in vivo* and *in vitro* models.(41) When ASCs are exposed to tumor-conditioned media secreted by breast cancer cell lines, they tend to proliferate, differentiate into myofibroblasts, enhance tissue stiffness through altered extracellular matrix deposition, secrete proangiogenic factors, and exhibit attenuated adipogenic differentiation.(41) ASCs preferentially contribute vascular and fibrovascular tumor-associated fibroblasts to the tumor stroma while bone marrow-derived mesenchymal stem cells contribute fibroblast-specific proteins.(34) Co-culture of ASCs with breast cancer cells can also facilitate tumor metastases.(15, 42, 43) These important translational data speak to the potential consequences of using purified ASC grafts in the presence of active cancer cells. They may lead to the identification of molecular markers to predict cancer recurrence after fat grafting(42) but do not necessarily translate directly to current clinical practice. Unlike the immunocompromised nude mice receiving purified ASC cultures,(43) immunocompetent human patients typically receive fat grafts containing a variable, but low (2 to 8%) fraction of ASCs.(44, 45)

The absence of an association between fat transfer and recurrence risk reported here is consistent with experimental studies showing that white adipose tissue may stimulate active but not dormant breast cancers. Human ASCs significantly increase their malignant potential when co-cultured with active, but not dormant, breast cancer cells *in vitro* and in a xenogenic murine recipient *in vivo* model.(15) Under experimental conditions, invasive breast cancer cells alter the phenotype of adjacent *mature* adipocytes which, in turn, may increase the malignant potential of local breast cancer cells.(40)

Our findings are applicable to patients undergoing fat transfer following prosthetic or autologous reconstruction of mastectomy defects in the setting of stage I-III breast cancer. Following mastectomy, the engrafted recipient site contains little to no breast tissue. While some studies have suggested that adipocytes or their progenitors may stimulate active breast cancer,(10, 16) this could be less problematic if susceptible tissues have already been extirpated. By contrast, a significant percentage of residual breast tissue remains following partial mastectomy, another context in which fat transfer can be used for subsequent contour correction.(1) While an oncologically permissible environment for fat grafting may exist

when residual disease is resected and appropriate adjuvant therapy administered, increased recurrence risk may exist when fat is transferred in the presence of residual breast tissue.(46–48) The European Institute of Oncology reported a locoregional recurrence rate of 0.4% per year following partial mastectomy among 2784 subjects.(49) However, a retrospective review of 143 partial mastectomy patients found that fat transfer was associated with a 2.07% per year increased rate of locoregional recurrence.(7) By contrast, and in support of our data, recurrence rates in mastectomy patients after fat transfer increased 1.38% per year,(7) versus 1.1% per year in a historical control group of 677 patients who did not receive fat transfer.(50) In the absence of a prospective trial, the authors of this multicenter retrospective review of 646 fat transfer patients recommended a cautious oncologic follow-up protocol.(7)

Fat transfer may be associated with recurrence after DCIS, which we did not include in our study population. In a matched cohort study of 321 patients, a significantly higher incidence of local and locoregional recurrence after fat transfer was found when analysis was limited to patients with *in situ* disease.(6) A subsequent study limited to 59 patients with *in situ* disease who received fat transfer and a matched cohort of 118 who did not, revealed a higher rate of locoregional recurrence in the fat transfer group (HR=4.5, 95% CI 1.1, 18.2).(8) Patients younger than fifty, high grade neoplasia, and a Ki-67 ≥ 14, were also associated with an increased rate of recurrence after fat transfer in this study.

In Petit's retrospective series, fat transfer was performed in 108 patients with *in situ* disease with a locoregional recurrence rate of 2.33% per year versus 1.44% per year in 405 patients with invasive carcinomas.(7) The molecular signature of the epithelial component of the tumor microenvironment that regulates extracellular matrix remodeling differs between DCIS and invasive ductal carcinoma.(51) Moreover, subtypes of DCIS can be differentiated by unique molecular signatures expressed by their fibroblasts, vascular, and inflammatory stromal cells.(52, 53) Recognizing these differences, Petit and colleagues(8) postulated that with fewer genetic perturbations than invasive carcinomas, intraepithelial neoplasias may be more efficient at responding to the stromal signaling that leads to malignant degeneration. Recently, this group re-analyzed their DCIS study population over a longer period of time, to increase the number of recurrence events evalauted.(26) Relative to controls, the recurrence rate was not higher in patients receiving fat transfer following mastectomy ($p=0.56$). It was somewhat higher in patients grafted following partial mastectomy, but the difference was not statistically significant ($p=0.20$). In addition, Gale and colleagues did not report an increased rate of recurrence following fat transfer in DCIS patients.(54) Fat transfer in these patients, however, was restricted to patients with clear margins and was delayed for 54 months after resection. By contrast, Petit waited a mean of 25 months and had positive or close margins in 42% of fat transferred patients but only 20% of controls, so the increased risk of recurrence may have been related to margin status.(8) Gale suggested that early fat transfer (≤2 years) after tumor resection may increase the impact of fat transfer on recurrence rates.(54) Kronowitz et al. - who also support the oncologic safety of fat transfer in their study - suggest that lumpectomy accompanied by intraoperative radiation only, may have also impacted recurrence rates in Petit's study.(22)

Evaluation of the oncologic safety of fat transfer to facilitate breast reconstruction is challenging because recurrence of local or regional breast cancer after mastectomy is a relatively rare outcome,(55) many years of follow-up are necessary to evaluate recurrence,(56, 57) and fat transfer has become common only recently. Thus, we used a retrospective case cohort approach. Our study was sufficiently powered to detect a risk ratio of 2 or greater, in terms of association between fat transfer and breast cancer recurrence. While a prospective, randomized controlled trial would be favorable over a retrospective analysis, it would be impractical to ask patients to agree to a control arm of no treatment for contour deformities. Finding an alternative control arm, such as temporary fillers or tissue rearrangement, would also be challenging. A prospective cohort study would also be useful but would require a substantially larger sample size and would not produce evidence for five to ten years. Finally, a study using existing large administrative or clinical datasets is not feasible because fat transfer does not yet have a unique billing code and is not routinely recorded in cancer registries. To address an urgent need for evidence on the safety of fat transfer to the breast,(58) we used a case-cohort study design, which is appropriate for assessing the probability of rare outcomes in a more timely fashion than a prospective cohort study.

The retrospective nature of this study is a limitation. In addition, we did not adjust for differences among fat transfer techniques due to a lack of consensus, nuanced technique differences not captured by retrospective review, and insufficient power to evaluate the impact of different fat transfer techniques on recurrence. Still, various methods of fat harvest and processing may affect adipocyte viability and stem cell fraction.(59–62) While optimization of the ASC-rich stromal vascular fraction of lipoaspirate may favor improved graft retention,(45) it may also increase the risk of exposure of ASCs to occult, residual tumor stroma.(45) All patients were treated at high-volume cancer centers and likely had access to timely cancer treatment and appropriate administration of adjuvant therapy.(48, 63) Thus, these results assume guideline-concordant care and may not be generalizable to all breast cancer patients. In addition, some of these patients may have sought a cancer center for their initial therapy but eluded detection of the institutional tumor registry for recurrences treated elsewhere. We only assessed patients having mastectomy and immediate reconstruction, a population that tends to be healthier, have greater economic resources, and have more favorable tumors than breast cancer patients overall.(64–66) Although we adjusted for some clinical variables, we did not adjust for health status or social factors. Future studies should include patients who have fat transfer after delayed reconstruction and after breast conservation therapy. As fat transfer to the breast becomes more common and acquires more indications, such studies ought to become more feasible.

CONCLUSION

Fat transfer was not associated with a higher probability of recurrence in this multi-site population of local and regional breast cancer patients treated with mastectomy and reconstruction. Although the precision of the study was somewhat limited, it provides evidence that fat transfer does not increase the probability of invasive breast cancer recurrence by a factor of at least 2.0. Future studies of a larger sample of immediate

reconstruction patients, and studies of fat transfer after delayed reconstruction or breast conservation therapy, are warranted.

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Table 1

Patient Characteristics

Patient Characteristics	Total Cohort*	Recurrence	No Recurrence
Age (SD)	47.78 (10.09)	44	48
BMI (SD)	26.49 (5.62)	25	25
TNM Stage	**N (%)**		
Stage I	585 (49)	77 (34)	508 (52)
Stage II	448 (37)	92 (41)	356 (37)
Stage III	164 (14)	56 (25)	108 (11)
Receptors			
HER2Neu+	215 (20)	29 (13)	205 (22)
ER+	875 (74)	134 (60)	741 (78)
PR+	713 (61)	101 (46)	612 (64)
Treatment			
Adjuvant XRT +	319 (27)	110 (49)	209 (22)
Adjuvant Chemotherapy +	689 (58)	153 (68)	536 (55)
Adjuvant Endocrine +	1 (0)	25 (42)	252 (74)
Neoadjuvant Chemotherapy +	250 (21)	82 (36)	168 (17)
Site			
MD Anderson	271 (23)	32 (14)	239 (25)
Memorial Sloan Kettering	794 (66)	166 (74)	628 (65)
University of Chicago	39 (3)	8 (4)	31 (3)
Washington University, St. Louis	93 (8)	19 (8)	74 (8)
Totals	1197 (100)	225 (19)	972 (81)

Abbreviations: BMI Body Mass Index, *TNM* Tumor Nodal Metastasis, *ER* Estrogen Receptor, *PR* Progesterone Receptor

*Values in parenthesis for Age and BMI represent standard deviation. All other values in parenthesis represent a percentage.

Table 2

Bivariate Time to Recurrence Models

Covariates	Hazard Ratio	95% CI	p-value
Age (for each 10 years)	0.81	(0.71, 0.93)	0.002
BMI (kg/m2)	0.98	(0.96, 1.01)	0.19
Stage II versus Stage I	1.5	(1.1, 2.1)	0.007
Stage III versus Stage II	2	(14, 2.8)	<0.0001
HER2Neu+ versus HER2Neu−	0.62	(0.42, 0.91)	0.02
ER+ versus ER−	0.51	(0.39, 0.66)	<0.0001
PR+ versus PR−	0.52	(0.40, 0.68)	<0.0001
Fat Transfer (yes versus no)	0.99	(0.56, 1.7)	0.99

Abbreviations: BMI Body Mass Index, *ER* Estrogen Receptor, *PR* Progesterone Receptor

Table 3

Multivariate Time to Recurrence Model

Covariates	Hazard Ratio	95% CI	p-value
Age (For each 10 years)	0.85	(0.75, 0.98)	0.02
BMI (kg/m2)	0.98	(0.96, 1.01)	0.11
Stage II versus Stage I	1.3	(0.95, 1.8)	0.13
Stage III versus Stage II	2.3	(1.6, 3.2)	<0.0001
HER2Neu+ versus HER2Neu−	0.48	(0.32, 0.72)	0.0004
ER+ versus ER−	0.48	(0.37, 0.63)	<0.0001
Fat Transfer (yes versus no)	0.97	(0.54, 1.8)	0.93

Abbreviations: BMI Body Mass Index, *ER* Estrogen Receptor, *PR* Progesterone Receptor