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The Oncologic Safety of Breast Fat Grafting and Contradictions Between Basic Science and Clinical Studies

A Systematic Review of the Recent Literature

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Abstract: Fat grafting is increasingly popular and is becoming a common practice in plastic surgery for postmastectomy breast reconstruction and aesthetic breast augmentation; however, concerns over the oncologic safety remains a controversial and hot topic among scientists and surgeons. Basic science and laboratory research repeatedly show a potentially dangerous effect of adipose-derived stem cells on breast cancer cells; however, clinical research, although limited, continually fails to show an increase in breast cancer recurrence after breast fat grafting, with the exception of 1 small study on a subset patient population with intraepithelial neoplasm of the breast. The aim of this review is to summarize the recent conflicting basic science and clinical data to better understand the safety of breast fat grafting from an oncological perspective.

Key Words: breast cancer, fat grafting, mesenchymal stem cells, adipose-derived stem cells

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In 1987, the American Society of Plastic Surgeons (ASPS) banned autologous fat grafting to breasts primarily over concerns of future cancer surveillance in the setting of fat necrosis, and secondarily because of inconsistency in graft retention.¹ In 2007, the ASPS established a task force to reevaluate the potential hazards and benefits of breast fat grafting concluding current radiographic technology can distinguish grafted fat from potentially dangerous lesions with acceptable risk and that autologous fat grafting to the breasts may be useful and safe, but lacks standardization.² In 2009, the ASPS lifted the ban on autologous fat grafting owing to lack of evidence; however, the ASPS Fat Graft Task Force stated that surgeons should exercise “caution when considering fat grafting procedure in patients at high risk for breast cancer”.³

Although breast cancer remains the most common cancer in women, fat grafting has become increasingly more popular and common in plastic surgery for postmastectomy breast reconstruction and also aesthetic breast augmentation.⁴ Fat grafting offers autologous tissue transfer without microsurgical expertise or resources, can be performed in the outpatient setting with fast patient recovery, and has minimal donor site morbidity. Although the technique of fat grafting has been widely studied and shown to have an acceptable minor complication risk, with the recent discovery of adipose-derived stem cells (ASCs) in fat tissue, the concern for oncologic recurrence risk remains a highly debated and controversial topic among surgeons and scientists.^{5–7} The ASCs are a subtype of mesenchymal stem cells (MSCs) and exhibit common characteristics of MSCs, such as the capacity to differentiate into different cell types (eg, osteocytes, chondrocytes), and secretion of growth factors.⁵ Under normal conditions, MSCs lay

dormant in certain niches in organs, but become activated in the case of injury (ie, surgery) to help tissue regeneration. It has been widely speculated that the growth factors secreted by activated MSCs may stimulate the growth and metastasis of cancer cells. Although clinical studies have yet to show an increased breast cancer recurrence risk after breast fat grafting with the exception of a subset population of epithelial neoplasms of the breast, basic science research is replete with evidence demonstrating that ASCs and breast cancer cells communicate and lead to increased migration and proliferation of breast cancer cells, as well as increased gene expression of typical malignancy markers (epithelial cell adhesion molecule [EPCAM], erythroblastosis oncogene B2 [Erbb2], lymphoidenhancer-binding factor 1 [LEF1], fibroblast growth factor receptor 4 [FGFR4], and synucleingamma [breast cancer-specific protein 1; SBCG]), and increased tumor growth and metastasis using in vivo xenograft models.^{8–11}

The aim of this review is to evaluate the recent data on clinical breast cancer recurrence after breast fat grafting and discuss it in the setting of the contradicting recent basic science studies that repeatedly demonstrate potentially dangerous effects of ASCs on breast cancer cells using both in vitro and in vivo xenograft models. Our intention is to shed light on the conundrum of the oncologic safety of breast fat grafting.

LITERATURE REVIEW

We carried out a literature search in PubMed and Google Scholar databases using “fat graft” or “fat grafting” or “lipomodelling” or “lipofilling” or “autologous fat” and “breast cancer” as search terms. We limited this review to recent literature and searched all the papers published from January 2010 to December 2014 (Fig. 1). In total, 16 clinical and 9 basic science studies were used.

Inclusion Criteria

Original articles pertaining to clinical studies of human patients undergoing fat grafting to the breast with mention of breast cancer recurrence were eligible for inclusion in this review. Basic science literature studying the interaction of ASCs and breast cancer cells, as well as studies using xenograft models for coinjection of ASCs and breast cancer cells, were also eligible.

Exclusion Criteria

Duplicate studies and studies with less than 25 patients and/or less than 12 months follow-up after breast fat grafting were excluded. In addition studies, without original data, including reviews, were excluded.

THE INTERACTION OF ASCS AND BREAST CANCER CELLS

As the controversy over the safety of breast fat grafting after breast cancer grows, many scientists and surgeons have turned to the laboratory to get a better understanding of ASCs and its interaction with breast cancer cells. Studies performed using different experimental models come to the common conclusion that MSCs, including ASCs, can create a microenvironment suitable for ramped up tumorigenesis potential of breast cancer cells. Ke et al¹² demonstrated that as few as

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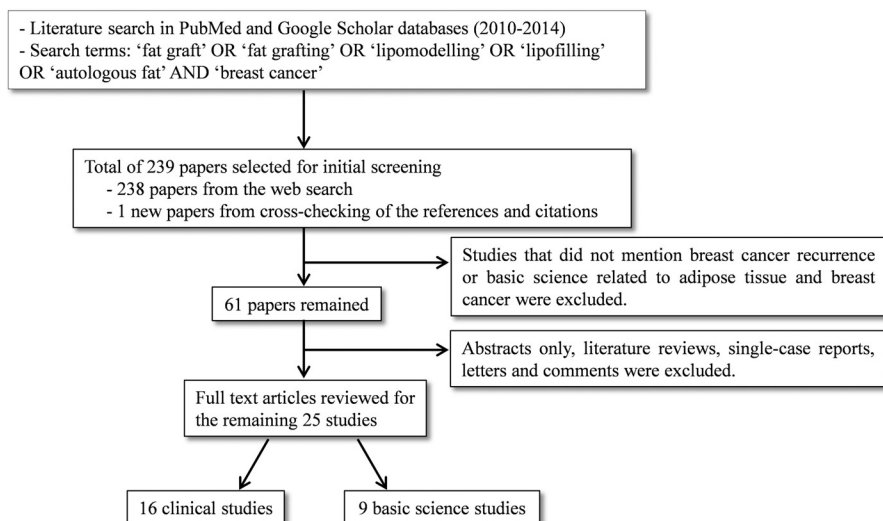


FIGURE 1. Study attrition chart.

5 breast cancer cells coinjected with MSCs in a murine model resulted in tumor development, not replicated without the addition of MSCs.

Researchers have proposed different mechanisms for the interactions between ASCs and breast cancer cells. Gehmert et al⁹ documented a direct communication between ASCs and breast cancer cells, whereas Zimmerlin et al¹³ used metastatic breast cancer isolates from pleural fluid to demonstrate ASCs increase breast cancer cell proliferation indirectly via secretion of growth factors.

Two concurrent studies by Orecchioni et al¹⁴ and Bertolini et al¹⁵ documented that 2 distinct populations of progenitor cells isolated from human adipose tissue play a role in increased cancer recurrence. In these studies, endothelial progenitor cells generated mature endothelial cells and capillaries within the tumor but their cancer-promoting effect in the breast was limited in the absence of ASCs, which supported new vessel formation and were more efficient than endothelial progenitor cells in promoting local tumor growth. Therefore, they concluded that ASCs and endothelial progenitor cells cooperate in driving progression and metastatic spread of breast cancer.¹⁴ Similarly, Rowan et al¹¹ discovered increased migration of breast cancer cells when cocultured with ASCs. More interestingly, they found increased micrometastasis in first pass organs, specifically the liver, lung and spleen, in a murine xenograft model suggesting a role of ASCs in angiogenesis and increased metastatic potential of breast cancer cells (Fig. 2).

Another theory on ASC-breast cancer cell interaction was direct intercellular contact between ASCs and breast cancer cells leading to morphological changes and increased expression of transcriptional genes for typical malignancy markers.¹⁰ Eterno et al⁸ studied the interaction between ASCs and primary breast cancer isolates from patients. They found a direct correlation between c-Met expression in breast cancer cells and susceptibility to tumorigenesis promoting effects of ASCs. The ASCs associated with increased tumorigenesis also showed increased expression of hepatocyte growth factor. Additionally, human donors with increased expression of c-Met on breast cancer cells developed cancer recurrence after fat grafting (Fig. 3). The authors concluded that a master role for hepatocyte growth factor/c-Met crosstalk in mediating a tumorigenic role of ASCs in breast cancer must exist.

Given the large volume of preclinical data available, of which only a small sample is reviewed above, adipose tissue is now considered not only an energy storage depot, but also an active endocrine tissue that interacts closely with the surrounding tissues. This is further supported by a study by Sturtz et al¹⁶ that revealed an upregulated expression of genes involved in inflammation, proliferation, invasion, and migration

in human adipose tissue adjacent to breast cancer, concluding adipose tissue is not inert, but plays an active fluent role in tumorigenesis. Therefore, the possible role of adipose tissue in breast tumorigenesis should be taken into consideration when planning fat grafting in a patient at increased risk for the development of breast cancer.

THE CLINICAL RISK OF FAT GRAFTING

In total, 16 clinical studies including 2100 patients were reviewed (Table 1). The overall rate of local breast cancer recurrence after fat grafting was 2.2% with recurrence noted in 47 patients. Various studies encompassed a diverse patient population undergoing a wide range of surgical procedures from fat grafting alone to fat grafting after autologous flap and/or implant placement. Some subjects underwent multiple fat grafting procedures as well. Breast cancer recurrence was limited to locoregional events; however, distant metastasis is discussed in the comments sections of Table 1 where applicable.

In summary, 6 clinical studies demonstrate no breast cancer recurrences in a number of patients ranging from 28 to 151 with a minimum follow-up of 12 months.^{21,23,25,29,31,32} Three published prospective trials including 158, 67, and 59 patients found breast cancer recurrence rates were 0.6%, 0.0%, and 5.1% with 1, 0, and 3 patients, respectively, discovered to have breast cancer recurrence at an average follow-up of 18, 12, and 34 months.^{19,21,30} Two clinical studies, including 60 and 137 patients, after a relatively long follow-up, with an average of at least 90 months, showed recurrence rates of 3.3% and 3.6%, respectively.^{17,28} Other retrospective analyses with shorter average follow up periods (<50 months) showed recurrence rates of 2.2%, 3.2%, and 3.1%.^{20,24,26}

The largest patient series was published by Petit et al¹⁸ in 2011. This was a multicenter analysis of 513 patients undergoing breast fat grafting after mastectomy or breast conserving therapy with invasive carcinoma and/or cancer in situ revealing a local recurrence rate of 2.4% (1.5% per year) and distant recurrence of 3.1% (1.9% per year).¹⁸ The following year, 321 consecutive patients were analyzed against a 1:2 match cohort with similar characteristics with local recurrence in 8 (2.5%) compared to 19 (3.0%) in the cohort control. However, when analysis was limited to a subset of 37 patients with intraepithelial neoplasms, 4 local recurrences existed (10.8% local recurrence rate) versus none in the cohort, a significant difference.²² The initial findings prompted the team to perform a matched cohort study of 59 patients with intraepithelial neoplasms undergoing breast fat grafting compared

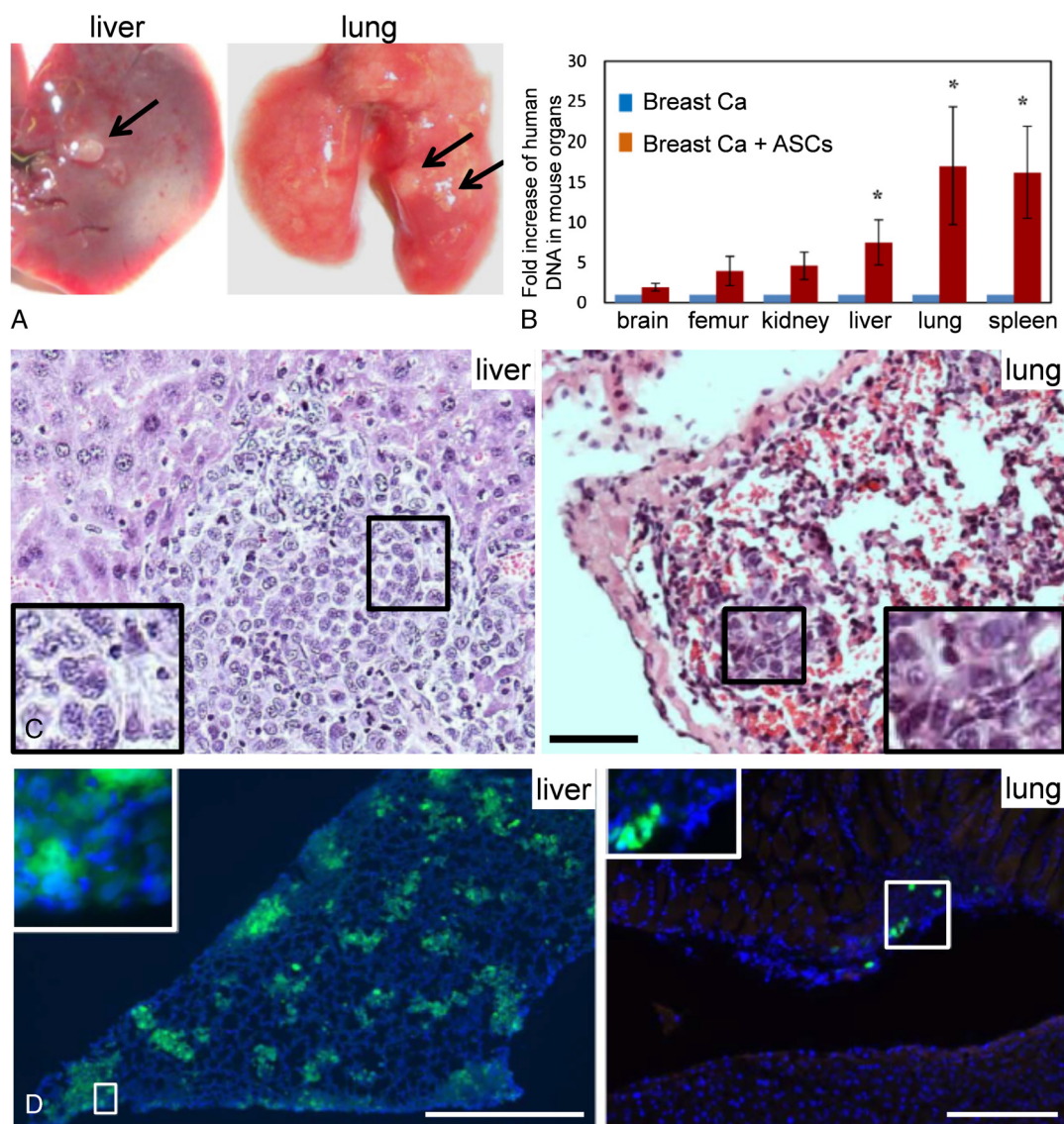


FIGURE 2. Metastasis of human breast cancer after coinjection with ASCs in a murine model. A, Human breast cancer cells showed increased macrometastasis to the liver and lung (first pass organs) after coinjection with ASCs. Black arrows point the metastatic foci in liver and lung. B, Graph shows the human DNA expression levels in various mouse organs after injection of human breast cancer with and without ASCs; note the significant increase in the spleen, liver, and lung with ASCs coinjection. C, Micrometastasis to the liver and lung after coinjection of human breast cancer cells and ASCs. Microbar is 100 μ . D, Liver and lung sections 40 days after coinjection of GFP labeled human breast cancer and ASC, showing metastatic multifocal lesions. Microbars are 400 μ and 100 μ , respectively. Figure adapted from Rowan et al.¹¹

to 118 matched patients not undergoing breast fat grafting, revealing an 18% 5-year cumulative risk of local recurrence in the breast fat grafting group compared to 3% in the cohort control ($P = 0.02$).²⁷

In summary, the overall local recurrence rate of 2.2% in patients undergoing breast fat grafting was comparable to the published breast cancer recurrence rates (5.2–10.6%) in patients without breast fat grafting after breast cancer surgery.^{33–37} However, fat grafting in the presence of known ductal or lobular intraepithelial neoplasms has up to an 18% 5-year local recurrence rate.

CURRENT FAT GRAFTING REGULATIONS

In 2011, a joint task force of the American Society for Aesthetic Plastic Surgery and the ASPS was created in response to raising concerns relating to stem cell therapies in aesthetic plastic surgery. The task

force recommended caution toward “stem cell breast augmentation” (as advertised), considering the lack of consistency in how these procedures are performed and how stem cells are incorporated into the procedure. The task force extended this caution to instructional courses which are designed to teach methods of stem cell extraction for aesthetic procedures, and specialized equipment being marketed to physicians for use in “stem cell procedures.”

The Task Force also conducted a systematic review of the peer reviewed medical literature on fat grafting and stated that the marketing and promotion of stem cell procedures in aesthetic surgery is not adequately supported by clinical evidence and recommended that, until further evidence is available, stem cell therapies in aesthetic and reconstructive surgery should be conducted under Institutional Review Board approval.³⁸

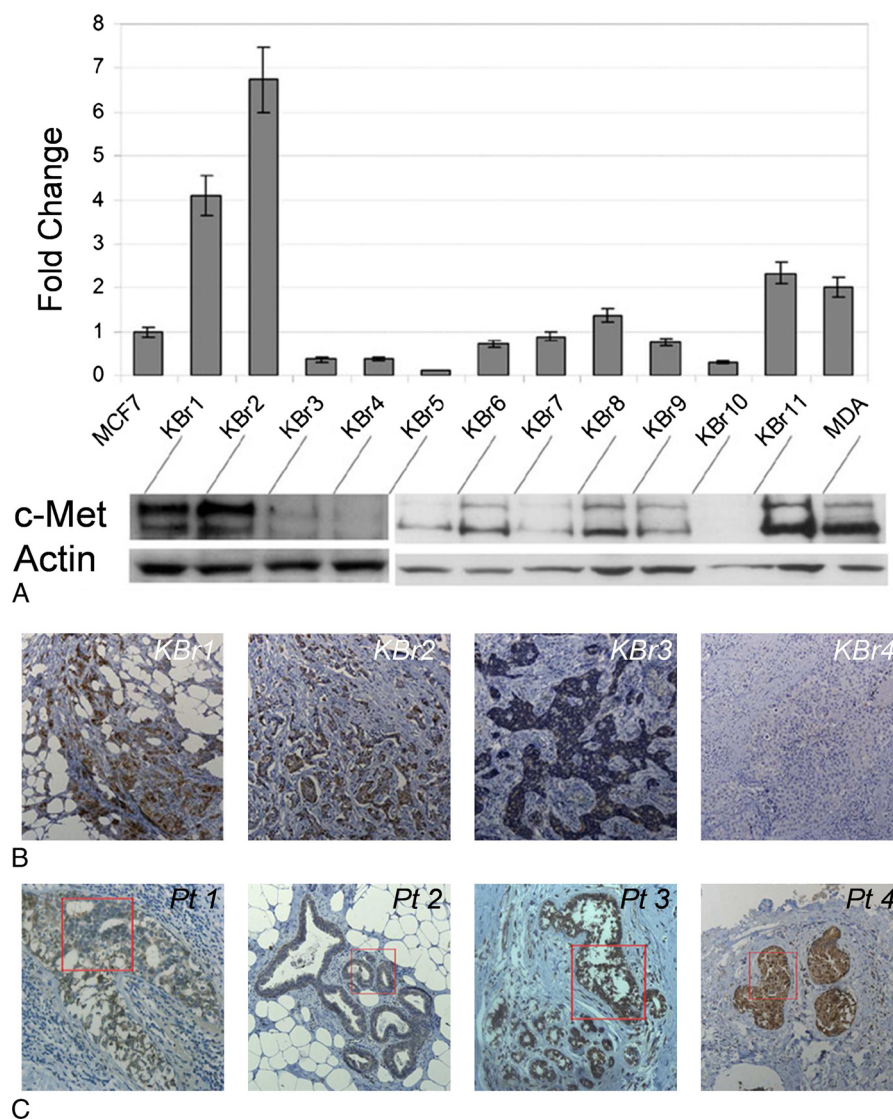


FIGURE 3. The correlation between the increased c-Met expression and breast cancer recurrence after breast fat grafting. A, Quantitative reverse transcriptase polymerase chain reaction results showing elevated c-Met expression in cell lines KBr1, KBr2, and KBr11. B, Immunohistochemical staining for c-Met expression, noted in KBr1 and KBr2, but not in KBr3 and KBr4. C, Histological biopsies of primary breast cancer samples showing high levels of c-Met immunohistochemical staining in patients 3 and 4, but low/no expression in patients 1 and 2. Patients 3 and 4 had local breast cancer recurrence after breast fat grafting at 4 and 7 months, but samples with low/no c-Met expression had no recurrence at 6 and 22 months after breast fat grafting. Figure adapted from Eterno et al.⁸

In December 2014, the US Department of Health and Human Services, Division of Food and Drug Administration published a draft guidance for human cell, tissues, and cellular and tissue-based products (HCT/P) from adipose tissue: regulatory considerations, labeled 21 CFR.³⁹ According to this publication, adipose tissue must meet the following requirements for clinical use: (1) minimal manipulation; (2) homologous use only; (3) no combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition does not raise new clinical safety concerns; (4) adipose tissue cannot have a systemic effect and be dependent upon the metabolic activity of living cells for its primary function, unless for autologous use, allogeneic use in a first-degree or second-degree blood relative, or reproductive use. It is also stated that HCT/P from adipose tissue for nonimplant augmentation would not be consistent with the basic function of breast tissue and

generally be considered a nonhomologous use. However, when HCT/Ps are removed from an individual and implanted in the same individual in the same surgical procedure, and as long as HCT/P does not undergo processing beyond rinsing, cleansing, or sizing, they are not required to comply with requirements in 21 CFR Part 1271. Despite recognizing autologous fat grafting to the breast as a nonhomologous use and therefore not compliant with its regulations, the Food and Drug Administration made an exception for certain surgical techniques that allows intraoperative harvest and injection, including the Coleman technique which utilizes intraoperative centrifuge.

CONCLUSIONS AND FUTURE DIRECTIONS

Currently, the basic science and clinical studies provide contradictory evidence with regard to the safety of breast fat grafting.

TABLE 1. Summary of Recent Literature on the Oncological Risk of Autologous Fat Grafting to the Breast

Study	Year	Patients (n)	Age, y	Follow-Up, mo	Surgery to Graft Time, mo	Cancer Stage	Cancer Operation	Br Ca Recurrence	Comments
Rigotti et al ¹⁷	2010	137	46.5 (20–68)	91.2 (37.2–229.2)	94 pts: 84 ± 72 43 pts: 20 ± 12	IV or less	MRM	5 (3.6%)	BFG was introduced into the author's practice in 2000. 137 pts with a minimal follow-up of 3 y were selected. The pts in group I (n = 94) were operated before, and pts in group II (n = 43) were operated after 2000. The patients were also divided into 2 periods, I: before BFG and II: after BFG; pts in group I had a much longer period I. Period I served as a control. A total of 16 pts (11%) had cancer recurrence (7 LRs, 7 DRs, 2 LRs and DRs). Of the 9 LRs, 4 LRs were in period I with a calculated annual recurrence rate of 9.1/1000 pt-y and 5 LR during period II at a rate of 7.2/1000 pt-y.
Petit et al ¹⁸	2011	513	52.1 (27.7–86.3)	19.2 (1–107)	39.7 (0–216)	In situ (108) Invasive (405)	Mastectomy (370) BCT (143)	29 (5.6%)	This was a multicenter study including 513 pts; pts who underwent treatment for cancer recurrence prior to BFG were excluded. Overall (local/distant) recurrence was 5.6% (3.6% per year). LR was 2.4% (1.5%/year) and DR was 3.1% (1.9%/year)
Rietjens et al ¹⁹	2011	158	48 (22–70)	18.3 (6–49)	50.5 (5.5–170)	0–IV	Mastectomy (93) BCT (62) Defect (3)	1 (0.6%)	158 pts (98% with a personal history of breast cancer) undergoing 194 BFG procedures were evaluated prospectively. One pt with LR was diagnosed 2 weeks after BFG, and was believed to be present and misdiagnosed at the time of BFG.
Doren et al ²⁰	2012	278	51 (21–81)	28 (0.56–168)	16.7	0–IV	Mastectomy (with TE/implant/flap/none)	6 (2.2%)	Single surgeon retrospective analysis of 278 pts undergoing mastectomy (lumpectomy pts were excluded) for a total of 448 breasts and 586 BFG procedures. 244 pts underwent mastectomy for breast cancer, whereas 203 of 448 breasts underwent prophylactic mastectomy, with subsequent BFG. At the most recent follow-up, 3 pts developed metastatic disease, 1 pt died of disease, and 6 pts (2.2%) had LR
Perez-Cano et al ²¹	2012	67	52 (37–68)	12	DNR	T2N0M0 or less	BCT	0 (0.0%)	The RESTORE-2 trial, a single-arm, multicenter, prospective trial of 71 post-BCT pts with T2N0M0 disease or less with 12 month follow-up completed by 67 pts with no report of LR.

Continued next page

TABLE 1. (Continued)

Study	Year	Patients (n)	Age, y	Follow-Up, mo	Surgery to Graft Time, mo	Cancer Stage	Cancer Operation	Br Ca Recurrence	Comments
Petit et al ²²	2012	321	45 (22–71)	Total: 56 (8–155) after fat grafting: 26 (1–128)	26 (2–128)	T3 or less	Mastectomy (196) BCT (125)	8 (2.5%)	321 consecutive pts operated on for primary breast cancer with subsequent BFG were analyzed versus a control of 2 matched pts with similar characteristics that did not undergo BFG. Eight LR existed in the BFG vs 19 in the control, which was not significant; similar results were confirmed when mastectomy vs BCT were analyzed separately and confined to invasive cancer (89% of tumors). Interestingly, when analysis was limited to intraepithelial neoplasm only (N = 37), BFG group had 4 LR versus 0 in the control. Regional nodal recurrence was found in 5 vs 9 and distant metastasis in 13 vs 27, for BFG and control, respectively.
Seth et al ²³	2012	69	49.4 ± 8.8	24.8 ± 5.9 (10–82)	18.3 ± 10.5	In situ to III	Mastectomy with immediate tissue expander	0 (0.0%)	Retrospective analysis of 886 consecutive pts (1202 breast) undergoing mastectomy with immediate tissue expander reconstruction with or without BFG; 7 pts were excluded due to lack of pathological data. Analysis of 812 pts (1106 breasts) in the non-BFG group with LR of 17 (1.5%) and survival 776 (95.5%) compared to 0 LR and 100% survival in BFG of 68 pts (89 breasts) revealed no significant difference between groups
Bonomi et al ²⁴	2013	31	55 (39–65)	21 (6–36)	<6 mo	DCIS/invasive	Flap with LM	1 (3.2%)	Retrospective analysis of 31 pts who underwent mastectomy and breast reconstruction surgery with latissimus dorsi flap ± implant or implant only with subsequent BFG within 6 months for symmetry. One pt (3.2%) developed LR, 4 years after mastectomy and 2 y after BFG.
Hoppe et al ²⁵	2013	28	52.4	31.2 (6–44.4)	67.2 (2–165.6)	DNR	Mastectomy	0 (0.0%)	Retrospective multicenter European trial of 28 postmastectomy (BCT pts were excluded) pts (25 breasts) who underwent a total of 135 water jet-assisted BFG (BEAULI) procedures with 0 LR
Ihrai et al ²⁶	2013	64	DNR	46.4 ± 21.4	78.8	In situ/invasive	BCT/Mastectomy with flap/implant	2 (3.1%)	Retrospective analysis of 100 BFG procedures in 64 pts with a minimum follow-up of 12 mo. Three (4.7%) DR and 2 (3.1%) LR were identified

Petit et al ²⁷	2013	59	49 (33–65)	38	25	Invasive ductal: 57 invasive lobular: 2 grade III or less	Mastectomy: 47 BCT: 12	6 (10.2%)	Matched-cohort study of 59 intraepithelial neoplasia pts undergoing BFG compared to 118 control pts. 5 y cumulative incidence of LR in BFG group (18%) was significantly higher than control group (3%) ($P = 0.02$). Ki-67 was the only significant factor found in univariate survival analysis of LR after BFG. After exploratory subgroup analysis, age <50 y, high-grade neoplasia, Ki-67 ≥ 14 and quadrantectomy procedure were all variables that increased the risk of LR after BFG.
Riggio et al ²⁸	2013	60	49.7 (36–68)	90	55	Stage I–III	Mastectomy + implant/flap	2 (3.3%)	60 pts undergoing mastectomy with implant/flap reconstruction and BFG (82 procedures) were included. Overall LR was 5%, 1 pt (1.6%) before BFG and 2 pts (3.3%) after BFG. All LR occurred in pts with stage II disease. The incidence of LR was 0.36 before and 0.43 after BFG. The estimated crude cumulative incidence after BFG was 7.25% for LR and 7.6% for distant metastases. The incidence rate related only to the stage II pts was 1.04 per 100 person-years. The LR occurred at 21 mo and 73 mo after initial BFG.
Sarfati et al ²⁹	2013	68	46 (28–73)	23 (4–50)	XRT to LF: 7 (6–180)	DNR	Mastectomy	0 (0.0%)	68 pts s/p mastectomy and radiotherapy were included. Patients received BFG before implant reconstruction with no LR; however, 1 pt developed contralateral breast cancer and 1 pt developed bone/liver metastasis. Patients at high risk for LR were excluded
Brenelli et al ³⁰	2014	59	50 $\pm$ 8.5	34.4 $\pm$ 15.3	76.6 $\pm$ 30.9	0–IIIA or unknown	BCT	3 (5.1%)	Prospective single surgeon evaluation of 59 pts (75 BFG procedures) s/p BCT for oncologic reasons. Pts with LR before BFG were excluded. Four pts had LR, but 1 case was suspected at the time of BFG and diagnosed 1 week later, which was not included in the data as LR. The LR rate was reported as 5.1% (3/59) with a LR per year of 1.4%.
Moltó García et al ³¹	2014	37	55 (22–64)	12–39	immediate	T2 or less Fibroadenoma: 8	BCT	0 (0.0%)	37 pts s/p lumpectomy for breast cancer (n = 29) or fibroadenoma (n = 8) underwent immediate BFG by closing the lumpectomy defect with absorbable sutures and injecting at a defect created distant to the lumpectomy cavity. Only T2 or less low risk pts were included. No LR have been recorded.

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TABLE 1. (Continued)

Study	Patients Year	Age, y	Follow-Up, mo	Surgery to Graft Time, mo	Cancer Stage	Cancer Operation	Br Ca Recurrence	Comments
Semprini et al ³²	2014	151 (40–72)	45 (17–76)	24 (9–29)	In situ/invasive	BCT	0 (0.0%)	151 pts s/p BCT for breast cancer with subsequent BFG at a later date reported no LR. 489 pts underwent BCT for breast cancer without BFG during the same time period with 4 LR (0.89%)

MRM indicates modified radical mastectomy; BCT, breast conservation therapy; TE, tissue expansion; DNR, did not record; DCIS, ductal carcinoma in situ; LM, lipomodelling; XRT to LF, radiation to lipofilling; BFG, breast fat grafting; pts, patients; LRs, local recurrences; DRs, distant recurrences; s/p, status post.

Although the reviewed basic science studies suggest that ASCs can encourage the proliferation, migration, and metastases of breast cancer cells both in vitro and in vivo, the concentrations of ASCs in these studies is significantly greater than what is typically seen in standard fat grafting. We know that fat grafts typically have $4.0 \times 10^5 \pm 2.0 \times 10^5$ ASCs per mL of lipoaspirate and $0.7 \times 10^6 \pm 0.1 \times 10^6$ stromal vascular cells per gram of adipose tissue.^{40,41} Even when using cell-assisted lipotransfer, described by Yoshimura et al,^{42–44} which combines processed stromal vascular fraction with adipose lipoaspirate to create an ASC-rich fat graft, the ASC concentration is much smaller than ex vivo expansion techniques used in the basic science studies. This may explain why most clinical studies looking at recurrence rates of breast cancer after fat grafting show no difference than nonfat-grafted breast cancer patients. With the exception of Petit et al who has shown there may be an increased risk of recurrence in patients with intra-epithelial neoplasms, there are no reports on increased risk of breast cancer recurrence associated with fat grafting to the breast.

At this point, there is not enough good data to make a definitive claim about the oncologic safety of breast fat grafting in patients. The best studies thus far suggest there is no increased risk of cancer associated with fat grafting, but these are limited by lack of standardization of surgical technique and fat harvest method, inadequate controls, retrospective analysis, and insufficient long-term follow-up. Although a prospective randomized trial is desirable, this will likely not occur. More well-controlled cohort studies with sufficiently long follow-up of a minimum of 120 months demonstrating similar findings that there is no increased cancer risk associated with fat grafting will provide clinicians and patients peace of mind when fat grafting to breast. Currently, patients with known intraepithelial tumors should be cautioned that there are studies to suggest increased recurrence rates associated with fat grafting. This conversation should be included in the informed consent of all patients considering fat grafting as part of their breast procedures.

Basic science studies often used banked breast cancer cell lines, which tend to be more durable and mutated compared to residual breast cancer cells after surgery in the average patient. Thus, basic science studies can be made more clinically relatable by using clinical breast cancer samples and ASCs harvested from the same patient to provide a more accurate clinical correlation.

Although there is no denying the aesthetic advantages of breast fat grafting especially in conjunction with implant or Brava system tissue expansion, surgeons should be sure to provide appropriate informed consent when performing breast fat grafting on breast cancer patients until more studies with longer follow-up are completed.^{45,46} We also believe surgeons performing breast fat grafting for aesthetic augmentation in young patients with a strong family history of breast cancer must inform their patients of the limited data available on cancer rates in high-risk patients after breast fat grafting to healthy tissue.

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