Breast fat grafting and cancer: a systematic review of the science behind enhancements and concerns

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Background: Autologous fat transfer (AFT) is gaining popularity in breast surgery, offering a natural-looking and minimally invasive approach for augmentation, reconstruction, and contouring. However, concerns about its impact on breast cancer necessitate an understanding of the interplay between transplanted adipose-derived stem cells (ADSCs) and the breast tissue microenvironment. Renowned for regeneration, ADSCs raise questions about their role in cancer promotion. This systematic review delves into the complex relationship between AFT and breast cancer, exploring how ADSCs may influence development, growth, and metastasis.

Methods: A systematic search of electronic databases, including PubMed, Embase, and BVS was conducted to identify relevant studies. The search strategy employed a combination of keywords, including "breast augmentation", "fat grafting", "breast enhancement", "mammoplasty", "cancer", "neoplasm" and related terms. Two reviewers independently screened titles and abstracts. Full-text articles were then retrieved for further evaluation based on their potential contribution to the review objectives.

Results: Two hundred and forty records were identified. Among these, 104 duplicates were removed, resulting in 136 reports available for title and abstract screening. Subsequently, 54 papers were deemed potentially eligible for inclusion, and all reports were retrieved.

Conclusions: *In vitro* studies reveal ADSCs dual role in breast cancer, influencing proliferation, migration, and drug resistance through complex signaling pathways. Animal studies highlight distinct ADSC subpopulations impacting tumor growth via direct interactions and extracellular vesicle cargo. *In vivo*, ADSC-enriched fat grafting is generally safe, showing no increased cancer recurrence risk compared to other methods. Notably, cases of invasive breast carcinoma warrant special attention. ADSC-enriched fat grafts exhibit potential benefits in graft retention and survival rates. Despite promising evidence, further studies are needed to comprehensively understand the intricate relationship between ADSCs and breast cancer for optimized clinical applications and potential therapeutic innovations.

Keywords: Breast fat grafting (BFG); autologous fat transfer (AFT); adipose-derived stem cells (ADSCs); breast cancer

Introduction

Breast fat grafting (BFG), or autologous fat transfer (AFT), is an increasingly popular technique in breast surgery. It involves harvesting adipose tissue from one body region and transplanting it into the breast. BFG is valued for its potential to provide a natural-looking and minimally invasive alternative for breast augmentation, reconstruction, and contouring. However, growing concerns have emerged regarding the implications of BFG on breast cancer, highlighting the need to understand the relationship between these two entities.

At the core of this issue lies the interplay between adipose-derived stem cells (ADSCs) in the transplanted fat and the breast tissue microenvironment. ADSCs have raised questions about their potential role in breast cancer promotion. Although renowned for their regenerative potential, ADSCs can also influence cellular behavior and even modulate tumor growth. The relationship between BFG and breast cancer is complex, encompassing both clinical and laboratory research. This systematic review explores the intricate mechanisms by which ADSCs could impact breast cancer development, growth, and metastasis, delving into the latest scientific findings and ongoing research in this domain. We present this article in accordance with the PRISMA reporting checklist (available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-23-54/rc).

Highlight box

Key findings
- This study confirms the safety and efficacy of autologous fat transfer in breast surgery.
- The study highlights adipose-derived stem cells (ADSCs) potential dual role in influencing breast cancer behaviors.

What is known and what is new?
- There are concerns about ADSCs regenerative properties and potential role in cancer promotion.
- We meticulously curate and synthesize the latest scientific advancements, offering a comprehensive and up-to-date resource for current knowledge.

What is the implication, and what should change now?
- The notable potential advantages of ADSCs enriched fat grafts lie in their ability to enhance graft retention and survival rates. This has the potential to revolutionize breast reconstruction options and introduce innovative therapeutic strategies aimed at improving overall patient outcomes.

Methods

Study design

This article presents a systematic literature review of published studies and scientific literature on fat grafting, ADSCs, and their association with breast cancer. The review encompasses studies conducted across multiple geographic regions and various publication dates until the knowledge cutoff date of November 1, 2023.

Search strategy

A systematic search of electronic databases, including PubMed, Embase, and Biblioteca Virtual em Saúde (BVS) was conducted to identify relevant studies. The search strategy employed a combination of keywords, including "breast augmentation", "fat grafting", "breast enhancement", "mammoplasty", "cancer", "neoplasm" and related terms.

Study selection

Two reviewers independently screened titles and abstracts. Full-text articles were then retrieved for further evaluation based on their potential contribution to the review objectives. Studies were included if they reported using fat grafting for breast augmentation, presented clinical outcomes, or provided relevant information on mechanisms, complications, and safety, regarding ADSCs and breast cancer. Literature reviews and case reports, as well as reports related to other malignancies, were excluded. Reviewers were unaware of each other's decisions. Discordances were solved through discussion and further agreement between reviewers. Rayyan software was utilized to ensure blinding and to ease the inclusion process, especially for screening titles and abstracts.

Data extraction and synthesis

Data from the included studies was extracted using a standardized form for each reviewer. Information extracted included author, publication year, study design, sample size, patient demographics, outcomes assessed, and key findings. The extracted data was then narratively synthesized, with the focus on summarizing the key findings and common themes across the studies.

Data analysis

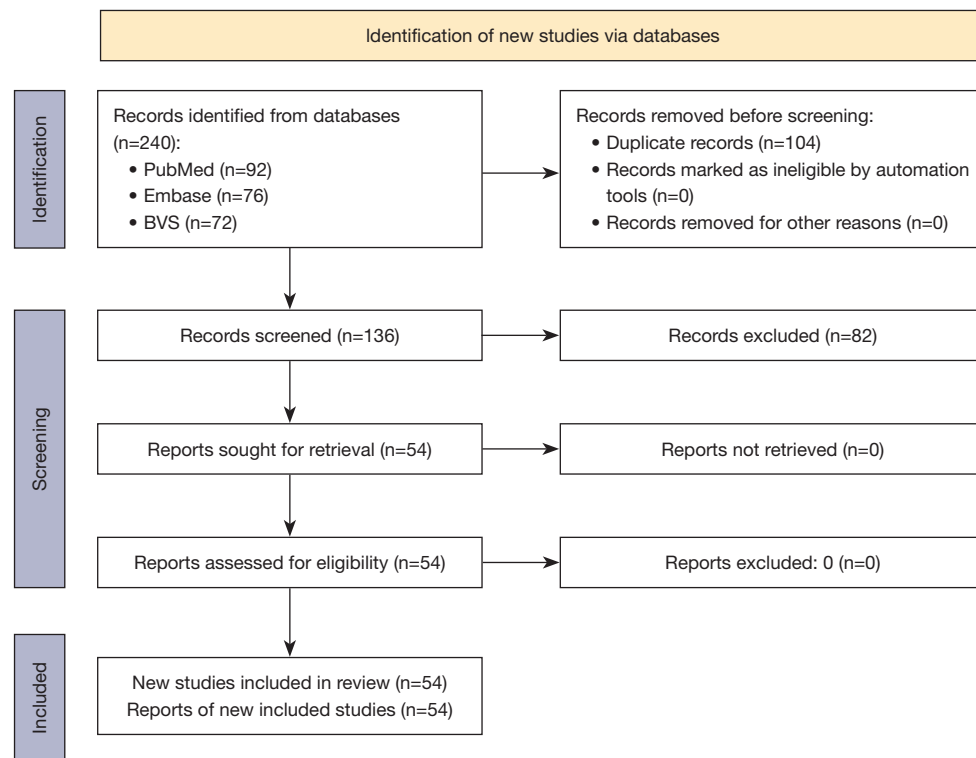Given the nature of this systematic review as a literature

Figure 1 Study selection workflow. BVS, Biblioteca Virtual em Saúde.

synthesis, it is essential to note that no formal statistical analysis, such as a meta-analysis, was conducted. The suitability and feasibility of meta-analyses rely on the availability of data from studies with comparable methodologies and outcome measures. As the included studies exhibited heterogeneity, both in design and objectives, a qualitative analysis approach was adopted. This involved the qualitative synthesis of findings to offer a comprehensive overview of breast augmentation through fat grafting.

Results

Following the search process, 240 records were identified. Among these, 104 duplicates were removed, resulting in 136 reports available for title and abstract screening. Subsequently, 54 papers were deemed potentially eligible for inclusion, and all reports were retrieved. The inclusion workflow is summarized in *Figure 1*.

Discussion

This section is delineated into three distinct sections, each

addressing a specific facet of the research inquiry. The inaugural segment meticulously examines *in vitro* studies, scrutinizing outcomes derived from controlled laboratory settings to elucidate nuanced aspects of the investigated subject. Following this, the subsequent section encapsulates experimental studies, which entail controlled experiments designed to simulate real-world conditions and thereby contribute meaningful insights. The conclusive portion of this study concentrates on clinical studies, presenting empirical observations and outcomes garnered from research conducted in human subjects. This strategic organization ensures a systematic and comprehensive exploration of the research topic, spanning foundational laboratory investigations to the pragmatic applications witnessed in real-world clinical scenarios.

In vitro

In 26 studies, outcomes pertaining to the connection between ADSCs and breast cancer cell lines were examined. It is crucial to highlight the distinctions in adipocytes between the breast and other areas, given that the majority of studies gather fat from the abdomen. ADSCs collected

from breast and abdomen have similar marker expression and differentiation potential. However, breast ADSCs presented higher self-renewal ability and a more unstable doubling compared with abdominal ADSCs (1).

The role of ADSCs in breast cancer progression *in vitro* is intricate and remains a subject of controversy in ongoing research. Co-culture of ADSCs and MCF-7 significantly increased MCF-7 migration rates, while the addition of a blocking anti-tenascin-C antibody in the medium didn't affect the migration rate (2). Furthermore, when compared to a fat-only medium, the ADSC medium demonstrated an elevation in cancer cell proliferation, migration, and the transcription of arginase-1, transforming growth factor-β, and vascular endothelial growth factor (3). In a separate experiment involving MCF-7, the presence of ADSCs exosomes notably amplified breast cancer cell proliferation (4). MDA cell line viability increased to almost 100% in ADSCs presence *in vitro* (5). ADSCs also increased migration in MDA-MB-231 co-cultures (6). Notably, when breast cancer cells collected *in vivo* were co-cultured with ADSCs obtained from the same patient, migration was nearly ten times higher (7). Co-culture of cell line T47D (inflammatory breast carcinoma), also found higher levels of transcriptional genes for typical malignancy markers (8). BT-474 co-culture also increased proliferation, with TNF-alpha upregulation (9). Natural tropism of ADSCs towards breast cancer cells has been evaluated after independent cultures were done in silicon chambers, then chambers were removed and ADSCs tropism was confirmed, thus indicating attraction of ADSCs to malignant breast cells (10).

The presence of adipocyte exosomes was observed to reduce early apoptotic cells in 5-fluorouracil-treated MCF-7, suggesting that ADSCs play a protective role against chemotherapeutic drug-induced apoptosis (4). This is reinforced by the identification of an increased tumorigenesis pathway and transformation gene expression in co-cultures of ADSCs with both MCF-7 and BT-474 (HER-2⁺ model) after 48 hours, with BT-474 co-culture showing downregulation after 96 hours (11). When *ex-vivo* breast cancer cells were co-cultured with ADSCs-enriched medium and tamoxifen, tamoxifen treatment simultaneously reduced the differentiation of ADSCs into adipogenic and osteogenic cells, while also inhibiting their proliferation in a dose-dependent manner (12). While these findings contradict the results of a study by Boemi *et al.*, which compared ADSCs from women with breast cancer who were taking tamoxifen to ADSCs from menopausal women, suggesting that tamoxifen (20 mg/day)

had no effect on ADSC apoptosis compared to the control group (13). MDA-MB-231 and ADSCs underwent treatment with paclitaxel (1.0 μM) or low-dose paclitaxel (0.1 μM) in combination with a histone deacetylase inhibitor, providing additional insights into the interaction between ADSCs and chemotherapy. The combined therapy induced cytotoxicity in MDA-MB-231 while preserving the viability of ADSCs, suggesting that a synergistic approach may enhance treatment outcomes (14). Furthermore, in the presence of doxorubicin, ADSCs' differentiation remained unaffected, highlighting the stronger affinity of doxorubicin and paclitaxel for BT-474 and MDA-MB-231 compared to ADSCs (15). These results emphasize the prospective application of chemotherapeutic fat grafts in the realm of breast reconstruction. Consistent with these observations, experimental data illustrated that ADSCs exhibit the capacity to uptake paclitaxel and subsequently release it, thereby furnishing supplementary substantiation for the aforementioned hypothesis (16).

In contrast, ADSCs were observed to stimulate both cell proliferation and cell apoptosis in MCF-7 and MDA-MB-231 models. This effect was attributed to the up-regulation of ATF4, a transcription factor known to induce cell apoptosis by disrupting translational processes (17). Further mechanisms were studied by Ejaz *et al.*, in which ADSCs inhibited MCF-7 proliferation in contact co-culture, by cell cycle arrest mediated by the retinoblastoma protein, as well as MDA-MB-231 proliferation (18). The conditioned medium derived from ADSCs exhibited suppressive effects on the proliferation and viability of MCF-7, MDA-MB231, and MDA-MB468 breast cancer cell lines. This suppression was accompanied by the activation of ATM-Chk2 signaling cascades specifically in malignant cell lines, such as MCF-7 and MDA-MB231, but not in non-cancerous M10/H184B5F5 cells. These findings imply distinct responses to ADSC-derived conditioned medium between cancerous and non-cancerous breast cells (19). The triggering of MEK-ERK pathway in breast cancer cells co-culture with ADSCs was also indicated through nuclear CBP recruitment which later upregulates human telomerase reverse transcriptase transcription and telomerase activity (20). In another indirect co-culture of ADSCs and MDA-MB-231, and direct co-culture demonstrated no growth effect on breast cancer cell lines, but stimulated migration (21). In metastatic pleural effusion cell lines, ADSCs culture increased 5-fold its proliferation, suggesting metastatic behavior, later, an experiment with active and dormant cells was conducted, with ADSC enhancing

growth of only active, not dormant cells (22). Additionally, it was observed that ADSCs did not possess the capability to induce the transformation of normal breast cells into a malignant phenotype. However, they demonstrated the ability to establish a susceptible microenvironment by inducing c-Met expression, a phenomenon validated through pharmacological inhibition (23). Therefore, AFT should be avoided until disease has been fully eliminated.

Animal models

Three papers exclusively focused on animal models, although certain *in vitro* studies also incorporated experimentation with these models. One study found ADSCs with low expression of CD90 (CD90low ADSCs) to significantly inhibit tumor progression compared to CD90 high ADSCs or fibroblasts (24). Tumor volume and mass were reduced with CD90low ADSC treatment versus other groups. Additional experiments explored the tumor-modulating effects of extracellular vesicles (EVs) derived from different ADSC subtypes. CD90low ADSC-derived EVs were significantly smaller in diameter than CD90 high ADSC-EVs. CD90low ADSC-EVs more potently suppressed breast cancer cell proliferation, migration, and induced apoptosis *in vitro* compared to CD90 high ADSC-EVs. The pro-apoptotic microRNA miR-16-5p was more abundant in CD90low ADSC-EVs and contributed to their enhanced anti-tumor activity.

Jin *et al.* and Millet *et al.* examined the impact of fat graft enrichment with ADSCs prior to transplantation in a mouse breast tumor model (25,26). Although the estimated tumor weight was similar between all groups, tumors in the highly enriched fat graft group exhibited significantly greater mass than those in other cohorts. In addition, the injection of ADSCs into the tumor site resulted in increased primary tumor growth and lung metastasis compared to the control group, as well as the fat graft and cell-assisted lipotransfer groups (3). Metastatic disease and tumor weight was also higher in an MDA-MB-231 and MCF-7 model in rats with ADSCs-high enhancement, with MDA-MB-231 being more aggressive (5). Higher vascular density was identified, as well as greater tumor growth, in tumors injected with ADSCs-enriched AFT, but not in AFT only models in Orbay *et al.* work (6). Proliferation marker Ki-67 staining indicated no difference in tumor cell proliferation between groups. Together these findings suggest ADSC enrichment of fat grafts may promote local tumor growth in animal models.

Paino *et al.* studied the inverse relationship between MCF-7 cancer cells and ADSCs, co-injecting MCF-7 cells and ADSCs in mice, with ADSCs integrating into the tumor, developing faster and bigger tumors than MCF-7 only cancer (27). Consistently, Rowan *et al.* did a similar experiment with MDA-MB-231 with human ADSCs that stimulated MDA-MB-231 multiple metastasis and increased angiogenesis (21). But when xenografts of CG5 tumor xenografts were injected with ADSCs enriched with paclitaxel (4 μM), tumor size was about 50% of controls, but lower doses (2 μM) rather increased xenograft growth (16). An interesting study involving the injection of ADSCs in a manner that encircled the tumor, leading to a reduction in growth and eventual disappearance within a span of 3 to 8 weeks. Remarkably, sustained complete recovery was observed and maintained for a minimum of 6 months throughout the study duration (28).

In summary, the animal studies collectively illustrate that various ADSCs subpopulations exert diverse regulatory influences on breast cancer progression. These effects are attributed to both direct interactions between tumors and ADSCs, as well as the secretion of EV cargo, particularly miR-16-5p, which exhibits antitumor functions. Further mechanistic investigations are essential to comprehensively understand the underlying pathways and mechanisms governing these observed effects.

In vivo

We've found 25 *in-vivo* studies in our search (detailed in *Table 1*). A retrospective case control study, elaborated on the recurrence risk in breast cancer after lipofilling, which included 412 women: 109 (26.5%) in the lipofilling group and 303 women in non-lipograft. In their study, lipofilling wasn't a predictive factor for recurrence, for overall survival or for distance metastasis. Although women treated for invasive cancer presented an independent predictive factor for local recurrence [$P<0.05$, hazard ration (HR): 5.06 (1.97–10.6)] (29). A further retrospective cohort study, involving the examination of 93 women who had undergone autologous fat grafting (AFG) following breast cancer treatment, revealed no discernible difference in tumor recurrence or distant metastases. Notably, a high degree of patient satisfaction was maintained throughout the study (34). Similarly, patients who underwent mastectomy with immediate breast reconstruction involving AFT subsequent to an incidental diagnosis of invasive ductal carcinoma did

Table 1 *In vivo* detailed studies assessment

Author, year	Design	Sample	Outcomes	Key findings
Berti, 2022, (29)	Retrospective, monocentric, case-control study	412 women, with 109 (26.5%) in the lipofilling group and 303 in the non-lipofilling group	In the overall study population, lipofilling did not show predictive significance for recurrence (HR =1.39, P=0.41), overall survival (HR =0.84, P=0.79), or distant metastases (HR =1.10, P=0.84)	In women treated for invasive cancer, the multivariate analysis indicated that lipofilling was an independent predictive factor for local recurrence (HR =5.06, P=0.04)
Mazur, 2018, (30)	The study investigated tumor recurrence in patients with autologous ADSC breast reconstruction *vs.* those without reconstruction over a 3-year observation period	56 reconstructed + SVF AFG *vs.* 252 without subsequent reconstruction	Cancer recurrence in patients treated with ASC-enriched fat for breast reconstruction was 3.7%, comparable to the control group (4.13%), with no observed adverse effects of therapy	Suggests safety of using ASC-enriched fat for breast reconstruction in terms of cancer recurrence
Toyserkani, 2017, (31)	Open-label, single-arm, single-center feasibility and safety study in patients with breast cancer-related lymphedema of the upper extremity	11 patients	Arm heaviness reduced from a baseline median score of 5.5 to 2.5 after 6 months (P=0.0030). Arm tension decreased from a baseline median of 5.0 to 2.5 after 6 months (P=0.0097). DASH score improved from 21.3 at baseline to 12.9 after 6 months (P=0.0168)	Autologous ADRC with scar-releasing fat graft proved safe over 6 months, effectively alleviating breast cancer-related lymphedema symptoms and reducing the need for conservative treatment
Myckatyn. 2017, (32)	Mastectomy with immediate breast reconstruction between 2006 and 2011, age older than 21 years, female sex, and incident diagnosis of invasive ductal carcinoma (stage I, II, or III)	n=1,197, consisted of all recurrences during the study period (n=225) and a 30% random sample of the study population (n=972)	The HR for disease recurrence with fat transfer was 0.99 (95% CI: 0.56–1.7), and after adjustment, it remained at 0.97 (95% CI: 0.54–1.8)	In breast cancer patients who had mastectomy with immediate reconstruction, no association with a higher risk of cancer recurrence
Vester-Glowinski, 2022, (33)	Double-blind, randomized controlled trial of breast augmentation with ASC-enriched fat grafting	20 women	After 1 year, ADSC-enriched fat grafts (54.0%, 95% CI: 30.4–77.6%) and placebo-enriched fat grafts (55.9%, 95% CI: 28.9–82.9%) demonstrated comparable volume retention in breasts (P=0.566, n=10 each)	Both groups had similar volume retention
Kempa, 2022, (34)	Monocentric cohort from all consecutive patients who underwent AFG after breast cancer from 2008 to 2020	93 women	The study showed low rates of local recurrence (1.1%), distant metastases (2.2%), and tumor-related death (1.1%), with 67.12% of patients expressing satisfaction with autologous fat grafting	Study aligns with the literature, showing a consistent low incidence of tumor recurrence and metastasis following AFG use
Calabrese, 2018, (35)	Long-term cancer recurrence risk of SVF + AFT compared to AFT, after nipple sparing mastectomy	41 women G1 (SVF + AFT), 64 G2 (AFT), and 64 G3 (control group)	Loco-regional recurrence rates were 2.4%, 4.7%, and 1.6% for G1, G2, and G3, while systemic recurrence rates were 7.3%, 3.1%, and 3.1%, respectively	No significant risk factors for loco-regional or systemic recurrence were identified among the variables, including SVF + AFT (G1) which showed no increase in oncological recurrence
Ito, 2017, (36)	Female breast cancer patients who underwent breast-conserving surgery and adjuvant radiotherapy. They received an autologous fat graft enriched with ADRC during adipose tissue harvest	n=10	Operation time: 188±30 min. Hospitalization: 1.2±0.4 days. No complications. No recurrence/metastasis in 7.8±1.5 years post-transplantation	ADRC-enriched autologous fat transplantation is safe without long-term recurrence and, a viable option for breast reconstruction, even following adjuvant radiotherapy
Kølle, 2013, (37)	Randomized, controlled, data assessor-blinded clinical trial. Participants undergoing breast augmentation. Intervention group: ASC-enriched fat grafts. Control group: conventional nonenriched fat grafts	n=16, 8 each group	ASC-enriched fat grafts demonstrated significantly higher retention rates (mean =80.2%) compared to conventional fat grafts (mean =45.1%). Clinical photos showed statistically superior results in the intervention group, as assessed by independent clinical experts	Potential use of ADSCs for both reconstructive and cosmetic volume restoration, presenting an attractive alternative to conventional fat grafting and implants
Gentile, 2013, (38)	Comparison of fat grafting with PRP to a control group using only centrifuged fat grafting	50 patients treated with fat grafting + PRP and a control group of 50 patients treated with centrifuged fat grafting	Patients treated with PRP added to autologous fat grafts showed a 69% maintenance of contour restoration and 3-dimensional volume after 1 year. The control group treated with centrifuged fat grafting showed a 39% maintenance	PRP + fat grafting leads to a significant improvement in maintaining breast volume in patients with breast soft-tissue defects compared to centrifuged fat grafting alone
Chiu, 2019, (39)	SVF-enriched fat grafting *vs.* conventional fat grafting	105 patients controls; 101 SVF-AFG	Survival rate of transplanted fat at 12 months: 67.9% in group A, 68.7% in group B. Postoperative complication rate: 3.8% in group A, 5.9% in group B. Statistically insignificant differences observed between the two groups	Study does not support the use of SVF in autologous fat grafting for breast augmentation
Hu, 2022, (40)	Breast augmentation with autologous fat transplantation alone compared to cell-assisted autologous fat transplantation, randomized	n=34, 17 each	The observation group had higher CC, SN-N, and N-MF, a statistically significant higher uplift value after surgery and MRI revealed greater postoperative fat retention compared to the control group	Suggested superiority of cell-assisted AFG compared to AFG alone
Salgarello, 2011, (41)	10% PRP + AFG *vs.* Coleman fat grafting	17 patients (40%) received fat enriched with 10% PRP (group A), while 25 patients (60%) received only Coleman fat grafts (group B)	10% PRP was not superior to Coleman fat grafting alone	The retrospective analysis does not show effect of 10% PRP on fat graft take compared to Coleman fat grafting
Kronowitz, 2016, (42)	Mastectomy for breast cancer or risk reduction and subsequent breast reconstruction with or without lipofilling	719 breasts for lipofilling group, 305 risk reduction, and 670 no-lipofilling	Locoregional recurrence rates at 5 years were 1.6% for cases (lipofilling) and 4.1% for controls (no lipofilling). Systemic recurrence rates were 2.4% for cases and 3.6% for controls	Supports the oncologic safety of lipofilling in breast reconstruction, as there was no increase in locoregional recurrence, systemic recurrence, or second breast cancer
Tukiama, 2021, (43)	Retrospective matched cohort. 1:3	42 patients treated for breast cancer who underwent AFG *vs.* control: 126 patients without AFG	Locoregional recurrence (7.1% *vs.* 6.3%; P=0.856). Local recurrence (7.1% *vs.* 5.6%; P=0.705). Distant recurrence (14.3% *vs.* 7.9%; P=0.238). Disease-free survival (21.4% *vs.* 19.0%; P=0.837). Overall survival (14.3% *vs.* 7.1%; P=0.181)	No evidence of increased risk in any of the survival outcomes, suggesting that lipofilling is a safe procedure for breast reconstruction after surgical treatment of breast cancer

Table 1 (*continued*)

Table 1 (*continued*)

Author, year	Design	Sample	Outcomes	Key findings
Juhl, 2018, (44)	Prospective, AFG reconstruction after breast conserving surgery	42 patients undergoing 1–3 AFG procedures	Calcifications: 21%; oil cysts: 85%; increased scarring: 3%	Considerable radiologic breast imaging changes induced by AFG after breast conserving surgery
Serra-Mestre, 2017, (45)	Fat grafting to reduce asymmetry in breast reconstruction, mastopexy, and augmentation	86 patients	Statistically significant reduction in mean intermammary distance. One capsular contracture in a breast reconstruction requiring capsulotomy and an oil cyst requiring aspiration	Safe remodeling of the medial cleavage of the breast
Kaoutzanis, 2016, (46)	Consecutive postmastectomy AFG	108 women with a total of 167 breast reconstructions	AFG + breast reconstruction resulted in a biopsy rate of 4.8%	Suggests AFG is a relatively safe procedure for refinement of the reconstructed breast in postmastectomy patients
			No cases of locoregional cancer recurrence	
			Suspicious imaging findings requiring biopsy showed fat necrosis, scar, or oil cysts without evidence of malignancy	
Gale, 2015, (47)	Case-controlled AFG in women with breast cancer history	211 participants (invasive carcinoma, n=184; ductal carcinoma *in situ*, n=27). Control subjects: matched 2:1	Local recurrence: 0.95% *vs.* 1.90% (P=0.33)	No evidence of increased oncologic risk associated with fat grafting in women previously treated for breast cancer
			Regional recurrence: 0.95% *vs.* 0% (P=0.16)	
			Distant recurrence: 3.32% *vs.* 2.61% (P=0.65)	
Klinger, 2022, (48)	Differences in LRR and LRFS were assessed between patients who underwent AFG and those who did not	n=6,592	LRR was 5.3% in the matched population, 3.9% in the AFG group, and 6.1% in the non-AFG group, suggesting non-inferiority of AFG (P=0.084)	Autologous fat grafting does not negatively interfere with cancer prognosis
			Kaplan-Meier curves confirmed non-inferiority of the AFG procedure for LRFS (aHR =0.73, 95% CI: 0.41–1.30, P=0.291)	
			Similar effects in terms of LRFS were observed among different biological subtypes (luminal-like group, HER-2 enriched-like, and TNBC)	
Yoshimura, 2008, (49)	SVF-AFG for breast augmentation	n=40	Postoperative atrophy of injected fat was minimal and remained stable after 2 months. Cyst formation or microcalcification was detected in four patients	Effective and safe for soft tissue augmentation and may outperform conventional lipoinjection
			Almost all patients reported satisfaction with the soft and natural-appearing augmentation	
Wang, 2015, (50)	SVF-AFG for breast augmentation	n=12	Fat Resorption was 51.84% (16.74%) at 6 months postoperatively	Little complications using SVF + AFG for breast augmentation
			Newly formed cysts and nodules in two cases; no calcification in MRI	
Shin, 2023, (51)	SVF-AFG for breast augmentation	n=384	Higher SVF cell number associated with greater retention volume. Greater retention volume in patients with soft breasts	Limiting arm movement, increasing SVF cell count, and improving skin tension may enhance retention rates
			Right breast retention rate (60.35%) lower than left breast (77.48%) at 18 months	
Jeon, 2021, (52)	SVF-AFG *vs.* AFG for correcting contour deformities of reconstructed breasts	n=20, 10 each group	Fat graft retention rate: Group 1 *vs.* Group 2 at 6 months: 73.8% *vs.* 62.2% (P=0.03); Group 1 *vs.* Group 2 at 12 months: 65.4% *vs.* 48.4% (P=0.03)	SVF is effective in increasing survival rates of autologous fat grafts for correcting volume deficit after breast reconstruction
			Group 1 showed higher satisfaction	
			Fat necrosis occurred in 1 patient in each group	
			No locoregional recurrence during follow-up	
Pérez-Cano, 2012, (53)	ADSC-AFG for breast conservation therapy contour defects correction	n=71	No serious adverse events associated with the ADRC-enriched fat graft injection procedure	Suggests safety and efficacy ADSC-AFG for breast conservative therapy contour defects
			No reported local cancer recurrences. Injection site cysts reported in ten patients	

HR, hazard ratio; ADSC, adipose-derived stem cell; SVF, stromal vascular fraction; AFG, autologous fat grafting; ASC, adipose-derived stromal cell; DASH, Disabilities of the Arm, Shoulder and Hand; ADRC, adipose-derived regenerative cells; CI, confidence interval; AFT, autologous fat transfer; PRP, platelet-rich plasma; CC, chest circumference; SN-N, sternal notch-nipple distance; N-MF, distance between nipple and inframammary fold; MRI, magnetic resonance imaging; LRR, locoregional recurrence rate; LRFS, locoregional recurrence-free survival; aHR, adjusted hazard ratio; TNBC, triple-negative breast cancer.

not exhibit higher rates of recurrence (32).

Calabrese *et al.* evaluated risk factors in long-term cancer recurrence risk in stromal vascular fraction (SVF), which is mainly composed of ADSCs, + AFT cases, AFT-only and control after nipple sparing mastectomy. In their analysis, comparable rates of loco-regional and systemic recurrences were observed between groups, with no distinction based on factors such as technique, age over 50 years, lympho-vascular invasion, oncological stage, adjuvant or neoadjuvant chemotherapy, adjuvant radiotherapy, and adjuvant hormone therapy, which were not deemed independent risk factors (35). Thus, sustaining a medium enriched with ADSCs exhibited no discernible difference in oncological recurrence. Likewise, the occurrence of cancer recurrence in ADSCs-enriched fat utilized for breast reconstruction did not exhibit statistical variation compared to patients without breast reconstruction over a follow-up period of 3 years (30). This aligns with data obtained from ten patients who underwent an ADSCs-enriched graft following breast-conserving surgery and adjuvant radiotherapy, with a mean follow-up duration of 7 years (36). In this sense, AFG is known as not being an independent risk factor for breast cancer local recurrence as shown in matched research (42,43,47). In contrast, there may be a time-dependent association, which non-enriched AFG done before 12 postoperative months was linked to local recurrence, but AFG after 12 months was not (54). However, a great Italian multi-center study with more than 6,500 patients confirmed no association between loco-recurrence and AFG, consistently (48). In enriched-AFG, multiple studies reject the loco-regional recurrence association, therefore supporting oncological safety.

The main advantage of ADSC-enriched fat for AFT lies in its inherent properties that enhance the survivability and integration of transplanted fat. This results in a superior retention of the graft, surpassing the retention achieved with AFT alone (55). In the context of this review, many papers provided information on graft survival rates, revealing minimal differences between enhanced and conventional AFT methods (33). AFG volume retention on soft tissue seems to be influenced by many factors, such as menstrual cycle phase, operation stage, lactation history, and certainly, enhancement with ADSCs improves considerably the retention rate (56-58). Kølle *et al.* (37) conducted a randomized clinical trial, comparing ADSCs to non-enhanced AFG, with surprising results. In their research, enhanced AFG showed a substantially higher retention rate (80.2%) compared to conventional fat grafts

(45.1%). Similarly, Xiong *et al.* presented that ADSCs and platelet-rich plasma (PRP)-enhanced AFG had higher retention rates compared to controls, even though there was no difference at 12 weeks in nude mice (59). Notably, Gentile *et al.* (38) showed that PRP-enhanced autologous fat grafts maintained 69% contour restoration and volume after 1 year, outperforming the control group with centrifuged fat grafts at 39% in breast reconstruction scenario. In contrast to this, its role in breast augmentation looks blurred, with contrasting results between ADSC enriched medium compared to control, from higher fat retention in cell-assisted AFG to dubious results. Despite the highly supportive evidence, low sample sizes research presenting no difference between AFG and enriched AFG exists (33,41). Therefore, results should be interpreted cautiously. In this context, Karam *et al.* conducted a meta-analysis comparing fat retention and necrosis, revealing a notable difference favoring ADSCs-enriched fat in terms of retention, however, no significant difference was observed in relation to necrosis (60).

Non-enhanced AFG after breast conserving surgery presented significant changes in radiological image, with 2 out of 10 developing calcifications, and 85% affected by oil cysts (44). Although highly present, these are benign changes, and when suspicious, had low biopsy rate and intervention needed (46). Similarly, SVF-AFG presented a small formation of 10% of oil cysts, while maintaining fat retention. Again, there was minimal formation of cysts, and no cases of fat necrosis. Jeon *et al.* (52) also found low rates of complications with SVF + AFG, with similar fat necrosis occurrence rates between SVF-AFG and AFG only, supporting procedure safety.

Enhancement fat grafting does not limit its use, as it can show prominent results even in scleroderma patients, with twice soft tissue after 6 months compared to control (61). Another successful trial used SVF in face lipotransfer, with significantly less loss of volume and higher grades by plastic surgeons. Notably, volume retention is only one of the benefits, with SVF-AFG better skin quality enhancement and volume compared to controls (62). Improvements in FACE-Q scores were present (63). Despite complete SVF enhancement working, platelet-derived growth factor (PDGF) alone does not improve results (64). These incremental improvements surely represent an incredible gain in patient satisfaction and surgical experience. SVF cell amount seems to influence fat retention, as higher cell amount in SVF associates with better volume retention (50,51).

Moreover, Toyserkani *et al.* investigated the application of ADSCs-enriched fat for breast cancer-related lymphedema of the upper extremity, yielding positive results in alleviating arm heaviness, tension, and dash scores. The study also reported a 6-month safety profile (31).

Purified AFG methods differ greatly, although mechanical and enzymatic digestion are the main ones. Gentile *et al.* (65) found out that enzymatic digestion was the best, with higher ADSCs amount and fat volume maintenance, while filtration was the best amongst mechanical methods. In concordance, Wu *et al.* (66) compared mechanical methods, also suggesting filtration superiority. Hence, it is suggested that the surgeon's choice should consider its reality, but given preference to enzymatic digestion or filtration.

The external validity of this review is inherently constrained by the limited and variable number of included studies, posing challenges to the generalizability of findings to the broader population of women with breast cancer. The diverse quality of the studies further complicates the overall interpretation of results, necessitating caution in extrapolating conclusions to diverse clinical scenarios. The variations in study quality and heterogeneity across the included studies may impact the overall robustness of the evidence and its applicability to broader patient populations.

In conclusion, the *in-vivo* studies reviewed in this report offer valuable insights into the safety and efficacy of ADSC-enriched fat for breast cancer patients. The evidence suggests that ADSC-enriched fat grafting does not appear to increase the recurrence risk of cancer or distant metastases in breast cancer patients. Furthermore, it has been associated with high patient satisfaction, potential in breast reconstruction, and the capability to minimize cancer-related lymphedema of the upper extremity

The properties of ADSC-enriched fat, including its ability to enhance the survivability and integration of transplanted fat, appear to confer advantages over AFT-only retention. While this review has some limitations, further research is warranted to better comprehend the long-term effects and optimal applications of ADSC-enriched fat in breast cancer treatment, given the promising current findings. Continued investigation into its potential clinical benefits is imperative.

Conclusions

In-vitro investigations have elucidated the dual role of ADSCs in influencing breast cancer cell behaviors, manifesting both promotive and inhibitory effects on proliferation, migration, and drug resistance. This nuanced modulation is orchestrated through diverse secreted factors and signaling pathways. Expanding on these insights, animal studies have demonstrated that distinct subpopulations of ADSCs differentially impact tumor growth, employing mechanisms that involve both direct interactions and the effects of EV cargo.

In contrast to *in vitro* evidence, the limited yet noteworthy clinical reports from *in-vivo* studies suggest that ADSC-enriched fat grafting is generally considered a safe procedure. Comparative analyses with fat grafting alone or no reconstruction indicate no increased risk of breast cancer recurrence or metastasis. However, special attention is warranted for cases of invasive breast carcinoma, where a recurrence following AFT has been observed. ADSC-enriched fat grafts exhibit potential benefits in enhancing graft retention and survival rates.

Despite the promising current evidence, there remains a need for further studies to comprehensively unravel the intricate relationship between ADSCs and breast cancer. These endeavors aim to optimize the clinical applications of ADSC-enriched fat grafts, potentially revolutionizing breast reconstruction options and introducing novel therapeutic strategies to enhance overall patient outcomes.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-23-54/rc

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