Aesth Plast Surg (2016) 40:380–386
DOI 10.1007/s00266-016-0634-9

REVIEW BREAST

# Potential Safety Loophole of Fat Grafting in Breast Cancer Patients

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Received: 26 October 2015 / Accepted: 16 March 2016 / Published online: 12 April 2016


**Abstract** Autologous fat grafting (AFG) accounts for 9.1 % of all cosmetic surgical procedures in the world. Its use has been increasing tremendously in breast reconstruction and produces satisfying outcomes. However, the lack of standard guidelines for routine screening protocols in breast cancer patients before and after AFG warrants consideration of the safety of AFG use in post-mastectomy and post-lumpectomy reconstruction. This manuscript examines AFG in breast reconstruction publications and details the complications, the mechanism of AFG, as well as the relationship between adipose stem cells (ASCs) and cancer recurrence. The ASCs transferred in AFG act as multiple potent stem cells, which can impact cancer recurrence in various ways. Both in vitro and in vivo studies show that ASCs can stimulate the recurrence of breast cancer. Based on a review of existing evidence, we provide recommendations and guidelines for AFG use in breast reconstruction to aid in clinical decision-making. Further investigations are needed to evaluate the long-term clinical safety of AFG as well as the proposed guidelines. *No Level Assigned* This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266

**Keywords** AFG · Breast cancer · Recurrence

## Introduction

Since Gustav Adolf Neuber harvested several small pieces of adipose tissue from the arm to fill a soft depression caused by osteomyelitis in the face of a 20-year-old man in 1893 [1], autologous fat grafting (AFG) has been used for numerous reconstructive and cosmetic procedures. Today, AFG is popular around the world. According to International Society of Plastic Aesthetic Surgery, more than 23 million cosmetic procedures were carried out across the world in 2013. Of these, 1,053,890 were cases of lipostructure, including lipofilling and stem-enhanced lipofilling [2]. This number represents 9.1 % of all surgical procedures and ranks lipostructure fourth among the most frequently performed cosmetic surgical procedures globally [2]. AFG has been used in numerous areas [3–6], especially in breast surgeries, such as breast augmentation and breast reconstruction [7].

In recent years, AFG has become a vital part of breast reconstruction. With the advancement of breast reconstruction philosophies and techniques, breast cancer patients who have undergone mastectomy or breast-conserving surgery can now select from multiple choices for reconstruction with superior aesthetic outcomes [8]. For post-mastectomy patients, these options include prosthetic implants and autologous tissue reconstruction [9]. Fat grafting can generate better aesthetic outcomes because it is capable of filling the folds and reducing recurrent

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contracture caused by prosthetic implants or myocutaneous flap and implant. Furthermore, repeat injections can adjust the volume of the reconstructed breast to achieve greater symmetry [10]. Also, in patients who received breast-conserving surgery, AFG can fill defects caused by surgery and achieve better contour.

AFG produces such good aesthetic outcomes that plastic surgeons have tried to use greater quantities of fat in surgery, even for the entire reconstruction. With the help of Brava to create a well-vascularized mega volume recipient place, Khouri et al. [11] performed complete breast reconstruction using fat grafting of 100–400 ml (225 ml average) to breasts in 488 patients. Meanwhile, AFG has also proven useful in the treatment of post-mastectomy pain syndrome. Caviggoli et al. [12] assessed 113 patients who suffered from post-mastectomy pain syndrome using a visual analogue scale for pain. Patients who underwent fat grafting (n = 72) showed a noteworthy decrease in pain compared to those who did not.

Despite the growing popularity and increasing breadth of application, long-term safety outcomes of AFG among breast cancer patients have never been rigorously evaluated. Screening guidelines for breast cancer patients pre- or post-AFG are nonexistent. Furthermore, both in vitro and in vivo results suggest that AFG may stimulate cancer recurrence. In this paper, we review the clinical outcomes and complications of AFG as well as basic science research and the role of adipose tissue stem cells, and offer a set of recommendations that can be used to improve the safety of AFG for breast cancer patients.

## Clinical Oncological Outcomes of Autologous Fat Grafting

In consideration of complications from AFG and the possibility that the graft might stimulate the occurrence or recurrence of breast cancer, the American Society of Plastic Surgeons prohibited this procedure in 1987 [13]. Although the ban was overturned due to lack of evidence in 2009, some plastic surgeons remain concerned about the safety of AFG and many studies have shown recurrence after injection [14, 15].

Petit et al. [16] performed a matched cohort study of patients involving 321 who received AFG after mastectomy or breast-conserving surgery and 642 controls who did not have AFG. There was not a significant difference between patients treated with AFG and those without AFG treatment, except that patients with intraepithelial neoplasia showed a higher rate of recurrence. In a second study of 59 intraepithelial neoplasia patients and corresponding control subjects, the 5-year cumulative incidence of local events for the AFG group was 18 % compared to 3 % among controls [17]. The authors concluded that ductal- or lobular-intraepithelial neoplasia cells connect with surrounding adipocytes more readily than invasive breast cancer cells because they have fewer genetic lesions. Thus, certain types of breast cancer may be more likely than others to recur after lipofilling.

Current clinical evidence for recurrence rate after AFG is inconclusive. Riaz et al. [18] completed a systematic review of oncological outcomes of breast cancer patients following AFG. Only six articles with a mean follow-up time of 27.4 months met the authors' criteria for quality of evidence. They showed a mean recurrence rate of 5.3 %, compared to 4.7 % among controls ($p = 0.10$). This difference was not statistically significant [18]. Although existing clinical evidence does not show significant associations between AFG and cancer recurrence, these clinical trials are limited by short follow-up time, biases, and weak methodology [13, 18]. To get a more definitive recurrence rate, longer follow-up and more meticulous experimental design are needed. Current clinical evidence is incomplete regarding the safety of AFG in terms of cancer recurrence. Therefore, it is necessary to understand the mechanism of AFG and analyze the potential impact of every step of it on cancer recurrence.

## In Vitro and in Vivo Studies of Autologous Fat Grafting

Breast cancer recurrence is closely related with peritumoral adipocytes. These adipocytes are involved not only in early cancer cell survival but also in cancer infiltration into surrounding adipocyte tissue [19]. This biological process is found through the paracrine pathway [20]. Celis et al. [21] found 359 proteins participated in this activity, including signaling molecules, hormones, cytokines, and growth factors. Meanwhile, grafted fat can cause hypoxia in the recipient place and induce expression of HIF-1α [22], which offers a tumor-permissive place. In addition, tumor cells can change surrounding extensive phenotypic of adipocytes. The new adipocytes, also called "cancer-associated adipocytes" (CAA), may increase the invasive capacity of tumor by overexpressing IL-6 [23]. CAA is also a fuel resource for tumor recurrence [24]. Lohsiriwat et al. [25] found that by endocrine, paracrine, and autocrine pathways, adipokines, such as Stromelysin-3, matrix metalloproteinase, and collagen VI, can stimulate breast cancer cells. The authors postulate that recurrence is induced by a "tumor-stroma interaction." In white adipose tissue, endothelial progenitors and pericyte progenitors together can increase breast cancer angiogenesis, development, and metastasis [26]. Considering the synergistic effect between tumor cell and peritumoral fat tissue as above, tumor would

have a higher recurrence rate when it is fully surrounded by fat.

Besides adipocytes, the surgery itself may also increase risks of recurrence. Placement of fat is considered as trauma to the breast. It requires inserting and advancing of the cannula repeatedly, as for a single pass, it is recommended that no more than 0.10 milliliters be placed [27]. Without a doubt, wound healing follows this trauma, which has proven to be important in breast cancer. Rigby et al. [28] recruited 67 women diagnosed with invasive breast carcinoma and 134 matched controls. Compared to the control group, breast cancer patients had 3.3-fold increase of trauma, such as falling and injuring the chest, prior to cancer diagnosis. The precise mechanism is unclear, but abundant evidence suggests that trauma and wound healing are involved in the development of breast cancer [29]. Segatto [30] and her team used wound fluids from breast cancer patient after surgery to culture breast cancer cells. The mammosphere forming efficiency was higher than the control group, indicating that wound fluid could stimulate self-renewal and stem cell-like phenotypes of breast cancer cells. Wound fluid also strongly activated STAT3, which participates in breast cancer cell proliferation and is essential for the progression of breast cancer initial cells.

## Adipose Stem Cell Use and the Recurrence of Breast Cancer

The safety of using Adipose-derived Mesenchymal Stem Cells (ASCs) in women who had breast cancer and received surgery raises concern. In recent years, many physicians prefer purifying and adding ASC into grafted fat to decrease the absorption rate [31]. This is also called cell-assisted lipotransfer (CAL). To get ASC, the first step is to digest adipose tissue from lipoaspirate by collagenase to get the stromal vascular fraction (SVF). Then ASCs are available after cell sorting or adherent culture of SVF [32]. A prospective clinical trial, RESTORE-2, was performed to evaluate cancer recurrence after CAL [33]. Sixty-seven patients who underwent breast conservation therapy received Adipose-Derived Regenerative Cell enriched fat grafting and were followed for 12 months without local cancer recurrence. However, because the follow-up time was relatively short, the study cannot definitively conclude that ASC grafting is safe for women who had breast cancer. Many in vitro experiments suggest that ASC and recurrence may be linked. Co-culturing of ASCs and cells from an inflammatory breast carcinoma line produced a tumorsphere structure, and the vesicles of the two types of cells were found in fusion, indicating cell–cell communication [34]. Moreover, cytokines suggestive of a more malignant breast cancer type were expressed at higher levels in the mixed culture. This research demonstrates that ASCs from fat transplantation may promote some specific types of breast cancer recurrence [34]. In mice, ASCs have also been shown to stimulate metastasis of MDA-MB-231 breast tumor xenografts. This process may occur via epithelial–mesenchymal transition [35].

Recent studies have found evidence that ASCs and tumor cells undergo mutual stimulation through a complex signaling network. By the HGF/c-Met pathway, ASCs can induce cancer cells to develop more invasive capabilities such as increasing growth rate and self-renewal ability [36]. ASCs also secrete interleukin 6 (IL-6), which motivates migration and invasion [37]. When Cofilin-1 was knocked-down, IL-6 dropped dramatically and the activity of ASC was lower, indicating that Cofilin-1 may mediate the expression of IL-6 in ASC. ASCs also appear to increase the amount of cancer stem cells [38]. The normal ability of adipogenesis of ASCs is reduced in tumor-conditioned media, which induces ASCs to differentiate into myofibroblast by cytokines, such as TGF-β, interleukin-8 (IL-8), and VEGF [39]. GRO-α and IL-8 in tumor condition media also recruit ASCs to surrounding tumor cells [40]. After treatment with ASC condition media, the percentage of $CD44^{high}/CD24^{low}$ cancer stem cells increases. This process depends on platelet-derived growth factors. When ASC was cultured in vitro 4–5 months, it would experience a spontaneous transformation and showed characteristics of tumor cells [41]. This variant ASC became tumorigenic when injected into mice. In light of many experimental findings, there is a need for further clinical evaluation of these potential safety risks and guidelines for ASC that address the risks to patients.

## Recommendations for Autologous Fat Grafting in Women After Breast Cancer Surgery

The number of breast cancer patients is enormous and screening, such as mammography, has been emphasized for years. In China, breast cancer is the most frequently diagnosed cancer and the sixth leading cause of cancer-related death among women [42]. The American Cancer Society recommends that women 20–39 have clinical breast examinations every 3 years, and women over 40 have annual mammograms and clinical breast examinations. Furthermore, all women over 20 should perform regular breast self-examinations [43]. However, there are no such guidelines for standard screening of breast cancer patients before or after AFG. Patients who opt for AFG should receive careful screening and examination to prevent potential synergistic interactions between ASCs and lingering tumor cells. Cancer may still exist even with negative margin results after partial mastectomy [44].

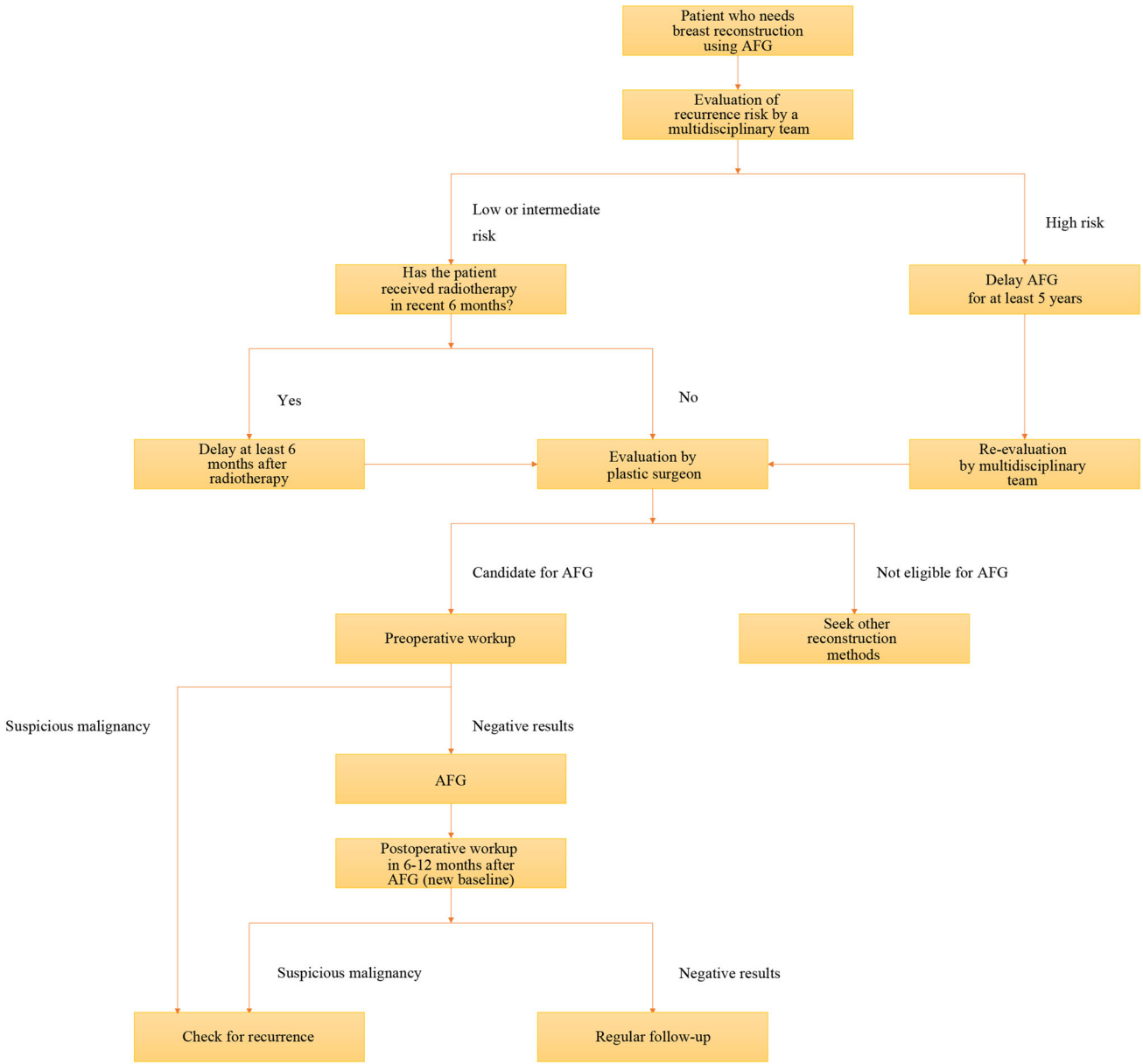


**Fig. 1** Recommendation for breast cancer patients who need AFG

Therefore, we propose a flow chart to guide screening and clinical decision-making surrounding AFG (Fig. 1) that is explained below.

For women with a high risk of recurrence, AFG is not recommended, because the long-term oncological safety remains unclear [45]. Two case-controlled studies of outcomes after AFG found very different locoregional recurrence rates after AFG, 0.4 and 1.87 % per year [16, 46]. The authors suggest that longer disease-free observation time between primary oncologic surgery and AFG, as was done by Katherine et al., can select for a relatively low-risk case group with a lower recurrence rate. Evaluation of high-risk patients is complex but important. There are numerous prognostic factors related. The TNM staging system is a classic tool to determine the extent and severity of breast cancer using uniform reporting criterions. It includes the size of the tumor (T), the range of involved positive axillary lymph nodes (N), and its spread to distant sites (M). The survival rate declined as the stage went higher [47]. Meanwhile, younger breast cancer patients showed more loco recurrences [48]. On the other hand, a higher histologic grade tumor predicted an increasing rate of distant recurrence [49]. Besides histopathological subtypes, molecular features were also related with patient outcome. Overexpression of the human epidermal growth factor receptor 2 (HER2) gene is associated with adverse

prognosis [50]. Also, triple-negative breast cancer, which is defined as ER negative, PR negative, and lacking overexpression of HER2, has a poorer outcome than other types due to lack of effective treatment [51]. Considering ovarian function is essential to breast cancer development, disease incidence increases after puberty, but this growth is less steep in postmenopausal women [52]. Additionally, in older patients, overall survival and the distant recurrence-free period are influenced by comorbidities [53]. In general, patients with the above characteristics have high risk of recurrence. Gene expression profiles of patients also demonstrate predictive value for cancer recurrence following AFG [54, 55]. Therefore, we strongly advise that patients consult with a multidisciplinary team and receive a careful and comprehensive evaluation prior to seeking AFG reconstruction. A multidisciplinary team should ideally include a breast surgeon, medical oncologist, radiation oncologist, pathologist, breast radiologist, and plastic surgeon [56]. It has been shown that breast cancer patients managed by this type of team experience better quality of life and survival rates [57]. Those with a high recurrent risk should delay AFG for at least 5 years and receive re-evaluation at that time [58, 59].

Low- and intermediate-risk patients who want to receive AFG after breast cancer surgery should undergo pre- and post-operative examinations to monitor possible malignancies. The examination components should be decided by the multidisciplinary team. As radiotherapy may affect the survival of transferred fat, AFG should be performed at least 6 months after radiotherapy [60]. Veber et al. [61] suggest that in healthy women, a combination of mammographic imaging and ultrasound should be performed preoperatively to distinguish between tissue alterations from surgery and malignant formation. Similar preoperative evaluation should be performed for post-surgery breast cancer patients. If abnormities are found, the risk of recurrence may be increased, and patients should not proceed with AFG but instead have further screening or treatment. Those who qualify for AFG should receive postoperative surveillance in addition to the patient education, physical examination, and annual mammography that typically follow breast cancer surgery [58, 62]. Patients should undergo mammography between 6 and 12 months after AFG [61]. Generally, if the results show scars or other changes resulting from AFG, this would become the new baseline for upcoming follow-up [63]. However, if the Breast Imaging Reporting and Data System (BI-RADS) III is reported, then short-term imaging should be implemented. If BI-RADS IV or V exists, pathologic confirmation of malignancy by ultrasound-guided fine-needle aspiration or core biopsy may be necessary [63, 64]. Magnetic resonance imaging is also recommended, as it is more sensitive for distinguishing liponecrosis from oil cysts and breast cancer, which can prevent unnecessary biopsies [65].

Considering that ASC may stimulate cancer recurrence, we do not suggest stem cell-enhanced injections to the breast in post-surgery patients [36]. Whether the number of ASCs in regular AFG is enough to cause recurrence is unclear. However, some suggest that ASC should be removed from cell suspensions before injection [66]. We consider that ASC in normal fat transfer is essential for successful transfer [67], but purifying, magnifying, and injecting it is dangerous for the target patients.

There are limitations to our review of the literature and recommendations: First, most evidence comes from basic science, which still needs further confirmation in patients. Second, there is a shortage of high-quality clinical evidence because many clinical studies have limitations and biases of their own. Third, future clinical evaluation is needed to see if our guidelines are useful for decreasing recurrence. Fourth, the cost-effectiveness of the proposed screening methods requires further discussion because it may be different according to the patient's financial situation and local healthcare provision.

## Conclusions

AFG is now globally and frequently used on post-surgery breast cancer patients. However, clinical evidence for its safety is incomplete due to short follow-up times and questionable methodology. Numerous basic research studies have shown that when ASC were mixed with tumor cells, tumor growth and metastasis may be stimulated. Also, trauma and wound healing caused by AFG may also be a risk factor. Still, there are no guidelines to choose qualified patients. Our recommendations (Fig. 1) can serve as a reference for plastic surgeons and oncologists making clinical decisions about AFG. They offer criteria to screen for suitable patients for AFG and to perform post-AFG surveillance for potential recurrence. Candidates with high risk factors should delay AFG until further clinical evidence is available. Expanded ASC injection is not indicated because it has a higher possibility of relapse. Although these proposed guidelines can help improve safety of AFG based on current evidence, we recommend further testing regarding feasibility and investigation of long-term clinical outcomes of AFG.

**Acknowledgments** The authors would like to acknowledge Xiaojun Wang, professor, and Xiao Long, professor, from Peking Union Medical College Hospital for their generous share of clinical experience.

**Compliance with Ethical Standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

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