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Oncologic Risks of Autologous Fat Grafting to the Breast

John K. Fraser, PhD; Marc H. Hedrick, MD; and Steven R. Cohen, MD, FACS

Abstract

As the frequency of fat grafting to the breast has increased, some investigators have raised the possibility that this procedure may potentially increase the risks associated with breast cancer. Their concerns included not only interference with cancer detection, but also promotion of tumor formation or recurrence mediated by mechanisms such as aromatase expression, angiogenesis, and tumor stromal cells. However, published clinical studies describing outcomes of fat grafting to the breast in more than 2000 patients have not reported any increase in new or recurrent cancers. The reason for this apparent disconnect may lie in the small sample sizes and relatively short follow-up, but it may also reside in the considerable gap between laboratory studies or theoretical considerations suggesting potential risks and the actual clinical practice. This review discusses potential risks of current and novel approaches to autologous fat grafting to the breast within the context of both the underlying science and clinical practice.

Level of Evidence: 3

Keywords

breast augmentation, breast reconstruction, breast cancer, autologous fat, fat injection

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Application of autologous fat grafting for breast augmentation and reconstruction following partial mastectomy is increasing.[1,2] Results of more than 2000 such cases, many with several years of follow-up including serial imaging, have now been published with no reports of an increase in the incidence of, or decrease in the ability to detect, new or recurrent breast malignancy (Table 1). In the most recent study, Rigotti et al[3] evaluated 137 patients treated with autologous fat grafting for cosmetic defects or radiolesions following modified radical mastectomy. All patients had at least three years of follow-up after fat grafting (median 7.6 years; range, 3.1 years to 19.1 years). The study evaluated local recurrence during two periods: the period between initial surgery and fat grafting, and the period between fat grafting and follow-up. The recurrence rate during the pregraft period was 9.1 cases per 1000 patient-years compared with 7.2 cases per 1000 patient-years in the period after fat grafting. Thus, the authors found no evidence of an increased incidence of recurrence in this group, nor in their total (more heterogeneous) population of 911 patients.

Nonetheless, concerns have been raised regarding the potential oncologic risks of these procedures. Concerns include a compromise of our ability to detect breast disease, the expression of protumorigenic factors by cells within the graft, and the transformation of stem cells within the graft.[4,5] Novel approaches, including supplementation of fat grafts with adipose-derived stem cell (ADSC) populations, could also impact oncologic risk.[6,7] The considerable recent growth in clinical and laboratory literature describing autologous fat grafting to the breast affords us the opportunity to review the data being published on these potential risks in the light of both the aesthetic and psychological benefits of breast reconstruction.[8]

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Table 1. Fat Grafting to the Breast: Clinical Experience Summary

Citation	Number of Patients	Setting	Comments
Delay et al[2]	880	83% reconstruction; 12% congenital;3% cosmetic;1% repair prior surgery	3% incidence of fat necrosis; 15% when the surgeon is less experienced; no increased risk of local recurrence or new breast cancer
Illouz and Sterodimas[14]	820	47% reconstruction; 46% augmentation, 7% congenital	49% incidence of breast imaging changes; no changes deemed suspicious (BI-RADS ≥4)
Zocchi and Zuliani[15]	181	60% augmentation or volume asymmetry 11% correction of surgery. defects	3.9% incidence of calcification; all imaging easily distinguished from neoplasia
Rigotti et al[3]	137	Post-modified radical mastectomy	9.1 cases per 1000 patient years before fat grafting; 7.2 cases per 1000 patient years post-fat grafting
Missana et al[10]	69	100% acquired contour deformity	7.2% incidence of fat necrosis
Fulton[60]	65	Augmentation	9% incidence of calcifications; all with benign appearance.
Yoshimura et al[16]	40	Augmentation with cell-assisted lipofilling	5% incidence of calcifications; all with benign appearance
Pierrefeu-Lagrange et al[61]	30	Breast reconstruction with latissimus dorsi flap and fat graft	13% incidence of calcifications; all with benign appearance One suspicious lesion; biopsy showed benign granuloma
Coleman and Soboeiro[1]	17	Augmentation and congenital	24% incidence of benign calcifications; two patients developed BrCA; one in area outside of fat graft; no delay in diagnosis or treatment
Yoshimura et al[6]	15	Augmentation following removal of conventional implants	No cysts or calcifications observed by MRI or mammography at 12 months

DETECTION OF NEW OR RECURRENT BREAST CANCER

Fat necrosis within the breast occurs under several circumstances, including radiation, trauma, biopsy, lumpectomy, flap-based reconstruction, reduction mammaplasty, implant removal, or (less frequently) from anticoagulant therapy, Weber-Christian Disease, or systemic lupus erythematosus.[9] It can also occur following implantation of a free fat graft into the breast.[10] As with wounds in other tissues, the early phase of response to the fat injury involves an inflammation, followed by fibrosis and remodeling. Over time, this fibrotic reaction can lead to calcification.[9]

Each of these response phases and the potential lesions are detectable with common breast imaging modalities (mammography, ultrasonography, and magnetic resonance imaging [MRI]).[11,12] In 1987, a committee of the American Society of Plastic and Reconstructive Surgeons (ASPRS; now the American Society of Plastic Surgeons, ASPS) proposed that calcifications resulting from fat necrosis subsequent to autologous fat grafting could compromise early detection of breast cancer and that, consequently, such procedures were unsafe.[4] However, in the years since this statement was issued, there have been substantial improvements in breast imaging modalities and in fat grafting techniques, as several pioneering surgeons continued to develop and optimize the procedure. In early 2009, ASPS published updated recommendations based on a review of 110 published studies covering 283 patients.[13] In the year since their recommendations were released, a voluminous body of new data has been published, many with large case series of patients who were followed-up for several years.

The largest published experience (880 patients over 10 years) was reported by Delay et al.[2] Their patient population consisted of 734 reconstructions, 106 corrections of congenital deformities, 30 aesthetic breast surgeries, and 10 procedures to correct previous surgeries. Imaging was performed with mammography, ultrasonography, and MRI. The authors concluded that "if lipomodeling was carried out in accordance with modern principles of fat transfer, it in no way hindered breast imaging." More importantly, the authors noted that 10 years of oncologic follow-up did not reveal any increased risk of local recurrence or development of a new cancer. Indeed, the authors commented that their clinical impression seemed to suggest a decrease in cancer incidence, although they acknowledged that such speculation was premature and that more studies are needed.

With respect to imaging, Delay et al they found that the incidence of fat necrosis in the first 50 patients treated was 15%; this declined to 3% in the last 100 patients, suggesting a surgical learning curve. The authors also noted the importance of strong communication between the surgeon and the radiologist, including assessment of the results by radiologists who specialized specifically in breast imaging.

Illouz and Sterodimas[14] reported results on 820 patients who received autologous fat grafts to the breast over a 25-year period. This included 381 patients who underwent unilateral breast reconstruction following tumor resection (the majority following removal of a silicone implant), 54 patients who were treated for congenital soft tissue defects (breast asymmetry and Poland syndrome), and 385 patients

Table 2. Incidence of Calcification Following Other Breast Surgical Procedures

Citation	Number of Patients	Setting	Comments
Abboud et al[62]	120	Reduction mammaplasty	11% incidence of calcifications
Danikas et al[63]	113	Reduction mammaplasty	25.6% incidence of calcifications
Peters et al[64]	404	Breast implants	100% incidence of calcification of first-generation implants; 42% of second-generation implants; Increased incidence of calcification with duration
Esserman et al[65]	43	Brachytherapy	19% incidence of calcifications
DiPiro et al[66]	5	Seat belt injury	60% incidence of calcification; one led to biopsy
Eidelman et al[67]	15	TRAM flap breast reconstruction	20% incidence of calcifications

who underwent fat grafting for bilateral breast augmentation. All patients had preoperative mammography and ultrasonography; the majority (670) underwent repeat imaging at six months and one year after treatment. Long-term follow-up data (two to 25 years; mean, 11.3 years) were available for 230 patients. Patients received between one and five grafting procedures (average, three) with a range of 25 mL to 180 mL of fat injected per procedure. Imaging revealed benign changes (including parenchymal asymmetrical densities, cysts, and benign-appearing calcifications) in just under half of the 670 evaluated patients. No suspicious lesions (BI-RADS Category 4 or greater) were observed.

Zocchi and Zuliani[15] reported results from 181 patients who received fat grafting into one or both breasts (326 breasts treated; average volume of fat grafted, 375 mL). All patients received preoperative and serial postoperative mammograms and ultrasound imaging of the breast. Three pseudocysts were detected; all three spontaneously resolved over six months. Seven cases of microcalcification were observed (3.9% of patients). The authors noted that with good communication between surgeon and radiologist, these artifacts were easily distinguished from those associated with neoplasia.

The other smaller studies listed in Table 1 report generally similar findings, with a relatively low incidence of calcification and little difficulty in distinguishing between calcifications secondary to fat graft necrosis and those indicative of malignancy. Published reports describing the addition of supplemental ADSC populations to the graft showed no evidence of an increased incidence of calcification (two of 40 patients in one study[16]; zero of 15 patients in a second[6]). To place this in context, the rate of calcification following fat grafting appears to be no greater than for other common surgical procedures of the breast (eg, breast reduction surgery or reconstruction with TRAM flaps; Table 2).

EXPRESSION OF PROTUMORIGENIC FACTORS

Aromatase

The higher incidence of breast cancer in postmenopausal women who are overweight or obese[17] is linked to the fact that adipose tissue expresses aromatase, a key enzyme in the biosynthesis of estrogen.[18] Indeed, adipose tissue is the primary source of estrogen following menopause. Before menopause, estrogen acts as a classical endocrine hormone—that is, at a distance from its site of synthesis. In postmenopausal women, it acts primarily as a paracrine factor, in a local manner.[18] Thus, estrogen levels in breast tumors of postmenopausal women are several times greater than they are in circulation or in normal breast tissue.[19,20] This is due to the ability of breast cancer cells to induce upregulation of aromatase expression in adjacent adipose tissue.[21]

Studies applying immunostaining, or the combination of laser capture microdissection and the quantification of aromatase expression, have shown that the enzyme is significantly increased in adipose tissue and stromal cells contained within the tumor as compared to adipose tissue not in close proximity to the tumor.[22,23] This indicates that upregulation of aromatase and the subsequently increased delivery of estrogen to the tumor is spatially restricted and, in order for adipose tissue to contribute in a meaningful manner to estrogen delivery to a breast tumor, that tissue must be in very close proximity to the tumor.

Given the extent of tumor resection, including surgical efforts toward reconstruction at the time of resection, it is very unlikely that adipose tissue transferred several months later will be delivered sufficiently close to an occult tumor to be of biological significance. More importantly, the standard of care for women with a history of breast cancer includes extended adjuvant therapy with estrogen-blocking agents such as tamoxifen, or with aromatase inhibitors such as exemestane or letrozole.[24,25] Consequently, even in the unlikely event that adipose tissue is grafted into a site immediately adjacent to an unrecognized tumor, these agents will effectively silence adipose-derived estrogen. This concept is supported by the studies of Delay et al and Rigotti et al, which found no increased risk of recurrent disease or development of new disease in women receiving fat grafting for postmastectomy breast reconstruction.[2,3] For women with no history of breast cancer undergoing fat grafting for augmentation or correction of congenital deformity, the risk of transferred fat being placed into a location where it will later come into direct contact with a new tumor is also low, particularly if the graft is placed into

the subcutaneous space or under the gland, rather than into the parenchyma.

Angiogenesis

Successful engraftment of a free fat graft requires the development of a new blood supply to the tissue through the process of angiogenesis.[26,27] For this reason, researchers have begun evaluating approaches that supplement grafts with cells capable of enhancing angiogenesis and thereby improving graft retention.[6,7] Graft revascularization is initiated by expression of proangiogenic factors by the implanted tissue and cells delivered with it in response to its ischemic environment.[26] However, Folkman's work has demonstrated that tumor development beyond a few millimeters is also dependent upon angiogenesis.[28] Consequently, it might be argued that delivering a source of proangiogenic stimulus to the breast could increase risk of new or recurrent malignancy.[5]

However, this argument ignores key facts about the biology of fat grafting and of breast cancer. For example, Nishimura et al showed that the angiogenic stimulus induced by fat grafting is transient, lasting for only approximately two weeks.[26] This is consistent with the well-described pattern of expression of proangiogenic factors such as vascular endothelial growth factor (VEGF), which is induced in response to ischemia and then silenced once the ischemic insult has been overcome.[29] That is, the angiogenic stimulus in fat grafting is abolished as soon as the graft becomes incorporated into the host vasculature and is no longer ischemic.[26] It should also be noted that fat grafting is not alone in this ability and that other common surgical procedures within the breast can result in transient upregulation of angiogenic and healing-related genes.[30,31]

In contrast, persistent growth factor expression and cell activation are relatively common consequences of breast reconstruction or augmentation with artificial implants. Specifically, capsule formation is associated with ongoing, low-level chronic inflammation with expression of several growth factors.[32,33] Recent evidence has linked both silicone and saline-filled implants with an increased risk of developing a rare form of anaplastic lymphoma within the breast.[34,35] Proposed mechanisms for this increase include the persistent activation state[36] and the similarity between the cells that comprise the capsule and those of tumor stroma.[37,38]

With respect to angiogenesis, there is substantial evidence that breast cancer requires little outside angiogenic support. Several studies have shown that autocrine expression of VEGF and other proangiogenic factors is a characteristic of early breast cancer. For example, expression of proangiogenic growth factors is evident in atypical ductal hyperplasia and ductal carcinoma in situ.[39] In another study of 64 breast cancer specimens, Relf et al detected the expression of at least six of seven proangiogenic factors in every sample.[40] This indicates that breast tumors have multiple endogenous means for stimulating angiogenesis; they are angiogenically independent. Hence, any transient delivery of proangiogenic factors as a result of fat grafting, with or without supplemental cells, will likely be irrelevant to a tumor that is angiogenically self-sufficient.

Stimulation of Tumor Metastasis or Growth by ADSC

In addition to a hormonal angiogenic stimulus such as that provided by VEGF, tumors also need cellular building blocks to generate blood vessels and associated stroma. Studies from small animal bone marrow transplant models have shown that these cells can be derived from bone marrow.[37] However, a population of cells with similar characteristics is present within adipose tissue[41] and there is evidence that such cells (ADSC) can migrate from adipose to nearby developing tumors.[42] In addition, several laboratory studies have shown that mixing cultured stromal cells with breast cancer cell lines can change the biology of the tumors.[43–45] This concern is potentially greater in approaches that supplement the graft with additional stromal cells.

In one such study, Karnoub et al[43] reported that when cultured marrow stromal cells (also referred to as mesenchymal stem cells, MSC) and human breast cancer cell lines were mixed and injected together into the subcutaneous space of immunodeficient mice, a two- to sevenfold increase in the rate of metastases in the lung was observed. Another study showed that implanting a mixture of cultured ADSC and the human breast cancer cell line MDA-MB-231 under the kidney capsule of immunodeficient mice resulted in increased invasiveness compared with the implantation of tumor cells alone.[44] Muehlberg et al[45] presented data showing that cultured ADSC promoted the growth of a mouse breast cancer cell line when mixed and coinjected into the subcutaneous space, or when the cells were delivered by intravenous infusion after the tumor cells had been implanted subcutaneously. These studies suggest the potential for ADSC to migrate from fat grafts and promote the growth or metastasis of new or recurrent breast tumors. However, a closer examination of these laboratory studies shows a considerable gap between the conditions applied in the laboratory and those existing in the clinic. To accurately assess the relevance of these studies to any realistic clinical risk, it is necessary to evaluate the extent of this gap.

First, all of the studies cited above relied on ectopic tumor growth. That is, in each case the breast tumor cells were injected into a site other than the breast (in the subcutaneous space[43,45] or under the kidney capsule[44]). This is a significant point in that we have known for many years that breast tumors, including the specific tumor lines in these studies, grow better within the breast than outside it.[46,47] Hence, the stimulatory effects observed in laboratory studies with ectopically-implanted tumors reflect the suboptimal growth environment of the ectopic site and do not speak to the natural environment of breast tumors, which is natively rich in adipose tissue and ADSC. For example, one study showed the ability of a breast tumor growing in an ectopic site essentially devoid of adipose tissue to recruit

stromal cells from an adipose graft.[42] This is interesting in terms of the ability of tumors to recruit stromal cells from sources other than marrow; however, the breast is not devoid of adipose tissue and hence any new or recurrent tumor within the breast has no shortage of local sources from which it can recruit.

Second, all stromal cells in these studies were cultured cell products. That is, to develop these cells, a native population was taken from its normal microenvironment (marrow or adipose) and placed into tissue culture, where the cells were expanded over a period of several days or weeks. This process involves activation of the cells such that they awake from their normal quiescent state and begin to proliferate. For example, stem cells within ADSC cultures actively divide such that the number of cells doubles every one to two days.[48] This is in sharp contrast to normal human adipose tissue, which is very quiescent. Studies have shown that stem cell-mediated production of new or replacement adipocytes in humans accounts for only 8.4% of all adipocytes over the course of a year.[49] Thus, while human ADSC placed in culture produce new cells at a rate of 100% every few days, in their normal environment they produce new adipocytes at a rate of only 8.4% per year. Radiolabeling studies in adult rats have found similar results, with less than 0.1% of stem cells engaged in active DNA synthesis at any time.[50] Thus, the cultured cells in these studies represent an activated population with characteristics that are very different from those in normal adipose tissue or in cells extracted from adipose before being placed in culture.

Third, these studies directly mixed breast tumor cells and ADSC such that the tumor cells were intermixed and placed in direct contact with activated stem cells. In one study that evaluated injecting the two-cell populations separately, the authors demonstrated that if the tumor cells and stem cells were injected adjacent to one another, no increase in metastasis was observed. In fact, the mechanism underlying this effect was dependent upon direct contact between tumor cells and stromal cells.[43] The second study suggesting an effect on tumor growth without mixing did not provide any data with breast cancer cell lines, but rather evaluated subcutaneous injection of a Kaposi sarcoma cell line or a prostate cancer line in combination with distal intravenous delivery of ten^4 immortalized, cultured stromal cells every day for six weeks.[42] The absence of data on breast cancer lines in this arm of the study is disappointing, given that the authors examined breast cancer lines in other studies included in this report.

Thus, while these studies provide scientific insights into the interaction between tumor cells and their microenvironment, they are of limited significance to the clinical setting for fat grafting to the breast. The major differences between these studies and the clinical setting can be summarized as follows: (1) they evaluated cells that had been activated by several weeks of cell culture; (2) they utilized purified stromal cells as opposed to the heterogeneous mixture of cells present within adipose tissue; (3) they investigated under artificial laboratory conditions by directly mixing together tumor cells and stem cells before implantation; and (4) they implanted tumors into ectopic locations (subcutaneously and under the kidney capsule) rather than into their native environment within the breast. Each of these differences has profound implications that effectively invalidate extrapolation of the findings of such studies to the clinical setting of fat grafting to the breast.

TRANSFORMATION OF STEM CELLS WITHIN THE GRAFT

As noted above, it is now well recognized that human adipose tissue contains a population of cells with the ability to self-renew (as evidenced by proliferation for considerable periods in vitro) and undergo multilineage differentiation.[41,51] These two properties are characteristics of adult stem cells. It is also recognized that many tumor types, including breast cancer, arise from tissue stem cells.[52,53] This association between stem cells and tumors suggests the possibility that stem cells within the adipose tissue could transform and give rise to new malignancy. Approaches that supplement fat grafts with cell populations containing additional ADSC could conceivably increase this risk.

Laboratory studies from one group have shown that taking freshly-isolated ADSC and placing them in cell culture for a prolonged period can cause the cells to transform and become tumorigenic.[54,55] In these studies, cells were subjected to intensive culture until they stopped proliferating and appeared senescent. When cultures were continued beyond this point, a cell subpopulation eventually grew that was capable of forming tumors when implanted into immunodeficient mice. However, the same study demonstrated that cells taken from cultures before they entered the senescent phase did not have the ability to form tumors and were chromosomally normal.[54] That is, the transformed phenotype was the result of selection pressure associated with prolonged cell culture rather than an intrinsic property of the cells themselves.[55] Indeed, it is well known that prolonged cell culture is associated with the risk of accumulation of genetic changes that can lead to transformation.[56] Thus, there is no evidence that cells present within the adipose tissue graft represent any meaningful risk of malignancy.

DISCUSSION

There are theoretical reasons why fat grafting might influence breast cancer growth or metastasis. Certain laboratory studies can be interpreted as supporting their negative impact on tumor development, metastasis, or recurrence. However, careful review of these concerns suggests that they arise from factors and situations that are not present to a significant extent in the clinical setting. A study that approximates more closely the clinical situation of fat grafting into the breast has been presented in poster form.[57] This study investigated an orthotopic model of breast cancer in which human breast cancer cells were implanted into the mammary fat pad of immunodeficient

animals, followed by placement of a human fat graft (with or without noncultured supplemental cells) immediately adjacent to the mammary fat pad containing the nascent tumor. The study found no increase in tumor growth with either an estrogen receptor-positive or an estrogen receptor-negative human breast cancer line. This is consistent with the absence of evidence for increased cancer risk in the many reports of fat grafting for breast reconstruction and augmentation. However, at this time, the number of patients with prolonged follow-up is only approximately 1000 and appropriate caution in proceeding is indicated.

Meticulous surgical technique must be applied both to maximize the aesthetic outcome and to reduce incidence of fat necrosis.[1,2,14,58] It must also be recognized that there is a learning curve with fat grafting, as with many surgical procedures. Baseline, prereconstruction breast imaging and patient counseling on all risks of this procedure, including those relating to cancer detection and development, are recommended.[13,14,59] This is particularly important in the case of women with a personal or family history of breast cancer, or those who are otherwise at increased risk of developing breast cancer.

CONCLUSIONS

The published literature shows a disconnect between the theoretical deleterious effects of fat grafting on breast cancer development and detection, and the data from many studies documenting the lack of clinical findings to support these suspicions. This disparity can be explained by the significant differences in conditions (injection site, cell treatment, etc.) between laboratory studies and actual clinical conditions. In the clinical setting, several studies note the importance of good communication between the surgeon and an experienced radiologist to ensure accurate interpretation of breast imaging findings. Incorporation of these steps into good clinical practice and timely reporting of outcome data, including long-term follow-up—preferably in the form of multi-center clinical studies or a robust international patient registry—will ensure that the field develops in a safe and appropriate manner.

Disclosures

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