Oncological Safety of Lipofilling in Patients with Breast Cancer: A Meta-analysis and Update on Clinical Practice

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Abstract. *Background: Lipofilling is an increasingly popular technique for breast reconstruction following both mastectomy and breast-conserving surgery (BCS). However, concerns remain over its oncological safety and its effect on cancer recurrence. Materials and Methods: A systematic literature review and meta-analysis was carried out. Patients who had undergone mastectomy or BCS were investigated separately in order to find out whether the addition of lipofilling had a significant effect on locoregional recurrence rate. Results: Eleven studies were used in the analysis, yielding a total of 2,382 patients. For patients undergoing mastectomy (mean follow-up=36.2 months, range=12-90 months) or BCS (mean follow-up=30.2 months, range=12-60 months), the addition of lipofilling was not found to significantly affect the locoregional recurrence rate. Conclusion: This meta-analysis demonstrates that lipofilling is an oncologically safe procedure to be incorporated into breast reconstruction following either mastectomy or BCS for breast cancer. However, a careful oncological follow-up is recommended. In the future, more adequately powered controlled clinical trials are needed in order to fully understand long-term outcomes after lipofilling.*

Lipofilling, or autologous fat transfer, is a technique which has been used for many years in the setting of aesthetic breast surgery. However, more recently, it has become popular in the management of breast reconstruction and treatment of volume defects following breast-conserving surgery (BCS), where its use can improve aesthetic results. Although gaining popularity in this setting, there are still questions regarding its oncological safety when used in patients being treated for breast cancer.

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There are a number of advantages associated with lipofilling in the setting of breast reconstruction. The technique, developed by Bircoll, involves grafting small amounts of autologous fat into the subcutaneous breast tissue, allowing improved contouring of the breast shape whilst causing minimal trauma and scarring (1). It has been used not only to treat volume defects following lumpectomy procedures, but also to enhance the contour of the breast and improve the aesthetic outcome following both implant-based and autologous tissue-based reconstruction (2).

The harvested adipose tissue is a source of pre-adipose stem cells, which can promote angiogenesis and neoadipogenesis. The Coleman technique, which is currently the most commonly used methodology, capitalises on this property of adipose tissue by increasing the content of stem cells through centrifugation. This is believed to result in better volume retention and aesthetic results (3). However, recent *in vitro* studies have raised concerns by suggesting that breast cancer cells show increased rates of proliferation by interacting with these stem cells (4).

To our knowledge, there is no *in vivo* evidence regarding the effect of fat-derived stem cells on human breast cancer tissue. Recent clinical studies have suggested that it is a safe option in such women (5). However, the majority of the studies available are single-centre case series, which could pose a difficulty in drawing reliable and definitive conclusions with regards to safety and viability of this procedure. This study aimed to systematically evaluate the current literature regarding the oncological safety of lipofilling in patients who underwent surgical treatment for breast cancer by performing a meta-analysis to investigate the recurrence rates and the incidence of complications.

Materials and Methods

Literature search. A computer-aided literature search using the PubMed and Ovid databases was carried out in order to identify relevant articles for inclusion in the study up to January 2016 with no lower limit. Search terms such as 'oncological safety AND lipofilling', 'breast cancer AND lipofilling AND safety' and 'breast

cancer AND lipofilling AND recurrence' were used to search for articles. The similar articles feature was also utilised when using PubMed and the bibliographies of relevant articles were analysed to ensure all eligible research was included. Possible abstracts were reviewed to identify full text manuscripts which could be reviewed for inclusion in the study.

Inclusion criteria. To be included in the meta-analysis, articles had to have investigated female patients who were being treated for breast cancer with either BCS or mastectomy. Patients had to be treated with lipofilling as part of their reconstructive surgery. Patients treated with lipofilling for purely aesthetic reasons were excluded from the study. Articles had to specify how many patients underwent BCS and mastectomy and the recurrence rate for each group.

Reviews, letters, commentaries and case studies were excluded from the study. Only articles written in English were included.

Data extraction. All articles deemed eligible for inclusion in the current meta-analysis were read in full by one of the authors in order to extract relevant data. Publication date, country of study, study design, number of participants, median age, number of patients undergoing mastectomy and BCS, number of recurrences in each group, use of radiotherapy and complication rate, including The nature of complications, were extracted from each article.

Statistical analysis. Following data extraction, a meta-analysis was performed to assess whether there was a significant oncological risk with the use of lipofilling, both for women treated with mastectomy and those treated with BCS. Meta-regression technique was used using lipofilling as the explanatory variable. All statistical tests were performed in the Comprehensive Meta-Analysis Software v2 (Biostat, Inc., NJ, USA).

Results

Our literature search yielded a total of 11 studies which reported on locoregional recurrence rate in patients who had undergone lipofilling as part of their breast reconstruction procedure. Ten out of 11 studies were carried out in Europe and one study was reported from Brazil. As discussed above, we analyzed data of those who had undergone mastectomy and those who had undergone BCS separately. The Coleman technique was the commonest method used and most studies did not report the fat volume transferred to the breast. The median total fat transferred to the breast was 99 cc.

Mastectomy. Nine studies reported on patients who had undergone mastectomy and subsequent lipofilling (5-13) (Table I) yielding 1,756 procedures. Six out of the nine studies were prospective and four used control groups. The mean age of patients across studies was 51.5 years. The mean follow-up was 36.2 months (median=29 months, range=12-90 months.) The mean locoregional recurrence rate was 3.2% with a median of 2.0% (range=0-8.5%).

A meta-analysis was performed using a meta-regression technique with historical controls (14-28). Results of the analysis are summarised in Figure 1. There was only a small

difference between the pooled values for locoregional recurrence rate of those who had undergone mastectomy and lipofilling and those who had undergone mastectomy only. The pooled estimate of logit recurrence rate in procedures without lipofilling was found to be -3.192, equivalent to a 4% locoregional recurrence rate. The slope of the regression curve represented the change in logit recurrence rate once lipofilling was performed after mastectomy. The slope was found to be -0.228, equivalent to a recurrence rate of 3.2%. However, this difference was insignificant ($p=0.497$). Therefore, we can conclude that practice of lipofilling does not significantly increase the locoregional recurrence rate after mastectomy.

Breast-conserving surgery. Ten studies reported on locoregional recurrence rate following BCS (5-7, 9, 10, 12, 29-32) (Table II) and lipofilling, three of which used controls. This yielded a total of 651 procedures. The mean follow-up was 30.2 months (median=27 months, range=12-60 months). The mean locoregional recurrence rate of those undergoing lipofilling was 4.5%, with a median of 1.3% (range=0-16.7%).

A meta-analysis was again performed using a meta-regression technique with historical control data to increase reliability (14-28). Figure 2 illustrates the result. The flat regression line indicates little difference between the pooled values. Again, using a meta-regression method using lipofilling as the explanatory variable, the intercept represented the pooled estimate of logit recurrence rate in procedures without lipofilling, in this case found to be -3.015, equivalent to a pooled locoregional recurrence rate of 4.7%. The slope represented the change in logit recurrence rate when lipofilling was performed after BCS, which was found to be 0.004, equivalent to a locoregional recurrence rate of 4.7%. However, this difference was insignificant ($p=0.992$). We can, therefore, conclude that lipofilling practice does not significantly increase locoregional recurrence rate after BCS.

Discussion

Lipofilling is a procedure which is growing in popularity and is increasingly used in breast surgery, and this is evident in the increasing number of publications on this subject. However, much of the literature concerns the technical aspect of the lipofilling procedure rather than the complications and outcomes. This is evidenced by the small number of published studies that used control groups for comparison (33).

Petit and colleagues conducted one of the largest studies investigating the use of lipofilling in 321 patients compared with 642 controls who did not undergo lipofilling (13). Controls were matched for surgery date (within 2 years), age

Table I. Studies regarding the use of lipofilling post-mastectomy for breast cancer.

Study	Ref	Design	Total procedures, n	Total mastectomies, n	Study group (with lipofilling), n	Control group, n	Locoregional recurrence in study group, n (%)	Locoregional recurrence in control group, n (%)
Silva-Vegara <i>et al.</i> 2016	6	Prospective	195	132	132	NA	8 (6)	NA
Chirappapha <i>et al.</i> 2015	7	Retrospective	137	85	85	NA	0 (0)	NA
Masia <i>et al.</i> 2015	8	Retrospective	214	214	107	107	6 (5.6)	6 (5.6)
Kronowitz <i>et al.</i> 2016	9	Prospective	1389	1230	639	591	8 (1.3)	11(1.9)
Petit <i>et al.</i> 2013	10	Prospective	177	141	47	94	4 (8.5)	3 (3.2)
Riggio <i>et al.</i> 2013	11	Prospective	60	60	60	NA	2 (3.3)	NA
Costantini <i>et al.</i> 2013	12	Prospective	22	14	14	NA	0 (0)	NA
Petit <i>et al.</i> 2012	5	Retrospective	963	588	196	392	4 (2.0)	18*
Petit <i>et al.</i> 2011	13	Retrospective	646	476	476	NA	8 (1.7)	NA

*Overall locoregional recurrence rate across all controls, including both mastectomy and breast-conserving surgery.

Table II. Studies regarding the use of lipofilling after breast-conserving surgery (BCS) for breast cancer.

Study	Ref	Design	Total procedures, n	Total number BCS, n	Study group (with lipofilling), n	Control group, n	Locoregional recurrence in study group, n (%)	Locoregional recurrence in control group, n (%)
Silva-Vegara <i>et al.</i> 2016	6	Prospective	195	63	63	NA	2 (3.2)	NA
Garcia <i>et al.</i> 2016	29	Prospective	37	37	37	NA	0 (0)	NA
Mestak <i>et al.</i> 2016	30	Prospective	77	77	32	45	2 (6.3)	2 (4.4)
Chirappapha <i>et al.</i> 2015	7	Retrospective	137	52	52	NA	0 (0)	NA
Semprini <i>et al.</i> 2014	31	Prospective	151	151	151	NA	0 (0)	NA
Kronowitz <i>et al.</i> 2016	9	Prospective	1389	152	79	73	1 (1.3)	4 (5.5)
Petit <i>et al.</i> 2013	10	Prospective	177	36	12	24	2 (16.7)	0 (0)
Costantini <i>et al.</i> 2013	12	Prospective	22	8	8	NA	1 (12.5)	NA
Petit <i>et al.</i> 2012	5	Retrospective	963	375	125	250	1 (2.4)	18*
Pérez-Cano <i>et al.</i> 2012	32	prospective	92	68	68	NA	0 (0)	NA

*Locoregional recurrence rate was of all controls, including both those who underwent mastectomy and those who underwent BCS.

(within 5 years), tumour size, histology, type of surgery and oestrogen receptor status. Eighty-nine percent of tumours were invasive. The median follow-up was 59 months from initial resection, and then 26 months from lipofilling procedure. They reported no significant difference in recurrence rate between the controls and the study group following mastectomy nor BCS, until analysis was limited to intraepithelial neoplasia, in which the use of lipofilling was found to significantly increase the risk of recurrence (10). This is echoed by results from Kronowitz and colleagues in a recent case-control study, who also found no significant difference in the rates of locoregional recurrence between those who had undergone lipofilling and those who had not. They found an increased locoregional recurrence rate in only one subgroup, those who had undergone hormonal therapy and lipofilling. They hypothesised that there may be a potential role for hormonal therapy in enhancing a tumorigenic microenvironment and perhaps

enhancing cross-talk between adipocytes and tumour cells. However, the authors stress that it is not known whether this does or even can occur (9).

Lipofilling has many inherent benefits for the use in breast reconstruction, being able to correct volume defects with minimal scarring, improving aesthetic results, and leading to an increased patient satisfaction rate (34). Another advantage cited for lipofilling is the near-limitless supply of high-quality donor material, which compensates for the post-filling loss of volume (1). Sarfati *et al.* also reported favourable results after preliminary lipofilling to the chest wall following mastectomy and irradiation, indicating that lipofilling may have wider indications than previously thought (35).

The main concern with the use of lipofilling in breast reconstruction is that it may increase the rate of recurrence. This is especially the case in the setting of BCS, where lipofilling is often used to repair the defect left by

Mixed effects regression (method of moments)

	Point estimate	Standard error	Lower limit	Upper limit	p-Value
Slope	-0.228	0.336	-0.887	0.430	0.497
Intercept	-3.192	0.236	-3.655	-2.730	0.000
Tau-squared	0.199278175				
	Q	df	p-Value		
Model	0.462	1	0.497		
Residual	13.028	15	0.600		
Total	13.490	16	0.637		

Figure 1. Regression of lipofilling on logit event rate. The left part of the graph presents the distribution of the local recurrence rate (expressed as logit) for studies where lipofilling was not applied following mastectomy. The right-hand side of the graph is the distribution of local recurrence rate (expressed as logit) for studies with lipofilling after mastectomy. In both cases, pooled values are on about the same level (the regression line is flat). The intercept of -3.192 represents the pooled estimate of logit recurrence rate for all studies without lipofilling and is equivalent to a 3.2% recurrence rate.

lumpectomy. Questions surrounding whether adipose tissue can promote growth of residual tumour cells have led to concerns regarding oncological safety. A number of *in vitro* studies have shown that adipocyte aspirate can induce tumour cell growth. Massa *et al.* conducted an *in vitro* study looking at the interaction of adipose tissue derived from lipofilling procedures with breast cancer cells from a number of cell lines and found that proliferation of cancer cells was enhanced when they were incubated with unfiltered lipo-aspirate. They also found that bone marrow fibroblasts, in comparison, did not induce significant increase in

proliferation of tumour cells. These findings suggest that a component of adipose tissue may be contributory to increased proliferation. This effect does not appear to be restricted to breast cancer cells (4). Perrot *et al.* reported an unusual case of osteosarcoma recurrence which occurred 13 years after the initial diagnosis and 18 months after lipofilling. It is unusual to see a recurrence of osteosarcoma so late, and preclinical models confirmed that adipocytes or their progenitor cells promoted osteosarcoma tumour growth (36). Despite such evidence from *in vitro* studies, these results have not been replicated or supported by *in vivo*

Figure 2. Regression of lipofilling on logit event rate. The left part of graph presents distribution of local recurrence rate (expressed as logit) for studies where lipofilling was not applied following breast-conserving surgery. The right-hand side of the graph is distribution of local recurrence rate (expressed as logit) for studies with lipofilling after breast-conserving surgery. In both cases, pooled values are on about the same level (the regression line is flat). Here the intercept of -3.015 represents the pooled estimate of logit recurrence rate for all studies without lipofilling that is equivalent to a 4.7% recurrence rate.

studies. Indeed, clinical trial data as collated in our meta-analysis suggest that these findings are limited to *in vitro* settings with no discernible translation *in vivo*, for reasons as yet unclear. This may be addressed by widening the ongoing debate regarding stem cell recruitment in breast cancer to consider the implications for implanted adipocyte-derived stem cells (37).

Another major concern regarding lipofilling is the loss of retained volume after grafting. This was recognised very early on, and was cited as the reason for the failure of earlier attempts of lipofilling to gain currency (38). This loss of volume is in part due to transplantation of non-viable material, and due to liponecrosis of the graft (39). The current methods of lipofilling improve retained volume through refinements of fat harvesting, and by processing the fat before implanting it in the recipient site. Previous techniques of lipofilling did not involve any processing of the tissue (38).

Described methods of fat harvesting are broadly similar. Donor tissue is engorged with tumescent fluid, which consists of saline, epinephrine, and a local anaesthetic. The fat is harvested through stab incisions using a blunt cannula (40).

Methods of fat processing can vary greatly. The canonical method described by Bircoll involved treating the fat with insulin (1). Others have recommended coenzyme Q10 and vascular endothelial growth factor (41, 42). However, the most prevalent method is the one described by Coleman, in which the fat is refined by centrifugation, allowing the supernatant fat and lower aqueous layers to be discarded, leaving only viable cells, which are less likely to be resorbed. The majority of the studies included in our analysis employed this method (43). At least one author recommended sedimentation as opposed to centrifugation (44). Cell-assisted lipo-transfer is a further refinement of

this technique, described by Matsumoto *et al.*, in which the fat is enriched with adipose-derived stem cells, either by centrifugation or by *ex vivo* culturing before implantation (45). This method showed promise in a recent randomised trial against placebo (46). Pèrez-cano *et al.* described the use of adipose-derived regenerative cell-enriched fat grafting, demonstrating the safety and efficacy of this procedure (32). Other methods prevalent include the Berlin autologous lipo-transplantation system, which is a proprietary closed circuit fat harvesting and processing system using water jets (47), and the BRAVA system, which involves mega-volume transfer of autologous fat after pre-expanding the breasts using proprietary BRAVA devices over a prolonged period of time (48, 49). However, externally validated studies comparing these various techniques are still very limited.

An early concern regarding the use of lipofilling in the breast was the potential for artifacts caused by lipofilling to interfere with radiological screening and follow-up. In fact, this was cited in an early recommendation of the American Society of Plastic Surgery (ASPS) against the use of lipofilling in the breast (39). However, subsequent studies have shown that the changes resulting from fat injection can be easily distinguished from neoplastic images, and would not interfere with radiological screening (50-52). Such evidence enabled the ASPS to revise their recommendation, withdrawing any reservations regarding lipofilling and breast screening (53).

Local complications associated with lipofilling include liponecrosis, oil cyst formation, calcifications, haematomas, infection, and donor site complications. Of these, liponecrosis is regarded as the of the more common of the complications of the procedure (29). However, more recent studies have shown relatively low liponecrosis rates: Petit *et al.* reported a liponecrosis rate of 2.0% in 646 procedures (13), as opposed to that reported by the ASPS, who reported a liponecrosis rate of 5.7% (52). However, a more recent study reported a liponecrosis and oil cyst formation rate of 7.2% in 319 procedures (6), and another reported a rate of 7% in an elderly population (7). Despite this, other studies have reported a rate of 0% (35, 47, 49, 54, 55). The varying rates of liponecrosis may be due to a number of factors: differing follow-up times, differences in investigation procedure for complications or differing patient population. It is also important to note that most of the liponecrosis described may not be clinically significant as a contributor to volume loss: one author described how many of the complications were discovered on routine ultrasound examination and were of no clinical significance (6). However, liponecrosis can on occasion lead to significant clinical sequelae, including sepsis and lymphadenitis (56). Therefore, the risk of liponecrosis cannot be completely discounted, and the factors

contributing to it should be better understood. Chirappapha *et al.* began this process in a recent study investigating complications of lipofilling. They found that there was no significant relationship between volume of fat injected, number of procedures, use of locoregional radiotherapy, age or comorbidity status and complication rate (7). However, this study was limited to an elderly population, which may not reflect the typical patient population.

This study is not without its limitations. Due to the small amount of published literature involving controlled trials with lipofilling in breast cancer, we had to use historical controls from previously published trials regarding recurrence after mastectomy or BCS. Additionally, the inclusion of studies only written English may mean that relevant studies were missed from the analysis. Moreover, the follow-up of the included studies varied widely, with the shortest being just 12 months (12) arguably not enough time to evaluate the recurrence rate. The included studies also did not report consistently on factors found to affect recurrence rate, such as tumour size, tumour stage and use of adjuvant therapies. The studies analysed had significant heterogeneity and therefore we had to use the mixed-effects rather than the fixed-effect model in the analysis. In the future, controlled trials need to be conducted which control for all these variables in order to identify patients who may not be suitable for lipofilling, if such a subset exists. Furthermore, the optimal interval between breast cancer surgery and lipofilling should be determined.

Conclusion

Through this analysis, involving 2,407 patients, we found no evidence that lipofilling significantly increases the risk of locoregional recurrence when used as part of a breast reconstruction procedure after either mastectomy or BCS for breast cancer and can be therefore considered an oncologically safe procedure in suitable patients with careful oncological follow-up. In the future, more long-term, adequately powered, multicentre controlled studies are needed. Additionally, more research should be carried out on the incidence of complications following lipofilling so that efforts can be made to prevent them and optimise fat graft survival.

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Conflicts of Interest

None of the Authors declare any conflicts of interest in regard to this study.

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