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Autologous fat transplantation in patients with breast cancer: “silencing” or “fueling” cancer recurrence?

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ABSTRACT

Lipotransfer can be considered a technical revolution in plastic surgery and widely performed for esthetic surgery. Recently the lipofilling has been indicated in breast reconstruction and deformity correction after breast conservative treatment. However, there is lack of understanding concerning the interactions between the potential tumor beds and the lipoaspirates grafts. Current literature underlines the efficacy of the technique as well as its safety. Nevertheless, many experimental studies provide data on the endocrine, paracrine, and autocrine activities of the transplanted fat tissues. Adipocyte, pre-adipocyte and progenitor cell secretions can stimulate angiogenesis and cell growth. The “tumor–stroma interaction” can potentially induce cancer reappearance by “fueling” dormant breast cancer cells in tumor bed. There is lack of translational research that proves this concern in clinical aspect. No study on the effects of lipotransfer on human cancer breast cells *in vivo* is available.

We provide direct and indirect effects of lipotransfer in breast cancer patients, highlighting pro and con related issues. To confirm the safety of lipotransfer in breast cancer patients we need clinical studies with control group based on long term follow up.

Introduction

The lipofilling technique has been used since many years and becomes rapidly popular especially in esthetic surgery. Breast reconstruction is also widely proposed to reduce the disabling effects of the mutilation.[1–5] Lipofilling can be associated to the usual techniques of breast reconstruction to improve the symmetry and the final cosmetic result. Fat grafting can also be performed to improve the cosmetic results of the conservative treatment, particularly in case of defect resulting from the tumorectomy followed by the radiotherapy[6–12](Fig. 1). For several teams, lipofilling becomes part of the armamentarium of the oncoplastic surgery.[6–23] The indications of lipofilling include micromastia, tuberous breasts, Poland’s Syndrome, post-lumpectomy deformity, post-mastectomy deformity, post radiotherapy sequelae, secondary reconstruction after flap or prosthesis reconstruction and nipple reconstruction.[7,11,24] However, the indication and case selection for lipotransfer should be standardized base on large series studies and long term follow up results, particularly in term of immediate surgical complications, fat necrosis/reabsorption and esthetic improvement.

Most studies published in the literature focus on technique, complications, fat graft survival and cosmetic results. Several studies are focused on breast cancer patient safety. They are mainly dealing with the risk of microcalcifications observed on the mammogram in the follow up. No data are available on the risk of recurrence due to the endocrine, paracrine and autocrine fat activity. In 2007, the French Society of Plastic Surgery addressed the question of cancer safety for the lipofilling technique in breast cancer patients. The Society sent a recommendation to the French plastic surgeons to postpone the lipofilling in the breast with or without breast cancer history unless it is performed under prospective controlled protocol. One year later, the American Society of Plastic Surgeons (ASPS) gathered 8 important American plastic surgeons in “The ASPS Fat Graft Task Force” to assess the indications, the safety and efficacy of autologous fat grafting.[24] Five major endpoints were identified: 1. What are the current and potential applications of fat grafting? 2. What risks and complications are associated with fat grafting? 3. How does technique affect outcomes of fat grafting? 4. What risk factors need to be considered for patient selection? 5. What advancements in bench research/molecular biology should potentially impact current or future methods of fat grafting?

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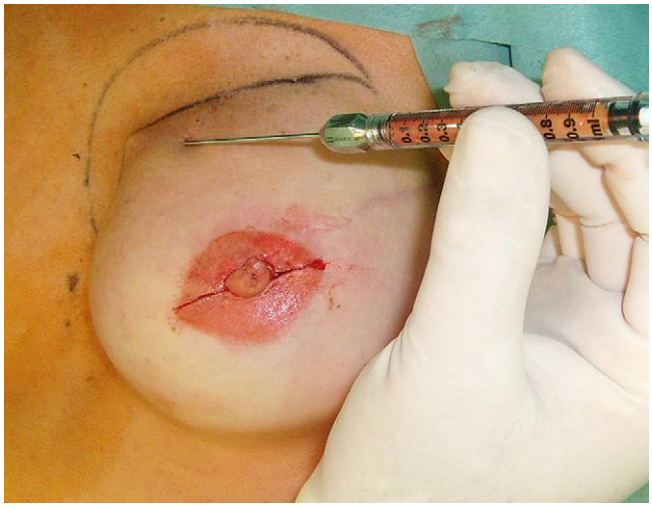

Fig. 1. Lipofilling procedure.

In the ASPS task force project, only 6 out of 111 cited literature references mentioned the potential impact of fat transfer on breast cancer detection.[11,16,17,25–27] There are reports concerning the radiological sequelae following autologous fat transfer, such as the finding of microcalcifications. Some data emphasized that not only mammography but also ultrasonography and MRI may be more accurate to distinguish between the changes associated with benign necrosis of breast tissue and changes associated with cancer.[25–27,80] Moreover, the task force also stated that "based on a limited number of studies with few cases … no interference with breast cancer detection has been observed; however, more studies are needed…". Despite the fact that post-lumpectomy and post-mastectomy are clearly included in the indications of fat graft, the task force did not discuss the issues of adipocyte–stroma interaction, and the risk of development of local recurrences.

Search strategy and selection criteria

Information for this Personal View were obtained by a search of PubMed using the following search term: "lipofilling", "fat grafting", "breast cancer", "breast conservative surgery", "oncoplasty", "adipocyte", "adipokine", "adiponectin", "leptin" and "adipocytokine". Only papers published in English were cited [The references no. [19] and [25] were published in French with English abstract available]. No limitation in date range was introduced. Publications and citations were selected within the issue of this review. The articles are selected according to each subheading purpose in the review.

What is fat grafting surgical procedure?

The first description of the use of adipose tissue as a filler was made in 1893 by Neuber. The results were ephemeral because of the resorption of the fat grafted. During the twentieth century, the surgical techniques were improved allowing more durable results with a low resorption rate.[19] At present, the technique used by the majority of surgeons was published in 1995 by Coleman[20]: adipose tissue is taken, centrifuged and injected in the area where a filling is necessary. Coleman's technique gives good and stable cosmetic results in many anatomic areas.[14,21,22] Lipofilling technique consists in a localized injection of fat into the area of breast previously subjected to excisional surgery for the removal of a breast cancer lesion.[6–15] Briefly, the fat is removed by liposuction from the subcutaneous tissue, usually from the abdomen or from the thighs according to the morphology of the patient. The specimen obtained is subjected to soft centrifugation to remove blood cell contaminants and obtain an adipocyte-enriched preparation. Recently, a number of new techniques have been described, mostly based on enzymatic treatments, with the ultimate goal to improve adipocyte purification. After harvesting and processing, the purified fat is finally injected into the area of the breast, which should be refilled to improve the shape. The revitalization of the injected fat acts as a graft. In approximately 30% of cases, reabsorption of the fat is observed. This represents a major hurdle to successful outcome of the lipofilling technique. This kind of complication can be circumvented with high density embryologic adipocyte preparations.[31–39]

Fat injection into the breast could result in fat necrosis, cyst formation, and indurations that could be mistaken as cancerous calcifications. Moreover the degree of reabsorption of the injected adipose tissue is unpredictable. Breast cancer surgeons use fat grafting to improve the results of breast reconstructions and to correct conservative treatments' sequelaes. One of the oncological concerns of the lipofilling in patients with breast cancer patient is related to the difficulty of radiological surveillance due to microcalcification occurence after lipofilling procedure. Rigotti et al.[10] demonstrated that lipofilling is more than just a filler: it also enhances skin trophicity (which is interesting after radiotherapy).

The aim of our manuscript is to critically review literature data questioning the safety of fat grafting in reconstructive surgery of patients with breast cancer.

Adipocytes and breast cancer

Experimental studies have shown that adipocytes can stimulate breast cancer cells. Adipokines are factors that can stimulate breast cancerous cells through endocrine, paracrine and autocrine pathways.[28,29] Lamszus et al. have proved that Hepatocyte Growth Factors stimulates tumor growth and neoangiogenesis in mice's mammary fat pads.[30] Numerous observations of the adipocyte proadipocyte, progenitor cells, adipokines, and adipokine–stroma interaction as potential actors in breast cancer tumorogenesis have been dispersedly reported in various reports during the last two decades.[40–74]

In 1992, an early experiment from Elliott et al.[57] showed that the subcutaneously or peritoneally co-transplantation of murine mammary carcinoma cell into adipose tissue rich environment regions led to tumor growth and metastasis. Later on, Manabe Y et al.[48] co-cultured mature adipocytes or preadipocytes with multiple models of breast carcinoma cell lines. The result also showed growth-promoting effects of mature adipocyte to estrogen positive tumor cells.

In 2002, Wiseman BS and Werb Z,[58] reviewed pathways involving soluble factors secreted from cells that surround tumors, the extracellular-matrix components, and interactions between stromal cells and tumor cells which create a specific and local peritumoral microenvironment. In the review, the role of adipocyte, which is the most abundant stromal cell, is emphasized either in promotion and protection against breast cancer.

The specific adipocyte products have been studied by microarray analysis, luciferase reporter assays,[46] serum analysis and interstitial fluid analysis.[59] Iyengar P et al.[46] also carried out an *in vivo* model to measure quantitatively the ability of adipocytes to facilitate growth potential of breast ductal epithelial cells faster than those fibroblast co-culture cells. Celis JE et al. registered a total of 359 unique proteins. Apart from providing a comprehensive overview of the mammary fat proteome and its interstitial fluid, their results offer some insight as to the role of adipocytes in the

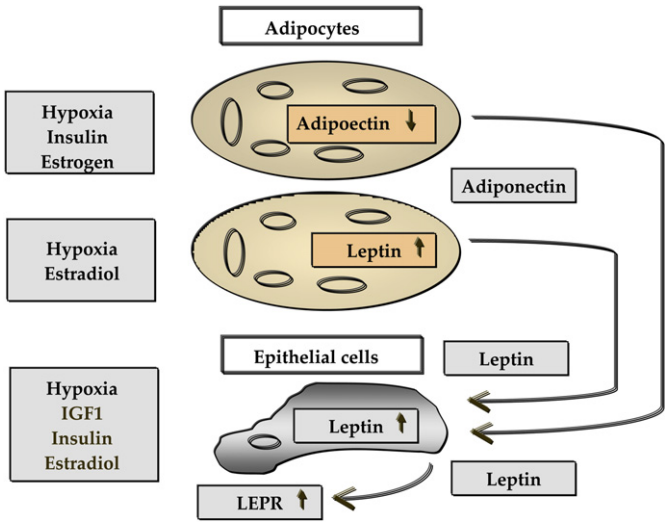

Diagram 1. Cross-talk of the adipokines leptin and adiponectin in breast cancer tumorigenesis (Adapted from Schaffler A et al.)

breast tumor microenvironment and their molecular cellular circuitry.[59]

Adipose organ can have influence to distant tumor site via endocrine function[44] and soluble factors secreted from peritumoral cells/extracellular-matrix components.[49] Trujillo ME and Scherer PE[44] reviewed endocrine function of the adipose organ which secretes adiponectin, resistin and other adipokines. The same description by Schaffler A et al.[49] stated that adipocytes have a role in breast-cancer tumorigenesis as they can promote tumorigenesis through soluble factors secreted from peritumoral cells, extracellular-matrix components. These soluble factors facilitate interactions between stromal cells and tumor cells and create a specific and local peritumoral microenvironment. Moreover, they reviewed the specific role of peritumoral adipose tissue which secretes adipokines [such as adiponectin and leptin] exerting endocrine and paracrine effects in breast cancer behavior. Meanwhile, the cellular and molecular basis of the peritumoral 'desmoplastic' tissue reaction is involved via tumor necrosis factor (TNF), interleukin 11 and matrix metalloproteinase 11. All these factors play role in breast cancer cell progression and adipocyte differentiation inhibition. Interactions between adipokines and breast cancer tumorigenesis are reported as shown in Diagram 1.

Adiponectin and breast cancer

Adiponectin is an adipocyte-secreted protein which has been implicated in the pathogenesis of insulin-resistant states, such as obesity and type 2 diabetes mellitus. Adiponectin levels are also associated with the development of endometrial carcinoma and breast cancer. The correlation of adiponectin level and breast cancer may especially link between breast cancer and obesity/insulin resistance via paracrine and endocrine pathway. The potential mechanisms of this relationship are not yet clarified even if the autocrine, paracrine or endocrine function may all be an explanation.[60–65]

Mantzoros C et al.[60] designed a case-control study in order to identify potential surrogate biomarkers of breast cancer tumorigenesis. They demonstrated an inverse correlation between serum adiponectin levels and breast cancer risk among postmenopausal women. This relationship was independent of possible effects of the IGF pathways, leptin, body mass index, sociodemographic variables, and other known risk factors for breast cancer. Körner A et al.[61] also observed that women with the higher adiponectin levels had a 65% reduced risk of breast cancer. This study was performed on 74 patients with breast cancer compared to 76 control patients. Their study demonstrated that the exposure of specific breast cancer cell lines to adiponectin can significantly inhibit the percentage of viable cells and cell proliferation with no effect on apoptosis. These studies suggested that adiponectin may relate to carcinogenesis and may constitute a molecular link between obesity and breast cancer.

Similar findings were described by Tworoger SS et al.[62] in 2007. The authors observed that adiponectin may be inversely associated with breast cancer risk in postmenopausal, particularly in a low-estrogen environment. Though the explanation of endocrine action seems to fit the hypothesis, the actions of autocrine and paracrine are still debatable. The specific effective role of adiponectin was demonstrated by Kang JH et al.[63] in 2005. They proved that adiponectin level within the range of physiological concentration could significantly suppress the proliferation of ER negative cancer cell line (MDA-MB-231) and also caused cell growth arrest and even apoptosis. Nevertheless, four out of five tested cell lines especially those with ER positive cancer cell line were unsuccessful to produce the same result.

In 2007, Barb D et al.[64] underlined that the circulating adiponectin concentrations are lower in patients with breast, endometrial, prostate, and colon cancer. Adiponectin may influence cancer risk not only through its well-recognized effects on insulin resistance, but it also acts on tumor cells directly. In 2008, an experimental study by Nakayama S et al.[65] showed that adiponectin treatment resulted in a significant dose-dependent growth inhibition of human breast cancer cell lines. The adiponectin can decrease breast cancer cell proliferation by inhibiting the entry into S-phase without inducing apoptosis, and this inhibitory effect is mediated through adiponectin receptor 1.

Leptin and breast cancer

Leptin is a cytokine-like protein secreted from adipose tissues. It is also recognized as a serum growth factor positively associated with body weight and/or body fat. The circulating leptin increases as body weight and fat mass increase. Leptin has been identified in regulation of cell proliferation and neovascularization[66] in malignant and normal cells of diverse origins, including lung, gastric, colonic, kidney, leukemic, hematopoietic and epithelial cells.[66] The expression of leptin has been described in normal human mammary tissues and in human breast tumor cell lines and breast cancer cell. Whether leptin is involved in the regulation of normal mammary gland development has not been clearly investigated.

In 2006, Miyoshi Y et al.[67] found the association between high serum leptin or high intratumoral leptin mRNA levels and poor prognosis. This seems to suggest that the leptin and Lep-R(L)/Lep-R(S) pathways are implicated in the growth stimulation of breast tumors. The process of this occurrence may be affected by autocrine, paracrine or circulating leptin.

In another report, Garofalo C et al.[68] claimed that leptin might also contribute to mammary tumorigenesis. They also discussed the biological functions of leptin and its signaling pathways, together with the effects of leptin on different cancer types in experimental cellular and animal models. They analyzed the epidemiological data on the relationship between obesity and the presence of cancer or cancer risk. The majority of data on relationship of leptin and cancer are based on epidemiological data and particularly related to its endocrine function as circulating leptin.

There are two case-control studies which used multiple logistic regression with adjustment by Mantzoros CS et al.[69] and Wu MH et al.[70] try to demonstrate the relation between serum leptin and

Table 1
Studies on adiponectin and leptin with evidences of relationship to breast cancer risk.

Reference	Year	Design	No of patients	Results	Notes
Mantzoros C, et al.[60]	2004	Case-control study	174	Inverse correlation between serum adiponectin levels and breast cancer risk among postmenopausal women	Odds ratio, 0.82; 95% confidence interval, 0.67–1.00). No significant association in pre-menopausal women
Körner A, et al.[61]	2007	Case-control and experimental study	74	Women with the higher adiponectin levels had a 65% reduced risk of breast cancer	Adiponectin significantly inhibit proliferation of tumor cells
Tworoger SS, et al.[62]	2007	Prospective case-control study	1477	Adiponectin inversely associated with breast cancer risk in postmenopausal women	Strongly inverse association in women who never used hormone replacement therapy
Kang JH, et al.[63]	2005	Experimental study *in vitro*	–	Cell growth arrest and induction of apoptosis by adiponectin in ER negative breast cancer cell lines	No evidence of antitumor activity in ER positive cancer cell lines
Nakayama S, et al.[65]	2008	Experimental study *in vitro*	–	Adiponectin decreases breast cancer cell proliferation by inhibiting the entry into S-phase without inducing apoptosis.	This inhibitory effect is mediated through adiponectin receptor 1
Miyoshi Y, et al.[67]	2006	Experimental study on tissue samples	91	Leptin and Lep-R(L)/Lep-R(S) pathways are implicated in the breast cancer tumorigenesis	Association of obesity and poor prognosis in patient with breast cancer may be explained by leptin levels
Mantzoros CS, et al.[69]	1999	Case-control study	83	Leptin does not appear to increase the risk of cancer in pre-menopausal patients	/
Wu MH, et al.[70]	2009	Case-control study	297	Higher leptin levels were significantly associated with an increased risk of breast cancer.	The associations of leptin with breast cancer risk remained after adjustment for obesity indices
Nkhata KJ, et al.[71]	2009	Experimental study *in vitro*	–	Increasing the adiponectin:leptin (A/L) ratio resulted in down-regulation of proliferation of MCF-7 and T47-D breast cancer cell lines.	/

breast cancer. Mantzoros CS et al.[69] concluded that serum leptin does not appear to increase the risk of cancer in pre-menopausal patients. In contrast, the results of latter study showed that the associations of leptin with breast cancer risk remained after adjustment for obesity indices. These results also suggested that leptin may have an independent role in breast tumorigenesis.

In 2009, an experimental study by Nkhata KJ et al.[71] was conducted on the adipocyte-derived adiponectin and leptin effect on breast cancer cell proliferation *in vitro*. They also examined the effects of varying adiponectin:leptin(A/L) ratios toward different breast cancer cell lines. The results showed that the effects of A/L ratio on mediating proliferation may have some specificity since the cell lines exhibited different responses as A/L ratio resulted in down-regulation of proliferation of only MCF-7 and T47-D breast cancer cell lines (Table 1).

Other adipocytokines and breast cancer

Besides the adiponectin and leptin which are well known adipokines, adipocytes also associated with other secretions such as Stromelysin-3,[72] matrix metalloproteinase,[53,72] and collagen VI[50] which may act through autocrine, paracrine and endocrine pathways. Some of them has been reported and studied clearly in the specific correlation with breast tumor cell development.

Andarawewa KL et al.[72] showed that adipocytes present at human breast tumor invasive front were induced by cancer cells to express ST3/Stromelysin-3/matrix metalloproteinase 11 (ST3/MMP11). That was associated with tumor invasion and poor prognosis. Thus, adipocytes are involved in initial cancer cell survival in connective tissue, and this effect is ST3 mediated. They also found the importance of a matrix metalloproteinase (MMP) in cancer cell-adipocyte crosstalk during early steps of connective tissue invasion. Motrescu ER et al.[53] demonstrated that MMP have collagenolytic activity. This activity is functional in fat tissue oncogenesis as well as during cancer invasive steps. These activities established through an epithelial/mesenchymal heterotypic cell interaction and induce dramatic remodeling of the adjacent connective tissue through desmoplasia, leading to the formation of the peritumoral stroma. Moreover, Iyangar et al.[50] in 2005 explored the bi-directional interactions between adipocytes and malignant ductal epithelial cells. They found that the absence of collagen VI delayed the onset of early hyperplasia while Collagen VI-secreting adipocytes were more permissive of breast tumor growth *in vivo* and had a greater impact on the progression of early tumor development. They concluded that adipocytes play a vital role in defining the extracellular matrix (ECM) environment for normal and tumor-derived ductal epithelial cells and contribute significantly to tumor growth at early stages through secretion and processing of collagen VI.

Not only the stimulatory effect but also the inhibitory effect of adipocyte were reported in fewer studies.[55,56,73,74] In 2001, Meng L et al.[73] studied epithelial–stromal interactions and demonstrated that adipocyte differentiation was inhibited by co-culturing fibroblasts with various breast cancer cell lines. On the other hand, inhibitory effect by adipocyte resistin was reported by Van Valckenborgh D et al.[74] They conducted both *in vitro* and *in vivo* experiments in mouse and revealed that resistin could significantly inhibit tumor growth in both experiments. Nevertheless this result was somehow contradictory to epidemiological studies that link obesity to a higher breast cancer risk, so the underlying mechanisms remain unclear regarding resistin and tumor growth association. Also Rahimi N et al.[56] have developed both *in vitro* and *in vivo* experiments in a mouse model to demonstrate that activation of TGF-β has a potent negative effect on adipocyte differentiation and murine mammary carcinoma growth. Other report stated that, under physiologic conditions, mature adipocyte would promote tumor growth, whereas pre-adipocyte would suppress tumor growth as well as their own differentiation.[55]

Discussion

Subcutaneously or peritoneally co-transplantation of murine mammary carcinoma cells into adipose tissue rich environment regions can lead to tumor growth and metastasis.[57] This is the main interesting concept of local effect acting via paracrine, autocrine or "tumor–stromal interaction" pathway that can also happen in

lipofilling procedures to the breast. We have evidence that both stimulatory as well as inhibitory effects can be observed in the experimental researches. Some of the studies tried to validate single type of cell or type of adipokine which may be responsible for some particular stages of breast cancer cell line development. However, the majority of those studies are from fundamental research and *in vitro* study and somehow difficult to link with the clinical model.

Indirect data that support safety of fat transfer are based on reconstruction using an autologous flap technique such as transverse rectus abdominis myocutaneous (TRAM) flap and deep inferior epigastric perforator (DIEP) flap. Despite the large amount of fat tissue transferred with the flap, no increased risk of cancer recurrence has been published in the literature. However both techniques should be distinguished. Autologous flap is made of a complex tissue with its own vascular system; the composition or ratio of the fat tissue in the flap is not altered. Lipotransfer fat composition is altered from original donor site ratio. Moreover new protocols try to select the proadipocytes and adult stem cells with specific enzymatic activities.[18,36,37,39,75] Several teams also introduced growth factor or biological active substance in the preparation process to increase the survival of the injected adipocytes.[76–78] After conservative treatment, the fat tissue is injected through the glandular tissue. Such injection of adipocytes are able to produce adipokines and several secretions which can potentially induce cancer reappearance by "fueling" dormant breast cancer cells in tumor bed through the "tumor–stroma interaction". We cannot conclude that the flap transfer does not have any tumor–stroma interaction. In the literature, few papers have shown the absence of local recurrence risk after TRAM flap reconstruction.[79] No study provides reliable comparative oncological outcome between flap reconstruction and lipotransfer in breast cancer patients.

The clinical series of oncologic data of lipotransfer in breast cancer patients is still limited. Illouz et al., reviewed a personal series of 820 patients with lipofilling, only 381 patients were cancer patients; other indications were for congenital breast asymmetry and cosmetic augmentation without cancer history.[23] However, they could not make the conclusion in term on oncological safety because almost half of the patients were lack of oncological data and follow up.

Rietjens M et al. reported one of the biggest series focus on lipotransfer in breast-cancer treatment and reconstruction. They followed 158 patients and found that postoperative complication rates are very low and there is little alteration in follow-up mammograms. Although they found only one recurrence in 18 months they concluded that and the potential risk of local 'dormant' tumor cells being stimulated to induce a local recurrence is still unclear.[80]

Another study based on cancer evolution by Rigotti G. Compared the number of LRR of the same group of patients in the pre and post lipofilling. Such methodology should be criticized, because the risk of LRR decreases with time and cannot be considered as equivalent in the pre and post lipofilling period. The authors excluded 104 breast conservative treatment patients from the whole study populations which breast conservative treatment patients could be the group at most risk of LRR. Without the translational research, this report concluded that autologous lipoaspirate transplant combines striking regenerative properties with no or marginal effects on the probability of post-mastectomy locoregional recurrence of breast cancer.[81]

In 2008 Chan CW et al.[82] reviewed 8 studies on autologous fat transfer with a focus on breast cancer surgery. In such review, most indications of lipofilling were not for breast cancer patients but for benign purpose. No specific oncologic follow up was mentioned. Chan stated in the conclusion that "…Owing to insufficient data, its (lipotransfer) use as an adjunct in breast reconstruction surgery has been slow to gain acceptance…".

The same concern of stimulatory effect of lipotransfer method is also found in other type of solid tumor. Recently, Perrot P and colleagues[83] reported a case of a late local osteosarcoma recurrence. They investigated the relationship of osteosarcoma tumor growth with fat injections in pre-clinical models and found that fat grafts or progenitor cells promoted osteosarcoma tumor growth.

There is increasing evidence that the stroma is important for driving tumor growth. When performing a fat transfer procedure we should consider the potential adipokines downstream effects on breast cancer tumorigenesis. Adipokines can potentially increase the interaction between tumor and stromal cells rather than conferring self-sufficiency to the tumor. Adipocytes, preadipocytes and adipokines can promote or inhibit breast cancer cell tumorigenesis through autocrine and paracrine mechanisms enhancing tumor–stroma interactions. These data question the safety of fat grafting in reconstructive surgery of the breast. Since November 2007, the French Society of Plastic Surgery (SOFCPRE) recommends not to use adipose tissue in breast surgery until its inocuity has been proved. Authors also underline that the autologous fat grafting to the breast is not a simple procedure and should be performed only by well-trained and skilled surgeons. The major complications can be observed when this procedure is performed by untrained and untutored physicians and the role of education in the lipofilling technique is of paramount importance.

Conclusion

We cannot state that lipofilling procedure is dangerous or should not be done in patients with breast cancer, since available data are balanced on suppressive or promoting effects of fat transfer on breast cancer progression. Therefore, we should promote translational research to evaluate the role of fat grafting in the development of breast tumor, to evaluate if fat grafting may induce cancer recurrence (especially after radiotherapy) and to evaluate whether cancer induction or recurrence depends on angiogenesis mediated by cytokines produced by the lipofilling. Clinical studies based on an accurate follow up of patients with breast cancer who underwent lipotransfer are required to definitively address all relevant questions. A prospective clinical registry including high volume multicenter collaborative data is warranted.

Authorship statement

Concept and design - Jean Yves Petit, Visnu Lohsiriwat; Writing manuscript - Giuseppe Curigliano, Visnu Lohsiriwat and Jean Yves Petit. Critically Revising - Mario Rietjens, Aron Goldhirsch.

Conflict of interest statement

The author and co-authors declare no conflict of interest.

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