Oncological Safety of Lipofilling in Healthy BRCA Carriers After Bilateral Prophylactic Mastectomy: A Case Series

Christophe Ho Quoc , Leonardo Pires Novais Dias , Oddone Freitas Melro Braghiroli , Nunzia Martella ,
Vincenzo Giovinnazzo , Jean-Marc Piat
Rhena Clinic, Sein Institute, Strasbourg, France

ABSTRACT

Objective: The germline breast cancer gene (BRCA) mutation confers a lifetime high risk for breast cancer (BC) and bilateral prophylactic mastectomy is the procedure which allows the highest risk reduction rate. Among other techniques, lipofilling (LF) can be used for breast reconstruction of these patients. However, there are some oncological safety concerns on the subject. The purpose of this study was to assess the oncological risk of LF in BRCA healthy patients.

Materials and Methods: A single institution case series was built including BRCA I/II mutated patients with no previous history of BC, who underwent bilateral prophylactic mastectomy followed by breast reconstruction with exclusive LF or combined with implants or latissimus dorsi flap. Data were collected regarding patient demographics, clinical information, reconstruction techniques used, and fat grafting details.

Results: From September 1999 till November 2017, we identified 18 BRCA carriers with no history of BC who had undergone bilateral prophylactic mastectomy, followed by breast reconstruction with LF. A total of 36 LF procedures were performed following an implant or latissimus dorsi flap, or as an exclusive fat grafting breast reconstruction. The average number of LF sessions was 1.4 with a mean volume of 108.8cc per breast. Median follow-up was 33.0 months after mastectomy and 24.5 months after the last LF intervention; no patients were diagnosed with BC during follow-up.

Conclusion: Germline BRCA mutation is a high-risk plight for BC. However, despite the limited follow-up, no BC was detected.

Keywords: BRCA mutation, breast cancer, prophylactic mastectomy, fat grafting, lipofilling, breast reconstruction

Cite this article as: Ho Quoc C, Dias LPN, Braghiroli OFM, Martella N, Giovinnazzo V, Piat JM. Oncological Safety of Lipofilling in Healthy BRCA Carriers After Bilateral Prophylactic Mastectomy: A Case Series. Eur J Breast Health 2019; 15(4): 217-221.

Introduction

The breast cancer genes (BRCA) I and II are two different tumour suppressor genes responsible for the repair of damaged deoxyribonucleic acid (1). When mutated, they carry a breast cancer (BC) lifetime risk up to 72% for BRCA I and 69% for BRCA II (2). Nowadays, identifying a BRCA-mutated patient has multiple implications, since it determines how the oncological team may individualize treatment of an affected patient, and provides the cancer-free related family members with access to preventive professional guidance (3, 4). Therefore, management strategies for non-affected germline BRCA carriers must be weighted, with the decision-making process involving a pivotal plight between closer clinical surveillance and prophylactic interventions. Amidst definitive procedures, bilateral prophylactic mastectomy (BPM) conceives the highest protection for BC, with a risk-reduction of more than 90% (5, 6).

Patients who undergo BPM procedures are driven by the distress of cancer risk and reconstructive techniques are offered to balance surgical burden (7). These reconstruction strategies are based on implants devices, autologous tissues or the combination of both procedures (8). More recently, lipofilling (LF) has become widely popular among surgeons. The technique has been demonstrated to be effective in breast reconstruction and can be used exclusively or associated with implants and flaps. Its versatility stems from correction of moderate sequelae until complete reconstruction of the breast contour (9-11).

Besides the comprehensive debate over the oncological safety of LF, actual data does not condemn this procedure (12-17). Nonetheless, there is currently a lack of knowledge pertaining to the subject. Additionally, the relation between LF and high-risk patients such as healthy mutated carriers is yet to be fully described. Bearing this in mind, the purpose of this study was to evaluate the oncological safety of LF on unaffected BRCA carriers, who experienced prior BPM.

Materials and Methods

This is a non-analytical observational study. Data was collected from prospectively maintained medical records. Study approval was granted by the Institut du Sein des Deux Rives – Clinique Rhena Ethical Committee before the study. Written informed consent was obtained from all patients.

Study population

Between September 1999 and November 2017, unaffected BRCA mutated women who had undergone BPM followed by LF, were elected to this cohort. Patients genetically classified as having a BRCA variant of unknown significance were excluded from the analysis, as were those found to have an occult breast carcinoma on the final pathology report after the BPM. All patients included underwent prophylactic and reconstructive surgical procedures at our institution. The study group included patients who had undergone BPM followed by immediate breast reconstruction, whether it be implant-based, with autologous tissue, or combination of both. Patients who had undergone expander and posterior final implant placement were included. The autologous flap employed was the latissimus dorsi (LD) flap. Fat grafting was used as a secondary technique, always performed when the previous reconstruction technique used did not need further re-interventions. The only exception was the complete fat grafting reconstruction, in which LF was the first procedure after the BPM.

Data research

Clinical files were reviewed to collect patient demographics, risk factors, BRCA statements, any previous oophorectomy procedures, prophylactic mastectomy and breast reconstruction details. Recipient and donor site complications were also reviewed. The follow-up was stated as the time between the last LF procedure and the last clinical visit. Clinical assessments and registered exams were analysed.

Technical aspects

The preoperative assessment included clinical interview and physical examination. Eligible patients underwent a preoperative imaging survey with mammography, breast ultrasound and breast magnetic resonance. All images were reviewed and approved by a radiologist.

All procedures were conducted under general anaesthesia. In order to formulate an individual surgical plan for each patient, the surgeon examined the morphology of the patient and explored the best possibilities for mastectomy and subsequent reconstruction in accordance with the individual characteristics of the patient. This was followed by a shared decision-making process. Both total and skin-sparing mastectomies (skin and nipple) were performed. For immediate reconstruction only, expanders, direct-to-implants and LD flaps were used. Exclusive LF was offered in a delayed timing of the procedure. We do not routinely perform sentinel node biopsy for prophylactic mastectomy.

Follow-up regimen for postoperative imaging and surveillance was scheduled with clinical visits at 1, 2, 6 and 12 months during the first year after BPM or LF procedures. Subsequently, clinical assessment was biannual. Imaging surveillance included magnetic resonance and mammogram, which were performed alternately every six months.

LF technique

The technique employed is a modified version of that described by Coleman (18). The choice of the donor site depended on each patient's morphologic distribution, and no previous subcutaneous infiltration was performed. The fat was primarily harvested from abdo-

men, thighs and lumbar areas. The donor site was then infiltrated with a solution composed of 500ml of saline, 1mg of epinephrine tartrate (Adrenaline Renaudin® 1mg/mL; Renaudin Laboratoire, Ixassou, Nouvelle-Aquitaine, France) and 150 mg of chlorhydrate of ropivacaine (Naropin® 7.5 mg/mL; AstraZeneca, Courbevoie, France). The collected fat was centrifuged for 20 – 30 seconds at 3000 rpm, isolating blood cells and plasma from the specimen. The purified fat was separated from the other contents and set for injection in 10mL BD Luer-Lok syringes (BD Plastipak™; Becton Dickinson, Grenoble, France). A 2 mm cannula was used for LF injection in both subcutaneous and muscle layers.

Statistical Analysis

Descriptive statistics such median, interquartile and range, or means and standard deviations were used to describe continuous values considering variable normality (assessed by graphical analysis and Shapiro-Wilk test) and outliers. Categorical variables are presented by their frequencies and proportions. Statistical analyses were conducted using Statistical Package for Social Sciences for Windows version 23.0 (IBM Corp.; Armonk, NY, USA) for Windows.

Results

General aspects

A background analysis identified 18 germline BRCA patients with no history of BC submitted to BPM and breast reconstruction with LF. The BPM and LF procedures were performed respectively from September 1999 until June 2016, and from October 2010 until February 2017. There were 77.8% (14/18) BRCA I patients and 22.2% (4/18) BRCA II. The patients' median age was 43 years (interquartile range [IQR], 36 – 49 years) at the first LF intervention. The median follow-up was 33.0 months after mastectomy, 4.5 months between BPM and LF, and 24.5 months after the last LF procedure. No primary BC was reported during follow-up surveillance. (Table 1)

Prophylactic mastectomy and immediate reconstruction details

Regarding the prophylactic procedures, there were 55.6% (10/18) nipple-sparing mastectomies, 38.9% (7/18) skin-sparing mastectomies and one 5.6% (1/18) total mastectomy. For immediate reconstruction, 44.4% (8/18) patients received expanders, 33.3% (6/18) went directly for implants, 16.7% (3/18) underwent LD flaps (no implant associated), and 5.6% (1/18) went exclusively for LF. All the patients that primarily received an expander, then proceeded to definitive silicone implant placement in a subsequent procedure. The mean breast weight was 472g ± 318g. No occult BC was detected on the final pathological analysis.

Lipofilling details

Most of the breasts (72.2%) (26/36) underwent only one LF intervention, and the mean session volume was 135±78cc per breast. Patients submitted for implants needed one (85.7%), two (3.6%) or three (10.7%) LF sessions. Patients submitted for LD flap reconstruction needed one (33.3%) or two (66.7%) sessions of LF and the exclusive reconstruction with fat required four interventions with a mean volume injected per session of 118cc, achieving a total of 474cc. Concerning the final reconstruction, the total mean volume injected per breast was 194±150cc, with an average total volume of 124±60cc for prosthesis and 429±117cc for LD flaps. (Table 2)

All the patients presenting with regular donor and receptor site hematoma were clinically assisted. No other complications were reported.

Table 1. Patients characteristics

Variable	All (n=18)
Age, yr (IQR)	43.8 (36–49)
BMI, (kg/m ² – mean±SD)	26.6±6.4
Diabetes	–
Hypertension	–
Smoking	1 (5.6)
Allergy	2 (11.1)
Type of mastectomy	
NSM	10 (55.5)
SSM	7 (38.9)
Total Mastectomy	1 (5.6)
Mastectomy weight, gr – mean±SD	472±318
Type of reconstruction	
Implant	14 (77.7)
LD flap	3 (16.7)
LF exclusive	1 (5.6)
Definitive implant volume, cc – mean±SD	367±124
FU after mastectomy, mo – median	33
FU from mastectomy to first LF, mo – median	4.5
FU after last LF, mo – median	24.5
All data presented as N (%) unless otherwise specified SD: standard deviation; BMI: body mass index; NSM: nipple sparing mastectomy; SSM: skin sparing mastectomy; LD: latissimus dorsi; LF: lipofilling; FU: follow-up	

Discussion and Conclusion

To date, the only study regarding LF in healthy BRCA patients was published by Kronowitz et al. (19) in 2016. This matched cohort described a group of thirty-three healthy BRCA patients submitted to BPM and LF reconstruction. They reported a mean follow-up of 33.6 and 18.4 months after BPM and LF, respectively, and no primary BC was detected during vigilance. Kronowitz analysed a group that underwent BPM and LF, respectively from 1981 until 2013, and from 2001 until 2014 (19). Other than the distant historical times between BPM and LF presented in their study, the results were consistent with those presented by our descriptive analysis (36.0 and 26.2 mean follow-up months after BPM and LF, respectively). As a natural response to the lack of data, specialties societies still recommend caution when performing LF on high-risk patients, particularly mutation carriers (20, 21).

To determine the oncological risk of LF on BRCA healthy individuals, it is crucial to discern the microenvironment path from normal to cancer cells and to identify which factors are related. Fat tissue is a known rich source of multipotent mesenchymal stem cells (MSCs), termed adipose stem cells, (22) and one of the physiological roles of the MSCs is the homing ability of being recruited to repair injured tissues (23). Several studies have suggested that MSCs have the ability to participate in primary and metastatic tumour development, thus playing an important role in tumour progression (24, 25). This is theoretically related to the similar microenvironment mechanism of wound healing and cancer cell proliferation (26). Cytokines and growth factors, such as platelet-derived growth factor and vascular endothelial growth factor, mediate a crosstalk between epithelial cells and surrounding stromal cells that are crucial for cancer initiation, progression and metastases (27). In a study by Massa et al. (28), an in vitro evaluation was performed with three BC cell lines in direct contact with human fat tissue and bone marrow fibroblasts. They observed a high proliferation

Table 2. Lipofilling characteristics (per breast)

Variable	Primary Reconstruction Procedures			
	All (n=36)	Implant (n=28)	LD flap (n=6)	LF exclusive (n=2)
Number of sessions – mean±SD	1.5±0.9	1.3±0.6	1.7±0.5	4.0±0.0
1	26 (72.2)	24 (85.7)	2 (33.3)	–
2	5 (13.9)	1 (3.6)	4 (66.7)	–
3	3 (8.3)	3 (10.7)	–	–
4	2 (5.6)	–	–	2 (100.0)
Volume injected per sessions, cc – mean±SD	135±78	107±48	270±65	118±1
Total volume injected, cc – mean±SD	194±150	124±60	429±117	474±2
<100 cc	11 (30.6)	11 (39.3)	–	–
101–200 cc	15 (41.7)	15 (53.6)	–	–
201–300 cc	2 (5.6)	2 (7.1)	–	–
301–400 cc	3 (8.3)	–	3 (50.0)	–
401–500 cc	3 (8.3)	–	1 (16.7)	2 (100.0)
>501 cc	2 (5.6)	–	2 (33.3)	–
All data are presented as N (%) unless otherwise specified LD: latissimus dorsi; LF: lipofilling; SD: standard deviation				

rate of BC cells in contact with unprocessed lipoaspirate tissue (2.31 folds in 48 hours) and apparently, no interaction between bone marrow fibroblasts and cancer cells (28).

The final LF injected specimen contains fibroblasts, adipose stem cells and preadipocytes at a different maturation stage. The act of infiltration provokes an injury at the receptor tissue site, which induces the adipose stem cells to differentiate and set up the wound healing micro-environment (22). It is considered perilous to perform this procedure on a site with the risk of containing dormant cancer. However, when LF procedures were performed in patients previously treated for BC, the cancer recurrence rates did not increase. In addition, it is worthy of note that regardless of the surgical treatment type, with lumpectomy or mastectomy, the result in terms of oncological control was the same (12-17). For instance, Petit et al. (16) published a large retrospective study with 513 patients submitted to LF after BC, in which 370 women underwent mastectomy, and the local regional recurrence rate was 1.38% with a mean follow-up of 19.2 months after LF. Consistent with this data, Silva-Vergara et al. (15) reported a 1:2 case-controlled study with 147 patients submitted for mastectomy followed by LF, and the cumulative relapse rate was 3.4% and 4.2% in cases and controls groups, respectively.

The liaison between adipose tissue and tumour cells is far more complex than expected. Cancer proliferation support apparently relies on mesenchymal stromal surroundings, which chemotactically sense the hypoxia and inflammatory activity of the tumour cells, and collectively enhance the cancer trophic environment. Besides the induction of collagen matrix deposit and vascular proliferation, there is a favourable ambience which blocks anti-tumour immune response, secretes anti-apoptotic factors and provides a propitious mitogenic context (14, 29). Concerning the aforesaid pathways, there is lack information about the trigger mechanism of silent tumour cells. In fact, the scientific knowledge so far indicates that the synergy between fat tissue, its stem cells, adipokines and vascular-inducing factors seems to organize and differentiate the adjacency tissue, and not induce the activation of dormant cancer cells (30).

The adipocyte microenvironment and its capacity to induce the replication of silent tumour cells is the tight-spot question for high-risk mutated patients. BRCA-affected patients are often submitted for other clinical treatments and the interaction between adipocytes and cancer cells may be underestimated in a mutated healthy patient. Without sustainable knowledge about subcutaneous tissue behaviour, its paracrine loop and influence on cells replication pathways, a definitive medical statement is still unwise.

In addition, some limitations should be mentioned. Firstly, this is a non-analytical study without a control group. In France, the consensus recommendation for LF in BRCA patients that had a history of BC presents some strict indications and should be performed with a minimum of two years' delay. Having said that, the affected sample taken from our database was limited and most patients were lost during follow-up. Secondly, the restricted sample size presented compromised statistical measurements and precluded significant relationships based on the collected data. Thirdly, there is a limited number of publications about the subject, which compromised the final statements.

To incorporate LF as a safe procedure, it is essential to be familiar with the physiology of the adipocyte microenvironment and whether it acquires a silent tumour replication capacity or not. Currently, LF does

not seem to increase BC incidence in patients with germline BRCA mutation who previously underwent BPM. It is important for patients to be aware that despite the LF being considered a low-risk procedure and our positive result, more data is needed to guide the oncological safety of LF for BRCA patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Institut du Sein Des Deux Rives - Clinique Rhena.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - C.H.Q., L.P.N.D.; Design - C.H.Q., L.P.N.D.; Supervision - J.M.P., V.G.; Data Collection and/or Processing - L.P.N.D., O.F.M.B., N.M.; Analysis and/or Interpretation - C.H.Q., L.P.N.D., O.F.M.B., N.M.; Literature Search - C.H.Q., L.P.N.D.; Writing Manuscript - C.H.Q., L.P.N.D.; Critical Review - C.H.Q., L.P.N.D., O.F.M.B., N.M., V.G., J.M.P.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Paul A, Paul S. The breast cancer susceptibility genes (BRCA) in breast and ovarian cancers. *Front Biosci (Landmark Ed)* 2014; 19: 605-618. (PMID: 24389207) [\[CrossRef\]](#)
2. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, Jervis S, van Leeuwen FE, Milne RL, Andrieu N, Goldgar DE, Terry MB, Rookus MA, Easton DF, Antoniou AC, McGuffog L, Evans DG, Barrowdale D, Frost D, Adlard J, Ong KR, Izatt L, Tischkowitz M, Eeles R, Davidson R, Hodgson S, Ellis S, Nogues C, Lasset C, Stoppa-Lyonnet D, Fricker JB, Faivre L, Berthet P, Hoening MJ, van der Kolk LE, Kets CM, Adank MA, John EM, Chung WK, Andrulis IL, Southey M, Daly MB, Buys SS, Osorio A, Engel C, Kast K, Schmutzler RK, Caldes T, Jakubowska A, Simard J, Friedlander ML, McLachlan SA, Machackova E, Foretova L, Tan YY, Singer CE, Olah E, Gerdes AM, Arver B, Olsson H. Risk of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA* 2017; 317: 2402-2416. (PMID: 28632866) [\[CrossRef\]](#)
3. Cobain EF, Milliron KJ, Merajver SD. Update on breast cancer genetics: clinical implications of detecting syndromes of inherited increased susceptibility to breast cancer. *Semin Oncol* 2016; 43: 528-535. (PMID: 27899183) [\[CrossRef\]](#)
4. Graffeo R, Livraghi L, Pagani O, Goldhirsch A, Partridge AH, Garber JE. Time to incorporate germline multigene panel testing into breast and ovarian cancer patient care. *Breast Cancer Res Treat* 2016; 160: 393-410. (PMID: 27734215) [\[CrossRef\]](#)
5. Hartmann LC, Lindor NM. The role of risk-reducing surgery in hereditary breast and ovarian cancer. *N Engl J Med* 2016; 374: 454-468. (PMID: 26840135) [\[CrossRef\]](#)
6. Ludwig KK, Neuner J, Butler A, Geurts JL, Kong AL. Risk reduction and survival benefit of prophylactic surgery in BRCA mutation carriers, a systematic review. *Am J Surg* 2016; 212: 660-669. (PMID: 27649974) [\[CrossRef\]](#)
7. McCarthy CM, Hamill JB, Kim HM, Qi J, Wilkins E, Pusic AL. Impact of bilateral prophylactic mastectomy and immediate reconstruction on health-related quality of life in women at high-risk for breast carcinoma: results of the mastectomy reconstruction outcomes consortium study. *Ann Surg Oncol* 2017; 24: 2502-2508. (PMID: 28612125) [\[CrossRef\]](#)

8. Panchal H, Matros E. Current trends in postmastectomy breast reconstruction. *Plast Reconstr Surg* 2017; 140: 7S-13S. (PMID: 29064917) [\[CrossRef\]](#)
9. Ho Quoc C, Delaporte T, Meruta A, La Marca S, Toussoun G, Delay E. Breast asymmetry and pectus excavatum improvement with fat grafting. *Aesthet Surg J* 2013; 33: 822-829. (PMID: 23908301) [\[CrossRef\]](#)
10. Groen JW, Negenborn VL, Twisk DJWR, Rizopoulos D, Ket JCF, Smit JM, Mullender MG. Autologous fat grafting in onco-plastic breast reconstruction: A systematic review on oncological and radiological safety, complications, volume retention and patient/surgeon satisfaction. *J Plast Reconstr Aesthet Surg* 2016; 69: 742-764. (PMID: 27085611) [\[CrossRef\]](#)
11. Manconi A, De Lorenzi F, Chahuan B, Berrino V, Berrino P, Zucca-Matthes G, Petit JY, Rietjens M. Total breast reconstruction with fat grafting after internal expansion and expander removal. *Ann Plast Surg* 2017; 78: 392-396. (PMID: 27387466) [\[CrossRef\]](#)
12. Agha RQ, Fowler AJ, Herlin C, Goodacre TE, Orgill DP. Use of autologous fat grafting for breast reconstruction: a systematic review with meta-analysis of oncological outcomes. *J Plast Reconstr Aesthet Surg* 2015; 68: 143-161. (PMID: 25591409) [\[CrossRef\]](#)
13. Waked K, Colle J, Doomaert M, Cocquyt V, Blondeel P. Systematic review: the oncological safety of adipose fat transfer after breast cancer surgery. *Breast* 2017; 31: 128-136. (PMID: 27837706) [\[CrossRef\]](#)
14. Gennari R, Griguolo G, Dieci MV, Guarneri V, Tavaniello B, Sibilio A, Conte P. Fat grafting for breast cancer patients: from basic science to clinical studies. *Eur J Surg Oncol* 2016; 42: 1088-1102. (PMID: 27265042) [\[CrossRef\]](#)
15. Silva-Vergara C, Fontdevila J, Weshahy O, Yuste M, Descarrega J, Grande L. Breast cancer recurrence is not increased with lipofilling reconstruction: a case-controlled study. *Ann Plast Surg* 2017; 79: 243-248. (PMID: 28542073) [\[CrossRef\]](#)
16. Petit JY, Lohsiriwat V, Clough KB, Sarfati I, Ihrai T, Rietjens M, Veronesi P, Rossetto F, Scevola A, Delay E. The oncologic outcome and immediate surgical complications of lipofilling in breast cancer patients: a multicenter study Milan-Paris-Lyon experience of 646 lipofilling procedures. *Plast Reconstr Surg* 2011; 128: 341-346. (PMID: 21502905) [\[CrossRef\]](#)
17. Ho Quoc C, Carrabin N, Meruta A, Piat JM, Delay E, Faure C. Lipofilling and breast cancer: Literature review in 2015? *J Gynecol Obstet Biol Reprod (Paris)* 2015; 44: 812-817. (PMID: 26321607) [\[CrossRef\]](#)
18. Coleman SR, Saboeiro AP. Fat grafting to the breast revisited: safety and efficacy. *Plast Reconstr Surg* 2007; 119: 775-785. (PMID: 17312477) [\[CrossRef\]](#)
19. Kronowitz SJ, Mandujano CC, Liu J, Kuerer HM, Smith B, Garvey P, Jaggi R, Hsu L, Hanson S, Valero V. Lipofilling of the breast does not increase the risk of recurrence of breast cancer: a matched controlled study. *Plast Reconstr Surg* 2016; 137: 385-393. (PMID: 26818270) [\[CrossRef\]](#)
20. Gutowski KA. Current applications and safety of autologous fat grafts: a report of the ASPS fat graft task force. *Plast Reconstr Surg* 2009; 124: 272-280. (PMID: 19346997) [\[CrossRef\]](#)
21. Société Française de Chirurgie Plastique Reconstructrice et Esthétique. Transfert graisseux pour reconstruction mammaire après mastectomie totale. SOF.CPRE (serial online) 2016; (4 screens). Available from: URL: <http://www.plasticiciens.fr/interventions/Fiches/513.pdf>
22. Chandler EM, Seo BR, Califano JP, Andresen Eguiluz RC, Lee JS, Yoon CJ, Tims DT, Wang JX, Cheng L, Mohanan S, Buckley MR, Cohen I, Nikitin AY, Williams RM, Gourdon D, Reinhart-King CA, Fischbach C. Implanted adipose progenitor cells as physicochemical regulators of breast cancer. *Proc Natl Acad Sci USA* 2012; 109: 9786-9791. (PMID: 22665775) [\[CrossRef\]](#)
23. Spaeth EL, Dembinski JL, Sasser AK, Watson K, Klopp A, Hall B, Andreoff M, Marini F. Mesenchymal stem cell transition to tumor-associated fibroblasts contributes to fibrovascular network expansion and tumor progression. *PLoS One* 2009; 4: e4992. (PMID: 19352430) [\[CrossRef\]](#)
24. Karnoub AE, Dash AB, Vo AP, Sullivan A, Brooks MW, Bell GW, Richardson AL, Polyak K, Tubo R, Weinberg RA. Mesenchymal stem cells within tumor stroma promote breast cancer metastasis. *Nature* 2007; 449: 557-563. (PMID: 17914389) [\[CrossRef\]](#)
25. Dwyer RM, Potter-Beirne SM, Harrington KA, Lowery AJ, Hennessy E, Murphy JM, Barry FP, O'Brien T, Kerin MJ. Monocyte chemoattractant protein 1 secreted by primary breast tumours stimulates migration of mesenchymal stem cells. *Clin Cancer Res* 2007; 13: 5020-5027. (PMID: 17785552) [\[CrossRef\]](#)
26. Liotta LA, Kohn EC. The microenvironment of the tumor host interface. *Nature* 2001; 411: 375-379. (PMID: 11357145) [\[CrossRef\]](#)
27. Lazenec G, Richmond A. Chemokines and Chemokine receptors: new insights into cancer-related inflammation. *Int J Cancer* 2007; 121: 1949-1957. (PMID: 20163989)
28. Massa M, Gasparini S, Baldelli I, Scarabelli L, Santi P, Quarto R, Repaci E. Interaction between breast cancer and adipose tissue cells derived from fat grafting. *Aesthet Surg J* 2016; 36: 358-363. (PMID: 26499941) [\[CrossRef\]](#)
29. Choi J, Cha YJ, Koo JS. Adipocyte biology in breast cancer: from silent bystander to active facilitator. *Prog Lipid Res* 2017; 69: 11-20. (PMID: 29175445) [\[CrossRef\]](#)
30. Bertolini F, Petit JY, Kolonin MG. Stem cells from adipose tissue and breast cancer: hype, risks and hope. *Br J Cancer* 2015; 112: 419-423. (PMID: 25584493) [\[CrossRef\]](#)