Original Article

Eur J Breast Health 2019; 15(4): 217-221
DOI: 10.5152/ejbh.2019.5013

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

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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, Giovinazzo 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 versatileness 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.

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Received: 28.05.2019
Accepted: 20.08.2019

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 abdomen, 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, Itxassou, 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)

		Primary Reconstruction Procedures		
Variable	**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 microenvironment (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 ambiance 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.

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