ARTICLE ORIGINAL / ORIGINAL ARTICLE

PREDICTORS OF INFLAMMATORY LOCAL RECURRENCE AFTER BREAST-CONSERVING THERAPY FOR BREAST CANCER: MATCHED CASE-CONTROL STUDY

http://www.lebanesemedicaljournal.org/articles/63-4/original1.pdf

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Akoum R, Abdalla EK, Saade M, Awdeh A, Abi-Aad F, Bejjani N, Ghossain A, Brihi E, Audi A. Predictors of inflammatory local recurrence after breast-conserving therapy for breast cancer: Matched case-control study. J Med Liban 2015 ; 63 (4) : 171-178.

ABSTRACT • Background : Inflammatory local recurrence (ILR) after breast-conserving surgery for noninflammatory breast cancer (BC) is associated with dismal prognosis. Risk factors for ILR are not well defined. **Methods** : Between 2001 and 2010, twelve patients at our hospital developed ILR after breast-conserving surgery, adjuvant chemotherapy, and radiotherapy for BC. We compared their clinico-pathological characteristics to those of 24 patients with noninflammatory local recurrence (non-ILR), 24 patients with distant metastases, and 48 disease-free controls, matched for age and observation period. **Results** : The median time to ILR was 10 months. In univariate analysis, extent of lymph node involvement ($p < 0.05$), multifocality ($p < 0.05$), c-erbB2 overexpression ($p < 0.05$), and lymphovascular invasion (LVI) ($p < 0.001$) affected the risk of ILR. Conditional logistic regression analysis showed a significant association between ILR and combined LVI and high histopathological grade. The odds ratio (OR) for ILR versus non-ILR was 6.14 (95% confidence interval [CI] 1.48-25.38) and for ILR versus distant metastases it was 3.05 (95% CI 0.09-97.83) when both LVI and high histopathological grade were present. Patients with family history of BC were more likely to present with ILR than non-ILR (OR 5.47; 95% CI 1.55-19.31) or distant relapse (OR 5.62; 95% CI 0.26-119.95). **Conclusions**: Pre- and postmenopausal women with high-grade BC and LVI are at increased risk to develop ILR, especially in the presence of family history of BC. Identification of risk factors for this lethal form of recurrent BC may lead to more effective preventive treatment strategies in properly selected patients.

Keywords : Inflammatory breast cancer, local recurrence, inflammatory local recurrence, chemotherapy, radiotherapy, mastectomy

Akoum R, Abdalla EK, Saade M, Awdeh A, Abi-Aad F, Bejjani N, Ghossain A, Brihi E, Audi A. Facteurs prédictifs de récidive locale inflammatoire après chirurgie conservatrice du cancer du sein : Étude comparative cas-témoins. J Med Liban 2015 ; 63 (4) : 171-178.

RÉSUMÉ • Objectifs : La récidive locale inflammatoire (RLI) après traitement conservateur du cancer du sein est associée à un mauvais pronostic. Les facteurs de risque d'une telle récidive ne sont pas encore bien connus. **Méthodes** : Entre 2001 et 2010, douze patientes présentant une RLI après chirurgie conservatrice, chimio- et radiothérapie adjuvantes ont été traitées dans notre département. Nous avons réalisé une analyse comparative des caractéristiques clinico-pathologiques de ces patientes avec 24 patientes présentant une récidive locale non inflammatoire, 24 patientes présentant des métastases à distance et 48 patientes en rémission persistante. La stratification a tenu compte de l'âge et de la date du diagnostic. **Résultats :** La RLI survenait après une période moyenne de 10 mois. L'analyse univariée a montré une corrélation significative des facteurs suivants: atteinte lymphatique ($p < 0,05$), multifocalité ($p < 0,05$), surexpression de c-erbB2 ($p < 0,05$) et invasion des vaisseaux lymphatiques (IVL) ($p < 0,001$). La régression logistique conditionnelle a montré une corrélation significative entre RLI et IVL associée au haut grade histologique [OR 6,14; CI 95% pour la comparaison RLI avec récidive locale non inflammatoire et OR 3,05; CI 95% pour la comparaison RLI avec métastases à distance]. La comparaison de ces mêmes groupes de patients en considérant la présence d'antécédents familiaux de cancer du sein a donné des ORs plus significatifs : 5,47 et 5,62. **Conclusion**: Les femmes pré- et postménopausées présentant un cancer du sein de haut grade histologique avec invasion lymphovasculaire sont à risque élevé de développer une RLI surtout en présence d'antécédents familiaux de cancer du sein. L'identification des facteurs de risque de cette RLI pourrait contribuer à l'élaboration d'une stratégie thérapeutique plus efficace.

INTRODUCTION

Ipsilateral breast tumor recurrence (IBTR) after breast-conserving surgery (BCS) and whole-breast radiation occurs in 4% to 10% of patients [1-3]. Late local recurrence (> 2 years) in a conserved breast can usually be treated by further surgery with curative intent and remains associated with a favorable prognosis [4-5]. Early local recurrence (< 2 years) may indicate a more aggressive clinicobiological behavior that heralds the appearance of distant metastases in many cases [1,6-7]. A small but important subset of patients with local recurrence develops inflammatory local recurrence (ILR), which is associated with a distinctly poorer prognosis. An uncommon finding representing 7% to 20% of recurrences [8-12], sometimes referred to as "secondary" inflammatory breast cancer, ILR typically occurs within two years of BCS, exhibits clinical and pathological characteristics of

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inflammatory breast cancer, and is surgically and oncologically difficult to control. Patients with ILR have only a 14% rate of 5-year overall survival compared to 50% for those with noninflammatory local recurrence (non-ILR) [4,8,13-15].

Pathological risk factors for IBTR after BCS include close or positive surgical margins [1,3,12,16], presence of extensive intraductal component (EIC) in and/or around the tumor [1,17-18], presence of lymphovascular invasion (LVI) with or without positive axillary lymph nodes [1,3,7,16,19], histological multifocality [7,16], high histopathological grade [16], negative hormonal receptor status [7], and c-erbB2 oncogene overexpression [20]. Clinical risk factors for IBTR include tumor size [16-17], young age [2-3,18-19], and gross multicentricity [9]; however, a strong family history of breast cancer has been associated with late IBTR and whether these are true recurrences or actually new tumors is controversial [21]. Skin involvement has been reported in 3% to 22% of breast recurrences in general [6,22].

ILR is diagnosed clinically, based on the appearance of diffuse redness and edema of the breast. The histopathological examination frequently reveals cancer emboli in the lymphatic vessels. However, the absence of this characteristic does not rule out the diagnosis. When the clinical criteria are missing, and a dermal lymphatic invasion is seen in the pathological specimen, the term "occult inflammatory breast cancer" has sometimes been used. However, whether occult inflammatory breast cancer carries as poor a prognosis as inflammatory breast cancer is still a matter of debate. Some studies report an outcome similar to that reported for inflammatory breast cancer [23-24]; others describe "occult inflammatory breast cancer" as a more benign process. This type of recurrence has been associated with multicentricity [7, 10-11], multifocality [25-26], positive resection margins [7,16], high number of positive lymph nodes [7,25], and LVI [4,7-8,12-15].

The aim of this study was to determine whether identifiable clinico-pathological characteristics in women with primary noninflammatory, invasive breast cancer affected their risk of ILR after BCS.

MATERIAL AND METHODS

Study design

To assess potential risk factors for ILR after BCS for breast cancer, we designed a case-control study in a hospital-based population. Data on cases and controls were extracted from the hospital radiotherapy registry. All cases and controls had primary noninflammatory, invasive breast cancer and were treated between 2001 and 2010 with BCS, doxorubicin and taxane chemotherapy, and radiation therapy at the same dose. Patients with a positive estrogen and/or progesterone receptor received hormonal therapy. Patients with c-erbB2 positive status treated after 2007 received adjuvant Trastuzumab.

Patients who developed ILR were compared with three control groups: • patients who presented with non-ILR (selected in a 2:1 ratio) • patients who presented with metachronous distant metastases (2:1) and • patients with no evidence of disease at least three years after the initial treatment (4:1). All controls received adjuvant chemotherapy containing a taxane and doxorubicin, and all of them received adjuvant radiation therapy delivering 50 Gy to the whole breast in 25 sessions, followed by a boost of 10 Gy in five sessions to the involved quadrant.

The following data were analyzed: age, tumor size, time to recurrence, pathological grading, lymph node status, surgical margins, lymphatic vessel invasion by tumor cells, multifocality, presence of EIC, and immunohistochemical staining for estrogen receptor (ER), progesterone receptor (PR), and c-erbB2 oncoprotein expression. Clinical data were also analyzed, including common comorbidities: diabetes mellitus, obesity, and infectious mastitis that had completely resolved on antibiotic therapy. The last updated follow-up was in 2011. Internal mammary relapse was considered as metastatic disease. Resection margins ≤ 1 mm in width were considered positive margins.

Local recurrences in cases and controls were histopathologically confirmed and found to be identical to the corresponding initial tumors with regards to grade and ER, PR, and c-erbB2 status.

Statistical analysis

The clinical and pathological variables were compared using χ^2 test, Fisher's exact test, and Student's *t* test. Family history, ER and PR status, menopausal status, c-erbB2 status, LVI, EIC, and multifocality were coded as dichotomous variables. Tumor size, grade, and lymph node status were coded as categorical variables. Logistic regression was used to evaluate the association of each potential risk factor with the occurrence of ILR. A conditional logistic regression model adapted for case-control studies with 2 or 4 matched controls per case was applied. The significance threshold was set at $p < 0.05$, and odds ratios (ORs) and 95% confidence intervals (CIs) were determined. Intercooled Stata software, version 9.0 (StataCorp, 2005), was used for the statistical analysis.

This retrospective review was conducted in accordance with institutional policy.

RESULTS

We identified 12 pre- or postmenopausal women with ILR, mean age 53 years (range, 30-65 years). All ILR cases exhibited intradermal lymphatic vessel invasion that was absent in their initial tumors (Figure 1). All ILR occurred within 20 months from the completion of therapy. The median time to recurrence was 10 months, significantly shorter than in the non-ILR and metastatic control groups (26 and 36 months respectively, $p < 0.001$).

Table I summarizes the baseline patient and tumor characteristics of cases and matched controls. Tumor size, EIC, negative ER and PR status, triple negative receptor

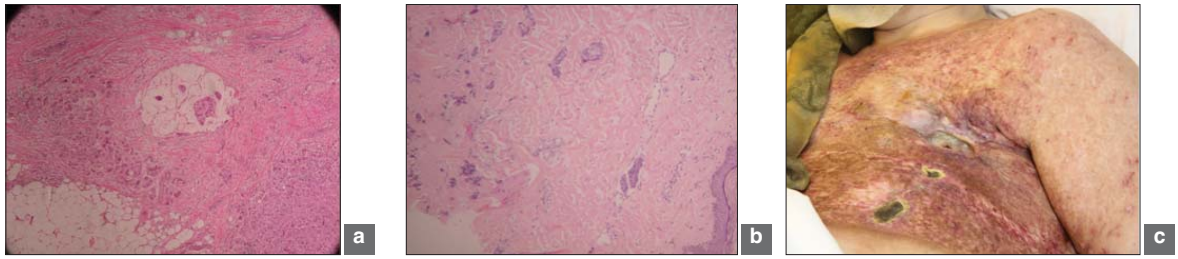

FIGURE 1

a. Photomicrograph of histopathological specimen from the initial breast tumor of a patient with a typical infiltrating ductal carcinoma of colloid type (hematoxylin and eosin x 20). **b.** Photomicrograph of the inflammatory local recurrence from the same patient showing tumor emboli within the intradermal llymphatic vessels (hematoxylin and eosin x 20). **c.** A photograph of the skin involvement in the same patient with inflammatory local recurrence despite chemotherapy and electron beam radiation to the skin.

TABLE I

BASELINE CHARACTERISTICS of PATIENTS with INFLAMMATORY LOCAL RECURRENCE and MATCHED CONTROLS

		Inflammatory local recurrence (n = 12)	Noninflammatory local recurrence (n = 24)	Distant metastases (n = 24)	NED (n = 48)	*p*
Mean age / years (range)		53 (30-65)	54 (29-65)	57 (32-66)	54 (29-67)	
Median TTR / months (range)		10 (3-20)	26 (4-130)	36 (8-130)		< 0.001
Grade	I	0	3 (13%)	3 (13%)	7 (15%)	
	II	4 (33%)	13 (54%)	15 (63%)	33 (69%)	
	III	8 (67%)	8 (34%)	6 (23%)	8 (17%)	0.06
T Class	1	0	4 (17%)	1 (4%)	22 (46%)	
	2	9 (75%)	17 (71%)	18 (76%)	24 (50%)	
	3	3 (25%)	3 (13%)	5 (21%)	2 (4%)	NS
N Class	0	1 (8%)	9 (38%)	2 (8.5%)	29 (62%)	
	1-4	3 (25%)	8 (34%)	15 (63%)	16 (34%)	
	> 4	8 (67%)	7 (29%)	7 (29%)	3 (5%)	< 0.05
Surgical margins	Free	8 (67%)	19 (79%)	17 (71%)		
	Free after re-resection	2 (16%)	3 (13%)	5 (21%)	3 (5%)	
	Positive	2 (16%)	2 (9%)	2 (8%)	1 (2%)	NS
Multifocality	No	7 (58%)	22	24		
	Yes	5 (42%)	2 (9%)	0	4 (9%)	< 0.05
EIC	No	6 (50%)	20			
	Yes	6 (50%)	4 (17%)	7 (29%)	21 (44%)	NS
ER	Positive		22	19 (79%)	37 (76%)	
	Negative	3 (25%)	2 (9%)	5 (21%)	11 (24%)	NS
PR	Positive	9 (75%)	19	14 (58%)	36 (74%)	
	Negative	3 (25%)	5 (21%)	10 (42%)	12 (26%)	NS
c-erbB2	Negative	2 (16%)	14 (58%)	14 (58%)	34 (70%)	
	Positive	10 (84%)	10 (42%)	10 (42%)	14 (30%)	< 0.05
Triple negative*	Yes	2 (16%)	1 (4%)	0	5 (11%)	NS
LVI	Absent	0	16	17	43	
	Present	12 (100%)	8 (34%)	7 (29%)	5 (11%)	≤ 0.001
Personal history	Positive	0	1 (4%)	1 (4%)	1 (2%)	NS
Family history	Positive	1 (8%)	3 (13%)	1 (4%)	4 (9%)	NS
Diabetes	Present	2 (16%)	2 (9%)	1 (4%)	1 (2%)	NS
Obesity	Present	3 (25%)	5 (21%)	4 (17%)	4 (9%)	NS
Mastitis **	Present	0			6 (13%)	< 0.0001
TTR	< 20 months	12 (100%)	12 (50%)	17 (71%)		
	> 20 months		12 (50%)	7 (29%)		0.05

NED: no evidence of disease **TTR**: time to recurrence **NS**: not statistically significant **EIC**: extensive intraductal component **ER**: estrogen receptor **PR**: progesterone receptor *__Triple negative__: negative ER, negative PR and negative c-erbB2 **LVI**: lymphovascular invasion **__Mastitis__: breast cellulitis complicating breast conservation surgery

status (ER, PR, c-erbB2), and positive surgical margins were not significantly correlated with the type of recurrence. The risk of ILR was significantly affected by the extent of lymph node involvement ($p < 0.05$), multifocality ($p < 0.05$), LVI ($p < 0.001$), and positive c-erbB2 status ($p < 0.05$). Histopathological grade did not significantly distinguish between recurrence groups ($p = 0.06$). Six disease-free controls (12.5%) developed infectious mastitis within 15 months from the BCS; none of these patients developed ILR, and none of the cases with ILR or the controls with non-ILR developed this benign postoperative condition ($p < 0.0001$). Obesity, diabetes mellitus, and personal and family history of breast cancer were not associated with the type of recurrence.

Survival analysis

Complete follow-up data were available on 100% of ILR patients. All ILR patients received cisplatin-based chemotherapy. Three patients developed distant metastases shortly afterwards. Four patients underwent mastectomy after a partial response to chemotherapy, and four patients developed extensive skin involvement; however, they all died with metastatic disease within 18 months. One patient remains alive with disease at current follow-up, four years after the ILR, with extensive centrifugal skin invasion without distant metastasis.

Univariate logistic regression

Histopathological grade III was significantly associated with the occurrence of ILR rather than non-ILR (OR 5.62; 95% CI 1.34-23.50; $p = 0.02$), distant metastases (OR 3.89; 95% CI 1.00-15.00; $p = 0.05$), or long-term remission (OR 9.11; 95% CI 2.31-35.80; $p = 0.002$). Lymphovascular invasion was significantly more likely to be associated with ILR ($p < 0.0001$) than with other outcomes. Multifocal tumors were more likely to predict ILR than to predict non-ILR (OR 27.70; 95% CI 1.28-598.00; $p = 0.001$), distant metastasis (OR 11.00; 95% CI 1.75-69.00; $p = 0.01$), or no evidence of disease (OR 11.25; 95% CI 2.44-51.70; $p = 0.002$). Positive margins, tumor size, lymph node status, EIC, ER, PR, and c-erbB2 status, and family history of breast cancer were not significant predictors of ILR (Table II).

Unconditional multivariate logistic regression

In comparing ILR cases with non-ILR controls using multivariate logistic regression, LVI, high grade, and multifocality were predictors of ILR (data not shown).

TABLE II

RESULTS of the UNIVARIATE LOGISTIC REGRESSION ANALYSIS of RISK FACTORS for INFLAMMATORY LOCAL RECURRENCE as COMPARED to NONINFLAMMATORY LOCAL RECURRENCE, DISTANT METASTASES, and NO EVIDENCE of DISEASE

Variable	Noninflammatory local recurrence (n = 24)		Distant metastases (n = 24)		No evidence of disease (n = 48)	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Tumor size (T2, T3)	1.00 (0.25-3.99)	NS	2.02 (0.54-7.59)	NS	17.03 (2.22-130.00)	0.006
Lymph node +	1.12 (0.99-1.26)	NS	1.09 (0.99-1.20)	NS	1.71 (1.14-2.55)	0.009
Grade (III)	5.62 (1.34-23.50)	0.02	3.89 (1.00-15.00)	<0.05	9.11 (2.31-35.80)	0.002
Margins (< 1 mm)	1.21 (0.27-5.35)	NS	1.90 (0.40-8.90)	NS	11.75 (1.83-75.10)	0.009
ER +	0.26 (0.05-1.10)	NS	0.09 (0.01-0.57)	< 0.01	0.36 (0.09-1.30)	NS
PR +	0.51 (0.12-2.08)	NS	0.18 (0.04-0.85)	0.03	0.23 (0.06-0.80)	0.03
c-erbB2 +	3.33 (0.77-14.30)	NS	2.80 (0.65-11.90)	NS	5.00 (1.29-19.30)	0.02
Family history +	4.60 (0.37-56.70)	NS	2.20 (0.27-17.90)	NS	2.25 (0.35-14.00)	NS
EIC present	3.40 (0.8-14.44)	NS	9.80 (1.80-51.00)	0.007	1.80 (0.51-6.71)	NS
Multifocality present	27.70 (1.28-598)	< 0.001	11.00 (1.75-69.00)	< 0.01	11.25 (2.44-51.70)	0.002
LVI present	*	< 0.001	11.2 (2.43-52.00)	< 0.001	*	0.000
TTR (< 20 months)	0.84 (0.74-0.96)	< 0.01	0.89 (0.80-0.99)	0.04	*	0.000

EIC: extensive intraductal component **ER**: estrogen receptor **LVI**: lymphovascular invasion **NS**: not significant
PR: progesterone receptor **TTR**: time to recurrence **+**: positive or positive findings *Variable "perfectly" predicts outcome

TABLE III

RESULTS of the CONDITIONAL LOGISTIC REGRESSION ANALYSIS of RISK FACTORS for the DEVELOPMENT of INFLAMMATORY LOCAL RECURRENCE as COMPARED to NONINFLAMMATORY RECURRENCE, DISTANT METASTASES, and NO EVIDENCE of DISEASE

Variable	Noninflammatory local recurrence (n = 24)		Distant metastases (n = 24)		NED (n = 48)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Grade (III)	4.72 (1.04-21.30)	0.04	2.50 (0.01-375)	0.70	150.20 (1.04-21699)	0.04
Margins (< 1 mm)	0.07 (0.00-2.70)	0.15	0.09 (0.00-10.80)	0.30	0.11 (0.00-1.70)	0.10
ER +	*	*	27.2 (0.04-17031)	0.30	3.96 (0.13-122)	0.43
PR +	*	*	27.2 (0.04-17031)	0.30	3.96 (0.13-122)	0.43
CERB-B2 +	*	*	14.4 (0.08-2445)	0.30	13.38 (0.89-201)	0.06
Family history +	3.53 (0.22-54.60)	0.35	48.4 (0.07-31287)	0.20	0.92 (0.06-12.8)	0.90
EIC present	0.41 (0.04-3.90)	0.40	0.45 (0.034-5.80)	0.54	5.4 (0.19-146)	0.31
Multifocality present	0.31 (0.02-4.80)	0.40	0.17 (0.003-8.49)	0.30	28.97 (1.49-560)	0.03
LVI present	44.8 (0.7-2781)	0.07	3.66 (0.03-429)	0.50	16.2 (0.9-292)	0.05

EIC: extensive intraductal component **ER**: estrogen receptor **LVI**: lymphovascular invasion **NS**: not significant **PR**: progesterone receptor **TTR**: time to recurrence **+**: positive or positive findings *Log likelihood not sufficient to enable conditional regression for these variables

In comparing ILR cases with distant metastases controls, LVI predicted ILR perfectly, whereas multifocality and high grade were less significantly predictors of outcome.

Conditional logistic regression

Based on univariate regression models, tumor grade, LVI, multifocality, EIC, negative ER and PR status, positive c-erbB2 status and family history were entered into conditional logistic regression models. These variables gave better fits by comparing the log likelihood of the models.

Comparison of ORs in the univariate and multivariate conditional logistic regression analyses further clarified the relationship of the association of two or more factors in the prediction of ILR. Odds ratios remained significantly high for LVI and pathological grading as predictors of ILR (Table III).

Family history of breast cancer had no significant role in predicting recurrence; however, patients with family history of breast cancer were more likely to present with ILR than with non-ILR (OR 3.53; 95% CI 0.22-54.60) or distant relapse (OR 48.40; 95% CI 0.07-31,287).

When all variables were included in the conditional logistic regression analysis to tease out the effects of each factor, controlling for the others, only LVI and grade III were strongly associated with ILR as compared to non-ILR, distant metastasis, and no evidence of disease (ORs: 6.14 [95% CI 1.48-25.38], 3.05 [95% CI 0.095-97.83], and 28.43 [95% CI 2.33-346.17], respectively, when both LVI and grade III were present). When family history of breast cancer was added to this combination of risk factors, the ORs remained greater than 4 (Figure 2).

DISCUSSION

This case-control study is the largest reported to date that examines risk factors for ILR that can be identified at the time of treatment of the primary tumor. The results of conditional multivariate regression demonstrated a consistent trend toward a higher likelihood of LVI and high grade among women with unilateral, invasive breast cancer who developed ILR compared with women matched for age, adjuvant treatment modalities, and diagnosis period who did not develop ILR. These characteristics were also potent risk factors for the development of ILR in patients with a positive family history of breast cancer. Until new molecular prognostic factors and new markers of inflammatory breast cancer are found, the presence of LVI and grade III could be signals of elevated risk of ILR.

Two previous studies attempted to correlate histological characteristics with the risk of ILR after BCS for non-inflammatory breast cancer [8,13]. One of them collected nine cases from 18 Japanese centers over a 9-year period [8]. The other collected seven cases from the New York Presbyterian Hospital over a 5-year period [13]. In both studies more than 10 risk factors were analyzed: tumor size and location, histological grade and type, lymph node

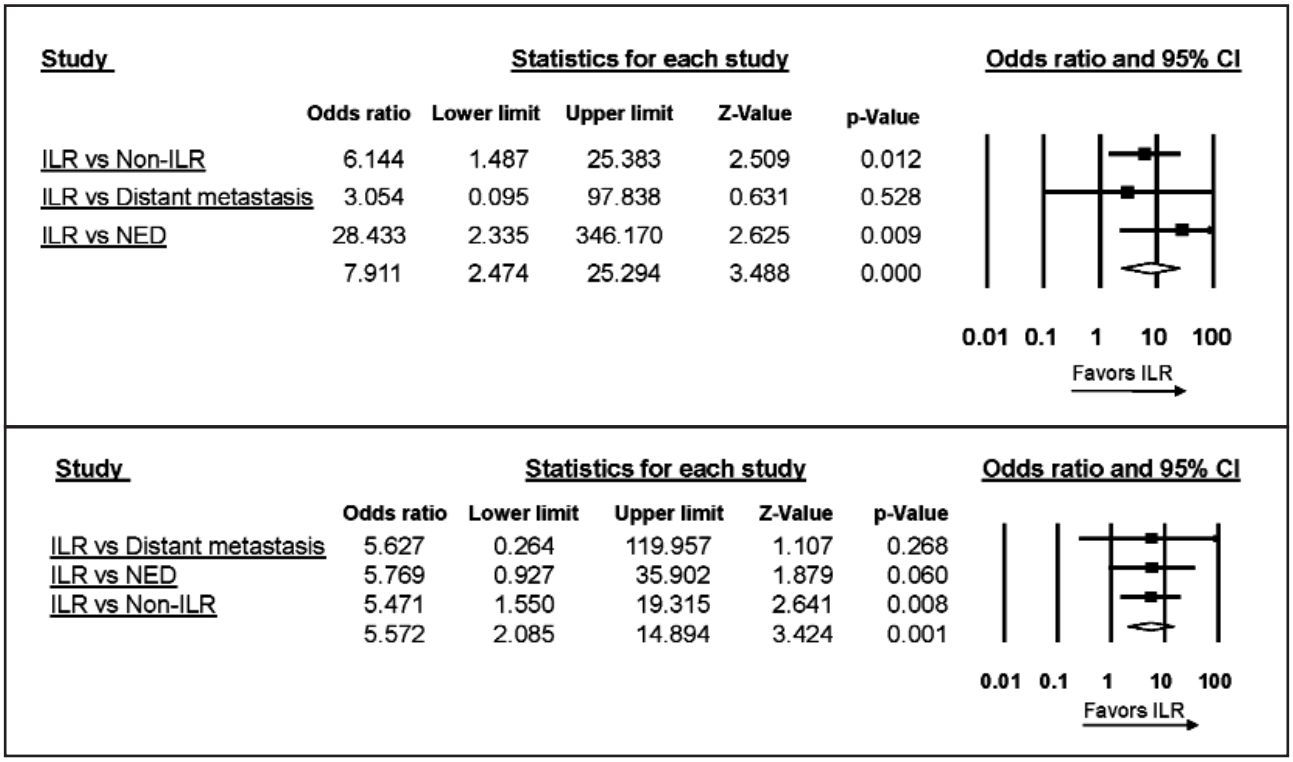

Figure 2. Results of multivariate conditional logistic regression analysis. Comparison of the odds ratios for inflammatory local recurrence of breast cancer when histopathological grade III and lymphovascular invasion (LVI) were present. • *Upper panel:* No family history of breast cancer • *Lower panel:* Family history of breast cancer present in addition to grade III and LVI.
ILR: inflammatory local recurrence **Non-ILR**: noninflammatory local recurrence **NED**: no evidence of disease.

involvement, resection margins, LVI, ER and PR status, and adjuvant treatment. In the first study, Nishimura *et al*., using a case-control design and unconditional logistic regression analysis, observed that LVI was the major predictor of ILR, whereas lymph node involvement, positive surgical margins, and lack of adjuvant radiation therapy were not predictors [8]. They concluded that ILR is mainly due to "occult" inflammatory breast cancer, since all recurrences occurred within 12 months. In the second study, only lymph node involvement and ER status were correlated with the time to ILR and with the overall survival time [13]. Unusual cases of ILR occurring 3 years after BCS were reported.

In a review of immunohistological c-erbB2 expression in 1,794 patients with primary breast cancer in Italy, Menard *et al*. found that ductal type, LVI, high nuclear grade, and negative ER and PR status were associated with high c-erbB2 expression [20]. Higher c-erbB2 expression was also associated with higher relapse rates, even in node-negative patients. However, conditional logistic regression in the present study did not highlight c-erbB2 expression as a major determinant in predicting ILR.

Some histological prognostic factors, such as LVI and multifocality, have not always been considered important enough to be incorporated into guidelines for more aggressive adjuvant therapy. Lymphovascular invasion has been associated with an increased risk of local failure in some series [1,7,19] but not all [17]. The importance of tumor grade in local recurrence is still controversial [7,16]. The current study highlights its role in association with LVI as a predictor of ILR. Hormonal receptor and c-erbB2 status are relevant prognostic factors [20], and multifocality has been associated with high risk of local recurrence [9,17], but these factors seem to be unrelated to the inflammatory nature of the local recurrence in this study.

Lymphovascular invasion is a widely recognized prognostic factor in node-negative breast cancer. Its significance as an independent prognostic factor in node-positive breast cancer remains uncertain [27]. The present case-control study demonstrated that LVI is a strong predictor of ILR in both situations, especially in coexistence with high-grade tumor and family history of breast cancer.

Cutaneous and subcutaneous LVI by cancer cells have been seen in up to 80% of inflammatory breast cancer, whereas less than 2% of operable noninflammatory cases exhibit such pathological features [28-29]. Recent studies have attributed these pathological findings to what is described as "occult inflammatory breast cancer," while recurrent tumors with obvious clinical features of inflammatory breast cancer are described as "secondary inflammatory breast cancer" [28-29]. As such, LVI may be a selection factor for more aggressive

treatment for these patients up front in order to lower their risk of post-treatment recurrence.

Whether ILR is a secondary characteristic acquired by the recurrent lesion or related to the primary cancer remains to be clarified. The findings of this study may be interpreted to indicate that the coexistence of high histological grade and LVI in a breast tumor suggests an aggressive behavior; thus, these findings could be used to alert the oncologist to higher risk of ILR and may formulate the basis of a future study population.

The main methodological limitation to this study is the relatively small number of cases, though this is the largest reported series of patients with ILR. However, matching controls to cases on the year of diagnosis and the age group minimized the effects of periodic or physiological differences. The study design, the homogeneity of therapeutic approaches, and the complete pathologic follow-up enabled relatively in-depth analysis of this rare condition.

Unfortunately, no therapeutic approach has been proven to prevent ILR. Whether our patients with high-grade tumors, family history of breast cancer, and LVI should have been initially more aggressively treated raises a relevant question in the era of growing tendency towards conservative surgery and sentinel lymph node biopsy in early-stage patients such as in the Z0011 trial [30].

Identification of patients at elevated risk of ILR could lead to more effective strategies of treatment at the time of therapy for the primary tumor, designed to lower the incidence of recurrence of this lethal disease. Next steps may include larger cohort and case-control studies or analyses based on prospective datasets that include more biochemical and molecular factors. These would identify more precisely which group of patients are at risk and allow development of methods of reducing the risk of such recurrences.

ACKNOWLEDGMENTS

The authors thank Faith Reidenbach for editorial assistance, which they sponsored, and declare to have no conflicts of interest to disclose.

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