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Molecular and epidemiological characteristics of inflammatory breast cancer in Algerian patients

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Abstract

Background—Inflammatory breast cancer (IBC) shows a high incidence in Tunisia and Egypt but epidemiological and molecular characteristics have not been described in Algeria.

Methods—We compared 117 IBC and 59 non-IBC locally advanced breast cancers (LABC), for estrogen and progesterone receptors, HER2, and EGFR protein expression by immunohistochemistry, and HER2 gene amplification by chromogenic *in situ* hybridization. Demographic, clinico-pathological and molecular variables were compared with chi-square and Fisher's exact tests to test for significance ($P < 0.05$, two-tailed). Overall survival (OS) and disease-free survival (DFS) were plotted using Kaplan–Meier curves and compared using the log-rank test.

Results—Tumor emboli were detected in 77% of IBC. Palpable masses were found in all LABC but only in 32% of IBC ($P < 0.001$). Recurrences were higher in LABC than in IBC (48% vs. 35%; $P = 0.14$) but OS was worse in IBC (68% vs. 71%; $P = 0.06$). There were no significant differences between IBC and LABC by demographics or by clinico-pathologic parameters. The majority of IBC and LABC tumors were luminal A (62% and 64%), followed by basal (~18%, each), triple negative (~18%, each) and HER2+ (~10%, each) subtypes. In multivariate analyses, grade was associated with worse OS ($P = 0.04$), and DFS ($P < 0.001$) in IBC; chemo- and radio-therapy were associated with improved OS and DFS, respectively ($P < 0.05$ for each) in LABC.

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Conflict of interest

The authors declare no conflict of interest.

Conclusions—IBC in Algeria shows similar characteristics to IBC described for Egypt and Tunisia with subtle molecular differences. Current therapeutic treatments were not very effective in this population and new approaches are much needed.

Keywords

Inflammatory breast cancer; locally advanced breast cancer; tumor emboli; tumor subtypes; hormone receptors; growth factor receptors; overall survival; disease-free survival

Introduction

Inflammatory breast cancer (IBC) is a rare but aggressive and lethal form of locally advanced breast cancer with clinical signs mimicking an inflammatory process such as diffuse breast erythema, peau d'orange, skin induration, and warmth. Tumor emboli are often identified in dermal lymphatics, although these are not always seen on skin biopsy [1–3]. While IBC is rare in the US, ~2.5% of American women diagnosed with breast cancer are affected by this disease [4], it is quite high in Northern Africa. Incidence in Tunisia [5] and Egypt [6] is 6% and 11%, respectively, while IBC remains under-investigated in Algeria. The etiologic factor(s) involved in these striking discrepancies between US and North African women remain unknown. Environmental factors such as high fat intake [7, 8], increased exposure to exogenous hormones, pesticides and herbicides [9–11], and infectious agents such as human mammary tumor virus sequences [12, 13] are plausible etiologic factors. Genetic or molecular factors have not been fully explored in IBC; some studies showed similar immuno-phenotypes between Tunisian and French patients [14, 15], but significant differences at the expression level of P-cadherin in Tunisian versus French women [16], and RhoC expression between US and Egyptian IBC patients have been reported [10]. Of interest, IBC Egyptian patients presented more often with high number of tumor emboli and RhoC levels as compared to non-IBC cases [10]. Because both P-cadherin and RhoC are associated with increased tumor cell motility and a more aggressive tumor phenotype, it was suggested that, in addition to other factors, these molecules may explain some of the differences seen in IBC within these populations [10].

In this study, we described the epidemiological and molecular characteristics of a relatively large set of Algerian IBC and matched non-IBC locally advanced breast cancer (LABC) patients, and analyzed prognostic factors and survival in the context of existing multimodality therapy.

Methods

Clinical specimens

Paraffin blocks from 117 primary IBC and 59 non-IBC LABC patients who were treated at Pierre et Marie Curie Cancer Center (PMCCC, Algiers, Algeria) from 2005 to 2009 were included in this study. This study was approved by the University of New Mexico Cancer Center (UNMCC) and PMCCC Institutional Boards. Formalin-fixed paraffin-embedded tissues were collected before any systemic treatment and used to build tissue microarrays (TMAs) as described elsewhere [17, 18]. Baseline clinico-pathological information was retrieved from medical records. The database included patient age, clinical presentation, tumor size, stage, pathologic axillary lymph node involvement, presence of tumor emboli, presence of palpable masses, histological type, presence/absence of distant metastases, nulliparity, age at first parity, number of pregnancies and children, family history of breast cancer, menopausal status (pre- or postmenopausal), rural versus urban residence, socio-economic status, chemo-, radio- and hormonal treatments received, and current status (alive or dead). Patient's residence was classified as suggested by Mourali et al. [19]: urban if the

women lived in a village or town with a population greater than 5,000, and rural if the community size was smaller. Obesity was assessed by using the patient height and weight at diagnosis to calculate the body mass index (BMI), obtained by dividing the weight in kilograms by the square of height in meters (kg/m^2). According to the criteria of the US National Institute of Health/National Heart Lung and Blood Institute (NCI/NHLBI) [20], women were classified as obese if BMI was $\geq 30 \text{ kg/m}^2$, overweight if BMI was between 25 to 30 kg/m^2 and normal/lean if BMI was $\leq 25 \text{ kg/m}^2$. IBC was clinically defined by a rapid onset (i.e., clinical evolution of less than 6 months) of breast edema, erythema and/or peau d'orange and/or warm breast with or without an underlying mass, and a histological proof of invasive breast carcinoma with or without evidence of dermal lymphatic invasion. The histological grading of the tumors was performed in accordance with the Bloom-Richardson classification. Nuclear grading was scored using the 1 to 3 grading system.

Neoadjuvant anthracycline-based chemotherapy was provided to IBC and LABC patients (detailed in Suppl. Table 1). A combination of tamoxifen and zoladex was provided to 56%, and 44% of IBC, and LABC patients, respectively. Aromatase inhibitors were provided to 44% of IBC, and 56% of LABC patients, respectively (Suppl. Table 1). 93% of IBC patients underwent mastectomy (Suppl. Table 1), while the remaining 7% of patients died before surgery could be performed.

Evaluation of ER, PR, HER2, and EGFR expression

ER, PR, HER2, and EGFR protein expression were determined by immunohistochemical staining (IHC) and HER2 gene amplification was detected using chromogenic *in situ* hybridization (CISH) at UNMCC. When only limited tumor sample existed in the two 1.5 mm TMA core or the core tissue was lost during the IHC procedure, a whole section from the original block was used for the study.

ER, PR, HER2 and EGFR expression levels were evaluated using standard procedures with the modified avidin–biotin complex method on the Ventana XT Benchmark auto-stainer (Ventana Medical Systems, Inc., Tucson, AZ) using antibodies against ER (Thermo Scientific, Fremont, CA; clone RB-9016; dilution 1:100), PR (Dako; Carpinteria, CA; clone PgR 636; dilution 1:100) and HER2 (Ventana; clone 4B5) as previously described [21]. EGFR expression was detected with the 31G7 clone (Zymed, Carlsbad, CA; Dilution 1:50). Breast tissues were used as positive controls; the same tissues, incubated with an isotype-matched antibody, were used as negative controls.

Detection of HER2 gene copy number by chromogenic *in situ* hybridization (CISH)

CISH was performed using the SPoT-Light® HER2 CISH Kit (Zymed, Carlsbad, CA), according to the method provided by the manufacturer.

Scoring of IHC and CISH results

Positive status for ER and PR was defined as having nuclear staining in at least 10% of invasive tumor cells. For EGFR, signal intensity was scored as 0 (negative), 1+ (weak), 2+ (moderate), and 3+ (strong). Any complete membranous staining ($>1+$) was considered positive. HER2 protein staining of the membrane was set at four levels, according to the manufacturers' instructions (0, 1+, 2+, and 3+). HER2 positive status was defined as an IHC score of 3+. The tumors with an IHC score of 1+ or 2+ were confirmed by CISH. HER2 amplification was scored according to the Test Interpretation Guide provided by the manufacturer. Samples showing diploid and polysomy status were considered negative; samples showing low and high amplification were considered positive.

Statistical analysis

Primary outcomes for this study were overall survival (OS) and disease-free survival (DFS). OS was calculated from the date of diagnosis with death scored as an event and censoring of other patients at the date of last follow-up or non-disease-related death. The DFS interval was calculated from the date of diagnosis to development of first recurrence. Patients without recurrence were censored at the time of last follow-up or death. Chi-square and Fisher's exact tests were used to compare demographic, clinical, and pathological data between IBC and LABC patients and IHC results between samples. The Spearman test was used to assess correlations between ER, PR, EGFR and HER2 status. For the analysis of ER, PR, EGFR and HER2 status, patients were divided into two groups (positive and negative) as described above. OS and DFS for the groups defined by ER, PR, EGFR and HER2 status and other variables (age, nodal status, lymphovascular invasion, nuclear grade, and chemo-, radio-, and hormone therapy treatments) were plotted using Kaplan–Meier curves and compared using the log-rank test. The Cox proportional hazard model with single covariates was used to obtain the hazard ratios (HRs) and associated 95% confidence intervals (CIs) for the groups compared. Primary multivariable analyses were performed using the Cox model, with candidate variables age (<50, ≥50 years), number of positive nodes (1–3, ≥4), lymphovascular invasion (yes, no), nuclear grade (2 vs. 3), chemo-, radio-, and hormone treatment (yes, no) and ER, PR, EGFR and HER2 status. Variables found to be statistically significant in univariate analyses were considered for inclusion in the multivariate model. Final multivariate models were obtained by a Cox step-wise procedure and verified by backward elimination [22]. For each ordinal variable, the lowest value was used as the reference in computing hazard ratios (HR). Survival rates and HRs are presented with their 95% CIs. Wald tests were used to test for significance of HRs. Two-tailed P values less than 0.05 were considered statistically significant.

Results

Patient characteristics

The majority of IBC and LABC patients were younger than 50 years old. The majority of tumors were infiltrating ductal carcinomas, followed by lobular and other (metaplastic, micropapillary and papillary) histological sub-types for the two series. LABC tumors were larger and palpable, while palpable masses were detected only in a minority of IBC patients (Table 1). However, the majority of IBC samples (77%) showed the presence of tumor emboli while these were absent in LABC cases (Table 1). Radio- and hormone therapy was equally provided to both IBC and LABC patients. However, a significant percentage of LABC did not receive chemotherapy (15% vs. 2% of IBC; $P < 0.001$; Table 1). Although we did not observe significant differences between IBC and LABC patients by other demographic features, IBC and LABC cases were more frequently found in urban patients, pre-menopausal women and affected women of both low and medium income (Supplementary Table 1). We observed higher OS (33.4 vs. 25.1 months) and DFS (27.0 vs. 21.5 months) in LABC as compared to IBC (Supplemental Table 2).

Tumor subtypes by immunohistochemistry

ER expression was observed in the majority of IBC and LABC tumors; about one third of IBC and LABC were PR-positive; HER2-positivity was found in approximately 20% each of the two series, and EGFR was detected in 15% and 17% of IBC and LABC, respectively (Table 1). To simplify the analysis, we restricted the analyses to the ductal non-metastatic IBC and LABC cases only, and classified both tumor categories into 4 molecular subtypes (Table 2). According to this classification, the majority of IBC and LABC tumors were luminal A, followed by basal, triple negative, and HER2+ subtypes without significant differences in the frequencies between the two series (Table 2). In IBC, ER expression

positively correlated with PR ($P<0.001$) but negatively with Her2 and EGFR expression ($P=0.02$ and <0.001 , respectively). PR expression showed a negative correlation with EGFR expression ($P<0.05$). In LABC, ER negatively correlated with EGFR ($P<0.001$), and HER2, positively with EGFR ($P=0.02$).

Response to treatment

A subset analysis representing the follow-up period (53.2 months) shown that in terms of response to treatment, LABC patients who underwent chemotherapy demonstrated a statistically higher breast cancer specific survival (BCSS) than IBC patients who underwent chemotherapy (88% vs. 70%, respectively; $P=0.02$); radiotherapy also showed a trend for better survival in LABC than IBC (84% vs. 67%; $P=0.06$; Table 3). IBC and LABC patients, treated with hormone therapy, showed similar BCSS (Table 3). Higher recurrences were observed in LABC than in IBC with chemotherapy and radiotherapy but the differences did not reach significance (Table 3). Hormone therapy alone was associated with higher recurrence in LABC than in IBC (47% vs. 24%, respectively; $P=0.02$). It should be noted that ~23%, each, ER- and/or PR-positive of IBC and LABC cases did not received hormone therapy because the ER and/or PR status was negative in the primary tumor biopsy at the time of treatment at PMCCC; however, these cases yielded ER and/or PR positivity when analyzed in a centralized laboratory at UNMCC using the same tumor block. Currently we are defining conditions aimed at improving the ER/PR detection at the PMCCC laboratory.

Univariate and multivariate analyses

Univariate analyses for IBC showed that grade was associated with worse DFS (median DFS, 21.5 months) but marginally with OS (median OS, 25.1 months); radio- and chemotherapy were associated with improved survival; hormone therapy, with improved DFS, and Her2-positivity was a factor of worse OS (Table 4). For LABC, radiotherapy was associated with improved OS and DFS; chemotherapy, with improved OS; and luminal A cases were associated with worse DFS (Table 4). In multivariate analyses, grade was a prognostic factor of worse OS and DFS in IBC; chemotherapy was associated with improved OS, and radiotherapy, of improved DFS in LABC (Table 4).

Discussion

This study has several strengths. First, IBC in all patients was confirmed using the same criteria by both clinical and histopathological methods [1]. Second, this study included a large number of IBC patients treated at a single institution, PMCCC, which is the main Cancer Center in Algeria. This may, to a certain extent, be well representative of the general population in Algeria. However, study participants were selected from a large pool of non-IBC patients who were matched with IBC patients on grade and histopathological type to eliminate variables that could confound the comparisons between the 2 groups. Third, several characteristics of the IBC patients recruited in this study were consistent with previous research reports from Egyptian [10] and Tunisian nIBC cases [14, 16], suggesting that the results are not likely to be affected by selection bias. Fourth, the higher incidence of IBC in a large sample of Algerian patients provides a unique opportunity to investigate the etiology and molecular abnormalities of IBC. These studies will give insights into the molecular characteristics of the disease, and will reveal new potential therapeutic targets. Fifth, to our knowledge, this is the first study to investigate the epidemiologic and molecular characteristics of Algerian IBC patients, who appear to exhibit a form of IBC that showed some molecular differences from Egyptian and Tunisian IBC patients.

The study also has limitations and drawbacks inherent to retrospective studies. The lack of reproductive data for the IBC and non-IBC patients is also a limitation. Data on these reproductive factors were searched for from the medical records, but this information was often not recorded.

The descriptive data presented in this study demonstrated no statistically significant differences between IBC and LABC cases. We did not find a significant association between BMI and IBC status, supporting findings of other groups [8, 23, 24]. It has been reported, however, that postmenopausal IBC obese women have significantly worse survival than their leaner counterparts [25]. Although a small matched case-control study from Pakistani women showed a significant familial link for IBC (20% vs. 5% in non-IBC; $P < 0.001$) [26], subsequent studies failed to show such association. In particular, family history of breast cancer was similar in series of French (18% vs. 26%; non-European women mostly from Algeria and Tunisian) and Tunisian (3% vs. 5%) [23], Egyptian (14% vs. 12%) [24], and American (13% vs. 8% in one study, and 40% vs. 36% in a second study from MD Anderson) [27, 28] IBC and non-IBC patients. Our findings of 10% of patients reporting family history of breast cancer for both IBC and non-IBC patients are in agreement with studies showing no familial link for IBC. There are some differences between Egyptian, Tunisian IBC and Algerian patients: The median age for Egyptian and Tunisian IBC patients is ~43 years old [8, 10, 14, 24], but Algerian IBC patients were older (median, 48.5 years). Furthermore, a high proportion of Egyptian IBC patients (83%) presented at diagnosis with palpable masses, high number of tumor emboli, and IBC patients typically lived in rural areas, although this last factor was not significant [24]. It has been suggested that farming-related exposures and exogenous hormones may be implicated in IBC patients [9, 11, 24, 29]. While our data showed that both IBC and LABC are more frequent in urban patients, we found no differences in the frequencies of IBC or LABC in the rural population (Supplementary Table 1). These findings are in contrast to IBC in Tunisia where living in a rural region was strongly associated with IBC [5]. Given the differences in the study design, we can only postulate that the difference may be explained by socioeconomic factors that are quite different in these countries: IBC in Tunisia has a rural predominance with a private health care system not affordable for everybody. In contrast, Algeria has a socialized health system that covers the entire population; more urban than rural population and higher gross income than Tunisia. Of note, when the analysis was restricted to residence and ER-positivity, we found similar ER frequencies in both IBC and LABC in the two populations (73% urban vs. 74% rural in IBC, and 70% urban vs. 73% rural in LABC). This may imply that both rural and urban populations are exposed to similar exogenous hormones, and that farming-related exposures may not have a similar effect in Algeria as opposed to the Egyptian population. There may be other factors implicated in IBC in the Algerian population and further studies are warranted. The presence of tumor emboli has been linked to positive lymph node involvement and worst outcome [30, 31]. Similar to the Egyptian IBC patients [10], the majority of Algerian IBC patients presented with tumor emboli but we did not find any association between tumor emboli and lymph node involvement with patient outcome.

At the biomarkers level, ER positivity (73%) in our IBC patients was higher than in IBC in Egypt and Tunisia (~60% and 47%, respectively) [10, 14, 16]. HER2 and EGFR cases were more frequent in Tunisia (33% and 23%, respectively) than in our population (15%) [16]. Of interest, the basal and HER2 tumor subtypes were more frequently observed in Tunisia (~33%, each), followed by luminal cases (29%) [16]. In our IBC population, luminal A was the predominant subtype, followed by basal, triple negative, luminal B, and HER2 subtypes (62%, 18%, 17%, 10%, 10%, respectively), pointing to molecular differences between these two neighboring countries. While genetic and environmental factors, briefly discussed above, may imprint a unique molecular pattern of IBC in each region, technical variations in

IHC assays (sample collection, storage, fixing procedures and time, and antibodies employed), biomarker grading, as well as study design and sample size may explain the molecular differences observed for the Algerian, Tunisian and Egyptian samples. Further collaborative studies to elucidate molecular differences between these populations with a centralized analysis of samples are warranted.

IBC is an aggressive disease associated with resistance to standard multimodality therapy translating into a dismal prognosis [32]. Because the molecular features of IBC have not been clearly defined, the ability of otherwise effective treatment modalities in non-IBC, such as hormone- and trastuzumab-based therapies have been limited in this population [1]. Although Algerian IBC patients were managed in a multidisciplinary fashion, comprising preoperative chemotherapy followed by surgery and radiotherapy (and hormone therapy for hormone receptor-positive tumors), we observed a worse breast cancer-specific survival in IBC patients independent of chemo-, radio- and hormone therapy. Along with technical improvements in ER and PR detection to cover a higher number of candidate IBC patients for endocrine treatment, new therapeutic approaches such as aromatase inhibitors may be a good option for ER /PR-positive IBC patients. Further, anthracycline-based chemotherapy with or without 1 year of trastuzumab (preoperative followed by adjuvant) demonstrated that the addition of trastuzumab significantly improved the pathological clinical response rates (38% versus 19%, $P = 0.001$) and event free survival (3-year event-free survival 71% versus 56%, HR 0.59, $P = 0.013$) in HER2-positive patients [33]. As indicated by the International IBC consensus, it is reasonable to administer a total of 1 year of trastuzumab among women with HER2-positive IBC tumors [1] in this population. Finally, lapatinib (a reversible inhibitor of EGFR and HER2) has shown encouraging results in the preoperative setting among women with HER2-positive IBC tumors [34–36]. Because about 20% of IBC patients were HER2-positive, lapatinib may potentially benefit in the IBC population, and implementation of clinical trials may be the next step to assess the effectiveness of these drugs in IBC patients.

The results of this study lay the foundation to our ongoing research aimed at investigating the correlation between epidemiologic and environmental risk factors, the molecular differences between tumor subtypes in IBC and non-IBC samples, and the molecular components of IBC in different ethnic groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Clinical and molecular characteristics.

Variable	IBC (%)	LABC (%)	P value*
Age ^(117, 59)			
50 yrs	70 (59.8)	34 (57.6)	0.87
>50 yrs	47 (40.2)	25 (42.4)	
Median ± Std. Dev.	48.5±12.3	50.1±13.8	0.30**
Range:	25–80	26–80	
Size ^(117, 59)			
2 cm /20 mm	14 (12.0)	0	0.003
> 2 cm / 20 mm	103 (88.0)	59 (100.0)	
Median ± Std. Dev.	50±34.4	52±32.0	
Range:	10–190	40–220	
Grade ^(117, 59)			
Mod. differentiated	74 (63.3)	39 (66.1)	0.74
Poorly differentiated	43 (36.7)	20 (33.9)	
Histological type ^(117, 59)			
Ductal	103 (88.0)	53 (89.8)	0.93
Lobular	8 (6.8)	4 (6.8)	
Other	6 (5.1)	2 (3.4)	
Stage			
3B	115 (98.3)	59 (100.0)	
4	2 (1.7)		
Lymph Node involvement ^(117, 55)			
0	14 (12.0)	5 (9.1)	0.71
1–3	20 (17.1)	12 (21.8)	
> 4	83 (70.9)	38 (69.1)	
Median ± Std. Dev.	6±6.7	6±6.9	
Range:	0–29	0–30	
Tumor emboli			
No	27 (23.1)		
Yes	90 (76.9)		
Palpable Masses ^(116, 59)			
No	79 (68.1)	0	<0.001
Yes	37 (31.9)	59 (100.0)	
Chemo therapy ^(117, 59)			
No	2 (1.7)	9 (15.30)	<0.001
Yes	115 (98.3)	50 (84.8)	

Variable	IBC (%)	LABC (%)	P value*
Radiotherapy ^(117, 59)			
No	18 (15.4)	10 (17.0)	0.83
Yes	99 (84.6)	49 (83.0)	
Hormone therapy ^(117, 59)			
No	54 (46.2)	23 (39.0)	0.42
Yes	63 (53.8)	36 (61.0)	
ER ^(101, 52)			
Positive cases	74 (73.3)	37 (71.1)	0.85
PR ^(103, 52)			
Positive cases	29 (28.2)	18 (34.6)	0.58
HER2 ^(101, 52)			
Positive cases	20 (19.8)	11 (21.1)	0.83
EGFR ^(102, 52)			
Positive cases	15 (14.7)	9 (17.3)	0.65

The number of evaluated IBC and LABC cases is shown in parenthesis;

* Fisher's exact test;

** Wilcoxon's test.

Table 2

Immunohistochemical classification of tumors.

Tumor subtypes	IBC (%)	LABC (%)	P value*
Luminal A ^(101, 52) (ER+ and/or PR+; HER2-)	43 (62.4)	33 (63.5)	1.00
Luminal B ^(101, 52) (ER+ and/or PR+; HER2+)	10 (9.9)	5 (9.6)	1.00
HER2+ ^(101, 52) (ER-; PR-; HER2+)	10 (9.9)	6 (11.5)	0.78
Basal ^(102, 53) (ER-; Her2-)	18 (17.7)	10 (18.9)	0.83
Triple negative ^(99, 50) (ER-; PR-; HER2-)	17 (17.2)	7 (17.0)	0.81

The number of evaluated IBC and LABC cases is shown in parenthesis;

* Fisher's exact test.

Table 3

Response to treatments.

Treatment	BCSS		P value [*]	Recurrence		P value [*]
	IBC (%)	LABC (%)		IBC (%)	LABC (%)	
Chemotherapy	68/97 (70.1)	42/48 (87.5)	0.02	34/97 (35.1)	23/48 (47.9)	0.15
Radiotherapy	58/86 (67.4)	37/44 (84.1)	0.06	32/86 (37.2)	22/44 (50.0)	0.19
Hormone therapy	42/58 (72.4)	44/53 (83.0)	0.26	14/58 (24.1)	25/53 (47.2)	0.02

BCSS, breast cancer specific survival;

^{*}Fisher's exact test.

Table 4

Cox proportional hazard models

Variable	Overall survival		Disease Free Survival	
	HR (95% CI)	P value*	HR (95% CI)	P value*
Univariate				
IBC				
Grade ^(103;103)	2.04 (0.89–4.65)	0.09	2.91 (1.36–6.21)	<0.01
Radiotherapy ⁽¹⁰³⁾	0.12 (0.03–0.43)	<0.01		NS
Chemotherapy ⁽¹⁰³⁾	0.28 (0.08–0.94)	0.04		NS
Hormone ⁽¹⁰³⁾		NS	0.49 (0.25–0.98)	0.04
Her2 ⁽¹⁰¹⁾	2.43 (1.01–5.85)	0.05		NS
LABC				
Radiotherapy ^(53,52)	0.16 (0.03–0.86)	0.03	0.23 (0.06–0.94)	0.04
Chemo ⁽⁵³⁾	0.02 (0.001–0.15)	<0.01		NS
Luminal A ⁽⁵¹⁾		NS	3.38 (1.09–10.54)	0.04
Multivariate				
IBC				
Grade ^(92,101)	2.39 (1.01–5.66)	0.05	3.2 (1.37–7.37)	<0.01
LABC				
Radiotherapy ⁽⁵¹⁾		NS	0.18 (0.04–0.80)	0.02
Chemo ⁽⁵³⁾	0.02 (0.001–0.15)	<0.01		NS

The number of evaluated IBC and LABC cases is shown in parenthesis; NS, not significant;

* Fisher's exact test.