Original Article

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Association Between GATA3 and Histopathological and Immunohistochemical Parameters in Early-Infiltrating Breast Carcinomas

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ABSTRACT

Objective: This study evaluated the frequency of GATA-binding protein 3 (GATA3) expression in early breast cancer and its relationship with histopathological and immunohistochemical parameters.

Materials and Methods: GATA3 was analysed by immunohistochemistry in histological sections of tumors from 105 female patients, with histological diagnosis of invasive breast carcinoma (BC), at clinical stages I, II and IIIA, who underwent primary surgical treatment. GATA3 nuclear expression was determined as the percentage of positive tumor cells and further categorized as high (positive expression in more than 95% of cells) or non-high (negative or low positive expression in up to 95% of tumor cells). GATA3 expression was analysed according to the patient age, tumor and node pathological stage, histological type, histological and nuclear grade, lymphovascular invasion, and estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), human epidermal growth factor 2 (HER2) status, and Ki-67 expression.

Results: GATA3 expression was positive in 103 cases (98.1%). High expression was significantly associated with low histological and nuclear grade, positive hormonal receptors, and less proliferative activity based on Ki-67 expression. A prominent feature was that 94.7% of the ER-positive/HER2-negative cases presented high-GATA3 expression, as 94.0% of the tumors showing high-GATA3 were ER-positive. In ER-negative/HER2-positive or ER-negative/HER2- negative, high-GATA3 was present in 25% while 75% were non-high-GATA3 compared with ER-positive/HER2- negative (4.1%) and ER-positive/HER2-positive (20%). Proliferative activity in triple-negative breast cancer tended to be higher among tumors with low-GATA3, irrespective of AR expression. In the group of ER-positive/HER2-negative tumors only three cases were low-GATA3 (85% and 80%), both with high proliferative activity.

Conclusion: High GATA3 expression is associated with favorable histopathologic and immunohistochemical BC prognostic factors.

Keywords: Breast cancer; GATA3 expression; immunohistochemistry; histopathology

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Key Points

- GATA3 is a transcription factor involved in estrogen receptor signaling in breast cancer.
- High-GATA3 expression is linked to favorable histopathological and immunohistochemical findings.
- Breast cancer responsiveness to hormone therapy is probably modulated by GATA gene expression.
- Further studies with GATA3 expression are warranted to determine its clinical role in specific situations, such as low ER tumors and ER positive/PR-negative tumors.

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Introduction

Transcription factors modulate gene expression by binding to their cognate DNA sequence and attracting the enzyme RNA polymerase II to the proper initiation site for transcription. The *GATA3* gene, at chromosome location 10p14, is a member of the GATA family with two GATA-type zinc-finger proteins and encodes the transcription factor GATA-binding protein 3 (GATA3), critical for luminal breast epithelium development and maintenance (1).

The GATA3 protein is linear, with more than 400 amino acids, that can be recognized by immunohistochemical analysis. Mutations of GATA3 and loss of the expression of its related protein are implicated in breast cancer (BC) development and aggressiveness (2, 3). GATA3 is a crucial regulator of estrogen receptor (ER) function and has been associated with a more favorable prognosis in patients with BC (4-6).

Precision oncology, with the identification of actionable genetic alterations, has progressed in the last decades. Currently, medical oncologists' decisions are based on prognostic and tumor predictive response factors, such as pathological and immunohistochemical parameters, and multigene tests. Nevertheless, additional prognostic factors are still needed. In this scenario, GATA3 is emerging as a candidate to broaden treatment options. Therefore, it is appropriate to better understand the role of GATA3 expression in BC and its relationship with other biomarkers.

The aim of this study was to assess the association between pathological and immunohistochemical parameters and GATA3 expression, in order to increase the understanding of BC development and expanding the evidence base for precision therapy.

Materials and Methods

In this prospective case series study, we analysed consecutive BC surgical specimens from patients attending a Mastology Reference Center (Clínica Prof. Alfredo Barros, São Paulo, Brazil). The research was approved by the board of the Ethics Committee of the University of São Paulo School of Medicine. Clinicopathological and immunohistochemical data from patients who fulfilled the inclusion criteria were collected from September 2017 to September 2020. All the cases were treated by the same surgeon (ACSDB) and all the pathological and immunohistochemical analysis were performed by the same pathologists (FMC and FNA).

Patients were eligible if they met these conditions: female sex, early BC (clinical stages I, II, and IIIA), and primary surgical treatment. The exclusion criterium was any patient who had received neoadjuvant treatment.

Histopathological and Immunohistochemical Analyses

All surgical specimens were fixed in a 10% buffered formaldehyde solution, embedded in paraffin, sectioned by handheld microtome, and stained with hematoxylin-eosin. The tumors were classified according to current recommendations (5). The following variables were analysed: Histologic type, nuclear grade, histologic grade, and lymphovascular invasion (LVI). LVI was defined as focal, when only one vascular space was involved, and multifocal, when more than one space had neoplastic emboli.

Estrogen receptor (ER) (clone SP1, Neomarkers, Fremont, CA, USA), progesterone receptor (PR) (PgR636, Dako, Carpinteria, CA, USA), androgen receptor (AR) (F39.4.1, Biogenex, Fremont, CA, USA), Ki-67 (MIB1, Dako, Glostrub, Denmark), and human epidermal growth factor 2 (HER2) (SP3, Thermo Scientific, Fremont, CA, USA) were determined by immunohistochemistry (IHC) staining, which was performed using Streptavidin Biotin Complex and EnVision methods (DakoCytomation). For ER, PR and AR, nuclear staining in more than 1% of the cells was considered positive. ER tumors with 1% to 10% of stained nuclei was reported as ER-low positive.

For HER2, cases with a score of 3+ by IHC, or 2 + with amplification by *in situ* hybridization method, were considered positive. The percentage of cells stained for Ki-67 was determined on the most representative area of the tumor after selecting three to five random fields within the tumor (both periphery and center), with at least 500 cells. Five fields were selected in cases with visually heterogeneous expression, while three fields were accepted for those with a homogeneous distribution of stained cells. The selected fields were transformed in digital images and percentage of Ki-67 stained cells were calculated using the software QuPath (https://qupath.github.io). The average was accepted as the final Ki-67 value.

For GATA3 staining a primary mouse monoclonal antibody was used, clone L 50-823 (Cell Marque - ref. 390 M - 16, CA, USA) at 1:1000 dilution. Nuclear staining in at least 1% of tumor cells was accepted as positive. The percentages in each case were assessed, and after observing their distribution, two GATA3 expression classes were empirically defined: high-positive (>95% of stained cells) and non-high-GATA3 (negative or positive expression in up to 95% of tumor cells).

As most of the cases were high-positive, and negativity was very rare, we grouped the results of the GATA3 expression in only two categories for statistical analysis: high and non-high (negative or low).

Statistical Analysis

The associations between GATA3 expression and qualitative variables were analysed by the chi-square test or Fisher's exact test. Correlation with quantitative variables was analysed by the Mann–Whitney test. MedCalc® Statical Software version 19.6.1 (Ostend, Belgium) was used for the analyses. A $p<0.05$ was considered significant.

Results

A total of 105 patients were included. GATA3 expression was positive in 103/105 (98.1%) cases. The percentage of stained cells ranged from 0 (n = 2 cases) to 100%, and no case presented with expression in the 1% to 19% range.

In this study the categories "negative", "low-positive", and "high-positive" for GATA3 expression were defined, and due to the very widespread expression of GATA3, the negative and low positive results were grouped together in a single category, the non-high GATA3 group. According to the proportion of stained cells, 84 cases (80%) presented >95% of positive cells (high-positive expression); 19 cases (18.0%) presented ≤95% of positive cells (low-positive expression), and two cases were negative (1.9%). Figure 1 shows examples of immunohistochemical findings.

There was a tendency to observe non-high expressions in younger patients, with a median age of 50.0 years in patients with GATA3 low or negative, and 60.5 years in the GATA3 high group ($p = 0.08$).

High-positive GATA3 expression was more frequent in samples with low histological grade and low nuclear grade (p<0.001). High-GATA3 expression was observed in all infiltrating lobular carcinomas. There was no association with tumor size, lymph node status, or LVI. These results are detailed in Table 1.

Immunohistochemical findings are shown in Table 2. Significant differences in ER, PR, AR, and Ki-67 were found when comparing the groups based on low/negative or high GATA3 expression.

As for immunohistochemical tumor subtypes classification, a prominent feature was that 94.7% of the ER-positive/HER2-negative

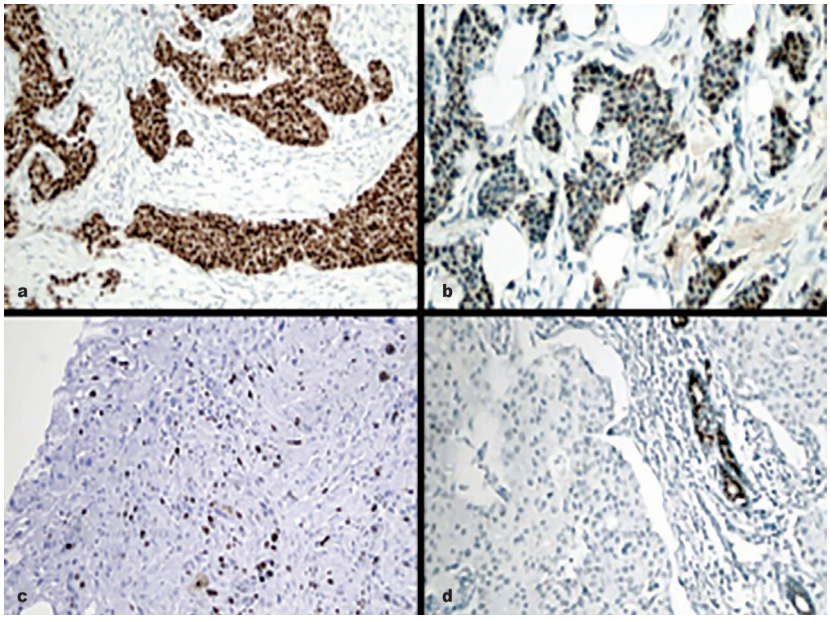

Figure 1. Immunohistochemical findings of GATA 3 expression in non-special type invasive breast carcinoma cells: **a)** high-positive with strong expression in 100% of tumor cells; **b)** low-positive with 70% of stained cells; **c)** low-positive with 20% of positive cells; **d)** negative

Table 1. Pathological parameters in the GATA3 expression categories

		Non-Hhigh	High	*p*-value
		N (%)	N (%)	
Histological type	Non-special type	17 (22.7)	58 (77.3)	0.130
	Lobular	0 (0)	14 (100)	
	Others	4 (25)	12 (75)	
Histological grade	I	1 (5.9)	16 (94.1)	<0.001
	II	4 (6.6)	57 (93.4)	
	III	16 (59.3)	11 (40.7)	
Nuclear grade	1	1 (7.7)	12 (92.3)	0.001
	2	2 (4.3)	44 (95.7)	
	3	18 (39.1)	28 (60.9)	
Lymphovascular invasion	Absent	15 (20.5)	58 (79.5)	0.423
	Focal	5 (26.3)	14 (73.7)	
	Multifocal	1 (7.7)	12 (92.3)	
pT	≤20 mm	12 (19.1)	51 (80.9)	0.286
	>20 mm e ≤50 mm	9 (25.7)	26 (74.3)	
	>50 mm	0 (0)	7 (100)	
pN	Positive	5 (13.8)	31 (86.1)	0.260
	Negative	16 (23.2)	53 (76.8)	

pT: pathological tumor size; pN: pathological node status

cases presented high-GATA3 expression, as 94.0% of the tumors showing high-GATA3 were ER-positive. in contrast, only 25% of cases with ER-negative/HER2-positive or ER-negative/HER2-negative evidenced high GATA3.

The two patients with GATA3 negative tumors (aged 50 and 30 years old) presented stage I triple-negative (TN) carcinomas, histological grade III, nuclear grade 3, AR-negative, and Ki-67 of 40% and 80%, respectively. Among the 13 TN cases, 9 (69.2%) presented with non-high-GATA3 expression, and of these 6 (66.7%) were AR-negative.

Discussion and Conclusion

Looking at clinicopathological parameters, high-GATA3 expression was associated with some favorable pathological features of BC, such as histological grade I and nuclear grade 1. In keeping with most of the previous studies, we did not find an association between GATA3 and tumor size and/or lymph node metastasis (6-8) despite one study, Querzoli et al. (9), reporting an inverse association with tumor size . A further study, Mehra et al. (10), reported low-GATA3 expression associated with lymph node metastases. Generally, our cohort findings linked high-GATA3 expression to favorable pathological features of BC.

It is well known that GATA3 plays a significant role in the normal development and function of the mammary gland, and as a marker of luminal identity in BC. As the most frequent transcription factor in luminal tumor cells, GATA3 became an important indicator of mammary differentiation in neoplasia of unknown origin, with better utility than mammaglobin and gross cystic disease fluid protein (3). Our results confirm this high GATA3 frequency in BC, as we found 98.1% positivity among all tumors. These results highlight the role of GATA3 as a reliable marker for primary tumor identification in occult BC found in lymph nodes or systemic metastases.

GATA3 is highly expressed in luminal BC, taking part in a gene set that identifies intrinsic tumor subtypes with distinct survival outcomes and is closely correlated with ER-alpha gene expression, an important fact to explain the role of GATA3 in hormone responsiveness (11-13). Notwithstanding, ER positivity is not a guarantee of a satisfactory response to hormone therapy and other factors must be considered. One of these factors is proliferative activity, evidenced by multigenic tests or by the expression of Ki-67 (14, 15). We found four patients with ER-positive/HER2-negative tumors and low-GATA3, all of them exhibiting a high-Ki-67 index. Although both *GATA3* and *ESR1* gene expression are correlated, probably other genes regulated by GATA3 are critical to hormone=responsiveness and possibly different types of mutation can impact its transcriptional function. Some of the other factors in the transcriptional apparatus include the cooperative action of the transcription factor FOXA1 and the genes *TP53*, *PIK3CA*, and *CDH1* (4, 16).

Given this complex scenario, it seems very difficult to establish a clear association between the categories of GATA3 expression–and gene mutations or epigenetic silencing (1). Probably when a strong and diffuse expression of GATA3 is observed, there is a whole transcriptional apparatus_functioning. A major challenge will be understanding the effect of differences in protein expression.

GATA3 is considered a prognostic marker in patients with biologically less aggressive tumors and is potentially useful to forecast sensitivity to anti-estrogenic treatment (17). In this regard, Parikh et al. (16)

Table 2. Immunohistochemical parameters by GATA3 expression category

		Non-Hhigh	High	*p*-value
		n (%)	n (%)	
ER	Positive	6 (7.1)	79 (92.9)	<0.001
	Negative	15 (75)	5 (25)	
ER	Negative	15 (75)	5 (25)	<0.001
	Low	2 (100)	0 (0)	
	Positive	4 (4.8)	79 (95.2)	
PR	Positive	3 (4.2)	69 (95.8)	<0.001
	Negative	18 (56.2)	14 (43.7)	
AR	Positive	10 (11.4)	77 (88.5)	<0.0001
	Negative	11 (61.1)	7 (38.9)	
HER2	Positive	8 (44.4)	10 (55.6)	0.005
	Negative	13 (14.9)	74 (85.1)	
kKi-67	≤20%	4 (8.5)	43 (91.5)	0.001
	>20%	17 (29.3)	41 (70.7)	
Subtypes	ER positive/HER2 negative	4 (5.3)	71 (94.7)	<0.0001
	ER positive/HER2 positive	2 (20)	8 (80)	
	ER negative/HER2 positive	6 (75)	2 (25)	
	ER negative/HER2 negative	9(75)	3 (25)	

ER: estrogen receptor; PR: progesterone receptor; RA: androgen receptor

remarkably observed that none of the responders to endocrine therapy was GATA3 negative, whereas 43% of the non-responders were GATA3 negative. A controversial group is the one with low expression of ER (1%-9% positive cells), which shares clinicopathological characteristics, biomarker profile, and outcomes with TN tumors (18, 19). In our cohort, we identified only two ER low positive carcinomas, both with-low GATA3 expression, a proportion closer to ER-negative rather than ER-positive cases.

Among ER-positive/HER2-negative tumors, the PR-negative subgroup has well-known lower responsiveness to endocrine therapy (20). Liu et al. (21) observed that the genomic analysis of this subgroup revealed that 16% are basal by PAM50 and present loss of GATA3. They developed an IHC-based classification-tool to discriminate non-luminal-like from luminal-like subtypes within the ER-positive/PR-negative/HER2-negative phenotype, showing that the non-luminal-like phenotype, characterized by GATA3-negative, CK5-positive and/or EGFR-positive tumors, received a limited benefit from adjuvant hormone therapy. In their turn, Tahiri et al. (22) observed that loss of PR expression correlates with higher tyrosine kinase activity in tumors that were HER2-negative.

The degree of benefit of hormone therapy in ER-positive/RP-negative cases remains debatable, and the possibility of using GATA3 for management decisions appears attractive. We had eight ER-positive/PR-negative/HER2-negative BC cases: 2 (25%) of them with GATA3 ≤95% and high Ki-67 (70% and 80%), and the other six cases with high GATA3 and Ki-67 between 5% and 30%. These data suggest that these tumors correspond to a heterogeneous group, and the therapeutic decision could be improved by additional data including the expression level of GATA3 and proliferative activity.

There is also a paucity of reliable data on the efficiency of hormone therapy in low-ER tumors. As convincing evidence remain elusive, it may be, at the moment, pragmatic to believe that the chance of good response with hormone therapy is higher in patients with low-ER tumors, but with preserved high-GATA3 expression.

Our results confirmed that high-GATA3 is much more frequent in ER-positive than in ER-negative tumors (92.9% *versus* 25%). Among our 13 cases of TN breast carcinomas, ten had low-GATA3 and, in this group, Ki-67 varied from 30% to 95%. In the three cases with high-GATA3, Ki-67 was 45%, 10%, and 18%. While all TN tumors with high-GATA3 expression were AR positive, only three low-GATA3 expressed AR, one of them with only 2% of positive cells. AR-positive TN carcinomas are associated with the luminal androgen receptor molecular subtype of these tumors. This subtype has hormonally regulated pathways that are active in the synthesis and metabolism of steroids, and share mutations with luminal carcinomas (23). These tumors are characterized by a low Ki-67 index and distinct clinicopathological presentation, and it is reasonable to conjecture that they preserve GATA3 functional integrity.

We analysed 18 HER2-positive carcinomas, ten of them ER positive and eight ER-negative. Although low-GATA3 was more frequent among ER-negative tumors (75% *versus* 20%), no statistical difference in proliferative activity, evaluated by Ki-67 expression, could be demonstrated (median 34% and 35% in both groups). This suggests that the role of GATA3 in HER2-positive carcinomas might be distinct, maybe because of the activity of tyrosine-kinase enzymes.

An association between non-high-GATA3 expression and high-grade tumors, in accordance with Lu et al. (24), was found. These characteristics are associated with poor prognosis, irrespective of molecular subtype, and Cakir et al. (6) estimated an 87% rate for GATA3-positive and a 78% rate for negative tumors in terms of five-year disease-free survival. For these authors, GATA3 was an independent factor for overall survival. In addition, Kouros-Mehr et al. (25), in an experimental model, observed that non metastatic cell lines have elevated GATA3 levels, whereas cells of metastatic lines have low GATA3 levels.

We acknowledge important limitations in our study, including the small sample size (particularly in the groups of ER-negative tumors), and the short follow-up period, which are insufficient for reliable outcome analysis. However, it opens new avenues to be explored concerning the role of GATA3 in the pathogenesis, evolution, and therapy of BC, mainly in the ER-low, ER-positive/PR negative, HER2-positive, and LAR TN subgroups. The results presented in these subgroups warrant further clinical investigation.

In conclusion, high expression of GATA3 protein in early infiltrating BC, is a surrogate marker of less aggressive disease. High-GATA3 expression is linked to greater tumoral differentiation and lower nuclear grade, lesser proliferative activity, and positivity of ER, PR, and AR. Regarding GATA3 expression in the various IHC subtypes, the highest rate was identified in luminal-like tumors (ER-positive and HER2-negative), and the lowest rate was found in basal-like tumors (ER-negative and HER2-negative). These results indicate that GATA3 expression can add important information about sensitivity and/or resistance to endocrine therapy, as well as possible chemosensitivity, especially in ER-positive tumors.

Ethics Committee Approval: The study was approved by the Ethics Committee of the University of São Paulo Medical School (CAAE: 562 69416.0.0000.0065; decision No.1.604.792).

Informed Consent: Due to the retrospective design of the research, informed consent was waived.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: P.M.S., A.C.S.D.B.; Microscopic Analysis: F.M.C., F.N.A.; Data Collection: P.M.S.; Supervision D.G., F.M.C., A.C.S.D.B.; Writing: P.M.S., A.C.S.D.B., D.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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