Clinicopathological characteristics of basal-like breast cancer: a comparative study between Egyptian and British patients

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Background
Clinicopathological features of basal-like breast cancer (BLBC) in African-American women have been extensively studied. Comparatively, less is known about these tumors in patients from countries in the North African region. The aim of this study was to assess the frequency and clinicopathological characteristics of BLBC in Egyptian patients in comparison with British patients.
Patients and methods
Tissue microarray blocks were constructed from primary invasive breast cancers from 321 Egyptian and 527 British patients with BC. Sections were stained immunohistochemically with estrogen receptor, progesterone receptor, epidermal growth factor receptor 2, CK19, CK14, EGFR, CK5/6, P53, and Ki-67. BLBC phenotype was identified by the lack of staining of estrogen receptor, progesterone receptor, and epidermal growth factor receptor 2, and positive staining for any of the CK14, CK5/6, and/or EGFR.
Results
The rate of BLBC phenotype was higher in Egyptian cohort (21%) than the British cohort (13%). BLBC tumors from both Egyptian and British patients were significantly associated with tumors of higher histopathological grade ($P<0.001$ and <0.001, respectively), higher proliferation rate ($P<0.001$ and 0.001, respectively), and higher rate of P53 expression ($P<0.001$ and <0.001, respectively). Compared with the British patients with tumors, BLBC in Egyptian women were significantly of larger tumor size ($P<0.001$) and were associated with more advanced lymph node stage ($P<0.001$).
Conclusion
BLBCs occurred more frequently in Egyptian patients compared with British women and are characterized by unfavorable biological features, akin to BLBC in African-American women. These findings warrant further studies to unravel the genetic background of BLBCs and whether their aggressive features are related to ethnic origin or other multifactorial and environmental variables.

Keywords:
basal like, breast cancer, British patients, comparative study, Egyptian

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Introduction

The term basal or basal-like breast cancer (BLBC) phenotype has emerged after the gene expression profiling of breast cancer (BC) as tumors expressing a transcriptome similar to that expressed by basal/myoepithelial cells of the mammary gland, hence its name (Sorlie *et al.*, 2001). Although BLBC was originally defined using gene expression profiling, its definition has been translated into immunohistochemical (IHC) definition (Abd El-Rehim *et al.*, 2004). IHC expression of one or more of the basal cytokeratins (CK5/6, CK14, and CK17) and EGFR has been widely accepted as a method for identification of BLBC (Abd El-Rehim *et al.*, 2004).

Triple-negative BC is identified by the negative IHC staining for the hormonal receptors – estrogen receptor (ER) and progesterone receptor (PR) – and for human epidermal growth factor receptor 2 (HER2). It has attracted increased attention in research over the past 15 years owing to its peculiar biological characteristics, poorer clinical outcome, and its lack of response to known chemotherapeutic BC agents (Rakha *et al.*, 2007). BLBC and TN tumors overlap, as they share several histopathological features. These tumors tend to be large sized, of high histopathological grade, with high proliferation rates, and are associated with higher rates of necrosis (Dufloth *et al.*, 2009; Rakha *et al.*, 2009a; Aleskandarany *et al.*, 2012).

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Recent studies reported variation of BLBC frequency among populations from different ethnic backgrounds, with variable reported rates (Troester *et al.*, 2018). Early studies reported that these tumors are estimated to account for 2–18% of BCs (Nagle *et al.*, 1986; Abd El-Rehim *et al.*, 2004) and that there are higher rates in some ethnic groups compared with others (Carey *et al.*, 2006; Parise *et al.*, 2010).

It has been known for a long time that BC morbidity and mortality is higher in Black women than in White women (Yang *et al.*, 2017). These differences were found to be owing to intrinsic biological characteristics rendering BC in these population more capable for lymph node (LN) and distant metastasis in addition to having rates of TN phenotype (Iqbal *et al.*, 2015). Enormous data characterizing BLBC in western and European women has been gained. Comparatively, this data is less in African and Asian population.

The aim of this study was to assess the clinicopathological characteristics of BLBC in Egyptian patients and to compare it with those from British patients.

Patients and methods

Patients

This study was conducted on 848 specimens of primary BC: 321 specimen from Egyptian patients and 527 from British patients.

Egyptian patients' cohort

Formalin-fixed paraffin-embedded blocks of 321 specimen from women diagnosed with primary invasive BC were obtained from the archives of the surgical Pathology Laboratory, Assiut University Hospital, Assiut, Egypt. These specimens represent a consecutive series of patients with primary BC, with LN stage I, II, and III, who presented to Assiut University Hospitals from year 2000 to 2011. Clinical data including patient's age at diagnosis, tumor site, tumor size, LN status, operation type, and treatment given were retrieved from the patients' hospital medical records. All hematoxylin and eosin-stained sections for each specimen were examined for detailed histopathological evaluation and for selection of a representative block for tissue microarray (TMA) construction. Ethical approval was obtained from the Assiut Faculty of Medicine Ethical Review Board (#29-7-2010).

Nottingham patients' cohort

For the purpose of this study, a well-characterized consecutive series of patients with early invasive primary operable BC (n=527) from patients presenting to Nottingham City Hospital were used. This consecutive list of specimens was taken from the main data set, which consisted of 2500 specimen. Tumors in these patients were equal to or less than 5 cm in diameter at the time of presentation (Abd El-Rehim *et al.*, 2005). Patients were uniformly treated according to standard protocol: primary surgery, with either mastectomy or wide local excision, followed by radiotherapy (Blamey *et al.*, 2007). Moreover, this cohort has been well investigated using a wide range of biological markers. Patients' clinical and pathological data including age, histological tumor type, primary tumor size, LN status, histological status, and vascular invasion were available and prospectively maintained. Moreover, data about a wide range of markers of close relevance to BC biology and outcome, including ER, PR, HER2, cytokeratins, cell cycle regulators, and others, were also available (Abd El-Rehim *et al.*, 2004; Abd El-Rehim *et al.*, 2005; Aleskandarany *et al.*, 2012).

Tissue microarray construction

For specimens from Assiut University, manual TMA construction was performed using the Arraymold kit B 150 core TMA [catalog no. IW-111, IHCWORLD, (www.ihcworld.com) according to the manufacturer's instructions]. The total number of BC specimens used was 321 specimens, with three cores (each of 1.5 mm diameter). Three TMA replicate blocks were constructed holding cores obtained from different areas of donor blocks according to a previously designed layout map. Two TMA blocks from each batch were sectioned for IHC staining.

For specimens from Nottingham, TMA blocks construction and IHC staining was described previously in several previous studies (Abd El-Rehim *et al.*, 2004; Abd El-Rehim *et al.*, 2005). Ki-67 was stained using whole sections.

Immunohistochemical staining

Tissue sections (4-μm thick) of each TMA block were stained with specific antibodies against ER, PR, HER2, EGFR-1, CK14, CK19, CK5/6, P53, and Ki-67 (Table 1) using standard IHC methods as described previously. For the visualization of the antibody–enzyme complex, 3,3-diaminobenzidine-tetrahydrochloride (TA-060-HDX; Thermo Scientific) was used.

Scoring of the immunohistochemical staining

Results of IHC staining were examined using light microscopy. Nuclear staining for ER, PR, P53, and Ki-67 was assessed as percentage of positive nuclei of invasive BC cells. Any positive staining for ER and for PR was considered ER-positive and PR-positive

Table 1 Technical details of the primary antibodies used in the study

Antibody	Source, type, catalogue and clone number	Dilution and incubation time with 1ry Ab	Antigen retrieval
ER	Thermo Scientific, Rabbit monoclonal RM-9101-S0(SP1)	1:100 1 hour RT	Heat induced, 10 mmol. Tween and EDTA, pH 8.0.
PR	Thermo Scientific, Rabbit monoclonal RM-9102-S0 (Sp2)	1:100 1 hour RT	Heat induced, 10 mmol. Tween and EDTA, pH 8.0.
EGFR-1	Genmed biotechnology 31G7 clone	1:50 1 hour RT	Pepsin enzyme at incubator 15 min.
HER2	Thermo scientific Mouse monoclonal MS-730-P0 (e2-4001)	1:300 1 hour RT	Citrate, pH 0.6 using microwave/800 W for 20 min..
CK14	Thermo Scientific, Mouse MonoclonalMS-115-P0 (LL002)	1:20 1 hour RT	Citrate, pH 0.6 using microwave/800 W for 20 min..
CK19	Thermo Scientific, Mouse Monoclonal MS-198-P0, (A53-B)	1:100 1 hour RT	Citrate, pH 0.6 using microwave/800 W for 20 min..
CK5/6	Thermo Scientific, Mouse Monoclonal MS-1814-S0 (D5/16B4)	1:10 overnight 4 C°	Citrate, pH 0.6 using microwave/800 W for 20 min..
P53	Thermo Scientific, Mouse Monoclonal MS-738-P0	1:200 1 hour RT	Citrate, pH 0.6 using microwave/800 W for 20 min..
Ki67	Rabbit polyclonal, RB-1510-P0	1:50 1 hour RT	Citrate, pH 0.6 using microwave/800 W for 20 min..

ER, estrogen receptor; PR, progesterone receptor; EGFR-1, epidermal growth factor receptor-1; RT, room temperature; mmol, millimole; W, watt.

tumor, respectively. For Ki-67, 14% was used as a cutoff point to identify the tumors with high proliferation index [Ki-67 positivity in>14% of tumor cell nuclei according to St Gallen consensus guidelines 2011 (Goldhirsch *et al.*, 2011)], whereas 10% was used for P53 (P53 positivity in≥10% tumor nuclei). Basal markers (CK14 and CK5/6) characteristically stain basal cells in normal ducts and were negative in luminal cells with heterogenous staining pattern in tumor cells (Fig. 1). EGFR-1 and HER2 showed positive membranous staining. Staining for EGFR, CK5/6, and CK14 was assessed by identification of the percentage of positively stained cells. The cutoffs for these markers were at least 10 for EGFR, CK5/6, and CK14. Results of HER2 were recorded according to the latest ASCO/CAP guidelines for HER2 testing using the 0, 1+, 2+, and 3+ scoring system (Wolff *et al.*, 2013). Tumors with HER2 overexpression (HER2 score 3+) were those having a strong and complete membranous staining in more than 10% of invasive tumor cells.

TN was defined as those tumors with negative staining for ER, PR, and HER2. BLBCs were those tumors within the TN phenotype which also expressed any of the basal cytokeratins (CK5/6 and/or CK14) and/or EGFR. All other BC specimens that did not fulfill any of these criteria were grouped as 'other BC' group. This classification was used to identify BLBC in both Egyptian and British specimens. The term BLBC in the present study therefore will be used to identify tumors that are negative for ER, PR, and HER2 and express at least one of the basal cytokeratin markers CK5/6 or CK14 and/or express EGFR.

Statistical analysis

The statistical analysis was performed using statistical package for the social sciences SPSS version 21 for Windows (SPSS Inc., Chicago, Illinois, USA). Associations between BLBC phenotype and clinicopathological data were assessed using the 2×2 cross-tables and χ^2-test. A P value of less than 0.05 (two-tailed) was considered significant.

Results

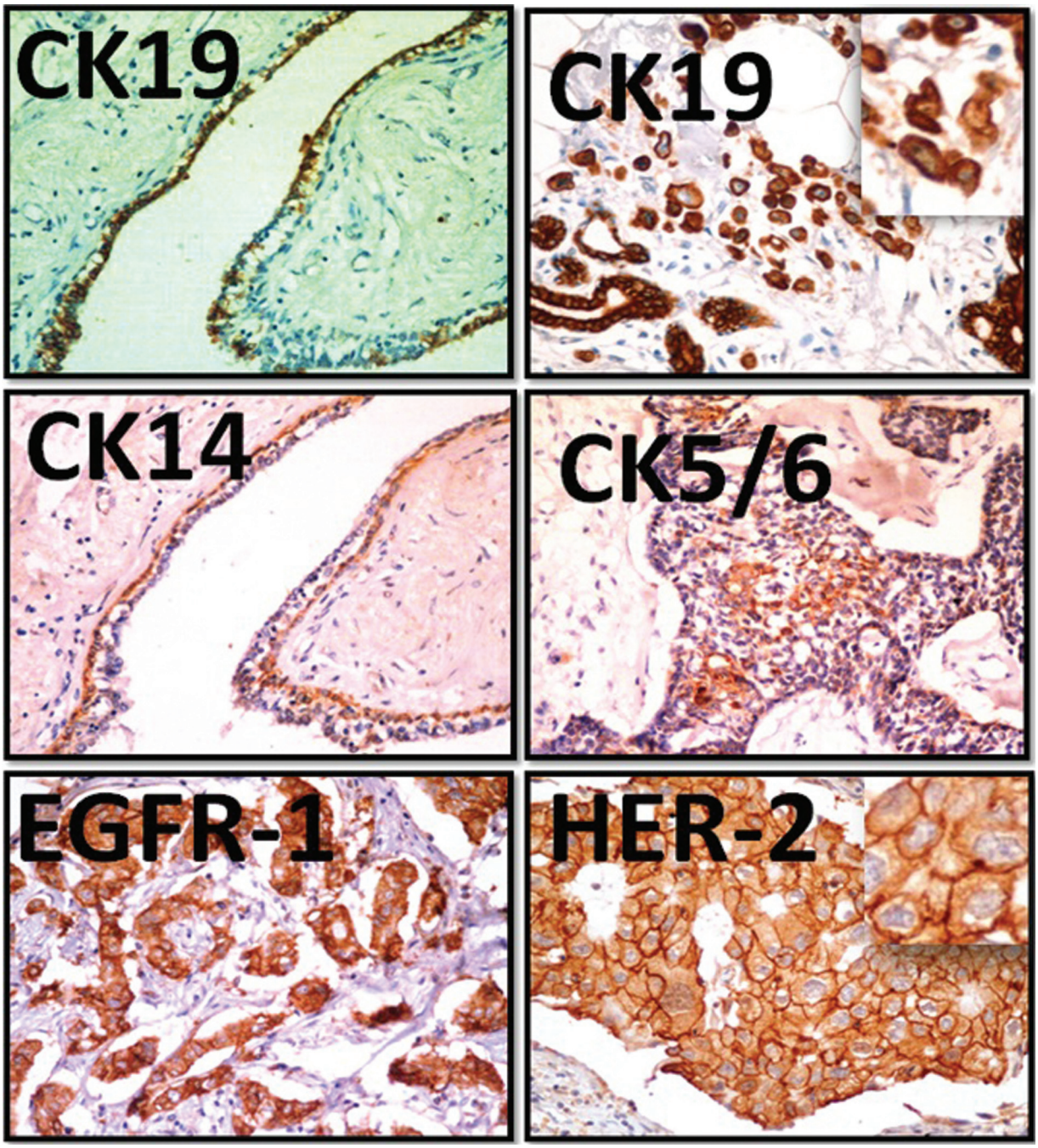
Egyptian cohort

TNBC was identified in 84/321 (26%) specimens, and BLBC was identified in 68/321 (21%) specimens. A significant association was seen between BLBC phenotype and tumors of high histopathological grade, where 82% of BLBC were grade 3 compared with 27% of other BC group (P<0.001; Fig. 2). A significant association was also seen between BLBC phenotype and LN stage (P=0.003), higher proliferation rate (P=0.001), and higher rate of P53 expression (P<0.001; Fig. 2). No significant association was detected between the BLBC phenotype and the patient age (P=0.163), tumor size (P=0.053), or with the presence of lymphovascular invasion (LVI) (P=0.639).

British cohort

Primary BC specimens from 527 patients were examined for TN and BLBC features. TN carcinomas were identified in 83/527 (16%) and BLBC in 67/527 (13%) specimens; both figures of TNBC and BLBC rates were significantly lower than those of the Egyptian cohort (P<0.001 and 0.001, respectively).

Fig. 1



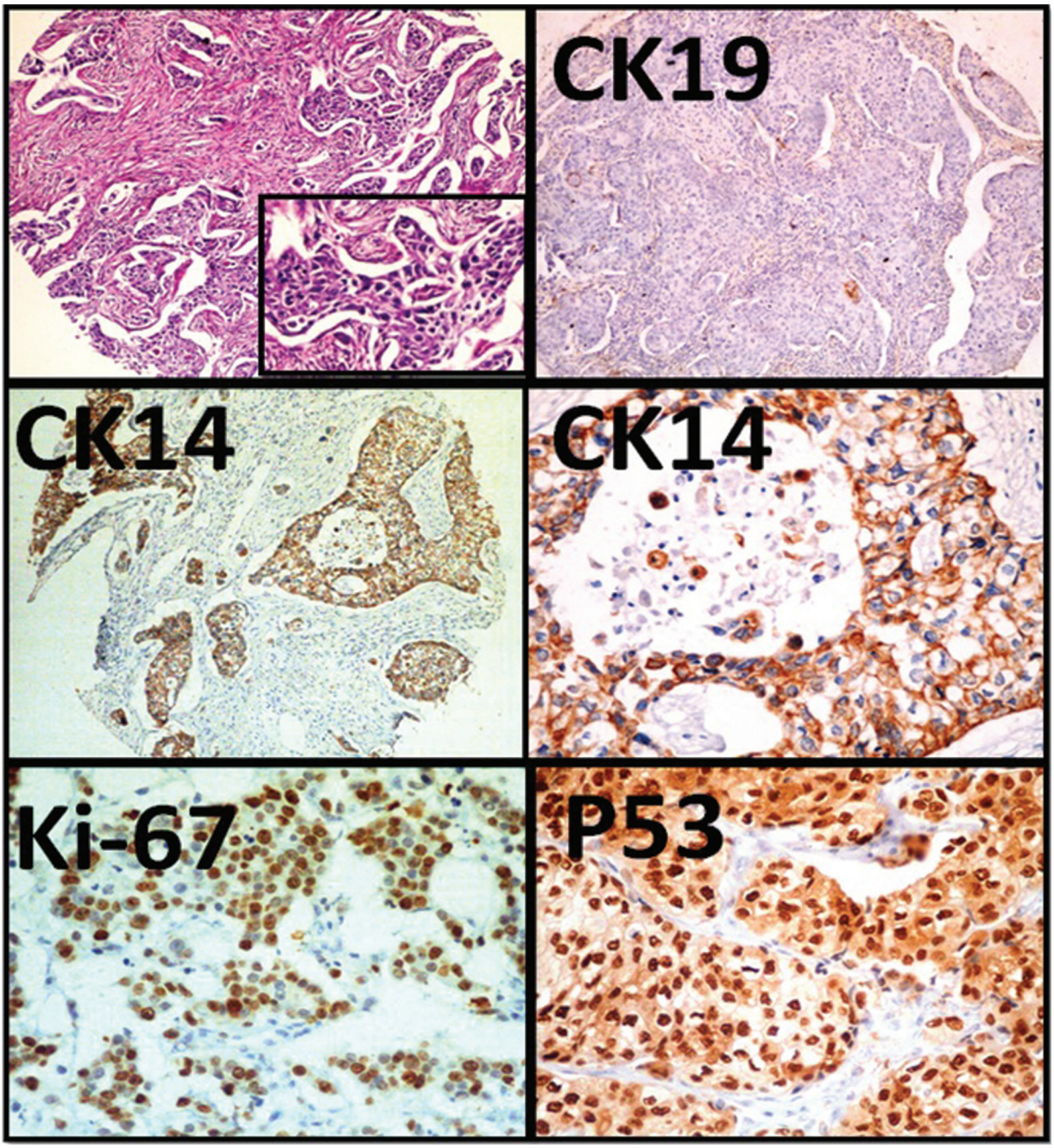
Different examples of breast tissue specimens showing the pattern of immunohistochemical staining of the markers used in the study. Upper panels: The luminal marker (CK19) shows positive membranous staining in luminal cells in normal ducts (left ×200) and tumor cells (right ×200 and inset ×400). Middle panels: show staining pattern for the basal markers; CK14 and CK5/6 both show positive staining in the basal cells in normal ducts (left ×200) with heterogenous staining in tumor tissue (right ×200). Lower panels: shows membranous staining pattern for both EGFR (×200) and HER-2 (×200 and inset ×400).

Specimens of the British cohort were similar to those of the Egyptian cohort in the significant association between BLBC and high-grade tumors ($P<0.001$), high proliferation rate ($P<0.001$), and high rate of P53 expression ($P<0.001$). Unlike Egyptian specimens, there was a significant association between BLBC phenotype in British specimens and patients younger than 50 years ($P=0.001$) and with tumors of larger size ($P=0.017$) but was not associated with LN stage ($P=0.230$). Further details are summarized in Table 2. An earlier report (Rakha *et al.*, 2009b) described detailed clinicopathological criteria of the BLBC subtypes in British patients.

Comparison of clinicopathological criteria between basal-like breast cancer in Egyptian and British specimens

The clinicopathological characteristics of BLBC in Egyptian patients were significantly different from

Fig. 2



A specimen of basal-like breast cancer phenotype. Upper left panel is staining with hematoxylin and eosin showing features of NST type with high histopathological grade (×100 and inset ×200). Upper right is immunohistochemical staining showing negative staining for the luminal marker CK19 (×100). Middle panels show positive staining for the basal marker CK14 (×100 and ×400). Lower panels show high proliferation rate (Ki-67) and high P53 expression rate (×400).

those of British patients. The BLBCs in Egyptian patients were significantly larger in size ($P<0.001$), had more frequent LN metastasis ($P<0.001$), and had a higher percentage of tumors with high proliferation rate ($P<0.001$) compared with the British cohort. No difference was seen between both populations regarding patient age ($P=0.304$), tumor grade ($P=0.065$), presence of LVI ($P=0.244$), or in the rate of P53 expression ($P=0.432$; Table 3).

Discussion

BLBC is a distinct molecular subtype of BC that is characterized by having a more aggressive behavior and confers a worse outcome. Several published reports described the molecular, pathological, and clinical features of BLBC in western and European women (Rakha *et al.*, 2007; Rakha *et al.*, 2009a; Rakha and Ellis, 2009); however, few studies were conducted to study those tumors in Egyptian patients.This study

Table 2 Clinicopathological characteristics of basal-like breast cancer specimens in Egyptian and British patients

		British				Egyptian			
Feature	Subgroups	BLBC	Other BC	Total	*P* value	BLBC	Other BC	Total	*P* value
Age	≤50	34 (52)	140 (30)	174 (33)	0.001	29 (43)	132 (52)	161 (51)	0.163
	>50	32 (48)	318 (70)	350 (67)		39 (57)	121 (48)	160 (49)	
Size (cm)	≤2	34 (51)	298 (66)	332 (64)	0.017	12 (18)	74 (29)	68 (27)	0.053
	>2	33 (49)	155 (34)	188 (36)		56 (82)	178 (71)	234 (73)	
Grade	1	3 (3)	107 (24)	109 (21)	<0.0001	0	4 (1.6)	4 (1)	<0.001
	2	0	183 (40)	183 (35)		12 (18)	182 (72)	194 (60)	
	3	65 (97)	163 (36)	288 (44)		56 (82)	67 (27)	123 (39)	
LN stage	Negative	49 (73)	289 (63)	338 (62)	0.230	19 (29)	78 (31)	97 (31)	0.003
	1–3 LNs	13 (19)	134 (29)	147 (28)		10 (15)	86 (34)	96 (30)	
	≥4 LNs	5 (8)	33 (7)	38 (7)		36 (55)	87 (34)	123 (39)	
Presence of LVI	Absent	40 (62)	242 (59)	282 (60)	0.344	32 (47)	127 (50)	159 (50)	0.639
	Definite	22 (34)	125 (31)	147 (30)		32 (47)	105 (42)	137 (43)	
	Probable	3 (5)	42 (10)	45 (10)		4 (6)	21 (8)	25 (8)	
PI	Low	6 (12)	134 (41)	140 (37)	<0.0001	40 (60)	215 (88)	255 (82)	<0.0001
	High	45 (88)	190 (59)	235 (63)		27 (40)	30 (12)	57 (18)	
P53	Low	33 (49)	314 (80)	347 (76)	<0.0001	37 (56)	196 (80)	233 (75)	<0.0001
	High	43 (51)	77 (20)	111 (24)		29 (44)	48 (19)	77 (25)	

BC, breast cancer; BLBC, basal-like breast cancer; LN, lymph node; LVI, lymphovascular invasion.

Table 3 Comparison between clinicopathological characteristics of basal-like breast cancer specimens in Egyptian and British patients

Feature	Subgroups	Egyptian Specimens	British specimens	*P* value
Age	≤50	29 (43)	34 (51)	0.304
	>50	39 (57)	32 (49)	
Size (cm)	≤2	12 (18)	34 (51)	<**0.001**
	>2	56 (82)	33 (49)	
Grade	1	0	3 (3)	0.065
	2	12 (18)	0	
	3	56 (82)	65 (97)	
LN	I negative	19 (29)	49 (73)	<**0.001**
	1–3 positive LNs	10 (15)	13 (19)	
	≥4 positive LNs	36 (55)	5 (8)	
Presence of LVI	Absent	32 (47)	40 (61)	0.244
	Definite	32 (47)	22 (34)	
	Probable	4 (6)	3 (5)	
PI	Low	40 (60)	6 (12)	<**0.001**
	High	27 (40)	45 (88)	
P53 (%)	<10	37 (56)	33 (49)	0.432
	≥10	29 (44)	43 (51)	

LN, lymph node; LVI, lymphovascular invasion; PI, proliferation index.

examined BLBC in 321 specimens from Egyptian patients and compared their features with 527 specimens from British patients. The prominent difference between both groups was the prevalence rate. In the British population, TNBC as a whole accounted for 16%, whereas the BLBC accounted for 13% compared with 26 and 21%, respectively, in the Egyptian patients. Two previous studies described the molecular types of BC in Egyptian patients. The first study identified TNBC in 274 specimens using ER, PR, and HER-2 expression regardless of the expression of basal markers. In this study, the rate of TNBC was 28.5% (El-Hawary *et al.*, 2012), which is very near to our observed rate of TNBC (26%). The second study was conducted on 200 BC specimen. BLBC tumors were identified using ER, PR, and HER-2 markers in addition to expression of CK5/6 and EGFR. BLBC in this study was 11% (Salhia *et al.*, 2011), which is lower than the figure observed in our series (16%).

There is variation in the frequency rates of TN and of TN-basal BC among studies either on Egyptian women or in other populations. This variation can be attributed to the difference in definition of TN and TN-basal BC among studies. Although TN and basal are deemed by some as synonymous, they are not (Rakha *et al.*, 2008). Analysis of

the microarray gene expression profile data found discordance of 20–30% between both groups (Prat *et al.*, 2013). First, a proportion of tumors identified as TN actually do not fall into the basal-like (BL) subtype category (Thike *et al.*, 2010). Second, the variation in the biological characteristics of BC differs among different ethnic groups (Curtis *et al.*, 2008; Maskarinec *et al.*, 2011; McCormack *et al.*, 2013), with a higher rate among Black (30.8%) compared with White women (11%) (Swede *et al.*, 2011) and in African-American (29%) compared with non-African-American women (13%) (Lund *et al.*, 2008). The rates were found significantly high in some African population, such as 47% in Nigerian women (Titloye *et al.*, 2016), but lower in Japanese patients (13%). Third, there is heterogeneity in TN group. Earlier studies found that TN-basal BC can be divided into six distinct subgroups: two BL (BL1 and BL2), an immunomodulatory, a mesenchymal, a mesenchymal stem-like, and a luminal androgen receptor subtype (Lehmann and Pietenpol, 2014). This heterogeneity was found to, not only, arise from the tumor cells themselves but from the tumor microenvironment as well (Prat *et al.*, 2013). Recent examination of the genomic and transcriptomic profiles of BLBC interestingly found that there is an expression signature that can distinguish between BLBC subtypes, and this signature can be claimed to the outcome heterogeneity of BLBC (Milioli *et al.*, 2017).

The association between clinicopathological features and BLBC in Egyptian women shared some similarities with those of the British population. In both groups, BLBC phenotype was associated with higher histopathological grade, higher proliferation rate, and higher rates of P53 expression. There was no difference, however, regarding the presence of LVI, as also reported previously (Rakha *et al.*, 2009b; Mohammed *et al.*, 2011).

This study found a significant difference between the clinicopathological features of BLBC in Egyptian patients compared with those from the British patients. The BLBC in British women occurs more frequently in younger patients. BLBCs in Egyptian cohort had significantly larger tumor size and were associated with the presence of LN metastasis. Association with tumor size and LN metastasis are features of tumors of unfavorable prognosis. Several studies reported variation in survival of BC among different ethnic groups. The question raised here is whether these ethnic disparities are owing to different genetic profile or owing to socioeconomic factors.

To find if unfavorable features we observed in BLBC in Egyptian cohort were specific to BLBC or is a general feature among BC specimens in the Egyptian patients, we analyzed the statistical difference in clinicopathological criteria between Egyptian and British specimens among other tumor types ('other' group comprises all tumors other than BLBC). The same differences were detected; specimens in the 'other' BC group were also associated with unfavorable prognostic features compared with the British patients. This indicates that the unfavorable prognostic features in Egyptian patients are not specific to BLBC.

Basal phenotype was originally described to have a transcriptome similar to basal cells within the mammary gland epithelium. On the contrary, emerging evidence from previous studies found that BLBCs have some similarities to the luminal progenitor cells (Lim *et al.*, 2009; Molyneux *et al.*, 2010). It has been then hypothesized that BLBC may arise from luminal progenitors or from mature luminal cells as a process of dedifferentiation. This dedifferentiation results from acquired genetic aberrations within a subpopulation of luminal tumor cells. It was found that silencing of some genes such as FOXA1 leads to growth arrest of a subpopulation of mature luminal cells and increases invasiveness and migration capabilities of other cell population, pushing the remaining cells to de-differentiate toward the basal phenotype (Bernardo *et al.*, 2013). These findings raise the possibility that some BLBC phenotypes may not be genetically determined; they start as luminal phenotype but undergo further genetic changes, resulting in appearance of the BLBC phenotype.

The higher rate of BLBC in Egyptian population is mostly because of the late presentation of tumors. Large proportion of Egyptian patients in this study were in stage II and III disease, whereas most of the British patients were stage I disease. Late presentation at diagnosis gives the tumor cells more time for genetic aberration, in a subpopulation of tumor cells, to occur where cells within this subpopulation undergo a process of dedifferentiation and acquisition of basal phenotype. The association between BLBC and LN stage in Egyptian patients but not in the British population supports this hypothesis.

Conclusion

BLBCs occurred more frequently in Egyptian patients compared with British women and are characterized by unfavorable biological features akin to BLBCs in

African-American women. These results warrant further studies to unravel the genetic background of BLBCs and whether their aggressive features are related to ethnic origin or other multifactorial and environmental variables.

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Conflicts of interest

There are no conflicts of interest.

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