

RESEARCH ARTICLE

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Clinical, Histopathologic Features and Outcome of Breast Cancer in UK Women of Ethnic Origin

Mohamed Zaakouk^{1,2,3*}, Aisling Longworth^{2,3}, Mervat Eldeftar¹, Noha Ezzat¹, Emad Elgemeie¹, Abeer M Shaaban^{2,3}

Abstract

Objective: Breast cancer (BC) in non-Caucasian females is understudied and its management is based on Caucasian data. 30 % of the West Midlands females are non-Caucasian. We aimed to elucidate the pathologic features, molecular profile, and outcome of non-Caucasian breast cancer. **Methods:** Breast cancers (BCs) of different ethnic origins diagnosed at a large Birmingham tertiary referral hospital between 2000 and 2016 were identified. Detailed clinical and histological data were collected and statistically analyzed. **Results:** Out of 7554 BC cases, 749 were of ethnic ancestry and median age of 51 years. These comprised 47 in-situ and 702 invasive carcinomas of presenting symptomatically in 86.2% of patients. 53.4% of the invasive carcinomas measured >20 mm. Cancers were predominantly of grade 3 (45%), and grade 2 (42.4%). Median NPI was 4.35. 65.1% of the ethnic carcinomas were of luminal subtype, 18.6% were Her2 positive and 16.2% triple-negative. Median overall survival was 62 months. Five and ten-year survival was 81.7% & 68.4% respectively. Ethnicity correlated with higher NPI ($p < 0.001$), larger tumour size ($p = 0.001$) and larger number of positive axillary nodes ($p = 0.007$). Negative correlations were found between age at diagnosis and both invasive tumour size & grade ($p < 0.001$) and between tumour grade and overall survival ($p = 0.006$). **Conclusion:** Compared with Caucasian breast cancer, non-Caucasian tumours presented predominantly symptomatically at younger age, were of larger size, higher grade with more unfavorable phenotypes and shorter survival. This is important in counselling, planning management and follow up of non-Caucasian patients.

Keywords: Breast cancer- Ethnic- non-Caucasian- racial differences

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Introduction

Breast cancer (BC) is the most common female cancer worldwide, and accounts for almost quarter (24%) of the estimated number of new cancer cases. In the UK, it is the most common cancer, accounting for 15% of all new cancer cases (2016-2018), where around 55,900 new breast cancer cases are diagnosed every year (2016-2018), 55,500 of them occurring in females. It is the second leading cause of cancer-related deaths in females (Sung et al., 2021).

Previous studies showed that BC survival in England is lower than in comparable countries (Møller et al., 2010a; Coleman et al., 2011). This is largely observed early after diagnosis, mostly because of late diagnosis with more advanced stage disease at time of diagnosis (Møller et al., 2010a).

According to latest (2011) census, persons of ethnic ancestry (other than white) constitute nearly 15% of the total population in England and Wales. This proportion is higher in the West Midlands, where they form 30% of the

population. It is noteworthy that UK data on ethnic breast cancer is sparse (Januszewski et al., 2014).

Breast cancer in females of non-Caucasian ethnic origin remains understudied, compared to its White-ethnicity counterpart. Most of the ethnic studies were performed in the US, investigating the racial disparity between African American and White America women. Ethnicity was found to be an independent prognosticator for poor outcome in African-American women (Newman et al., 2006). Similarly, Copson et al, in the POSH study, demonstrated that UK Black women had a significantly worse survival than whites (Copson et al., 2014).

It is increasingly recognized that these disparities may indeed be due to certain genetic and other non-genetic biological differences (Iqbal et al., 2015; Deshmukh et al., 2017). However, socioeconomic differences, deprivation and access to health care such as screening services have also been proposed as risk factors underlying such racial disparities (Gathani et al., 2021b).

We therefore aimed to describe the clinico-pathologic characteristics, molecular profile and survival of a large

¹Cancer Pathology Department, National Cancer Institute, Cairo University, Cairo, Egypt. ²Department of Cellular Pathology, Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom. ³Institute of cancer and genomic sciences, University of Birmingham, Birmingham, United Kingdom. *For Correspondence: mohamed.zaakouk@nci.cu.edu.eg

cohort of BC in UK women of non-Caucasian ethnic origin, who have equal access to health care facilities as Caucasian white women. This will provide insight on the presentation and outcome of the UK breast cancer in black and ethnic minorities and help with counselling, screening planning and management of breast cancer in those understudied groups.

Materials and Methods

The work has been conducted on UK women of minor ethnicities, diagnosed with BC between 2000 and 2016 at Queen Elizabeth Hospitals Birmingham, UK; a large tertiary referral centre providing South Birmingham Breast Screening and symptomatic service. This time frame has been selected to provide at least 5 years of follow-up. Histopathological characteristics, clinical data, imaging findings, medical treatment, types of surgery and survival data, where available, were retrieved from the digital patient records and pathology electronic system. Clinical data included age at diagnosis, presentation (whether screening detected or symptomatic) and imaging findings included size (by ultrasound, mammography, or both), focality and presence/absence of nodal/distant metastasis at time of diagnosis.

Type of breast and axillary surgery, oncological treatment including neoadjuvant/adjuvant chemotherapy were collected. Overall survival (OS) defined as duration from date of diagnosis till the patient was last seen or death has been calculated. Disease histopathological characteristics included tumour histology, invasive size, molecular type, tumour grade, Nottingham prognostic index (NPI), lymphovascular invasion ('LVI), nodal status (positive vs negative) and number of pathologically proven involved axillary lymph nodes.

Statistical analysis

Data was statistically analysed using the IBM statistical package for the social sciences (SPSS, version 27). The non-Parametric Mann-Whitney and Kruskal-Wallis tests were used as appropriate. Survival was analysed using

Kaplan-Meier survival curves. Comparisons were double sided and considered statistically significant when p value ≤ 0.05 .

Results

Patients' breakdown

We identified 7554 primary BC of different ethnic origins using the above inclusion criteria. The following groups were excluded; British/white ancestry, those missing confirmed ethnicity/diagnosis, patients with sparse histological/clinical data and male patients (Figure 1). The remaining 749 cancers were of non-Caucasian patients, of whom 47 were ductal carcinoma in situ (DCIS) and 702 invasive cancers.

Patients' demographics

The distribution of identified minor ethnicities are illustrated in Table 1. Out of these ethnicities, Indian, Pakistani, and Caribbean constituted 65.4% (459/702) of the cases, representing nearly two thirds of the cases.

Data regarding type of presentation was available in nearly half of the cases, and most of these cases were symptomatic at time of presentation (324/376; 86.2%). Radiologically, imaging (whether ultrasound, MRI or

Table 1. The Distribution of Non-Caucasian Ethnicities in the Studied Cohort

| Ethnicity | Number | Percentage |
|-----------------------|--------|------------|
| African | 28 | 4.0 |
| Bangladeshi | 18 | 2.6 |
| Caribbean | 98 | 14.0 |
| Chinese | 22 | 3.1 |
| Indian | 194 | 27.6 |
| Mixed | 30 | 4.3 |
| Other Ethnicity | 134 | 19.1 |
| Other Asian Ethnicity | 11 | 1.6 |
| Pakistani | 167 | 23.8 |
| Total | 702 | 100 |

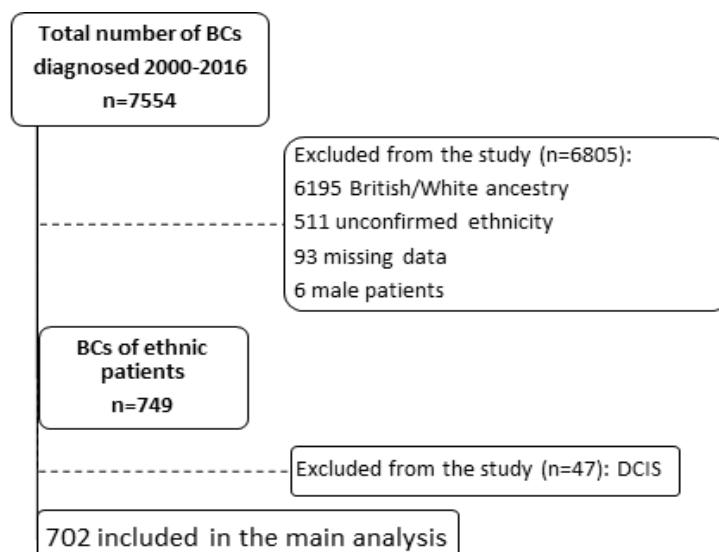


Figure 1. Schematic Presentation of Patient Inclusion and Exclusion Criteria

Table 2. Histologic Types Identified in the Studied Breast Cancers

| Histologic type | Number | Percentage |
|---|--------|------------|
| Infiltrating duct carcinoma (NOS), 8500/3 | 436 | 62.2 |
| Lobular carcinoma NOS, 8520/3 | 44 | 6.3 |
| Tubular carcinoma, 8211/3 | 17 | 2.4 |
| Mucinous adenocarcinoma, 8480/3 | 11 | 1.6 |
| Invasive micropapillary carcinoma of breast, 8507/3 | 4 | 0.56 |
| Glycogen rich carcinoma, 8315/3 | 1 | 0.14 |
| Cribiform carcinoma NOS, 8201/3 | 5 | 0.74 |
| Metaplastic carcinoma NOS, 8575/3 | 6 | 0.88 |
| Adenoid cystic carcinoma, 8200/3 | 1 | 0.14 |
| Solid papillary carcinoma with invasion, 8509/3 | 1 | 0.14 |
| Mixed carcinomas | 36 | 5 |
| Unknown | 140 | 19.9 |
| Total | 702 | 100.0 |

both) at time of diagnosis revealed a median tumour size of 22 mm (IQR: 14-30) and axillary nodal metastasis in half of patients. Median age at diagnosis was 51 years (IQR: 42-59) and 47.1% of these patients presented below the age of 50.

Among the different histologic types, no special

Table 3. Clinical and Histopathological Characteristics of the Ethnic Breast Cancers

| | | Total | n | % |
|-------------------------|------------------------------|-------|------------|------|
| Age | Median (interquartile range) | 702 | 51 (42:59) | |
| Presentation | Symptomatic | 376 | 324 | 86.2 |
| | Screening-detected | | 52 | 13.8 |
| Molecular Type | Luminal | 557 | 361 | 64.8 |
| | Her2-positive | | 107 | 19.2 |
| | TNBC | | 89 | 16 |
| Tumour Grade | Grade 1 | 603 | 76 | 12.6 |
| | Grade 2 | | 257 | 42.6 |
| | Grade 3 | | 270 | 44.8 |
| Tumour T-stage | T1 | 408 | 190 | 46.6 |
| | T2 | | 185 | 45.3 |
| | T3 | | 33 | 8.1 |
| Nodal Status | Positive | 518 | 234 | 45.2 |
| | Negative | | 284 | 54.8 |
| | N0 | | 504 | 284 |
| | | | | 56.3 |
| | N1 | | 158 | 31.3 |
| | N2 | | 42 | 8.3 |
| | N3 | | 20 | 4.1 |
| Lymphovascular invasion | Yes | 361 | 138 | 38.2 |
| | No | | 223 | 61.8 |

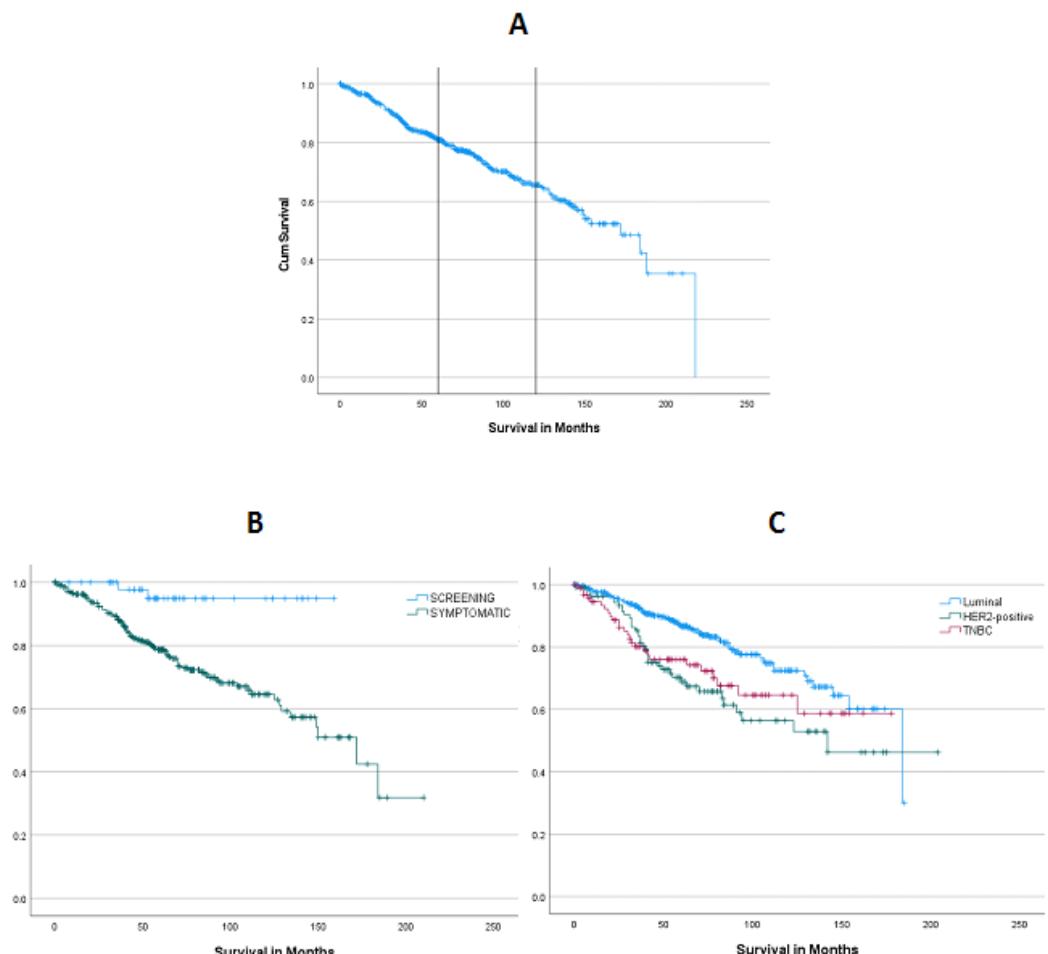


Figure 2. Kaplan-Meier Survival Curves of Non Caucasian Patients: (A) Five and ten year OS, (B) Relation between OS and type of presentation (screen detected versus symptomatic) & (C) Relation between OS and the molecular subtype of cancer.

type (NST) carcinoma was the commonest type (62.2%; 436/702), followed by lobular (44/702) and mixed (36/702) carcinomas, representing 6.3% and 5%, respectively. All identified histologic types are presented in Table 2.

The largest proportion of carcinomas were of grade 3 (44.8%). More than half of the tumours (53.4%; 218/408) measured more than 20mm (T2 & T3). Within surgical excisions, lymphovascular invasion (LVI) was identified in 23% of the cases. The NPI ranged from 2.1 to 7.62 and the median was 4.32 (IQR: 3.385-5.19). Among the molecular types, luminal phenotype was the predominant (65%), followed by the Her2 positive (19.2%) and triple negative phenotype (TNBC, 16%). The above-mentioned characteristics are summarised in table 3.

The overall survival ranged from 0 to 240 months and the median was 77 months (IQR: 46-114). Five and ten year overall survival was 81.7% & 68.4%, respectively (Figure 2-A).

Younger age at diagnosis correlated significantly with larger histological tumour invasive size ($p < 0.001$), larger tumour imaging size ($p = 0.017$), higher tumour size T-stage ($p = 0.003$) and higher grade ($p < 0.001$). Symptomatic cancers correlated significantly with higher grade tumours ($p < 0.001$), larger tumour size (histological and imaging) ($p < 0.001$), larger number of positive axillary nodes ($p = 0.048$), higher NPI ($p < 0.001$) and worse overall survival ($p = 0.002$). Her2 positive & TNBC cancers had worse overall survival ($p = 0.003$), higher NPI ($p = 0.004$) and larger tumour size ($p = 0.008$). Kaplan-Meier curves displaying relation of OS to presentation (Figure 2-B) and type (Figure 2-C).

Discussion

Racial disparity in diseases and particularly cancer has recently been a health and political issue with a focus on enhancing equality, diversity, and inclusion of patients of various racial background in research and trials. UK breast cancer research has been lagging behind that in Caucasian women but recent studies have highlighted the need for more research into breast cancer and ethnicity (Gathani et al., 2021a). While some recent useful epidemiological studies of ethnic breast cancer in England have emerged (Gathani et al., 2021c), there is lack of high quality detailed data including clinicopathological data on the clinical presentation, imaging, histological including receptor data. Our previous review of the Indian high-risk breast and ovarian literature highlighted heterogeneity of data and lack of histological information including receptor status of the reported breast cancer (Sharma-Oates et al., 2018).

One of the most important findings in this study is the younger age at diagnosis and the predominant symptomatic presentation. Nearly half of the patients in the current study were under the age of 50. Previous studies also showed that BC in patients of non-Caucasian origin presented at a younger age than Caucasian patients (Jack et al., 2009; DeSantis et al., 2016; Gathani et al., 2021b). Because of being diagnosed before age of screening, most

of the cases (74%) presented symptomatically. This has important implications into planning the onset of breast cancer screening in the ethnic populations since starting at the current age of 50 is likely to miss a significant proportion of breast cancer in those women. In the UK, screening uptake has decreased by 5% between 2005/06 (74%) and 2019/20 (69%) (UK). Access to health care facilities, deprivation and barriers to early detection and screening were all among the risk factors that have been proposed to underly the racial/ethnic disparity in clinical outcome between Black and White women (Iqbal et al., 2015).

In the current study, breast carcinomas were predominantly of high grade (87.4%), where grade 3 formed 45% and grade 2 represented 42.4%. This is in markedly different from the distribution of histological grade in the UK screening-detected patients, where grade 3 cancers were the smallest proportion (18%) (Group, 2021). More than half of the tumours (53.4%) measured more than 20mm (T2 & T3). The large size and higher grade of cancers in the present study may also be a reflection of the symptomatic presentation. Lower grade and smaller cancers are expected in screening detected cases, in view of early detection of the disease in its natural course.

Regarding molecular subtypes, the more unfavourable phenotypes including Her2-positive and triple negative phenotype cancers represented 19.2% and 16%, respectively. These proportions are higher than what is reported in the Caucasian white patients, where Her2 positive and triple negative cancers represent 13.7% and 14%, respectively (Gayther et al., 1998).

Within the resection specimens, presence of lymphovascular invasion (LVI) was confirmed in approximately a quarter (24%) of the cases, while in UK Breast Screening Programme, LVI was identified only in 13% of the cases. This high incidence of LVI was reflected in the high percentage of nodal involvement (45%).

Similar findings were reported in studies conducted on non-White American patients (Warner et al., 2015). UK women of non-European ancestry were found to present with larger tumours, higher proportion of the triple negative phenotype (19-34% compared to 14%), more advanced stage (stage 3 in 13-22% compared to 11%) and shorter survival than Caucasian patients (Hall et al., 2009; Warner et al., 2015; Sharma-Oates et al., 2018).

Our cases characteristically presented symptomatically, at a younger age at diagnosis, with higher proportion of the Her2-positive and TNBC cancers. These characteristics correlated significantly (p values ranging from 0.048 to < 0.001) with bad prognosticators, namely high grade & large size tumours, high NPI, large number of involved axillary nodes as well as short OS. UK women have shorter OS than those reported in other industrialized countries, though this gap has diminished over the last few years (Coleman et al., 2011). Similarly, women in England have shown shorter OS, compared to women in Norway and Sweden, particularly for older patients (Møller et al., 2010b). Young UK women with BC in the POSH study showed racial/ethnic differences in survival,

where Black and Asian women had shorter OS than whites. The differences in survival were most noted between Black and white women (Copson et al., 2014).

Research into ethnic differences in breast cancer can be challenging. Ethnic populations are not uniformly distributed in the UK and therefore large scale studies have been lacking. In addition, detailed data on ethnicity is not comprehensively documented in patients' records in many institutions. Our centre serves as a large tertiary referral hospital covering the West Midlands County which is characterized by larger proportion of non-Caucasian ethnicity (30%), compared to 15% in England and Wales with accurate records of patients' ethnicities and a stable population thus enabling us to perform this study.

However, a limitation of the study is its retrospective nature rendering it difficult to capture unrecorded data. As a tertiary referral centre some patients originated elsewhere and therefore, we attempted to retrieve this data, as much as possible, from other hospitals. Another general limitation, which has been reported in previous studies is the non-uniform/missing reporting of ethnicity, particularly in the earlier years of the study, that resulted in many cases (n=511) with un-identified ethnicity. Those have been excluded from the study.

To conclude, our data showed that non-Caucasian patients' BCs present at a younger age, predominantly symptomatic and comprised high histological GRADE and with higher proportions of the unfavourable molecular subtypes compared with white Caucasian patients. Young age at diagnosis and the symptomatic presentation were associated with poor prognosticators and shorter overall survival.

Further epidemiological and pathological studies into UK women of non-Caucasian background are required to better describe breast cancer in these patients and to inform screening and management strategies.

Author Contribution Statement

All authors contributed to the work. Conception and design of study: all authors; Collection of data: MZ and AL; Data analysis: MZ; Data interpretation: all authors; Preliminary draft of the manuscript was written by MZ; Revision and editing of manuscript: all authors; Approval of final version of manuscript: all authors.

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General

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Approval

The study was approved by the Institutional Review Board (IRB) of National Cancer Institute (NCI), Cairo University.

Ethical Declaration

Data was coded, and patient names or identity did not appear in any of data collection forms or during statistical analysis.

Data availability

The data are available from the corresponding author, on a reasonable request.

Conflict of Interest

Authors declare no conflict of interest.

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