Clinicopathological features of pregnancy-associated breast cancer at Chris Hani Baragwanath Academic Hospital, South Africa

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Background. Pregnancy-associated breast cancer (PABC), defined as cancer diagnosed during pregnancy or up to 1 year postpartum, tends to present with tumours displaying more adverse prognostic pathological features compared with those diagnosed outside of pregnancy. It is unclear if this is due to the more aggressive tumour biology associated with early-onset breast cancer, or influenced by the pregnancy independently.
Objectives. To compare the clinicopathological features of patients presenting with PABC with their age-matched non-PABC controls.
Methods. Records of females of reproductive age diagnosed with breast cancer from 1 October 2006 to 31 October 2020 were retrospectively reviewed using the Chris Hani Baragwanath Academic Hospital Breast Unit electronic database. Cases of PABC were identified, and non-PABC cases were selected as age-matched controls at a 2:1 ratio to each PABC case.
Results. A total of 1 056 patients were eligible for inclusion, with 63 meeting criteria for PABC. After excluding 10 cases, 53 PABC cases were age-matched to 106 controls. The incidence of PABC was 1.5%, with a median age of 36 years. Over 90% of patients presented with palpable breast masses. PABC patients presented with significantly larger tumours (5.5 cm v. 4.0 cm) and higher nuclear grades compared with age-matched controls. PABC patients also demonstrated more oestrogen (40% v. 23%) and progesterone receptor (47% v. 28%) negativity compared with controls.
Conclusion. PABC patients from our population presented with more adverse clinicopathological tumour characteristics than their age-matched controls. These findings align with existing literature, and would likely contribute to a worse prognosis in this patient group.

Keywords: pregnancy-associated breast cancer, clinicopathological features, prognosis

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Breast cancer (BC) is the most common female cancer worldwide, and the leading cause of cancer-related deaths in women.[1] In South Africa (SA), a low- to middle-income country, BC accounted for the highest number of new cancer cases across genders in 2022, making it an important medical condition that contributes significantly to the burden on the healthcare system.[2]

Pregnancy-associated breast cancer (PABC) is commonly defined as BC diagnosed during pregnancy or up to 1 year postpartum.[3-6] Although relatively rare, with an incidence of 0.2% - 3.8% of all BC cases, it remains the most frequently diagnosed malignancy during pregnancy.[3-5] The global incidence of BC is increasing owing to a combination of lifestyle factors, reproductive changes and an ageing population.[3-9] The mean age at diagnosis of PABC ranges from 33 to 38 years.[4,5,7,10] Studies from Africa have pointed towards a higher overall burden of PABC, as demonstrated in both Dusengimana[11] (10.3%) and Hou's[12] cohorts (21.2%), a finding that is thought to be linked to larger young populations in Africa compared with Western populations.[9,11,12] Additionally, cultural and economic factors contribute to inadequate health education and poor adherence to contraception, which further increases the likelihood of multiparity occurring in these populations and the possibility of BC being associated with pregnancy.[11,12]

Pregnancy and multiparity have been shown to confer a long-term protective effect against the development of BC. However, this effect is preceded by a transient period of augmented susceptibility with an increased risk of BC after the first pregnancy, persisting for as long as 5 - 10 years post delivery.[13-15] Additionally, the risk of developing BC in the postpartum years is higher in first-time mothers aged >35 years, with the probability increasing the later the initial pregnancy occurs.[9,13-16] As a result, definitions of PABC are inconsistent in the literature, ranging from 1 to 10 years after delivery, depending on the extent of this perceived risk.[15] However, the most widely agreed-upon definition of PABC is BC occurring during pregnancy or up to 1 year post delivery, which will be used to define PABC in this study.

PABC presents similarly to BC in non-pregnant patients, often with a palpable mass, overlying skin changes, or a bloody nipple discharge, with self-discovered breast mass reported as the most common presenting feature of PABC in >80% of cases.[5,6,17] Clinical examination of the breast during pregnancy and lactation is challenging due to physiologically increased breast density and nodularity, which may lead to significant delays in identification and work-up of suspicious breast lumps and, subsequently, more advanced stage disease at diagnosis.[3,5,6,16,18] In sub-Saharan Africa, delays to diagnosis are exacerbated by system inadequacies and barriers to accessing healthcare.[19]

Furthermore, PABC appears to demonstrate intrinsically more adverse tumour characteristics, including larger, higher nuclear grade cancers with increased axillary node involvement, and higher stage disease at diagnosis.[6,7,9,12,20-22] In addition, these tumours have

a greater propensity for oestrogen (ER) and progesterone receptor (PR) negativity with human epidermal growth factor receptor-2 (HER2) positivity, features contributing to a worse overall prognosis. The most common histological subtype in PABC is invasive ductal carcinoma, occurring in 75 - 90% of cases, with multiple studies supporting these findings.[6,10,12,15-17,21,22] However, there are currently no published SA studies, and only two African studies from Rwanda and Tunisia, with small cohorts, corroborating these conclusions in African populations.[11,23]

It remains unclear whether these unfavourable tumour traits are due to the distinctively aggressive tumour biology expected in young BC patients, or if they are independently influenced by pregnancy. Various hypotheses have been proposed to explain the biological mechanisms driving PABC: the distinctive hormonal milieu of pregnancy that causes breast cell proliferation, and potentially promotes malignant transformation in cells that have accumulated mutations; pregnancy-related immunosuppression allowing mammary tumour cells to proliferate; and breast involution in the postpartum period, which creates an inflammatory microenvironment and a pro-oncogenic state.[7,9,14,16,17] Gene-expression analysis in Pena-Enriquez *et al.*'s[7] study further highlighted the unique biological triggers in PABC, with evidence of aberrant DNA damage repair and transformed immune check-point molecules that support oncogenesis. Nevertheless, disparities in outcome data may be the effect of small study cohorts and a lack of robust data, owing to the relatively infrequent occurrence of PABC.[5,10,22,24,25]

Overall, the diagnosis and management of PABC is complex, and although there is increasing evidence in the literature, it remains poorly understood, with a limited number of high-quality studies.[19] There are no published articles in SA, and a paucity of data on this condition in Africa. Therefore, this study aimed to investigate PABC in a local SA context by evaluating the incidence, presentation and clinicopathological features of PABC to enhance our understanding and optimise diagnosis and management strategies.

Objectives

To compare the clinicopathological features of PABC with non-PABC in age-matched controls at Chris Hani Baragwanath Academic Hospital (CHBAH) Breast Unit.

Eligible patients with confirmed BC at the CHBAH Breast Unit from 1 October 2006 to 31 October 2020 were included in this analysis, and the study objectives were:

(*i*) to determine the incidence of PABC in all patients of childbearing age diagnosed with breast cancer;

(*ii*) to describe the demographic characteristics of PABC patients compared with their age-matched controls;

(*iii*) to identify the presenting signs and symptoms in patients diagnosed with PABC v. non-PABC; and

(*iv*) to determine the clinicopathological characteristics of PABC, including tumour size and grade, stage of disease and receptor status, and compare these with those of non-PABC in age-matched controls.

Methods

This was a retrospective descriptive analysis of the CHBAH Breast Unit electronic database. After obtaining ethical approval for this study from the Human Research Ethics Committee of the University of the Witwatersrand, and permission from the CHBAH management and the gatekeeper of the Breast Unit electronic database, female patients who met the eligibility criteria were included in the study.

Inclusion criteria were female patients of reproductive age (18 - 45 years) with confirmed BC at CHBAH between 1 October 2006 and 31 October 2020.

Exclusion criteria for the PABC group only were patients diagnosed with BC prior to pregnancy or >1 year postpartum.

The CHBAH electronic breast database was used to identify eligible women during this 14-year time period. Patients meeting the criteria for PABC were identified using specific keywords in an advanced terminology search on the database, including: 'pregnant', 'pregnancy', 'breastfeeding', 'lactation', 'postpartum', 'delivery', 'gestation', 'baby' and 'infant'. The principal investigator also evaluated included patient records to ensure that PABC cases were not overlooked. Patients not meeting the criteria for PABC were identified as controls for comparison. The study aimed to include 62 PABC patients, based on the literature-reported PABC incidence of 0.2 - 3.8%[3-5] and an estimated incidence of 1.5% in our total cancer registry of 4 116 patients. To determine the clinicopathological characteristics of PABC (objective *iv*), two control patients were age-matched precisely to each PABC case using Stata software (StataCorp, USA).

Information from included patient records was captured on an Excel (Microsoft, USA) datasheet for further analysis. Extracted variables were age at diagnosis, pregnancy/lactation status, presenting sign(s)/symptom(s), tumour size, nodal involvement (based on imaging findings), tumour node metastasis staging, histological grade (Nottingham Histologic Score System) and subtype, receptor status (ER/PR and HER2) and Ki67% (cell proliferation index). To ensure accuracy in the size of the tumour recorded, the measured dimensions on the pathological specimen were used in patients who had upfront surgery, while the image-determined tumour size was utilised for those that underwent neoadjuvant therapy.

Data analysis was performed using the Stata software with the assistance of professional statisticians. Statistical differences between comparable groups were calculated using Pearson's χ^2 or Fisher's exact test for categorical variables, and the Mann-Whitney U test for continuous variables. $P<0.05$ was considered statistically significant.

Ethical approval

Ethical approval was obtained from the Human Research Ethics Committee of the University of Witwatersrand (ref. no. M210804) on 20 October 2021, as well as the chief executive officer of Chris Hani Baragwanath Hospital. Owing to the retrospective nature of this study, no patient informed consent was obtained; however, the privacy rights of human subjects have been observed.

Results

A total of 1 056 patients from the BC registry of 4 116 patients satisfied criteria for inclusion during the defined study period. Of these, 63 patients met the case definition for PABC. Ten cases were excluded due to incomplete records of clinicopathological data, specifically the Ki67% and HER2 equivocal results without corresponding fluorescence *in-situ* hybridisation (FISH) results. This yielded 53 PABC cases for evaluation. Each PABC case was then age-matched to two controls, producing 106 age-matched non-PABC controls (Fig. 1). The incidence of PABC in this study was 1.5%. Notably, most cases of PABC (55.6%) in this study were detected during the final 3 years of the 14-year study period.

Demographic and clinical characteristics

Table 1 shows the demographic and clinical characteristics of the study population. The median (interquartile range (IQR)) age at diagnosis in the PABC group was 36 (32 - 39) years, identical to that of non-PABC control participants because of age-matching ($p>0.99$). Overall, the median (IQR) age at diagnosis of BC in all females of reproductive age (n=1 056) was 39 (35 - 43) years. In terms of race, the majority of study participants in both groups (90.6% of PABC

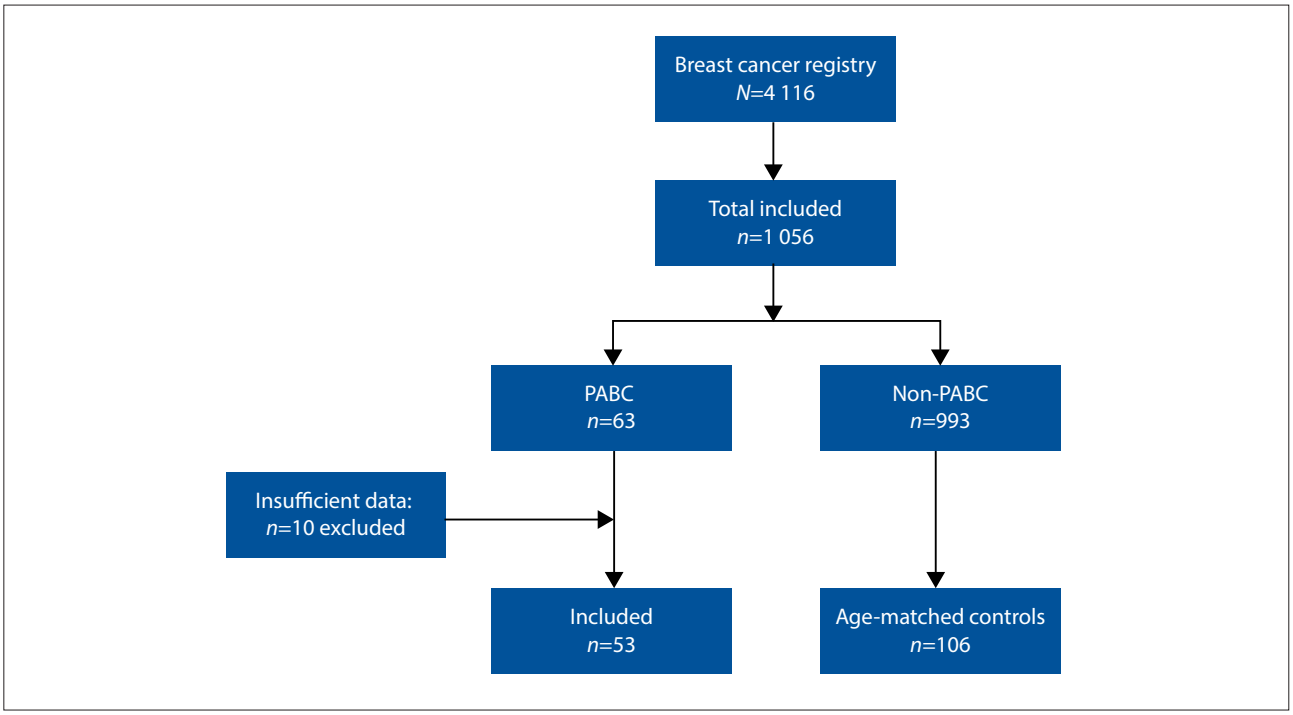

Fig. 1. Flow diagram of study participants. (PABC = pregnancy-associated breast cancer.)

Table 1. Demographic and clinical characteristics of PABC patients v. non-PABC age-matched controls (*N*=159)

Parameter, *n* (%)*	PABC (*n*=53)	Age-matched controls (*n*=106)	*p*-value
Age, years, median (IQR)	36.0 (32.0 - 39.0)	36.0 (32.0 - 39.0)	>0.99
Race			0.761
Black	48 (90.6)	98 (92.5)	
White	5 (9.4)	3 (2.8)	
Coloured	0 (0)	3 (2.8)	
Other	0 (0)	2 (1.9)	
Presenting sign: mass	49 (92.5)	103 (97.2)	0.223
Tumour size, cm, median (IQR)	5.5 (3.8 - 5.5)	4.0 (3.0 - 5.5)	0.027
Node positivity	41 (77.4)	88 (83.0)	0.39
De novo metastatic	13 (24.5)	18 (17.0)	0.257
Stage			0.151
I	2 (3.8)	5 (4.7)	
II	11 (20.8)	40 (37.7)	
III	27 (50.9)	44 (41.5)	
IV	13 (24.5)	17 (16.0)	

PABC = pregnancy-associated breast cancer; IQR = interquartile range.
*Unless otherwise indicated.

and 92.5% of non-PABC patients) were black. This race distribution is broadly reflective of the SA population, with black Africans constituting 81.4% of the overall population, while 98.5% of the local population served by CHBAH is black.[26]

As shown in Table 1, a palpable breast mass was the presenting sign in >90% of patients in both groups (p=0.223). Patients with PABC presented with significantly larger tumours of 5.5 cm at diagnosis, compared with 4.0 cm in age-matched controls (p=0.027). Both groups had predominantly axillary node positive disease on presentation: 77.4% in the PABC group v. 83.0% in age-matched controls (p=0.39). In comparison, *de novo* metastatic disease was marginally more frequent in the PABC group at 24.5% v. 17.0%, respectively (p=0.257). Patients in the PABC group had significantly higher disease stage at diagnosis overall, compared with the non-PABC population, with 22.2% v. 13.8% in those with stage IV disease, respectively (p=0.018; data not shown). However, the significance was lost when compared with age-matched controls. Likewise, early-stage BC was less prevalent in the PABC group compared with non-PABC controls for stage I and II disease (Table 1 and Fig. 2).

HIV status

In this study population, 32% of patients overall were HIV positive, while 68% were HIV negative (Table 2). A greater percentage of patients with PABC were HIV positive compared with controls (34% in PABC v. 27.3% in non-PABC). However, this finding did not reach statistical significance.

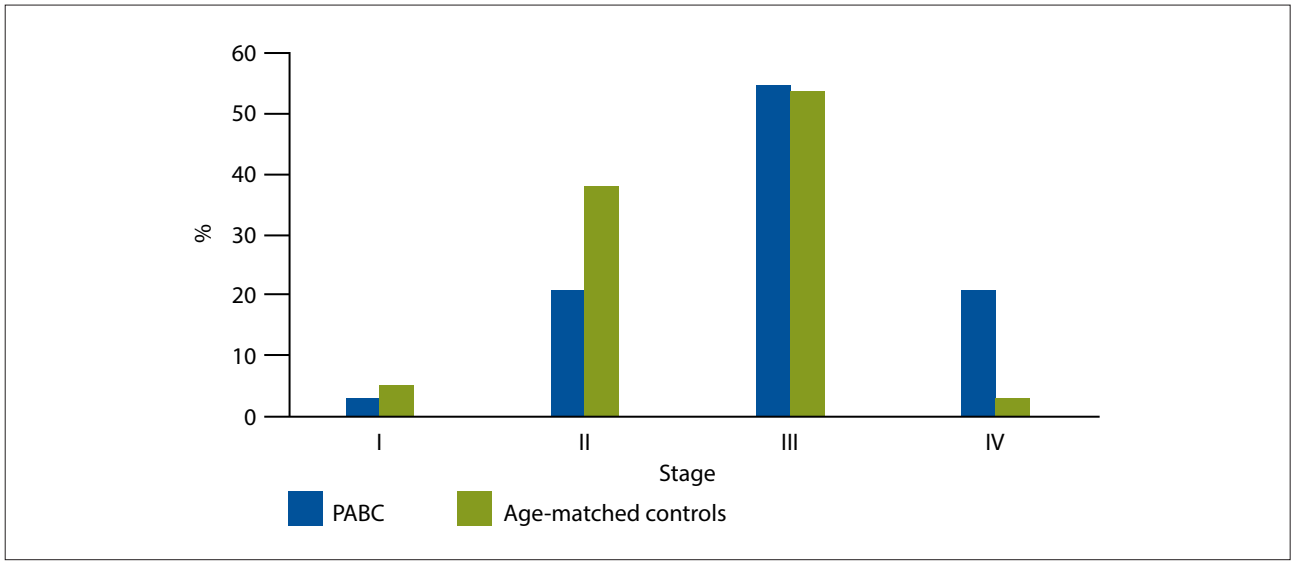

Fig. 2. Disease stage in pregnancy-associated breast cancer (PABC) v. non-PABC age-matched controls.

Table 2. HIV status of PABC patients v. non-PABC age-matched controls (*N*=159)

HIV status, *n* (%)	PABC (*n*=53)	Age-matched controls (*n*=106)	*p*-value
Positive	18 (34.0)	29 (27.3)	0.404
Negative	31 (58.5)	68 (64.2)	
Not recorded	4 (7.5)	9 (8.5)	

PABC = pregnancy-associated breast cancer.

Table 3. Pathological characteristics of PABC patients v. age-matched controls

Parameter, *n* (%)*	PABC (*n*=53)	Age-matched controls (*n*=106)	*p*-value
Grade			0.042
1	0 (0.0)	10 (9.5)	
2	29 (54.7)	48 (45.7)	
3	24 (45.3)	47 (44.8)	
Histological subtype			0.551
Invasive ductal	53 (100)	103 (97.2)	
Other	0 (0.0)	3 (2.8)	
Hormone receptor status			
ER			0.025
+	32 (60.4)	82 (77.4)	
–	21 (39.6)	24 (22.6)	
PR			0.018
+	28 (52.8)	76 (71.7)	
–	25 (47.2)	30 (28.3)	
HER2			0.56
+	24 (45.3)	48 (45.3)	
–	29 (54.7)	58 (54.7)	
Ki67%, median (IQR)	50 (25 - 70)	40 (25 - 60)	0.116

PABC = pregnancy-associated breast cancer; ER = oestrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor-2; Ki67% = cell proliferation index; IQR = interquartile range.
*Unless otherwise indicated.

Pathological characteristics

The histological subtype was almost exclusively invasive ductal carcinoma, occurring in 100% of PABC v. 97% of non-PABC patients (Table 3). The PABC group exhibited a significantly higher number of grade 2 and 3 tumours compared with age-matched controls (p=0.042), with no grade 1 tumours identified in the PABC group. In addition, in PABC v. age-matched controls, significantly more ER-negative (40% v. 23%, p=0.025) and PR-negative (47% v. 28%, p=0.018) disease was observed (Fig. 3 and Table 3). Both groups demonstrated a preponderance of HER2 negative disease. No significant differences in the Ki67% index was found between the PABC v. age-matched control patients (p=0.116).

When comparing the clinicopathological features between the PABC group and the entire non-PABC study population (i.e. all patients aged 18 - 45 years with non-PABC, n=993), the significant differences identified in both the grade and ER/PR hormone receptor

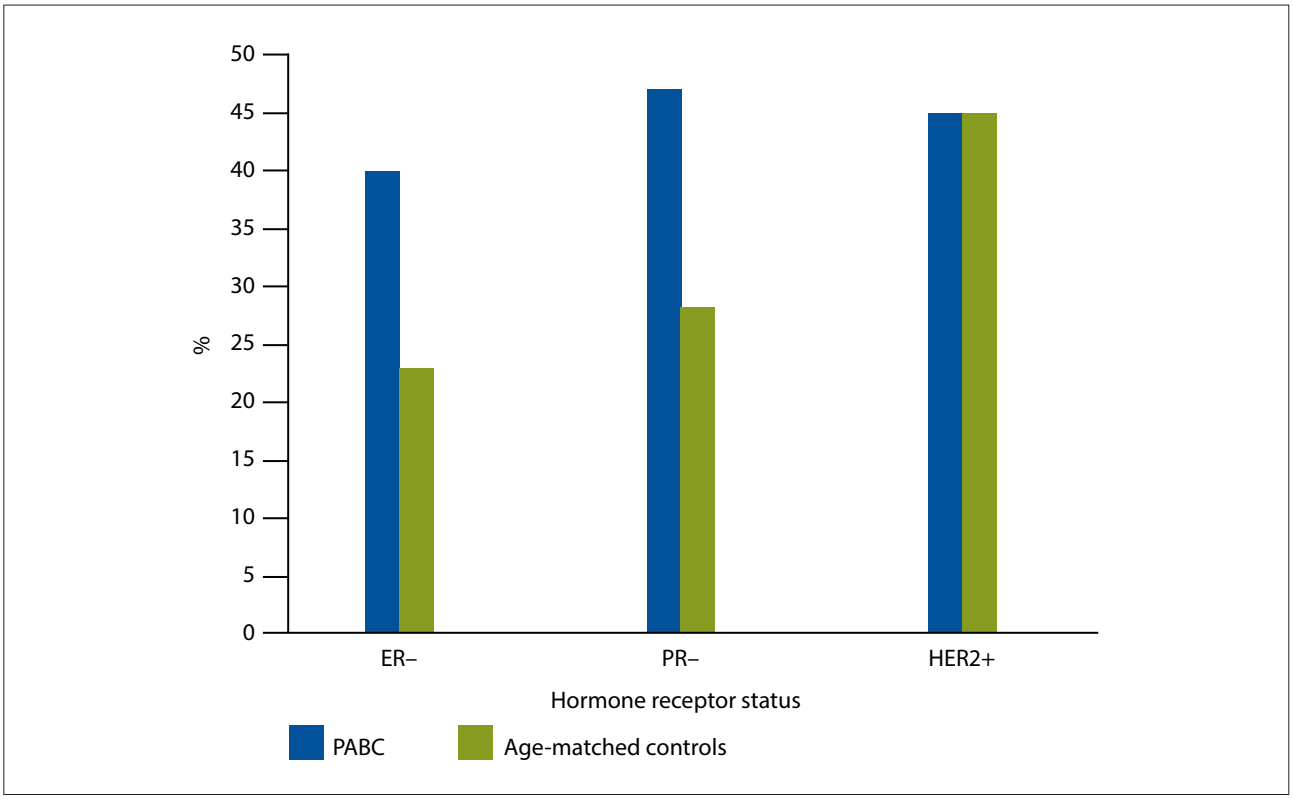

Fig. 3. Hormone receptor status in pregnancy-associated breast cancer (PABC) v. non-PABC age-matched controls. (ER– = oestrogen receptor negative; PR– = progesterone receptor negative; HER2+ = human epidermal growth factor receptor-2 positive.)

status no longer reached statistical significance. This demonstrates the relevance of age-matching in this young BC population to enhance accuracy in analysis and interpretation of the results.

Discussion

Our study was conducted at CHBAH, a tertiary referral centre in Soweto township and the biggest hospital in the southern hemisphere. CHBAH serves almost 2 million Soweto residents and a substantial catchment area across Gauteng Province.[27] The Soweto area represents a significant number of South Africans facing poverty and high unemployment rates, where barriers to healthcare are commonplace, which further exacerbates diagnostic delays such as those observed in PABC.

Patients were evaluated over a 14-year period, producing a large study population that achieved the required PABC sample size despite the condition's low incidence. The use of a substantial electronic database, where records are accurately documented and regularly updated by clinicians, patient-navigators, oncology nurses, research staff and information technology personnel, meant precise age-matching was feasible, and this was performed with the assistance of a professional statistician to further aid accuracy.

A total of 53 PABC cases were eligible for further evaluation, with a median age of 36 years, which is consistent with previous studies.[4,11,16] Age-matching was utilised to eliminate age as a confounding factor and reduce its impact on the perceived aggressiveness of tumours in this patient group.

PABC in this single-centre study is a relatively rare entity, with an incidence of 1.5%, which aligns with the international reported incidence of 0.2 - 3.8%.[3-5] Yet this is likely an underestimation of the true frequency of PABC in this population, particularly when compared with similar African studies.[11,12] Korbi *et al.*[23] reported a PABC incidence of 4.8% in Tunisia, while Dusengimana *et al.*[11] observed a rate of 10.3% among women in Rwanda. Hou *et al.*[12] documented a substantially higher incidence of 21.2% in their Nigerian cohort. However, broader criteria for inclusion were employed in these studies, with a wider definition of PABC in the Nigerian study (including patients up to 2 years postpartum), and an extended age range for females of reproductive age (18 - 50 years) in the Rwandan study.[11,12] Notably, a recent systematic review and meta-analysis reported that the highest incidence of PABC occurs in Africa, estimated at 27.4 per 100 000.[9] The lower incidence of PABC in our study may be due to under-recognition of the association between pregnancy, lactation and BC by both patients and clinicians. This was particularly evident prior to 2018 (a 12-year period), during which time only 44.4% of the total PABC cases were diagnosed. After 2018, during the last 2 years of the 14-year study period, 55.6% of all PABC cases were identified, suggesting a growing awareness of PABC over time resulting in an increased detection rate.

The hypothesis that PABC presents with tumours that have more adverse prognostic clinicopathological characteristics appeared to hold true in this study. The majority of patients in both the PABC and non-PABC age-matched control group presented with palpable breast masses, denoting more advanced, clinically detectable disease. However, patients in the PABC group presented with significantly larger tumours than their control group counterparts. In addition to generally unfavourable tumour biology, this finding may also be explained by the physiological changes occurring in the breast during pregnancy and lactation. Increased breast density and nodularity peripartum renders clinical examination challenging and, subsequently, suspicious breast masses may not be detected, resulting in diagnostic delays and larger tumours at diagnosis.[3,5,6,16-18] These diagnostic delays may have impacted the stage of disease noted in the PABC group in this study, where PABC patients presented with more stage III and IV disease at diagnosis

compared with non-PABC patients, parallel with recent findings from the literature.[20]

Further contributing to the adverse pathological tumour traits in PABC, these patients were more likely to have tumours with a significantly higher nuclear grade as well as ER and PR negativity when compared with age-matched controls. These findings accord with international data.[21,22] However, in contrast to the literature, the majority of patients in this study had HER2-negative tumours, which may have resulted from the inconsistent documentation of the FISH result. When tumours are HER2 equivocal on initial biopsy, further characterisation with a FISH test is required to determine HER2 status. During the study period, the National Health Laboratory Service system underwent an update, and access to the previous database was unavailable, making it challenging to retrospectively trace missing data. Therefore, three PABC cases with equivocal HER2 results were excluded, potentially contributing to the difference in HER2 status seen in this study compared with existing literature.

Although PABC patients in this study presented with marginally increased *de novo* metastatic disease compared with non-pregnant controls, this did not reach statistical significance, in keeping with both African[9] and international literature.[21] One factor potentially influencing this, in our study, is the method by which staging of newly diagnosed PABC patients was determined. The European Society for Medical Oncology guidelines suggest staging should be performed with a computed tomography (CT) scan of the chest, abdominal imaging (ultrasound, CT or magnetic resonance imaging) and a bone scan in all patients with clinically positive axillary nodes, large tumours >5 cm, aggressive tumour biology and clinical signs/symptoms or laboratory values suggestive of metastatic disease.[28] However, owing to the risk to the fetus of radiation exposure associated with a CT scan in PABC patients, in addition to limited access to cross-sectional imaging in our resource-constrained environment, CT is not routinely performed as a first-line investigation in this population. Therefore, pregnant patients underwent basic investigations for metastatic screening, including blood tests, a liver ultrasound and a shielded chest X-ray at initial diagnosis, which could have resulted in an underestimation of *de novo* metastatic disease in this group.

Study limitations

In this retrospective record review, identifying a PABC case at diagnosis was contingent on the attending clinician establishing an association with pregnancy or breastfeeding. If this was not recognised during the initial consultation, it may have been overlooked as a case of PABC and, therefore, not recorded as such in this study, potentially, leading to under-reporting of PABC. In addition, 10 PABC cases were excluded from the final analysis as the Ki67%, an important marker of tumour proliferation with prognostic significance, was not reported by the laboratory. Prior to 2011, the laboratory did not routinely record the Ki67% value. Therefore, PABC cases detected during this period were ineligible for inclusion if the Ki67% was unavailable. Three of these excluded cases also had HER2-equivocal results, for which a FISH test could not be traced, further justifying their exclusion but, ultimately, contributing to a reduced sample size.

Lessons learnt and future research

Given that PABC appears to demonstrate more adverse prognostic pathological features with more advanced disease stage, as demonstrated by this study, prompt diagnosis and improved management strategies are essential. These can be achieved through enhanced awareness among both clinicians and patients to ensure thorough investigation of new breast lumps in the peripartum period. In addition, creating mandatory fields for pregnancy and lactation in the electronic database will facilitate identification of PABC patients. Further studies should consider a prospective analysis and evaluation of treatment strategies between PABC and age-matched controls to fill current data gaps. However, our study has generated valuable clinicopathological data on PABC in a SA context, which has not been published previously.

Conclusion

PABC patients from our population tended to have larger tumours, exhibiting more unfavourable characteristics, than aged-matched controls. These factors are likely to adversely affect prognosis in these young patients. There was also a trend to more advanced stage of disease at diagnosis in the PABC group, which may be attributed to the diagnostic delays in pregnant and lactating patients, in addition to the complex hormonal milieu of pregnancy potentially affecting tumour growth. However, larger prospective studies are required to assess the true association of these factors with PABC and to enhance our understanding of this complex condition, thereby enabling improved management strategies in our resource-constrained environment.

Data availability. The data analysed in this study are available from the corresponding author upon reasonable request, but are not publicly available owing to ethical/privacy restrictions.

Declaration. This research was undertaken in partial fulfilment of the requirements for LL's MMed degree in the Department of Surgery at the University of the Witwatersrand.

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Author contributions. LL: conceptualisation and design; acquisition and interpretation of data; writing – original draft; final approval of the version to be published. DK: conceptualisation and design; formal analysis and interpretation of data; supervision; writing – review and editing; final approval of the version to be published. HC: conceptualisation; interpretation of data; supervision; writing – review and editing; final approval of the version to be published. NM: conceptualisation and design; interpretation of data; supervision; writing – review and editing; final approval of the version to be published.

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