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ORIGINAL RESEARCH

Impact of Ethnic Differences and HER2 Protein Expression on the Age at Breast Cancer Diagnosis: A Mixed Methods Study

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Video abstract

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Purpose: Despite advances in breast cancer (BC) research, a significant research gap remains in understanding the interplay of ethnicity, Human Epidermal Growth Factor Receptor 2 (HER2) protein expression and age at BC diagnosis, particularly in under-represented minority populations from Africa. We analyzed variations in HER2 protein expression and ethnic differences in age at BC diagnosis across indigenous Namibian and American women diagnosed with BC.

Methods: Using a mixed methods study, we analyzed case series cohort from 1,953 women all diagnosed with invasive BC, including 98 indigenous Namibian women and 1855 American women retrieved from the cBioPortal database. HER2 positivity rate was obtained by staining breast tissue biopsies and quantifying HER2 protein expression, with this study accessing the data retrospectively. We stratified participants by ethnicity and compared age at BC diagnosis and HER2 status to elucidate disparities. Chi-square test for proportions, *t*-test for independence and the cumulative probability analysis curves were used for statistical analysis. A p-value of <0.05 was considered significant.

Results: Indigenous Namibian women were diagnosed with BC significantly with a younger age compared to American women (White, $p<0.0001$, and African American $p=0.0035$). In a logistic regression analysis, African American women with BC had significantly lower odds of HER2-positive status compared to White women (OR = 0.52, $p < 0.001$). The cumulative probability analysis further delineated the probabilities for age at BC diagnosis according to ethnic disparities with indigenous Namibian, Asian, and African American women showing significant higher probabilities for younger ages at BC diagnosis compared to White women ($p<0.0001$, $p=0.0035$, and $p=0.0057$, respectively).

Conclusion: Ethnic disparities and the variations in HER2 protein expression and age at BC diagnosis between indigenous Namibian and American women diagnosed with BC necessitate tailored population genetics and geographical differences in BC screening approach to address global BC screening equity.

Keywords: breast cancer, human epidermal growth factor receptor 2, immunohistochemistry, age at breast cancer diagnosis, ethnicity, Namibia

Introduction

Breast cancer (BC) remains the leading cause of cancer-related morbidity and mortality among women worldwide, with over 2.3 million new cases and 666,000 BC-related deaths reported globally. This is accounting for 23.8% and 15.4% of all cancer cases and deaths in women, respectively.[1,2] In the United States alone, BC incidence rate is significantly higher than in Namibia, with the latter reporting 34.5 cases per 100,000 women.[3,4] Despite these alarming statistics, there exists a substantial gap in understanding how the age at BC diagnosis and molecular features, specifically Human Epidermal Growth Factor Receptor 2 (HER2) status, vary across geographically different ethnicities.[5–7] This gap is well pronounced in underrepresented populations, where limited data due to a very small population scale hinders the development of

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effective, tailored population-specific interventions.[4,8] Currently, there is limited data on how age at BC diagnosis and HER2 molecular status vary across geographically different ethnic groups.[6,9–11]

Age at BC diagnosis is a critical prognostic factor influencing tumour biology, treatment response, survival outcomes and long-term quality of life.[12] Certain ethnic groups are diagnosed with BC at a younger age compared to their White counterparts in the same or different geographical location, which may reflect various underlying biological and genetic differences.[5,13–15] This aspect of cancer epidemiology is especially pivotal in resource-poor settings like Namibia, where BC data is limited due to the low population scale.[4,16,17] In such settings, understanding age-related patterns in diagnosis can significantly enhance early detection efforts, crucial for improving survival rates in environments with limited healthcare resources.[18–20] Furthermore, the biological and genetic underpinnings of these age variations in BC could hold key insights into the disease's pathophysiology, potentially revealing novel biomarkers and therapeutic targets.[4,6,21,22]

HER2 status plays a pivotal role in molecular diagnosis of BC, offering insights into tumour biology and guiding therapeutic decisions. HER2, a protein expressed in approximately 20% of BC cases, is associated with aggressive tumour behaviour and poorer prognosis.[23–25] However, its expression varies significantly across ethnicities, underscoring the need for a deeper exploration of these differences.[5,26,27] Variability in HER2 positivity rates has been reported, with African populations often exhibiting lower HER2 positivity compared to Western cohorts. This disparity points to potential biological differences in tumour characteristics, which could influence treatment responses and outcomes.[5,6,13] Yet, data from African minority populations remain markedly underrepresented in global cancer research, leading to a substantial knowledge gap in BC research.[4,28] We hypothesize that HER2 expression profiles, along with age at BC diagnosis, may vary significantly among different ethnic groups and continents.[29–32] These variations hold key biological implications for personalized BC screening, and treatment efficacy.[33–35] By investigating these aspects, we will provide new insights into the molecular epidemiology of BC, potentially reshaping screening and treatment paradigms when confirmed in a large cohort study.[36,37] This approach is particularly important when considering the inclusion of underrepresented African cohorts from minority populations, offering a unique perspective in the global understanding of BC biology.[4,6,38]

To address our hypothesis, this study is designed with dual objectives: (i) to investigate the ethnic variations in age at BC diagnosis and (ii) to elucidate the differential expression of HER2 status across diverse ethnic groups from two continents.

Methodology

Ethics

This study adhered to ethical guidelines, with all procedures being approved by relevant institutional review boards. Informed consent was obtained from all participants involved in primary data collection, ensuring confidentiality and compliance with ethical standards. Ethics clearance number (**17/3/3 MSK**) was sought and obtained from the Namibia Ministry of Health and Social Services (MOHSS) ethics committee and the Namibia University of Science and Technology (NUST) higher degree committee. Permission from the respective Medical Imaging departments was sought to carry out this study in the different departments. This study complies with the Declaration of Helsinki.

Study Design

A cross-sectional study incorporating both primary and secondary data sources with different ethnic backgrounds from two continents.

Data Source and Sample Size

From Namibia

Primary data from 98 Namibian women with complete demographic data and ethnicity from minority populations diagnosed with BC from 2018 to 2020, from a tertiary hospital. These Namibian women belong to indigenous African ethnic groups, primarily the Ovaherero and Nama communities, to address the gap of disparities in age at BC diagnosis in African indigenous populations.[20,28,32] All patients were recruited from the Medical Imaging Department at AB May Oncology Center, Windhoek Namibia. This was the only center with accessible BC data for research in Namibia during

the study period. All Namibian biospecimens were formalin-fixed, paraffin-embedded (FFPE) primary tumour tissues, collected at diagnosis.

From the cBioPortal

Secondary data of 1855 American women was retrieved retrospectively from the cBioPortal database in the TCGA study named: The BC MSK, Cancer Cell 2018 (https://www.cbioportal.org/study/clinicalData?id=breast_msk_2018), which encompasses of age at BC diagnosis and HER2 status of women diagnosed with BC across three American ethnicities.[39]

Data Collection

We enrolled only women diagnosed with invasive BC (N=1953). We recorded the genetic and molecular profiles of BC cases from 1855 American women similar to a published study.[40] The dataset encompassed mainly three studied American ethnic groups. HER2 status and age at BC diagnosis were the primary data points utilized in our study. The age at BC diagnosis was recorded and HER2 status was determined using data retrieved retrospectively. We included all BC patients recruited from the cBioPortal BC MSK, Cancer Cell 2018 study because of the availability of data for HER2 status, ethnicity, and age at BC diagnosis. The inclusion criteria for the prospective study were as follows: Namibian women with complete demographic data from indigenous African populations above the age of 18 who were diagnosed with BC from year 2018–2020 at Medical Imaging Department at AB May Oncology Center, Windhoek Namibia. For the retrospective study, we included all women diagnosed with BC from the BC MSK, Cancer Cell 2018 study (https://www.cbioportal.org/study/clinicalData?id=breast_msk_2018). The exclusion criteria for the Namibia data were male gender and women who were not Namibian citizens. This was a setup for only Namibian women in order to reduce discrepancies in the misrepresentation of African indigenous populations from other African counties. HER2 data was not available for Namibian cohort due to limited laboratory capacity.

Data Specificity for Each Ethnic Group

To ensure the accuracy and relevance of the data across studied ethnic groups, the following steps were meticulously followed:

(i) Ethnic classification: The cBioPortal database categorizes patients into specific ethnic groups based on self-reported information and genetic ancestry data.[41,42] This classification was crucial for our subgroup analyses.
(ii) Data segregation: The data were segregated to include detailed demographic information specific to each group.
(iii) Data verification: Each ethnic group's data were cross-verified with additional sources within the TCGA database to ensure consistency and reliability. This involved checking for congruence in patient information and molecular data.[42]
(iv) Quality control: Rigorous quality control measures for data cleaning were implemented to eliminate any potential biases or errors. This included double-checking HER2 status and validating age at BC diagnosis records.[42]

DNA Isolation and Analysis

DNA was isolated from the BC tissue samples using standard extraction protocols. This DNA served as a template for subsequent molecular analyses, including Polymerase Chain Reaction (PCR) and gene sequencing, to validate and complement the findings as detailed in a published study.[43]

HER2 Laboratory Analysis

The determination of HER2 status was conducted through a rigorous protocol involving HER2 tests. Initially, all samples underwent analysis using the anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody.[44,45] The staining procedure was performed according to the manufacturer's instructions, ensuring consistent application across all samples. Briefly, BC tissue samples were collected from diagnosed patients, following standard biopsy procedures. Tissue sections were prepared and mounted on slides, ensuring optimal conditions for staining. HER2 staining process utilized primary antibodies specific to the HER2 protein, slides were treated to visualize HER2 protein expression.[39,46] Our study accessed HER2 data retrospectively.

Data Interpretation and Scoring Systems

The interpretation of results for HER2 status was based on the updated American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines.[47–49] HER2 status scores were assigned as follows: 0 (no staining observed or membrane staining in <10% of tumour cells), 1+ (faint/barely perceptible membrane staining in >10% of tumour cells), 2+ (weak to moderate complete membrane staining observed in >10% of tumour cells), and 3+ (strong complete membrane staining in >10% of tumour cells). Cases scored as 2+ were considered equivocal. Cases with scores of 0 or 1+ were considered HER2-negative, while 3+ indicated HER2 positivity.[50–52]

Quality Control Measures and Reference Standards

For samples with an equivocal HER2 score of 2+, FISH testing was performed to confirm the HER2 protein expression status. The FISH analysis utilized the Vysis PathVysion HER-2 DNA Probe Kit, which probes for the HER2 gene and the CEP17 reference.[53–55] A ratio of HER2 to CEP17 signals greater than 2.0 was considered positive for HER2 amplification.[46] To ensure the accuracy and reproducibility of the HER2 status results, several quality control measures were implemented: (i) All HER2 status analyses were conducted by experienced technicians trained in the specific protocols. (ii) Positive and negative controls were included in each batch of tests to verify the staining and hybridization processes. (iii) A subset of samples was randomly selected for re-testing to confirm the consistency of the results. (iv) All interpretations of HER2 results were performed by two independent pathologists to mitigate subjective bias.[46,56,57] The methodology for HER2 status determination adhered to the highest reference standards, as outlined by the ASCO/CAP guidelines.[47–49] These guidelines were used as the benchmark for all procedural and interpretative aspects of HER2 testing, ensuring that the results are comparable to internationally recognized benchmarks.[43,58]

Statistical Analysis

Statistical tests were conducted using R statistical software (version 4.3.3). All continuous variables (eg, age at diagnosis) were evaluated for normality using the Shapiro–Wilk test and visual inspection of Q–Q plots. Descriptive statistics were computed to summarize the dataset, with the age at BC diagnosis detailed through mean, standard deviation (SD) and median values to illustrate the central tendency and dispersion within the cohort. Outliers that reflected data entry errors or implausible biological values (eg, age <10 or >100) were excluded; otherwise, they were retained to preserve real-world heterogeneity. Chi-square test for independence was utilized to assess the relationship between racial categorizations and HER2 status, scrutinizing the distribution of HER2 across different populations similar to a published study.[57] An independent samples *t*-test was used only when comparing the mean age at diagnosis between two groups with normally distributed data.[59] We used Chi-Square for independence test to assesses whether the difference between the two categorical variables of interest was statistically significant: Variable 1 was "Ethnicity" (African American, Asian, Namibian, and White) and variable 2 was "Age group" (Early-onset, Mid-age, Late-onset). The goal was to compare the differences in age at BC diagnosis distributions across multiple ethnic groups whether the age group of BC diagnosis distributions varies between ethnic groups.[30,60]

For comparisons involving more than two groups (eg, ethnicity), ANOVA was initially considered, but due to non-normal distributions and unequal sample sizes, we employed the Kruskal–Wallis *H*-test instead. For two-group comparisons, independent samples t-tests were used only when both groups met normality assumptions; otherwise, the Mann–Whitney *U*-test was applied. We performed Empirical Cumulative Distribution Function (ECDF) analysis with age distributions within a BC case series cohort. We used additional statistical analyses using Mann–Whitney *U*-Test in case-series and Kruskal–Wallis H-test to assess statistical significance across groups. Logistic regression analysis was used to model the odds of HER2 positivity, accounting for both age and ethnicity. To ascertain the predictive accuracy of HER2 status on the age of BC diagnosis, ROC curve analysis was performed, and the AUC was computed using the trapezoidal rule. A p-value < 0.05 was considered significant, and all analyses employed two-tailed testing procedures.

Results

Cohort Demographics

A brief demographic profile of 1,953 women diagnosed with BC is shown in Table 1. The ethnic composition of our cohort was White (73.99%), followed by African American (18.02%), Namibian (5.02%), and Asian American (2.97%) populations. The mean age at BC diagnosis was 56.42 (26–80), with a significant majority (69.53%) being diagnosed above age 50 years ($p<0.001$, effect size 39.06%), while about 25% of all HER2 results were negative (Table 1).

Disparities in Age at BC Diagnosis Across Different Ethnicities

Analyzing disparities in age at BC diagnosis across different ethnicities was vital for identifying at-risk populations, enabling early intervention, and tailoring preventive public health strategies.[61,62] The description of BC patients by age groups and ethnicities revealed a broader range of disparities for age at BC diagnosis across populations (Figure 1A). Age at BC diagnosis showed a trend suggesting potential disparities in the timing of BC onset and detection across these groups (Figure 1A). To investigate on ethnic and age-related patterns in HER2 status was important in order to understand the biological diversity of BC in relation to age at BC diagnosis.[63] There was a significant predominance of HER2-negative status across the study cohort ($p < 0.0001$, Figure 1B). Also, HER2 negative status was dominant in both age groups, below 50 years and above 50 years (Figure 1B). The comparison of HER2 status between African American and White women revealed significant differences in the HER2 statuses within their groups ($p < 0.001$, Figure 1B). However, there were no statistically significant differences observed in this analysis in HER2 positivity rates between White and African American women.

Ethnic Disparities in Age at BC Diagnosis

We studied ethnic disparities in age at BC diagnosis to uncover potentially unique risk factors and disease progression patterns among different populations, which can inform targeted early detection strategies and culturally appropriate interventions.[13,32]

Our findings show a statistically significant younger age at BC diagnosis for African American women compared to White women ($p=0.0037$). Namibian women were diagnosed with BC at a significantly younger age than White women in America ($p<0.0001$). Asian women show a diagnosis age distribution that is significantly different from White women ($p=0.0043$) both in America, indicating potential biological or cultural factors influencing the age of BC onset that warrant further investigation. No significant difference in the age at BC diagnosis between Namibian and Asian women. The age at diagnosis between African American and Asian women did not significantly differ ($p=0.1549$), which could

Table 1 Study Demographics and Descriptive Statistics

Characteristic	Total Count	Mean (SD, Range)	Median (IQR)	Categories	Frequency (%)	Effect Size	p-value
Diagnosis age	1953	56.42 (12, 26–80)	56 (48–65)	Above 50 years Below 50 years	1358 (69.53) 595 (30.47)	39.06% *	**<0.001**
IHC-HER2	736	N/A	N/A	Positive Negative Equivocal Indeterminate	115 (6.45) 450 (25.22) 160 (8.97) 11 (0.62)	0.23**	**<0.001**
Race	1953	N/A	N/A	Namibian African American White Asian American	98 (5.02) 352 (18.02) 1445 (73.99) 58 (2.97)	4.11***	**<0.001**

Notes: * For Diagnosis age, the difference in proportions between "Above 50 years" and "Below 50 years" is 39.06% (Proportion difference). **For IHC-HER2 Status, Cramer's V (a measure of association strength for categorical variables) is provided to quantify the relationship. ***For Race, a relative risk comparing the majority group (White) to all other groups combined. All significant p-values are bolded.

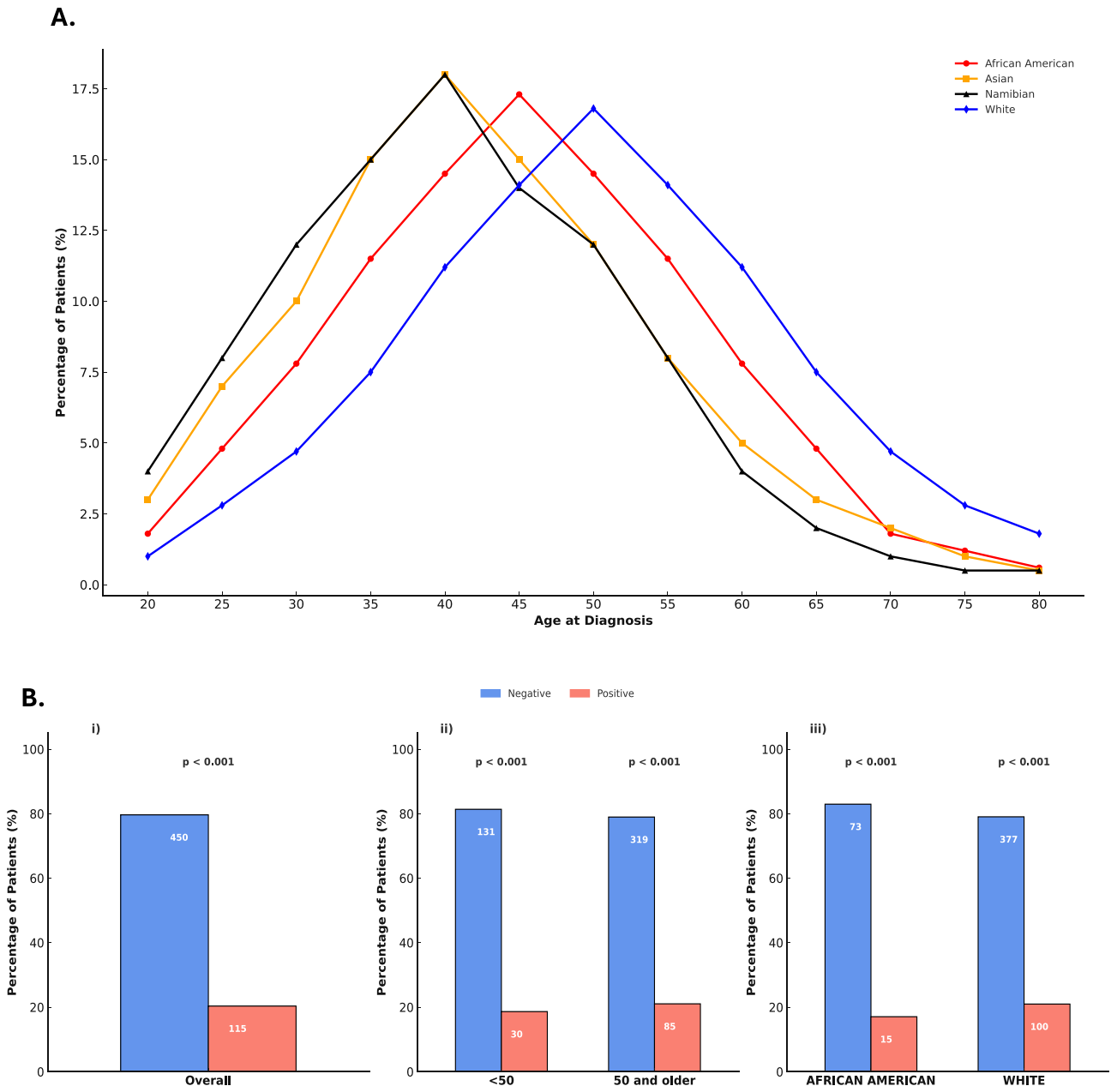

Figure 1 Age distribution and IHC-HER2 status across ethnic groups. (**A**) Age-specific density plots show the percentage of BC patients diagnosed according to their age at BC diagnosis across the four ethnic populations. Namibian, Asian, and African American women demonstrated earlier peaks in diagnosis (age 40–45), while White women had a late-shifted peak (age 50–55). (**B**) (i) Overall distribution of IHC-based HER2 status showing a statistically significant predominance of HER2-negative tumours. (ii) Age-stratified analysis reveals consistent dominance of HER2 negativity in both age <50 and age ≥50 years subgroups. (iii) Race-stratified data show similar trends of high HER2-negative tumours across African American and White patients. Binomial tests comparing HER2-negative vs HER2-positive distributions within each group demonstrated statistical significance ($p < 0.001$ for all subgroups).
Note: All significant p-values are bolded.

indicate similar epidemiological patterns in BC onset between these ethnicities. Namibian women were diagnosed with BC at a significantly younger age than African American women (p=0.0035), highlighting the stark differences even within the African descent groups and suggesting unique contributing factors for geographical regional differences (Figure 2A–F).

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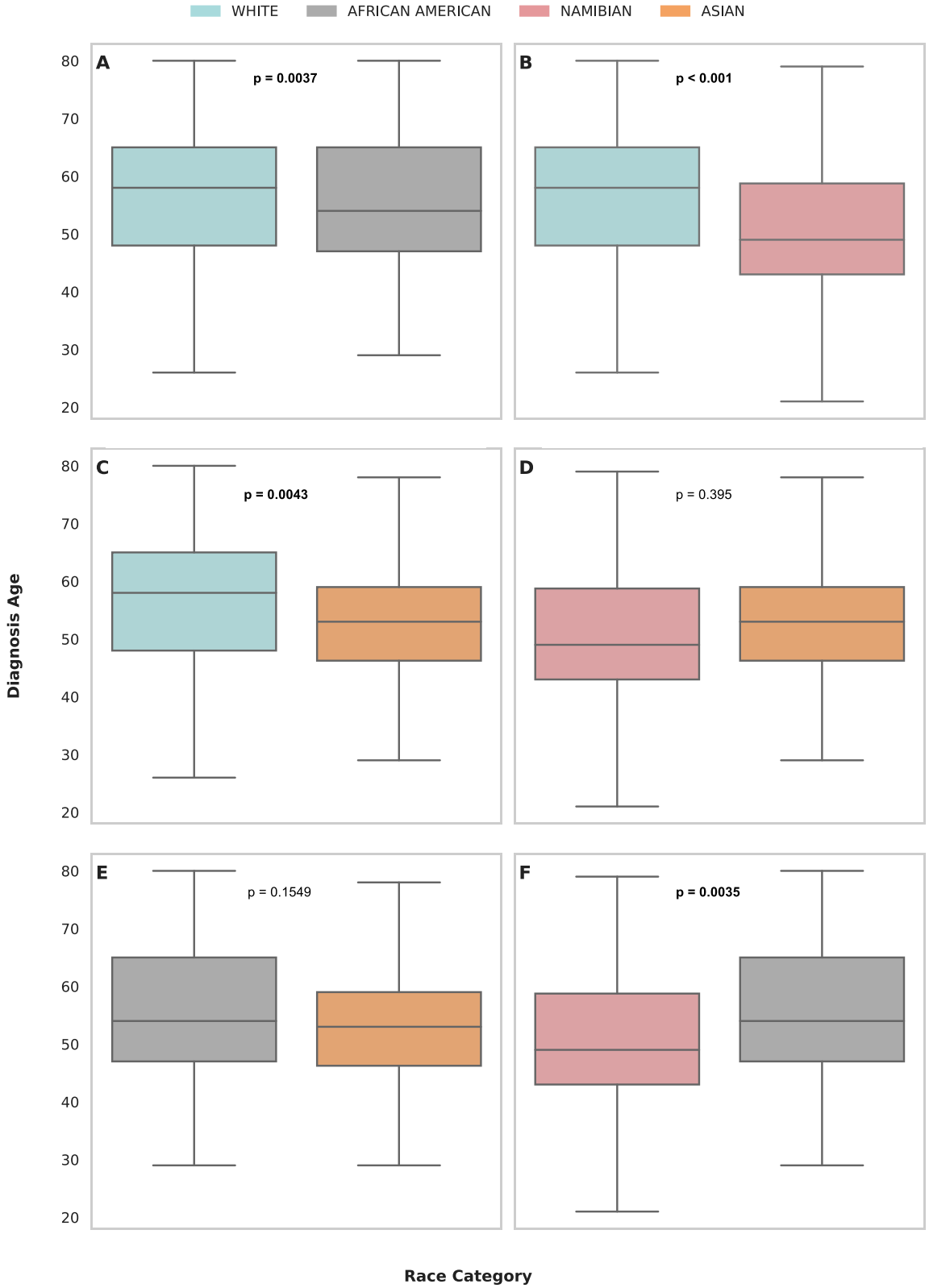

Figure 2 Box plot analyses for the age at BC diagnosis among different ethnic groups in the study cohort. (**A**) Statistically significant younger age at diagnosis for African American women compared to White women. (**B**) Namibian women are diagnosed at a significantly younger age than White women. (**C**) Asian women show a diagnosis age distribution that is significantly different from White women. (**D**) No significant difference in the age at BC diagnosis between Namibian and Asian women. (**E**) The age at diagnosis between African American and Asian women did not significantly differ. (**F**) Namibian women were diagnosed at a significantly younger age than African American women.

Note: All significant p-values are bolded.

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Furthermore, to address age structure of the study population, we analysed the distribution of BC cases across three age groups as follows:

(i) Early-onset (<40 years),
(ii) Mid-age (40–60 years), and
(iii) Late-onset (>60 years)

This was done for four ethnicities: African American, Asian, Namibian, and White. There was a statistically significant difference in age groups at BC diagnosis between four different ethnicities (Table 2). Notably, Namibian women show the highest proportion of early-onset cases (18.37%), followed by Asian women (15.52%). In contrast, White women have the highest percentage of late-onset cases (42.98%), while mid-age diagnoses were particularly prominent among Asian (63.79%) and Namibian (59.18%) groups. The differences in age distribution across these ethnic groups were confirmed to be statistically significant ($p = 0.0012$, Table 2).

Cumulative Probability Analysis for Age at BC Diagnosis Across Different Ethnic Groups

Understanding the cumulative probability for age at BC diagnosis across different ethnic groups is fundamental for identifying potential disparities in age distribution across the study cohort.[32,64] We performed cumulative probability analysis for age distributions within a BC case series between different ethnic groups, providing a novel perspective on how ethnicity may influence the timing of BC onset (Figure 3). In the cumulative probability analysis using ECDF plots for all study populations, there was a significant difference in cumulative probability for age at BC diagnosis for all populations ($p<0001$, Figure 3A). There was a statistically significant difference in cumulative probability for age at BC diagnosis between Namibian women and African American women ($p = 0.0045$, Figure 3B). Also, there was a statistically significant different in cumulative probability for age at BC diagnosis for Namibian women compared to White women ($p < 0.0001$, Figure 3C). In addition, there was no statistically significant difference in cumulative probability for age at BC diagnosis between Namibian women and Asian women (Figures 3D) and between White and African American women and women (Figure 3E). Also, there was no statistically significant difference in cumulative probability for age at BC diagnosis between Asian and African American women (Figure 3F); however, the difference between Asian and White women was statistically significant ($p = 0.0035$, Figure 3G).

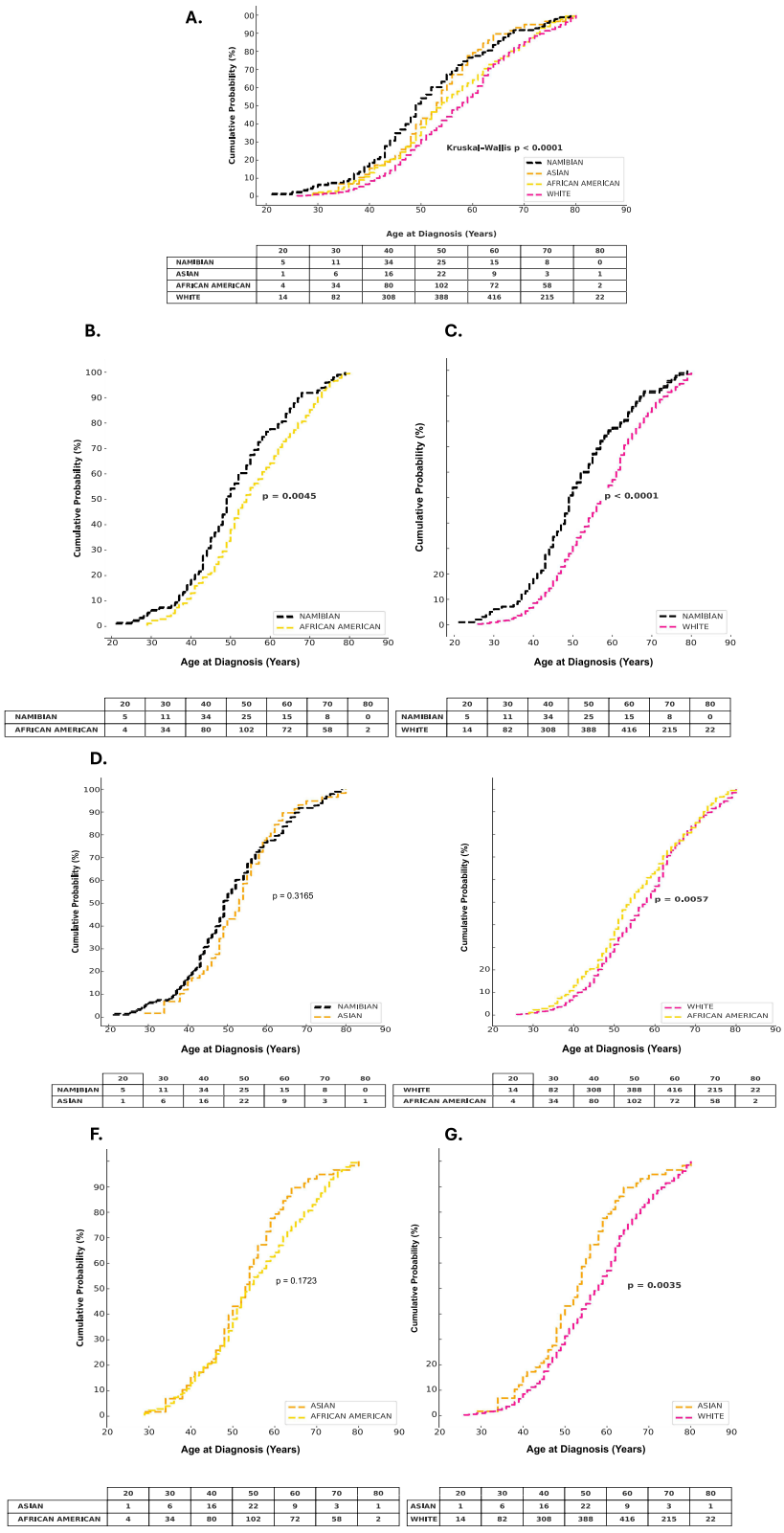
Logistic Regression Analysis of Age and Race Associated with HER2-Positive BC

Analysing age and racial disparities in HER2-positive BC is crucial for understanding variations in disease biology and treatment outcomes. African American patients, who are underrepresented in clinical trials, often exhibit worse BC outcomes, making this disparity particularly relevant for tailoring interventions and improving equity in care.[65] Age-specific trends in HER2 status further may inform personalized treatment strategies and risk stratification for patients across different life stages, emphasizing the importance of integrating demographic and molecular data to refine therapeutic approaches and address disparities in BC management.[66,67] To evaluate the association between age, race, and HER2-positive BC we performed a logistic regression analysis among age groups. In unadjusted logistic regression,

Table 2 Analysis of Age Groups at BC Diagnosis According to Ethnicity

Ethnicity	Early-onset (%), <40 yrs	Mid-age (%), 40–60 yrs	Late-onset (%), > 60yrs	*p-value
African American	13.07	51.14	35.8	**0.0012**
Asian	15.52	63.79	20.69	
Namibian	18.37	59.18	22.45	
White	8.51	48.51	42.98	

Note: * Chi-Square for independence test between ethnicity and age group. The significant p-value is bolded.



	20	30	40	50	60	70	80
NAMIBIAN	5	11	34	25	15	8	0
ASIAN	1	6	16	22	9	3	1
AFRICAN AMERICAN	4	34	80	102	72	58	2
WHITE	14	82	308	388	416	215	22

Figure 3 Empirical cumulative distribution function (ECDF) plots to compare cumulative probability for age at BC diagnosis between different ethnic groups. (**A**) Show a significant difference in cumulative probability for age at BC diagnosis for all populations. (**B**) There was a statistically significant difference in cumulative probability for age at BC diagnosis between Namibian women and African American women. (**C**) There was a statistically significant different in cumulative probability for age at BC diagnosis for Namibian women compared to White women. (**D**) There was no statistically significant difference in cumulative probability for age at BC diagnosis between Namibian women and Asian women. (**E**) There was no statistically significant difference in cumulative probability for age at BC diagnosis between White and African American women. (**F**) There was no statistically significant difference in cumulative probability for age at BC diagnosis between Asian and African American women. (**G**) There was a statistically significant difference between Asian and White women (**3G**). **Note**: All significant p-values are bolded.

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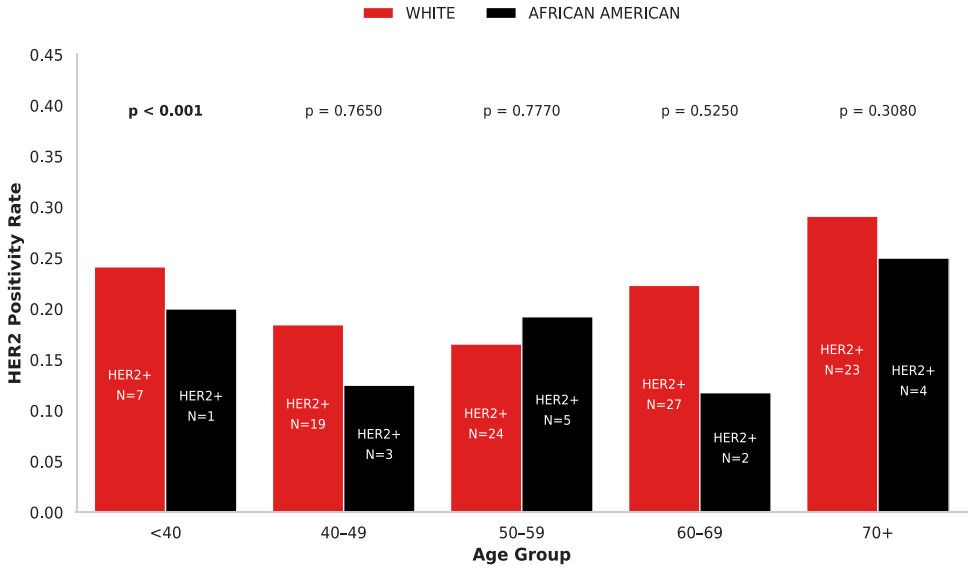

Figure 4 HER2 positivity rates across age groups stratified by race. HER2-positive rates were compared between White and African American women within five age strata (<40, 40–49, 50–59, 60–69, and ≥70 years). Each bar shows the proportion of HER2-positive cases, with in-bar annotations indicating HER2+ sample sizes. Only the below 40 years group showed a significant disparity (**p < 0.001**), with White women markedly more likely to be HER2 positive. The accompanying table below summarizes the exact HER2+ counts with total sample sizes, and Fisher's test results, reinforcing the observed intergroup differences across age strata.
Note: Fisher's exact test was used to assess statistical differences between races in each age group. The significant p-value is bolded.

only the age below 40 years group showed a significant disparity in HER2 positivity ($p < 0.001$), with White women markedly more likely to be HER2 positive (Figure 4) and Table 3. Adjusted logistic regression revealed significantly lower odds of HER2 positivity among African American patients after adjusting for age ($p < 0.001$, Table 4).

Table 3 Age-Stratified Odds of HER2 Positivity in White and African American Women with BC (Unadjusted)

Age Group	HER2+ (White)	HER2+ (African American)	Total (White)	Total (African American)	Odds Ratio	p-value
< 40	7	1	29	5	30.33	**0.0001**
40–49	19	3	103	24	1.48	0.7650
50–59	24	5	121	26	1.04	0.7770
60–69	27	2	79	17	3.59	0.5250
≥ 70	23	4	126	16	0.70	0.3080

Note: A significant p-value is bolded.

Table 4 Adjusted Odds of HER2 Positivity by Age Group and Race (Multivariable Logistic Regression)

Variable	Coefficient	Odds Ratio (OR)	CI Lower	CI Upper	p-value
Intercept	0.154	1.17	0.79	1.73	0.444
Age 40–50*	0.009	1.01	0.64	1.59	0.971
Age 50–60*	−0.392	0.68	0.43	1.06	0.091
Age 60–70*	−0.177	0.84	0.53	1.31	0.442
Age >70*	0.418	1.52	0.94	2.45	0.085
Race: African American**	−0.647	0.52	0.37	0.73	**<0.001**

Notes: The significant p-value is bolded. *Reference category: Age <40 years. **Reference category: White race.
Abbreviation: CI, Confidence Interval.

Discussion

We conducted a cross-ethnic retrospective study using a case series cohort involving a total of 1,953 women pathologically diagnosed with invasive BC from two different geographical areas, Africa and America. We combined primary and secondary datasets and uncover significant disparities in HER2 positivity status and age at BC diagnosis, with an emphasis on underrepresented Namibian minority indigenous populations. This work addresses a significant gap in understanding how age at BC diagnosis varies across underrepresented populations, particularly in resource-limited settings. We report significant younger age at BC diagnosis in women of African origin either genetically or geographically compared to other ethnicities, a finding that highlights the importance of individualized screening guidelines and suggests biological diversity in BC across different ethnicities. Additionally, the observation that African American women have significantly lower odds of HER2-positive BC compared to White women suggests critical variations in tumour biology that could impact therapeutic responses and outcomes. However, another potential explanation for this observation could be a difference in the HER2 status quality. These findings provide compelling evidence for the need to consider ethnicity-specific patterns in BC diagnosis and molecular characteristics to optimize screening and treatment strategies globally. Also, we emphasize on the scientific necessity of genetic and biological studies tailored to diverse minority ethnic groups especially from Africa.

Although Figure 1B shows that the raw percentages of HER2 positive BC appear similar between White and African American patients, our multivariate logistic regression (Table 4) revealed significantly lower odds of HER2 positivity among African American patients after adjusting for age. This apparent discrepancy is due to the confounding effect of age at BC diagnosis, which differs significantly between racial groups in this study. Therefore, when age is accounted for, our statistical model uncovers a meaningful disparity in HER2 expression that is not apparent from crude proportions alone.

The significant findings on the differences on cumulative probability and age at BC diagnosis (Figure 3) between White, African American, and Namibian women, despite Namibia's small population scale, are a pivotal finding that magnifies the global importance of biological and epidemiological diversity in BC onset[4,64,68] This underscores the necessity of including small populations in large-scale studies to ensure that the resultant data and subsequent healthcare recommendations are truly inclusive, thus preventing a "one-size-fits-all" approach. Our study poses questions about the genetic and environmental factors unique to populations of African origin and further highlights how data from smaller populations can reveal cumulative risk that may be obscured in broader studies, underscoring the importance of including diverse ethnic groups in BC research.[32,69–71] We justify the need for tailored intervention strategies in resource-limited settings and address potential underlying genetic or environmental factors influencing earlier age of BC onset in different ethnicities. Given these findings, healthcare providers and policymakers should consider population-specific screening programs to address the unique risks and trends observed among different ethnic groups.[1] The high proportion of younger age of onset of BC in populations of African origin, as indicated in our results, may point to the potential role of hereditary factors.[31,72,73] Hereditary factors are contributing to genetic predispositions, such as mutations in *BRCA1* and *BRCA2* genes or other less characterized genomic variations that are more prevalent in African populations.[72–75]

The high proportion of younger age at BC diagnosis in women with African ancestry (Namibian and African American women) may suggest that there may be intrinsic biological factors, possibly founder mutations or epigenetic changes, that predispose this ethnic demographic to earlier BC onset.[73,76] However, there was no significant difference in the age at BC diagnosis between African American and Namibian women compared to Asian women, suggesting that these groups may share common factors affecting the age at BC onset or could be due to a small sample size of both populations.[77,78] In addition, the observed BC disparity in age at diagnosis in this study underscores the need for personalized screening in BC according to underlying genetic, socioeconomic, epidemiology, geographical locations, and environmental factors which may affect disease development. This is further supported by the variations in HER2 statuses, pointing towards potential differences in tumour biology and pathology across ethnicities similar to previous findings by Villareal-Gaza et al.[79] Our results reinforce the concept that genetic and geographical diversity can yield critical insights into disease mechanisms that are universally applicable.[80]

The differences in HER2 expression, particularly the higher incidence of HER2-negative BC among certain ethnicities, demand a re-evaluation of the biological factors driving BC across diverse populations. This raises questions

about the interplay between genetic predispositions and environmental or lifestyle factors that may contribute to these observed patterns.[81] Previous studies found that BC with HER2-positive status is more aggressive and tends to be diagnosed with at a younger age compared to those with negative or equivocal HER2 status.[82–84] Our findings suggest that younger patients of African origin may face more aggressive BC types due to early onset. However, when we performed Receiver Operating Characteristic (ROC) curves analyses, HER2 status could not predict age at BC diagnosis in this study population (Supplementary Figures 1 and 2).

The lower odds of HER2-positive BC among African American women compared to White women (Figure 4) suggests critical racial disparities in tumour biology. Our results should be interpreted with caution since our sample size for this analysis was very small. However, these findings align with three previous BC studies which observed similar patterns in White versus African American women populations.[5,13] The implications of these findings are profound, suggesting that ethnicity-specific treatment protocols may be necessary, as the effectiveness of HER2-targeted therapies may vary across ethnic lines. This new insight can drive a more nuanced approach to treatment that better serves the genetic and molecular profiles of diverse patient groups. The lower incidence of HER2-negative and positive status in African American women could indicate ethnicity-specific biological pathways influencing low HER2 expression, justifying the need for more ethnically inclusive research to guide precision oncology. However, Stringer-Reasor et al reported a higher incidence of HER2 negativity in African Americans in their study population.[65] This discrepancy with our findings could be due study populations may not be genetically homogeneous, leading to variability in HER2 status incidence.[85]

The strengths of our study include the following: (i) Innovative approach of mixing primary data from small populations in Namibia and secondary data from publicly available databases like the cBioPortal and TCGA. This provides a wide-ranging analysis of demographics with a large sample size to improve the statistical power, (ii) Inclusivity of minority populations typically underrepresented group of indigenous African Namibian women alongside American women provides a broad, geographically diverse perspective often lacking in BC research. This diversity enhances the study's ability to identify unique patterns, cumulative risks, and contributes to more inclusive and personalized healthcare recommendations, (iii) the use of cumulative risk plots and the logistic regression model to compare the trends of age at BC diagnosis over time in different ethnicities, (iv) New insights, particularly the younger age at BC diagnosis in women of African origin specifically minorities Namibian women, represent a novel contribution to the field, highlighting the inclusive of certain underrepresented African populations and suggesting potential biological underpinnings worthy of further investigation, (v) The analyses of HER2 status across ethnicities provide interesting observations to contribute to the field of precision oncology, with the potential to influence future research directions, public health policies, and clinical practices in BC personalized screening and treatment.

The limitations are as follows: (i) comparability of the Namibian cohort and the MSK dataset which includes metastatic, hormone receptor-positive (HR+) BC cases with a subset resistant to endocrine therapy. This poses a significant difference from the Namibian cohort, which may not share the same clinical characteristics. However, HER2 status from these patients was analysed after confirmed diagnosis of invasive BC and before treatment hence resistance to hormonal and endocrine therapy did not interfere with HER2 results or age at BC diagnosis,[86] (ii) our findings using this small cohort of African indigenous populations from Namibia should not be generalizable to all women in Namibia or to African populations more broadly, (iii) limited sample size for some ethnic groups and missing HER2 status data with a significant proportion of women with unknown HER2 status including Namibian women, which could mask true incidence rates and impact the robustness of the associations made between HER2 status and age at BC diagnosis, (iv) Single marker tumour genetic analysis primarily on HER2 status which does not account for other genetic, molecular, or hormonal factors that influence BC, (v) Variations in BC screening, diagnostic practices, geographical locations, and healthcare access across different countries and ethnicities may influence the age of BC diagnosis, which this study might not fully account for.

Acknowledging these limitations is crucial for the proper interpretation of our study's results and for guiding future research to build on the foundational work provided here to address our limitations.

Conclusions

This study suggests significant ethnic disparities in age at BC diagnosis and HER2 positivity, uncovering that Namibian women are diagnosed at a significantly younger age compared to African American and White women, while African American women have markedly lower odds of HER2-positive BC. While the crude HER2 positivity frequencies appeared similar across racial groups, multivariable logistic regression modelling revealed a significant difference in the adjusted odds of HER2 positivity, exposing the importance of age-stratified interpretation of HER2 positive disparities. These findings show the need to contextualize BC biology within specific ethnic and regional frameworks, shedding light on the interplay of genetic, environmental, and healthcare access factors influencing disease presentation. This is a translational implication for designing ethnicity-informed BC screening programs, particularly in younger women where HER2 biology diverges across populations. The observed disparities in this study suggest the critical need for inclusive genomic studies that incorporate underrepresented groups to avoid "one-size-fits-all" approaches in HER2 biomarker-driven screening and treatment. Our results support the prioritization of ethnic diversity in BC genomics to ensure equitable precision medicine globally. When confirmed in a larger cohort, our findings advocate for a -personalized BC screening and treatment strategies from minority African populations, emphasizing on the importance of genetic, geographical, and epidemiological diversity. Embracing our global genetic diversity especially in minority groups is not only a step towards equity but also a stride towards individualized approach in BC screening. We highlighted the intersection of ethnicity with BC age at diagnosis and molecular differences, providing a compelling comparison for incorporation of ethnic-specific factors and genetic diversity in BC management.

Institutional Review Board Statement

This study adhered to ethical guidelines, with all procedures being approved by relevant institutional review boards. Ethics clearance number (**17/3/3 MSK**) was sought and obtained from the Ministry of Health and Social Services (MOHSS) ethics committee and the Namibia University of Science and Technology (NUST) higher degree committee. Permission from the respective Medical Imaging departments was sought to carry out the study in the different departments around Namibia with regard to the diagnostic reports, and permission was granted in January 2022.

Data Sharing Statement

The data underpinning this study's findings are derived from a combination of publicly accessible resources and direct clinical observations. The cBioPortal platform can be accessed at (https://www.cbioportal.org/), where users can review the data collection protocols, data types, and specific datasets utilized in this study. Clinical data from Namibian patients, collected in accordance with ethical standards and patient consent protocols. Aggregated data, stripped of any potential identifiers, and detailed methodologies employed in data collection and analysis are available from the corresponding author upon request and in alignment with the ethical approval guidelines governing this research.

Informed Consent Statement

Informed consent was obtained from all prospective participants involved in primary data collection, ensuring confidentiality and compliance with ethical standards.

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Disclosure

The authors declare no conflicts of interest in this work.

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