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Research Article

Racial Comparison of Receptor-Defined Breast Cancer in Southern African Women: Subtype Prevalence and Age–Incidence Analysis of Nationwide Cancer Registry Data

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Abstract

Background: Receptor-defined breast cancer proportions vary across Africa. They have important implications for survival prospects and research priorities.

Methods: We studied estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor statuses in two multiracial Southern African countries with routine diagnostic immunohistochemistry. A total of 12,361 women with histologically confirmed breast cancer diagnosed at age ≥20 years during (i) 2009–2011 from South Africa's national cancer registry (public sector) and (ii) 2011–2013 from Namibia's only cancer hospital were included. Crude, age, and age + laboratory–adjusted ORs of receptor status were analyzed using logistic regression, and age–incidence curves were analyzed using Poisson regression.

Results: A total of 10,047 (81%) women had known ER status. Ranking of subtypes was consistent across races: ER^+/PR^+HER2^- was most common (race-specific percentage range, 54.6%–64.8%), followed by triple-negative (17.4%–21.9%), ER^+/PR^+HER2^+ (9.6%–13.9%), and $ER^-PR^-HER2^+$ (7.8%–10.9%). Percentages in black versus white women were 33.8% [95% confidence (CI), 32.5–35.0] versus 26.0% (24.0–27.9) ER^-; 20.9% (19.7–22.1) versus 17.5% (15.4–19.6) triple-negative; and 10.7% (9.8–11.6) versus 7.8% (6.3–9.3) $ER^-PR^-HER2^+$. Indian/Asian and mixed-ancestry women had intermediate values. Age–incidence curves had similar shapes across races: rates increased by 12.7% per year (12.2–13.1) across ER subtypes under the age of 50 years, and thereafter slowed for ER^+ (1.95%) and plateaued for ER^- disease (−0.1%).

Conclusions: ER^+ breast cancer dominates in all Southern African races, but black women have a modest excess of aggressive subtypes.

Impact: On the basis of the predominant receptor-defined breast tumors in Southern Africa, improving survival for the growing breast cancer burden should be achievable through earlier diagnosis and appropriate treatment. *Cancer Epidemiol Biomarkers Prev; 23(11); 2311–21. ©2014 AACR.*

Introduction

Improvements in breast cancer survival are needed in sub-Saharan Africa, where this cancer is currently the most common cancer in women and the second most common cause of cancer-related death (1). The potential to achieve such improvements will be curtailed if more aggressive tumor phenotypes are overrepresented. In the clinical setting, estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor statuses are used to determine breast cancer prognosis, therapeutic management, and, of particular relevance in sub-Saharan Africa, have implications for treatment costs and the time window to achieve earlier diagnosis (2–4). In this region, estimates of the percentage of breast tumors that are the poorer prognosis ER-negative (ER^-) subtype are extremely wide ranging, from 30% to 40% (5–7) to 60% to 76% (8–11). In African American women with breast cancer, the comparative ER^- percentage of 39% is lower than many of the estimates from studies conducted in indigenous African patients with breast cancer, but it is 10% to 20% higher than in their age-matched white American counterparts (12). If higher ER^- estimates dominate across sub-Saharan Africa, there would be major implications for research priorities appropriate for this setting, as well as for strategies to improve prognosis, especially concerning the use of hormonal therapy.

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Within sub-Saharan Africa, heterogeneity in ER^- estimates may arise from variations in age and stage at diagnosis, calendar time trends, and attributable genetic and environmental etiologies (13–15). This reproduction-related cancer is greatly influenced by fertility patterns, specifically those that lead to delayed age at first childbearing and lower parity, which increase the risk of ER^+ but decrease that of ER^- breast cancer (16). African countries are at different stages of the fertility transition, evidenced by declining parity and lengthening birth intervals (17, 18). Notably, parity, inversely associated with breast cancer risk, ranges from 2.3 children per woman in South Africa to 8 in Niger (18). However, along with real differences in subtype distributions, there remains the possibility that heterogeneity in breast cancer receptor distributions were influenced by selection biases and false negatives due to the quality of histopathologic processing as routine receptor determination has historically been lacking (19, 20).

The Southern African countries of Namibia and South Africa provide unique settings in which to study receptor-defined breast cancer epidemiology because ER, PR, and HER2 are routinely determined at diagnosis in 14 public-sector diagnostic laboratories. Both countries also have coexisting multiracial patient populations diagnosed within the same hospitals and laboratory systems, thus allowing a direct racial comparison of breast cancer receptor distributions. On the basis of over 12,000 incident breast cancers in black, white, mixed-ancestry, and Asian women, we examined race-specific and racial differences in receptor-defined breast cancer subtypes in these two countries, and, for the first time in sub-Saharan Africa, examined ER-defined age–incidence curves (21, 22).

Materials and Methods

Setting

The racial composition of Namibia's 2 million population is 87% black, 6% white, and 7% mixed-ancestry and the estimated age-standardized breast cancer incidence rates in 2012 was 24 per 100,000 women (cf. 93 in the United States; ref. 1).

In South Africa, the population of 52 million is 79% black, 9% white, 9% mixed-ancestry (or "Colored"), 3% Indian/Asian, and <1% of other/unknown race. Indians make up the majority of the "Indian/Asian" population, and mixed-ancestry refers to a population with mixed-heritage. IARC Globocan estimated age-standardized breast cancer incidence rates in 2012 were 42 per 100,000 women (1); however, rates vary by race. The South Africa cancer registry estimated breast cancer incidence rates to be 3.7-fold higher in white and 2.5-fold higher in mixed-ancestry and Indian/Asian than in black women in 2006 (23).

Neither South Africa nor Namibia has population-based breast cancer screening; thus, late-stage tumors are prevalent in the public sector (~50%–60% stage III/IV) and *in situ* tumors are rare (5).

Study population

In Namibia, we included all women ($n = 440$) diagnosed with invasive breast cancer at age 20 years or older at the country's only public-sector oncology facility, Windhoek Central Hospital, from January 2011 to April 2013. This hospital also treats private patients, who were included in this analysis. Age at diagnosis, race, grade and ER, PR, and HER2 receptor status, routinely conducted during this time period, were extracted from patient files.

In South Africa, the National Cancer Registry (NCR) is a pathology-based cancer registry for the entire country (23). The NCR receives information on new cancer patients diagnosed in the public sector from the National Health Laboratory Service (NHLS), a single integrated nationwide diagnostic laboratory service for all public hospitals. Public-sector cancer patients are predominantly those without medical scheme coverage and comprise approximately 90% of black, 80% of mixed-ancestry, 50% of Indian/Asian, and 30% of the white population (24). At breast cancer diagnosis, the NHLS routinely performs histology and immunohistochemistry (IHC) for ER, PR, and HER2. For the present study, we included all public-sector female breast cancer cases diagnosed at the age of 20 years or older between 2009 and 2011 inclusive ($n = 11{,}921$). Data on date of birth, date of breast cancer diagnosis, hospital, province, laboratory name, laboratory reports (approximately 2 per patient), and race were obtained from NCR. NCR predicts race using a surname analysis hot-deck imputation algorithm and provides plausible race-specific cancer distributions (Supplementary Methods). The NCR also obtains information on cancer patients diagnosed in the private healthcare sector; however, this information was not available for 2009–2011 at the time of extraction, nor were 2011 data available for one South African province, KwaZulu-Natal.

The study was approved by University of Witwatersrand (M130117, 25/01/2013) and the Ministry of Health and Social Services, Namibia (17/3/3).

Breast cancer receptor information

Breast cancer hormone receptor testing is routinely performed in the South African public sector. Receptor testing is conducted on core breast biopsies at one of 13 NHLS laboratories in South Africa (Supplementary Table S1.1), each of which provide diagnostic services to set of referral hospitals in its catchment area. In Namibia, receptor determination was conducted at the Namibia Institute of Pathology (Supplementary Table S1.1). Receptor expression was evaluated by IHC and, in some instances, by FISH for HER2 if IHC results were equivocal (score 2). Receptor status and tumor grade, entered in various formats across 22,122 free-text e-laboratory reports, were extracted primarily using an automated algorithm, supplemented by manual checks where status was not found (Supplementary Methods). As the primary information was extracted from pathology reports, data on tumor staging was missing for over 80% of women and so was not included in the analysis.

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Our analyses focused principally on ER, which was the receptor most frequently determined. PR and HER2 statuses were only included for those women for whom ER status was known [i.e., almost all of those with PR/HER2 status known (>99%)]. ER and PR were considered positive if >1% staining was present, as per international guidelines (19) and HER2 as positive if FISH was positive or HER2 score was 3.

Statistical analysis

For each race, among women with known receptor status, we calculated the percentage of breast cancers that were ER^-, PR^-, and $HER2^+$ and their exact binomial 95% confidence intervals (CI) in 5-year (for ER only) and 10-year age-at-diagnosis categories. ORs for the binary outcomes receptor status known/unknown and, if known, receptor positive/negative were analyzed using logistic regression. Subtypes were classified in patients with all 3 receptors known ($n = 7{,}246$) using standard definitions (ref. 3; Table 3, footnote) and ORs associated with each subtype, compared to luminal A, were estimated using multinomial logistic regression. We examined ORs of receptor status associated with race adjusted for (i) age only and (ii) additionally adjusted for an indicator of the laboratory where receptor testing was conducted. The latter was intended to control for potential systematic histopathologic–processing differences; however, it may be an overadjustment, explained as follows. As a consequence of South Africa's apartheid legacy, there is an unequal geographical distribution of racial groups. If there were no systematic between-laboratory processing differences that affected receptor status, adjusting for this "laboratory factor" may inadvertently adjust for race, as the uneven distribution of racial groups creates a laboratory–race correlation, i.e., race differences in the case mix.

We also compared ER^- percentages in black and white women with corresponding values in US-SEER incident invasive breast cancers diagnosed 2008–2010 (25).

Within each race in South Africa, if public-sector breast cancer patients represent the same proportion of all (public + private) patients with breast cancer across age groups, then ER-specific and age-specific (5-year age bands) breast cancer "proportional" incidence rates can be calculated as number of ER-specific public sector cases divided by the corresponding age-specific population. This assumption held approximately (Supplementary Fig. S1.1), and thus proportional ER and age-specific breast cancer incidence rates were plotted against age for each race. We used Poisson regression models to estimate the rate of acceleration of incidence rates per year of age (Poisson regression of log case count in 5-year age bands, with a log offset of corresponding population at risk, separately by race and ER-specific cases). We conducted analyses with an *a priori* stratification at the age of 50 years to allow examination of Clemmesen's hook—the term used to describe the rapid increase in breast cancer incidence rates with age until 50 years, beyond which ER^+ incidence rates continue increasing albeit at a slower rate while ER^- rates plateau (26).

Results

A total of 12,361 women with breast cancer were included in this study (Supplementary Table S2.1). Black women were both the largest (56%) and youngest patient group. ER status was known for 10,047 women (81%), PR for 70%, HER2 for 68%, and grade for 56%. Within provinces, missing ER status was not associated with race or age, but was more common in smaller provinces (24%–41% missing) and in KwaZulu-Natal (Supplementary Table S2.2). Missing patterns for PR and HER2 were similar (not shown), except for one laboratory which only tested for PR in younger patients; thus, its PR and subtype data are included only in age-adjusted and age-specific analyses.

Overall, 31.8% of tumors were ER^-, 46.3% PR^-, and 25.2% $HER2^+$. For each race, receptor prevalence by age and grade are provided in Table 1 and Supplementary Fig. S2.1 and their associated ORs are given in Table 2. The latter were stratified by age (<50 and $\geq$50 years) because of nonlinear age effects. ER^- and PR^- percentages peaked at ages 50 to 54 years for all races (Table 1) and the reduced odds of ER^- and PR^- tumors with increasing age were restricted to $\geq$50 years. In contrast, lower odds of $HER2^+$ breast cancer with older age held at all ages. Higher grade tumors were strongly associated with ER^- status, especially in non–black women, and were also more likely to be PR^- but were not associated with HER2 status.

The percentage of ER^- breast cancers was lowest in white women [26.0% (95% CI: 24.0–27.9)], followed by Indian/Asian [28.4% (23.4–33.5)], mixed-ancestry [31.1% (28.8–33.4)], black [33.8% (32.5–35.0)], and women of other/unknown races [36.4% (32.7–40.1); Table 1]. For any given race, laboratory-specific ER^- percentages varied up to 20% and a positive within-laboratory correlation was present (Supplementary Fig. S2.2a). Table 3 presents age-adjusted ORs for each receptor associated with race, before and after adjustment for laboratory. Under the age of 50 years, white women with breast cancer were less likely to have ER^- (OR 0.78) and PR^- (OR 0.81) tumors, when compared with age-matched black women, but the reduced ER^- odds in white cases was partly attenuated and became nonsignificant after adjustment for laboratory. At age $\geq$50 years, white, mixed-ancestry, and Indian/Asian cases were less likely to have ER^- and PR^- tumors than black women. Lower PR^- odds in non–black women persisted after laboratory adjustment and ER^- ORs (0.67, 0.79, and 0.73 in white, mixed-ancestry, and Indian/Asian women) were attenuated (to 0.77, 0.91, and 0.84, respectively) and only remained significantly reduced for white compared with black women. In absolute terms, there were 7.8% (95% CI: 5.5–10.0) less ER^- breast cancers in white than black patients (crude, all ages) which reduced, after adjusting for laboratory and stratifying by age, to 5.9% less (2.9–8.9) over the age of 50 years and to no significant difference under the age of 50 years. These

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Table 1. Race-specific distributions of ER, PR, and HER2 status by age at diagnosis and grade; calculated among histologically confirmed female breast cancer cases in South Africa (2009–11, public sector) and Namibia (2011–13), restricted to women with known receptor status (n = 10,047 for ER, 8620 for PR, 8251 for HER2)

	Black		White		Mixed ancestry		Indian/Asian		Other/unknown	
ER	***N* = 5,559**	**% ER$^-$ (33.8)**	***N* = 1,963**	**% ER$^-$ (26.0)**	***N* = 1,556**	**% ER$^-$ (31.1)**	***N* = 313**	**% ER$^-$ (28.4)**	***N* = 656**	**% ER$^-$ (36.4)**
Age at diagnosis										
20–29	116	27.6	18	38.9	27	48.2	2	50.0	12	50.0
30–39	756	34.3	155	25.8	137	38.0	28	25.0	84	33.3
40–49	1,364	33.3	350	28.6	368	33.2	59	32.2	161	41.6
50–59	1,372	38.5	476	34.5	399	34.8	92	27.2	151	41.1
60–69	1,015	31.6	513	23.2	354	27.7	72	30.6	114	34.2
≥70	936	30.2	451	17.7	271	22.1	60	25.0	134	27.6
Grade										
1	475	17.9	210	9.1	181	13.8	27	11.1	44	20.5
2	2,025	28.0	581	20.7	440	25.2	88	22.7	233	31.3
3	1,265	51.2	360	47.5	267	58.4	42	54.8	140	54.3
NK	1,794	32.3	812	24.6	668	28.7	156	27.6	239	33.9
PR[a,b]	***N* = 5,131**	**% PR$^-$ (47.7)**	***N* = 1,465**	**% PR$^-$ (39.0)**	***N* = 969**	**% PR$^-$ (43.6)**	***N* = 263**	**% PR$^-$ (36.1)**	***N* = 576**	**% PR$^-$ (52.3)**
Age at diagnosis										
20–29	104	41.4	18	55.6	23	69.6	2	50.0	11	54.6
30–39	702	46.7	127	37.8	99	52.5	22	31.8	74	54.1
40–49	1,271	44.1	275	39.6	264	41.7	52	46.2	149	55.0
50–59	1,262	55.4	366	48.6	271	51.7	83	33.7	138	57.3
60–69	945	47.9	399	39.1	229	41.5	56	35.7	103	53.4
≥70	889	44.4	345	34.5	171	41.5	53	34.0	117	41.9
Grade[b]										
1	456	37.5	166	27.1	126	28.6	22	22.7	39	41.0
2	1,940	41.7	508	34.8	339	43.7	75	33.3	223	47.1
3	1,216	63.7	311	60.1	210	62.9	38	60.5	136	71.3
NK	1,561	46.5	545	38.7	382	44.0	133	33.8	194	47.9
HER2[a]	***N* = 4,686**	**% HER2$^+$ (24.9)**	***N* = 1,569**	**% HER2$^+$ (25.3)**	***N* = 1,249**	**% HER2$^+$ (27.6)**	***N* = 244**	**% HER2$^+$ (20.5)**	***N* = 503**	**% HER2$^+$ (24.3)**
Age at diagnosis										
20–29	97	24.7	14	42.93	21	19.1	2	0.0	10	10.0
30–39	636	30.7	128	25.0	109	30.3	23	34.8	66	40.9
40–49	1,140	27.3	281	31.0	287	26.5	45	22.2	131	26.0

(Continued on the following page)

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Table 1. Race-specific distributions of ER, PR, and HER2 status by age at diagnosis and grade; calculated among histologically confirmed female breast cancer cases in South Africa (2009–11, public sector) and Namibia (2011–13), restricted to women with known receptor status ($n = 10,047$ for ER, 8620 for PR, 8251 for HER2) (Cont'd)

HER2[a]	N = 4,686	% HER2$^+$ (24.9)	N = 1,569	% HER2$^+$ (25.3)	N = 1,249	% HER2$^+$ (27.6)	N = 244	% HER2$^+$ (20.5)	N = 503	% HER2$^+$ (24.3)
50–59	1,176	26.5	375	25.9	343	29.5	71	14.1	116	25.9
60–69	851	21.7	412	23.5	271	24.7	58	19.03	86	12.8
≥70	786	18.1	359	21.7	218	29.4	45	24.4	94	21.3
Grade										
1	413	20.8	176	17.1	146	19.1	25	12.0	36	22.2
2	1,785	24.5	511	24.3	386	25.9	76	17.1	193	27.5
3	1164	26.0	335	29.9	236	33.9	37	27.0	114	21.9
NK	1,324	25.8	547	26.1	481	28.5	106	22.6	160	23.1

[a]PR and HER2 are included only if ER is known.
[b]Data from one laboratory (women of all ages) were excluded from total statistics for PR, due to age-related missing PR status. That laboratory included age-specific numbers; hence, the total number is less than the sum of the age-specific numbers.

overall black–white differences held within individual laboratories that had at least 50 cases from each race-pair (Supplementary Fig. S2.3). There was no suggestion of racial differences in HER2 status, with the exception of lower HER2$^+$ odds in mixed-ancestry compared with black women younger than 50.

In the 7,246 women with all three receptors known, concordance was high for ER and PR (81%) and low for HER2 and ER (35%) and HER2 and PR (42%). Ranking of subtype frequencies was consistent across races: luminal A tumors were the most common (54%–65% of tumors in each race), followed by triple-negative (TRN; 17%–23%), luminal B, and HER2-enriched (8%–14%; Fig. 1). The proportion of luminal A tumors increased with age, whereas luminal B and TRNs declined after a peak at age 50 to 59 years (Fig. 1; Supplementary Table S2.3). Under the age of 50 years, the subtype distribution did not differ significantly by race, with the exception of a high proportion of TRNs in women of mixed-ancestry and of other/unknown races (Table 3). Above the age of 50 years, all non–black races had significantly lower odds of TRN tumors than black women (ORs 0.63–0.86), but upon laboratory adjustment, the difference between black and white women was the only one that remained significant (OR 0.75). White breast cancer patients also had 33% (8–50) lower odds of HER2-enriched tumors than black patients or, in absolute terms, 2.4% (0.3–4.6) less HER2-enriched tumors.

Restricting the analysis to cases from South Africa only, ER$^+$ and ER$^-$ breast cancer incidence rates increased steeply up to the age of 50 years in all races [Fig. 2; test for interaction of age*race $P = 0.59$ (ER$^+$), $P = 0.52$ (ER$^-$), ER*age $P = 0.72$)]. The combined rate of increase at these ages was 12.7% (12.2–13.1) per year (race and ER-specific values are provided in Fig. 2). At ages 50 years and older, ER$^+$ incidence rates accelerated at a slower rate (1% to 3% per year), whereas ER$^-$ rates plateaued, or, in white women, declined slightly. Visual examination shows some convexity in the ER$^+$ curves.

When compared with data from the SEER database, ER$^-$ percentages in black women ages 40 to 70 years from this study overlapped with those for recently diagnosed U.S. black women (Fig. 3). For younger patients, proportions were lower than in the United States and over age 70 they were higher. In contrast, white women generally had a greater proportion of ER$^-$ disease than their U.S. counterparts, except for women diagnosed at extremely young or old ages.

Discussion

A strong evidence base for receptor-defined breast cancer is lacking in sub-Saharan Africa, yet such data are fundamental to informing breast cancer control. Amidst a background of heterogeneous estimates, we present recent, robust, and large-scale data that reveal that breast cancer subtype rankings are consistent across black, white, mixed-ancestry, and Indian/Asian women in

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Table 2. ORs for receptor-defined cancer associated with grade and age, by race[a]

	Black	White	Mixed ancestry	Indian/Asian	Other/unknown	Interaction with race[b] (*P*)
			OR for ER^- vs. ER^+ breast cancer (95% CI)			
Linear trend, per 10 years						
All ages	0.96 (0.93–1.00)	0.84 (0.78–0.90)	0.84 (0.78–0.92)	0.97 (0.80–1.17)	0.88 (0.79–0.99)	0.002
<50	1.01 (0.87–1.16)	1.04 (0.74–1.45)	0.83 (0.62–1.11)	1.09 (0.47–2.52)	1.27 (0.84–1.92)	0.56
≥50	0.85 (0.79–0.92)	0.67 (0.58–0.76)	0.78 (0.67–0.91)	0.99 (0.71–1.38)	0.74 (0.61–0.92)	0.01
Grade[c]						
2 vs. 1	1.76 (1.36–2.27)	2.57 (1.53–4.30)	2.09 (1.30–3.336)	2.41 (0.65–8.89)	1.58 (0.71–3.50)	0.70
3 vs. 1	4.71 (3.63–6.11)	8.86 (5.28–14.87)	8.49 (5.19–13.84)	9.99 (2.58–38.79)	4.03 (1.78–9.13)	0.07
NK vs. 1	2.17 (1.68–2.80)	3.32 (2.02–5.48)	2.52 (1.60–3.98)	3.26 (0.92–11.50)	1.76 (0.80–3.87)	0.59
			OR for PR^- vs. PR^+ breast cancer (95% CI)			
Linear trend, per 10 years						
All ages	1.00 (0.97–1.04)	0.92 (0.85–0.99)	0.92 (0.84–1.00)	0.94 (0.77–1.15)	0.89 (0.80–0.99)	0.06
<50	1.01 (0.88–1.17)	1.01 (0.73–1.41)	0.67 (0.48–0.93)	0.89 (0.38–2.10)	1.06 (0.70–1.61)	0.25
≥50	0.84 (0.78–0.90)	0.77 (0.68–0.87)	0.85 (0.72–1.00)	1.11 (0.80–1.55)	0.76 (0.62–0.93)	0.27
Grade[c]						
2 vs. 1	1.18 (0.96–1.46)	1.40 (0.95–2.07)	1.97 (1.26–3.08)	1.78 (0.58–5.42)	1.11 (0.55–2.25)	0.38
3 vs. 1	2.91 (2.32–3.64)	3.91 (2.59–5.90)	4.23 (2.61–6.85)	5.10 (1.54–16.73)	3.10 (1.46–6.60)	0.45
NK vs. 1	1.45 (1.17–1.80)	1.70 (1.16–2.50)	1.99 (1.28–3.10)	1.88 (0.64–5.52)	1.16 (0.57–2.37)	0.72
			OR for $HER2^+$ vs. $HER2^-$ breast cancer (95% CI)			
Linear trend, per 10 years						
All ages	0.87 (0.83–0.91)	0.90 (0.82–0.97)	1.01 (0.92–1.10)	1.01 (0.79–1.29)	0.82 (0.71–0.95)	0.03
<50	0.92 (0.78–1.09)	1.07 (0.71–1.56)	0.92 (0.64–1.31)	0.97 (0.37–2.57)	0.72 (0.45–1.16)	0.79
≥50	0.82 (0.75–0.90)	0.90 (0.78–1.04)	1.00 (0.86–1.18)	1.50 (0.99–2.29)	0.88 (0.67–1.17)	0.02
Grade[c]						
2 vs. 1	1.20 (0.92–1.56)	1.52 (0.98–2.37)	1.47 (0.91–2.35)	1.48 (0.38–5.75)	1.35 (0.57–3.24)	0.90
3 vs. 1	1.26 (0.96–1.65)	2.02 (1.28–3.20)	2.18 (1.33–3.57)	2.69 (0.65–11.17)	0.95 (0.38–2.42)	0.18
NK vs. 1	1.27 (0.97–1.66)	1.72 (1.11–2.66)	1.68 (1.06–2.65)	2.13 (0.58–7.86)	1.02 (0.42–2.49)	0.61

[a]Contributing numbers for known ER, PR, and HER2, by race, are provided in Table 1.

[b]Interaction of categorical race (black, white, mixed ancestry, Indian/Asian, and Other/NK) with age (linear) or grade (indicator). χ^2 test on 4 d.f. Interaction of race with age at all ages is not reported, as age associations differed within each race under and over the age of 50 years.

[c]ORs for grade are adjusted for age in 10-year categories.

Southern Africa. Better-prognosis luminal A tumors are the most common subtype in every race (at least 55% of tumors), followed by TRN (∼one in five), luminal B, and HER2-enriched tumors. Over the age of 50 years, black women have an absolute excess of up to 9% ER^- tumors compared with white women, comprised of smaller excesses of TRN and HER2-enriched tumors; mixed-ancestry and Indian/Asian women have intermediate values. Furthermore, age–incidence curves revealed the characteristic Clemmesen's hook (21).

The observed racial differences in the subtype proportions are likely to be real, as they were present both nationally and in women originating from the same laboratory. Systematic processing biases would have affected all races, because tumor collection, handling, and processing protocols are similar across all NHLS laboratories. This within-laboratory comparison overcomes the confounding inherent in comparing results from different locations. We observed strong associations of grade with receptor status, as expected, suggesting that random misclassification of receptor status was unlikely to be large, but if present would have underestimated racial differences. Black–white differences were also consistent with observations in the United States; however, they were of a smaller magnitude (12), because while the ER proportion was very similar in age-matched black South African and black American women with breast cancer, South African white women had higher ER^- percentages than in U.S. whites. The availability of public-sector–only cases in South Africa may have made this a study of more socioeconomically comparable, largely unscreened groups and thus accounted for the smaller difference. Future comparisons with white South African private sector patients would be useful. Unknown ER status in 15% to 20% of women was comparable with U.S. SEER data for 1998–2002 (22) and, although not strongly

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Table 3. Age-adjusted and age + laboratory–adjusted ORs for receptor-defined breast cancer associated with race, under and over age 50

	Individual receptors			Breast cancer subtypes[a]		
Outcome vs. reference	ER^- vs. ER^+	PR^- vs. PR^+	$HER2^+$ vs. $HER2^-$	Luminal B vs. luminal A	HER2-enriched vs. luminal A	Triple-negative vs. luminal A
Number of cases (outcome/reference)						
All ages	3,199/6848	3,992/4,628	2,083/6,168	967/4,062	735/4,062	1,482/4,062
<50	1,207/2430	1,437/1,756	848/2,142	440/1,433	276/1,433	526/1,433
≥50	1,992/4,418	2,555/2,872	1,235/4,026	527/2,629	459/2,629	956/2,629
	OR (95% CI)					
Under age 50						
Age-adjusted						
Black	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
White	0.78 (0.63–0.97)	0.81 (0.66–1.01)	1.07 (0.85–1.35)	0.90 (0.66–1.25)	0.77 (0.51–1.15)	0.92 (0.67–1.25)
Mixed-ancestry	1.08 (0.89–1.32)	1.06 (0.85–1.31)	0.95 (0.75–1.21)	0.79 (0.55–1.14)	0.72 (0.45–1.13)	1.39 (1.03–1.87)
Indian/Asian	0.87 (0.55–1.38)	0.90 (0.56–1.43)	0.88 (0.51–1.52)	0.74 (0.36–1.56)	0.64 (0.25–1.66)	0.83 (0.42–1.65)
Other/unknown	1.30 (0.99–1.14)	1.48 (1.13–1.18)	1.09 (0.79–1.21)	1.05 (0.69–1.61)	1.22 (0.75–1.98)	1.41 (0.96–2.05)
Age + laboratory–adjusted						
Black	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
White	0.85 (0.67–1.07)	0.79 (0.62–0.99)	0.94 (0.72–1.22)	0.91 (0.64–1.30)	0.75 (0.48–1.18)	0.98 (0.69–1.38)
Mixed ancestry	1.14 (0.90–1.45)	0.92 (0.71–1.19)	0.75 (0.56–1.00)	0.77 (0.51–1.17)	0.62 (0.36–1.05)	1.32 (0.92–1.90)
Indian/Asian	0.90 (0.56–1.45)	1.08 (0.66–1.78)	0.97 (0.54–1.71)	1.00 (0.46–2.16)	0.68 (0.25–1.80)	0.88 (0.43–1.79)
Other/unknown	1.33 (1.01–1.74)	1.40 (1.06–1.85)	1.07 (0.77–1.47)	1.11 (0.72–1.72)	1.14 (0.70–1.88)	1.36 (0.92–2.00)
Age 50 and over						
Age-adjusted						
Black	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
White	0.67 (0.58–0.77)	0.70 (0.61–0.81)	1.08 (0.92–1.27)	1.00 (0.79–1.26)	0.63 (0.48–0.84)	0.70 (0.57–0.86)
Mixed ancestry	0.79 (0.67–0.92)	0.83 (0.70–0.98)	1.31 (1.10–1.56)	0.92 (0.69–1.24)	1.15 (0.86–1.53)	0.86 (0.68–1.08)
Indian/Asian	0.73 (0.54–0.99)	0.52 (0.38–0.70)	0.76 (0.51–1.13)	0.54 (0.29–1.00)	0.64 (0.35–1.15)	0.63 (0.41–0.97)
Other/unknown	1.04 (0.84–1.30)	1.06 (0.85–1.32)	0.89 (0.66–1.19)	0.75 (0.48–1.17)	0.82 (0.53–1.28)	0.98 (0.72–1.34)
Age + laboratory–adjusted						
Black	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
White	0.77 (0.66–0.89)	0.72 (0.62–0.83)	1.00 (0.83–1.19)	1.08 (0.84–1.38)	0.67 (0.49–0.92)	0.75 (0.60–0.93)
Mixed ancestry	0.91 (0.76–1.09)	0.78 (0.64–0.95)	1.09 (0.89–1.35)	1.00 (0.72–1.40)	1.13 (0.80–1.60)	0.89 (0.67–1.17)
Indian/Asian	0.84 (0.60–1.16)	0.63 (0.45–0.89)	0.85 (0.55–1.30)	0.88 (0.45–1.70)	0.66 (0.35–1.27)	0.89 (0.55–1.43)
Other/unknown	1.09 (0.88–1.37)	1.03 (0.82–1.29)	0.90 (0.67–1.22)	0.81 (0.52–1.26)	0.85 (0.54–1.33)	1.00 (0.73–1.37)

[a]Subtypes defined immunohistochemically: luminal A (ER^+/PR^+HER2^-), luminal B (ER^+/PR^+HER2^+), HER2-enriched ($ER^-PR^-HER2^+$), and triple-negative ($ER^-PR^-HER2^-$). ORs adjusted for age as a linear term and laboratory as an indicator variable.

associated with race or age within provinces, we have previously found missing status to be associated with late-stage, possibly ER^-, tumors (5). Missing ER data from KwaZulu-Natal reflect a technical problem at the time of extraction and is unlikely to have introduced bias.

Genome and transcriptome sequencing has advanced the understanding of the diversity of breast carcinomas (27), but in a sub-Saharan African setting, ER, PR, and HER2 receptors remain the most relevant for clinical management (28). The one third ER^- proportion in black South African women agrees with several sub-Saharan African estimates (5–7), but contrasts with other higher estimates (e.g., >70%; refs. 8–10). ER assessment is known to be vulnerable to false negatives if preanalytic factors are not tightly controlled, including the duration of fixation, type of fixative used, and speed and completeness of dehydration (19). Such factors are unlikely to have had a major impact on the present study, because the ER^- proportion was low and at diagnosis, prechemotherapy IHC was routinely conducted in an established laboratory system.

The shapes of the age–incidence curves for both ER^+ and ER^- breast cancer were remarkably consistent across races and with international observations, notably with a decline in the rate of increase of incidence rates of ER^+ breast cancer after the age of 50 years and a stabilization of ER^- rates beyond this age. This feature, known as Clemmesen's hook, is well established in breast cancer epidemiology, but to our knowledge it has never been investigated within a sub-Saharan African country. The different age–incidence curves by ER status have been

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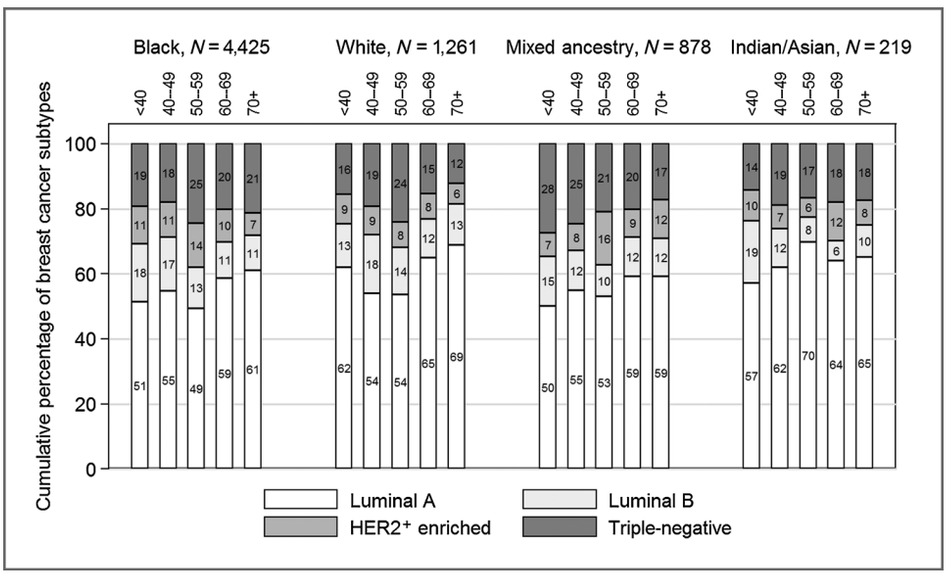

Figure 1. Age-specific percentages of luminal A, luminal B, HER2-enriched, and triple-negative tumors in patients with breast cancer, by race. Numbers within bars indicate subtype percentages.

attributed to etiologic heterogeneity in these two diseases. However, we cautiously estimated the shape of the age–incidence curve and did not estimate absolute incidence rates; thus, we were unable to assess whether the higher TRN proportion in black than in white women derived from higher absolute TRN incidence rates, as has been observed in the United States (29). Convexity in the cross-sectional rather than longitudinally derived age–incidence curves for ER^+ breast cancer may reflect positive birth cohort effects. Younger generations of South African women are growing up in a post-apartheid South Africa and, when compared with their mothers' generations, maintain lifestyles associated with higher ER^+ breast cancer risk profiles (30). Notably, South Africa has seen a 30% decline in births per woman between 1940s and 1970s birth cohorts (31), there is widespread use of oral and injectable contraceptives (32), more than 30% of women are obese, attributed to nutritional changes as well as reduced physical activity (33), and age at menarche has declined (34). Such trends may also account for the cross-sectional ER^- peak at ages 50 to 54 years observed in this study, in contrast with the monotonic declines in the ER^- proportion observed in other populations (26).

Biases aside, breast cancer subtypes may truly differ among Africa's genetically diverse populations which are also at varying stages of epidemiologic, and particularly, reproductive transitions (35, 36). The average number of children born to South African women is considerably less than to women from other sub-Saharan African countries (18), and heterogeneity in ER proportions on a national scale in South Africa may echo larger-scale trends across sub-Saharan Africa. Indeed, the three South African

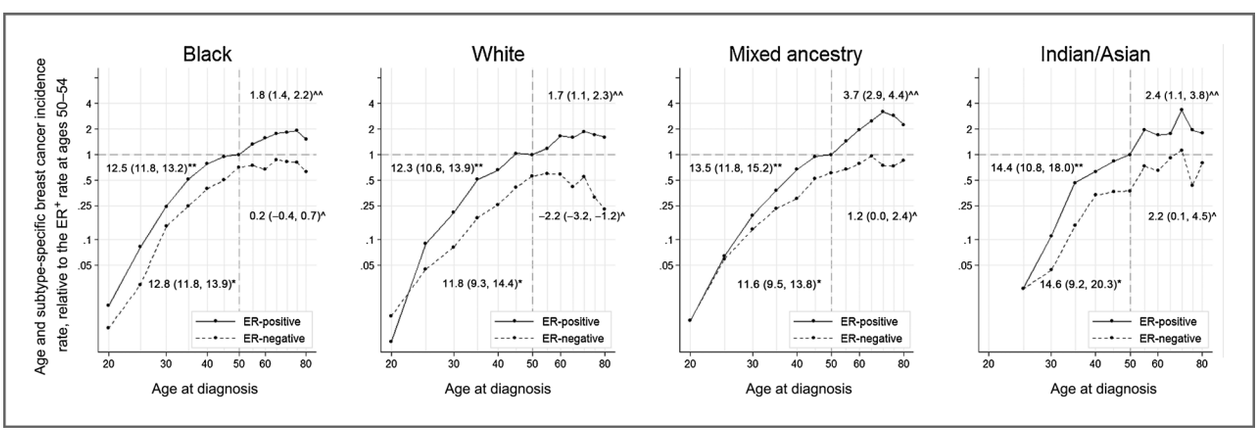

Figure 2. Age–incidence rate curve of ER^+ and ER^- breast cancer in South Africa's public sector, 2009–2011, for Black, White, Mixed ancestry, and Indian/Asian women. Age-specific incidence rates in 5-year age bands are expressed as a ratio of the ER^+ rate at ages 50 to 54 years in the same racial group. The percentage increase in incidence rates (95% CI) per year of age under 50 for ER^- (*) and ER^+ (**) and at ≥50 years for ER^- (∧) and ER^+ (∧∧) breast cancer are noted. Axes are plotted on logarithmic scales. A reference line at age 50 and for ratio = 1 at ages 50 to 54 years is overlaid.

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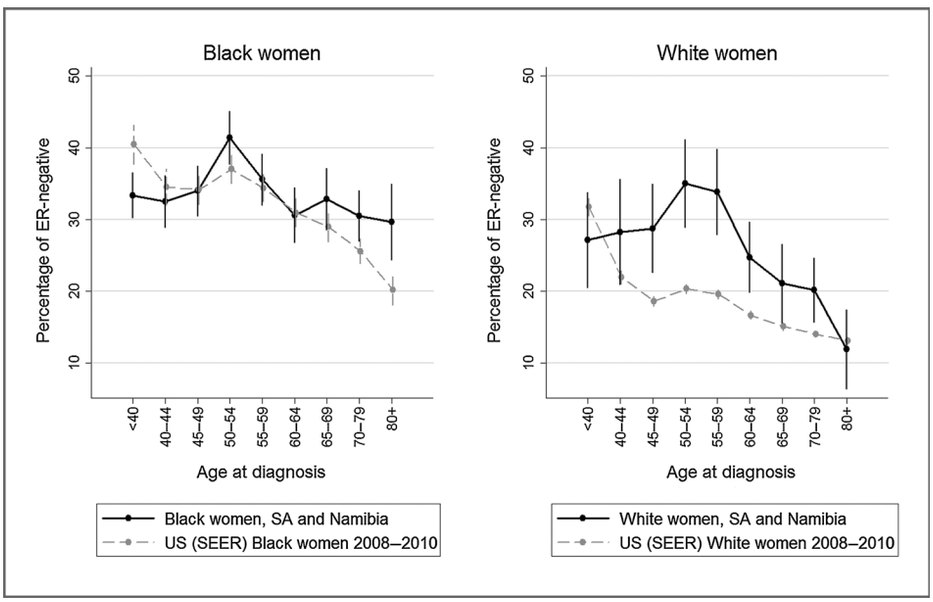

Figure 3. Age-specific percentage of ER$^-$ breast cancer in Black and White women in South Africa and Namibia compared with race-matched estimates from U.S. SEER 2008–2010 invasive breast cancers.

provinces with the highest ER$^-$ proportions in black women also have the country's highest parity. Furthermore, women of other/unknown races, a group most likely containing more immigrants from other Southern African countries, had the highest ER$^-$ proportion. An earlier diagnostic stage in South Africa compared with other sub-Saharan African settings [~50% stage III/IV in South Africa (5) vs. 60%–80+% elsewhere] may also partially contribute to the differences reported across the continent (37–39). Thus, in the epidemiologic transition giving rise to higher overall breast cancer incidence rates in South Africa, the subtype composition of the breast cancer burden may also be evolving.

Breast cancer survival indicators for sub-Saharan Africa are poor, as exemplified by a mortality-to-incidence rate ratio of 0.51, i.e., 3-fold higher than in the United States (0.16). This study's findings shed a positive light on the prospects for addressing improvements in survival in Southern Africa. These issues are pertinent today because the burden of this cancer is projected to increase by at least 30% between 2012 and 2025 (1). The Breast Health Global Initiative recommended four key areas to optimize breast cancer management in such settings which included both early detection and treatment (40). Earlier breast cancer detection is needed across Africa, where 50% to over 80% of patients are diagnosed at stages III to IV (5, 37–39). Late stage at diagnosis may be due to a faster tumor growth rate or to delayed diagnosis. The findings of a majority ER$^+$ disease subtype, as opposed to a faster-growing more aggressive ER$^-$ or TRN disease, suggests that most tumors may have similar growth rates to those in Europe and America, and thus later diagnosis stage is more attributable to delays in presentation and in referral. Furthermore, the mean duration of symptoms is often reported to be between 6 and over 18 months (38, 41, 42); thus, tumor sizes are for the most part consistent with models of breast tumor growth. Earlier presentation and faster referral may be possible, as has been demonstrated in certain South African public hospitals, with a stage migration from 70% to 50% stage III–IV disease in just 5 years (5). Further research on setting-specific barriers to early diagnosis and how to overcome them are needed, for which ongoing trials of clinical breast examination in similar settings will be informative (43). In terms of treatment, with at least two thirds of breast tumors in South Africa and Namibia being better prognosis ER$^+$ tumors (3), they would be expected to respond to endocrine therapy if diagnosed early (44). Tamoxifen in particular offers an attractive therapeutic option due to its relative affordability (2) and ease of oral administration. It has been successfully introduced in Ethiopia (45), although a Nigerian study has highlighted 25% early nonadherence to tamoxifen, particularly among younger patients (46).

Nevertheless, poorer prognosis breast cancers still amounted to a sizeable proportion. One in ten breast cancer patients had HER2-enriched tumors, which may benefit from treatment with trastuzumab, which is not currently available in the South African public sector. A further one in five patients had triple-negative breast cancer for which there is no targeted treatment at present. Prognosis from these tumors in other settings is poor (3), and survival studies are needed in African settings to assess prognosis of these, and indeed all, breast cancer subtypes.

In conclusion, these data provide strong evidence that at least two thirds of breast cancer patients being diagnosed in Southern Africa have better-prognosis ER$^+$ tumors. Such women may benefit from a combination of early diagnosis and available treatment that could realistically translate into avoidance of death from breast

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cancer. Furthermore, the age–incidence curves suggest that these ER^+ tumors will increase in proportion as the mean age of breast cancer patients increases, as forecasted by population ageing. The predominant tumor breast cancer biology in this region should thus not curtail the prospects for improved prognosis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C. Dickens, D. Kielkowski, V.A. McCormack
Development of methodology: C. Dickens, V.A. McCormack
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Zietsman, H. Cubasch, P. Kellett
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C. Dickens, V.A. McCormack
Writing, review, and/or revision of the manuscript: C. Dickens, R. Duarte, H. Cubasch, P. Kellett, J. Schuz, D. Kielkowski, V.A. McCormack
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C. Dickens, R. Duarte, H. Cubasch, P. Kellett
Study supervision: D. Kielkowski, V.A. McCormack

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Cancer Epidemiology, Biomarkers & Prevention

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Racial Comparison of Receptor-Defined Breast Cancer in Southern African Women: Subtype Prevalence and Age –Incidence Analysis of Nationwide Cancer Registry Data

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