

https://dspace.org/

The association of HIV status with triplenegative breast cancer in patients with breast cancer in South Africa a crosssectional analysis of caseonly data from a prospective cohort study

J Duber; Al Neugut; Maureen Joffe; Daniel S O'Neil; Oluwatosin Ayeni ...

https://hdl.handle.net/10539/44499
WOS

Downloaded from a DSpace repository. https://dspace.org/

The association of HIV status with triple-negative breast cancer in patients with breast cancer in South Africa: a cross-sectional analysis of case-only data from a prospective cohort study

Jacob Dubner, Alfred I Neugut, Maureen Joffe, Daniel S O'Neil, Oluwatosin A Ayeni, Wenlong Carl Chen, Ines Buccimazza, Sharon R Čačala, Laura W Stopforth, Hayley A Farrow, Sarah Nietz, Nivashini Murugan, Boitumelo Phakathi, Judith S Jacobson, Katherine D Crew, Valerie McCormack, Paul Ruff, Herbert Cubasch, Yoanna S Pumpalova

Summary

Background Breast cancer is the most common malignancy diagnosed among women in South Africa, with the aggressive triple-negative subtype comprising approximately 15% of breast cancers in this population. South Africa has the largest population of people with HIV in the world. This study aims to evaluate the association between HIV status and the proportion of patients with breast cancer with the triple-negative subtype.

Methods We did a cross-sectional analysis of case-only data from the South African Breast Cancer and HIV Outcomes (SABCHO) study, a prospective cohort study recruiting patients with newly diagnosed breast cancer at six public hospitals in South Africa. We analysed data from patients who enrolled in SABCHO between Jan 1, 2015, and Jan 18, 2022. Women aged 18 years or older with newly diagnosed and histologically confirmed invasive breast cancer were eligible. Participants were classified as HIV-positive or HIV-negative by use of an ELISA-based HIV test done at the time of enrolment. We developed multivariable logistic regression models to test for an association between HIV status and the proportion of triple-negative relative to non-triple-negative breast cancers while adjusting for demographic and reproductive risk factors.

Findings Of the 4122 patients enrolled in the SABCHO cohort within our study timeframe, 239 patients were excluded due to unknown breast cancer subtype (n=141), HIV status (n=97), or race (n=1). 3883 women with breast cancer were included in the study, of whom 637 (16·4%) had triple-negative breast cancer, 894 (23·0%) were HIV-positive, and 186 (4·8%) had triple-negative breast cancer and HIV. Triple-negative breast cancer accounted for 186 (20·8%) of 894 breast cancers among women who were HIV-positive and 451 (15·1%) of 2989 breast cancers among women who were HIV-negative (p<0·0001). In the fully adjusted logistic regression model, HIV-positive status was associated with an increased proportion of triple-negative breast cancer (adjusted odds ratio [OR] 1·39, 95% CI 1·12–1·74, compared with women who were HIV-negative). When compared with women who were HIV-negative, the association between HIV-positive status and the proportion of triple-negative breast cancer was strongest among the subgroup of women with a duration of HIV infection of 2 years or longer (1·57, 1·23–2·00) and those on antiretroviral therapy (ART; 1·47, 1·16–1·87).

Interpretation Patients with breast cancer and chronic HIV who are on ART are more likely to have triple-negative breast cancer than patients with breast cancer without HIV. This association is independent of age, race, and reproductive factors.

Funding US National Institutes of Health, University of the Witwatersrand, South Africa Medical Research Council Common Epithelial Cancers Research Center, Conquer Cancer Foundation, and Varmus Global Scholars Fund.

Copyright © 2024 World Health Organization. Published by Elsevier Ltd. This is an Open Access article published under the CC BY NC ND 3.0 IGO license which permits users to download and share the article for non-commercial purposes, so long as the article is reproduced in the whole without changes, and provided the original source is properly cited. This article shall not be used or reproduced in association with the promotion of commercial products, services or any entity. There should be no suggestion that WHO endorses any specific organisation, products or services. The use of the WHO logo is not permitted. This notice should be preserved along with the article's original URL.

Lancet Glob Health 2024; 12: e1993–2002

Department of Medicine, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, USA (J Dubner BA, Prof A I Neugut MD, Prof K D Crew MD, Y S Pumpalova MD); **Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY, USA** (Prof A I Neugut, J S Jacobson DrPH, Prof K D Crew, Y S Pumpalova); **Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA** (Prof A I Neugut, J S Jacobson, Prof K D Crew); **Strengthening Oncology Services Research Unit** (M Joffe PhD, Prof P Ruff MMed, O A Ayeni PhD, W C Chen PhD), **Sydney Brenner Institute for Molecular Biosciences** (W C Chen), **Department of Surgery** (S Nietz MD, N Murugan MBBCh, H Cubasch MD), **and School of Clinical Medicine** (Prof P Ruff), **Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; Division of Radiation Oncology, Department of Radiation Sciences, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa** (O A Ayeni); **Section of Medical Oncology, Department of Internal Medicine, Yale School of Medicine, Yale University, New Haven, CT, USA** (D S O'Neil MD); **Yale Cancer Center, Yale University, New Haven, CT, USA** (D S O'Neil); **South African National Cancer Registry, National Health Laboratory Service, Johannesburg, South**

Introduction

Breast cancer is the most common malignancy diagnosed among women in South Africa, with an age-standardised incidence rate of 48·7 per 100 000 women in 2022.[1] Triple-negative breast cancer—a subtype without oestrogen or progesterone receptors and without HER2 (also known

Africa (W C Chen)**; Department of Specialized Surgery, Inkosi Albert Luthuli Central Hospital, University of KwaZulu-Natal, Durban, South Africa** (I Buccimazza MBChB, Prof B Phakathi PhD)**; Division of Surgery, Tygerberg Hospital and University of Stellenbosch, Cape Town, South Africa** (S R Čačala FRACS)**; Departments of Surgery and Radiation Oncology, Grey's Hospital, University of KwaZulu-Natal, Pietermaritzburg, South Africa** (L W Stopforth MBChB, H A Farrow RN)**; International Agency for Research on Cancer, Lyon, France** (V McCormack PhD)

Correspondence to: Dr Yoanna S Pumpalova, Department of Medicine, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA **yp2184@cumc.columbia.edu**

Research in context

Evidence before this study

We searched PubMed in January, 2023, with different permutations of the terms "HIV", "breast cancer", "triple-negative breast cancer", and "sub-Saharan Africa" for articles published between Jan 1, 1986, and Jan 1, 2023. No language restrictions were applied. One study of 210 patients with breast cancer in Mozambique found a positive association between HIV-positive status and the proportion of triple-negative breast cancer, but all other identified articles that assessed the association between HIV status and breast cancer subtype in sub-Saharan Africa did not find an association. Two articles (published in 2013 and 2019) were most relevant to this study because they included patients with breast cancer who were recruited from public hospitals in South Africa. Although these studies did not find an association between HIV status and breast cancer molecular subtype, their patient sample sizes were small; specifically, the numbers of patients who had both HIV and triple-negative breast cancer (38 patients and 24 patients). Additionally, these studies did not adjust for reproductive risk factors, such as parity and breastfeeding history, which are differently associated with the risk of triple-negative breast cancer versus other breast cancer subtypes.

Added value of this study

Given the chronic immune dysregulation associated with HIV and evidence supporting a link between host immune function and triple-negative breast cancer pathogenesis, our study analysed the association between HIV and the proportion of triple-negative breast cancer using, to our knowledge, the largest sample size to date in sub-Saharan Africa. It is also the first study, to our knowledge, to adjust for reproductive factors that have been linked with breast cancer subtype.

Implications of all the available evidence

Our study shows that patients with breast cancer with chronic HIV who are on antiretroviral therapy are more likely to have triple-negative breast cancer than those without HIV. This association is independent of age, race, and reproductive variables. Although previous studies of HIV and breast cancer subtype did not find an association between HIV and the proportion of triple-negative breast cancer, our results are considered to be more reflective of the true epidemiological patterns of disease among patients with breast cancer, given that our sample size was larger than those of previous studies, which gives our analysis greater statistical power. The observed relationship might reflect increased absolute rates of triple-negative breast cancer, decreased absolute rates of hormone receptor-positive breast cancer, or both, among women with HIV. This association could be mediated by the direct effects of chronic HIV pathobiology on tumour oncogenesis through host immune dysregulation and hormonal shifts. It could also reflect the effects of HIV-associated exposures, such as chronic antiretroviral therapy. Regardless of mechanism, women who are HIV-positive who develop breast cancer are more likely to have the aggressive triple-negative breast cancer subtype. Any breast cancer symptom in a woman with HIV should prompt a full evaluation by a provider with breast cancer expertise, regardless of the woman's age, race, or reproductive history.

as ERBB2) overexpression—has a short survival time and high mortality rate due to its aggressive spread, few targeted therapeutics, and high rate of relapse.[2] In 2019, triple-negative breast cancer accounted for approximately 15% of breast cancers among women in South Africa.[3]

Previous studies have identified west African ancestry, low socioeconomic status, younger age at first birth (<25 years), and increased parity without breastfeeding as factors that increase the risk of triple-negative breast cancer compared with other breast cancer subtypes.[4–7] However, most of these studies were done in high-income settings and did not evaluate the association of HIV with breast cancer subtype. South Africa has the largest population of people with HIV in the world, with an HIV prevalence of 24·1% among all Black women and 36·0% among Black women aged 25–49 years.[8] Overall rates of breast cancer in South Africa do not differ by HIV status,[9] but it remains unclear whether HIV affects the distribution of breast cancer subtypes.

HIV infection is associated with profound immune dysregulation that is partly attenuated, but not fully reversed, by treatment with antiretroviral therapy (ART).[10,11] Previous studies support a strong association between host immune function and triple-negative breast cancer pathogenesis,[12,13] prompting us to investigate an association between HIV and triple-negative breast cancer. Several previous studies conducted in sub-Saharan Africa did not find an association between HIV status and the proportion of the triple-negative breast cancer subtype,[3,14–17] but these studies had small sample sizes and did not control for relevant demographic and reproductive risk factors that differ by HIV status, such as parity and breastfeeding history. In this study, we used data from the prospective South African Breast Cancer and HIV Outcomes (SABCHO)[18] study to test the hypothesis that patients with breast cancer and HIV are more likely to have triple-negative breast cancer than patients with breast cancer without HIV.

Methods

Study design and data source

We used a case-only study design within the SABCHO cohort to do a cross-sectional analysis of the association of HIV with breast cancer subtype. SABCHO is a prospective cohort study that began enrolling patients with breast cancer from six public hospitals in South Africa in January, 2015.[18] Participating study sites were Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg;

Chris Hani Baragwanath Academic Hospital, Johannesburg; Grey's Hospital, Pietermaritzburg; Ngwelezana Hospital, Empangeni; and Addington Hospital and Inkosi Albert Luthuli Central Hospital (analysed as a single site), Durban. All study hospitals either had medical, surgical, and radiation oncology services available in house, or had clear referral pathways for women diagnosed with breast cancer. For this analysis, we included women enrolled in SABCHO between Jan 1, 2015, and Jan 18, 2022. The study was approved by the University of the Witwatersrand Human Research Ethics Committee (Medical; M1911203) and the Institutional Review Board of Columbia University (AAAQ1359).

Participants

Women aged 18 years or older with newly diagnosed and histologically confirmed invasive breast cancer from one of the participating centres and no previous self-reported history of cancer were invited to join SABCHO. All participants provided written informed consent. Participants were classified as HIV-positive or HIV-negative by use of an ELISA-based HIV test done at the time of enrolment through the South African National Health Laboratory Services. If testing results were not available, self-reported HIV-positive status was used. Those who self-reported HIV-negative status but did not have a confirmatory ELISA test were excluded (appendix 1 p 5). Women with missing data on breast cancer subtype or self-reported race were excluded (appendix 1 p 5).

Procedures

The primary outcome in this analysis was triple-negative breast cancer versus non-triple-negative breast cancer subtype. Pretreatment tumour oestrogen and progesterone hormone receptor expression and HER2 expression were assessed via immunohistochemistry at each study hospital. Tumours with equivocal HER2 immunohistochemistry (ie, 2+ staining intensity, which indicates moderate HER2 expression) underwent confirmatory HER2 fluorescent in-situ hybridisation testing. Tumours with equivocal HER2 immunohistochemistry without confirmatory testing were classified as HER2-negative (n=282). Tumours that were hormone receptor-negative (<1% oestrogen receptor or progesterone receptor nuclei staining) and HER2-negative were classified as triple-negative breast cancer. Tumours that were hormone receptor-positive, HER2-positive, or both, were classified as non-triple-negative breast cancer.

Data were collected during baseline interviews and conducted by dedicated study nurses, including HAF. Date of birth, race, family history of breast or ovarian cancer, age of menarche, menstrual status, age of menopause, number of full-term pregnancies, age at first full-term pregnancy, breastfeeding history, use of oral or injectable contraceptives, use of hormone replacement therapy (HRT), history of hysterectomy or bilateral salpingo-oophorectomy (BSO), and history of smoking and alcohol use were recorded at the time of enrolment via a face-to-face interview. Sex data were not explicitly collected because all enrolled participants were biological women. Height and weight were measured at enrolment and were used to calculate BMI. For women who were HIV-positive, year of HIV diagnosis, $CD4^+$ T-cell count, HIV viral load, and ART treatment history were recorded.

We calculated duration of HIV infection as the time interval between July 2 (midpoint of the calendar year) of the reported year of HIV diagnosis and the date of breast cancer diagnostic biopsy, rounded to the nearest year. HIV viral load was classified as detectable (≥50 copies per mL blood) or undetectable (<50 copies per mL blood). As previously described in published literature, a wealth index ranging from 1–5 was derived via principal component analysis of data from a survey of household possessions and facilities;[19] a wealth index of 5 indicates the greatest wealth. Self-reported age at menarche outside ages 8–24 years was considered unreliable and were imputed as 15 years (cohort median), as were ages for women who reported having gone through menarche but did not report an age. Women who reported menses in the past 12 months and who had not had a hysterectomy or BSO were classified as premenopausal. Women who reported no menses in the past 12 months and who had not had a hysterectomy or BSO were classified as having gone through natural menopause. Women who had a BSO were classified as having gone through surgical menopause. Women who had a hysterectomy without BSO were classified as having unknown menopausal status. Self-reported breastfeeding history was used to calculate the average duration (in weeks) of breastfeeding per livebirth. Women with an average breastfeeding duration greater than or equal to 1 week were classified as having breastfed.

See Online for appendix 1

Statistical analysis

The study size was the number of patients who had enrolled in SABCHO at the time this analysis was initiated, and we deemed it appropriate to have sufficient statistical power to draw conclusions about our association of interest. The patient cohort was stratified as triple-negative breast cancer versus non-triple-negative breast cancer and contingency tables were constructed to compare the two groups at the time of enrolment. We calculated associations between covariates and triple-negative breast cancer status using linear model ANOVA for continuous variables and Pearson's χ^2 test for categorical variables. Univariable logistic regression was used to calculate odds ratios (ORs) and 95% CIs for the association of each covariate with triple-negative breast cancer. For logistic regression models, Wald's χ^2 test was used to evaluate statistical significance ($p<0{\cdot}05$). Covariates associated with triple-negative breast cancer were considered for inclusion in stepwise multivariable logistic regression models. Known confounders of breast

	Non-triple-negative breast cancer (n=3246)	Triple-negative breast cancer (n=637)	Total (n=3883)	p value*
Age group, years	..	..	..	0·023
<40	458 (14·1%)	76 (11·9%)	534 (13·8%)	..
40–49	735 (22·6%)	167 (26·2%)	902 (23·2%)	..
50–59	757 (23·3%)	161 (25·3%)	918 (23·6%)	..
60–69	699 (21·5%)	143 (22·4%)	842 (21·7%)	..
≥70	597 (18·4%)	90 (14·1%)	687 (17·7%)	..
Median age (IQR)	55·0 (45·0–66·0)	54·0 (45·0–65·0)	55·0 (45·0–66·0)	0·38†
Race	..	..	..	0·0079
Black	2594 (79·9%)	538 (84·5%)	3132 (80·7%)	..
Non-Black‡	652 (20·1%)	99 (15·5%)	751 (19·3%)	..
HIV status	..	..	..	<0·0001
Positive	708 (21·8%)	186 (29·2%)	894 (23·0%)	..
Negative	2538 (78·2%)	451 (70·8%)	2989 (77·0%)	..
BMI, kg/m²	..	..	..	0·85
<25	622/3083 (20·2%)	118/612 (19·3%)	740/3695 (20·0%)	..
25–30	827/3083 (26·8%)	169/612 (27·6%)	996/3695 (27·0%)	..
>30	1634/3083 (53·0%)	325/612 (53·1%)	1959/3695 (53·0%)	..
Unknown§	163	25	188	..
Median BMI (IQR)	30·6 (25·8–35·6)	30·4 (26·0–35·8)	30·6 (25·8–35·7)	0·95†
First degree relative with breast or ovarian cancer	..	..	..	0·35
Yes	305/3172 (9·6%)	52/618 (8·4%)	357/3790 (9·4%)	..
No	2867/3172 (90·4%)	566/618 (91·6%)	3433/3790 (90·6%)	..
Unknown‡	74	19	93	..
Alcohol user	..	..	..	0·43
Yes	614 (18·9%)	129 (20·3%)	743 (19·1%)	..
No	2632 (81·1%)	508 (79·7%)	3140 (80·9%)	..
Smoker	..	..	..	0·50
Yes	387 (11·9%)	82 (12·9%)	469 (12·1%)	..
No	2859 (88·1%)	555 (87·1%)	3414 (87·9%)	..
Wealth index¶	..	..	..	0·0038
1	647/3166 (20·4%)	110/621 (17·7%)	757/3787 (20·0%)	..
2	609/3166 (19·2%)	148/621 (23·8%)	757/3787 (20·0%)	..
3	616/3166 (19·5%)	142/621 (22·9%)	758/3787 (20·0%)	..
4	638/3166 (20·2%)	119/621 (19·2%)	757/3787 (20·0%)	..
5	656/3166 (20·7%)	102/621 (16·4%)	758/3787 (20·0%)	..
Unknown§	80	16	96	..
Study site	..	..	..	0·41
CHBAH	1436 (44·2%)	281 (44·1%)	1717 (44·2%)	..
CMJAH	846 (26·1%)	170 (26·7%)	1016 (26·2%)	..
Durban	469 (14·4%)	76 (11·9%)	545 (14·0%)	..
Grey's	437 (13·5%)	98 (15·4%)	535 (13·8%)	..
Ngwelezana	58 (1·8%)	12 (1·9%)	70 (1·8%)	..

Data are n (%) unless otherwise stated. CHBAH=Chris Hani Baragwanath Academic Hospital. CMJAH=Charlotte Maxeke Johannesburg Academic Hospital. SABCHO=South African Breast Cancer and HIV Outcomes. *Calculated using Pearson's χ^2 test unless otherwise specified. †Calculated with linear model ANOVA. ‡In the analysis, non-Black race was self-reported as either White, Coloured, or Asian. §Participants with unknown data were not included in analyses. ¶As previously described in published literature, a wealth index ranging from 1–5 was derived via principal component analysis of data from a survey of household possessions and facilities,[19] with 5 indicating the greatest wealth.

Table 1: **Demographic and socioeconomic features of the SABCHO cohort, by breast cancer subtype**

cancer subtype, such as age, were included in the logistic regression models regardless of statistical significance. All models were adjusted for study site.

The first multivariable model compared triple-negative breast cancer with non-triple-negative breast cancer with respect to HIV and demographic factors (age group, race, wealth index [continuous], and hospital [fixed effect]). The second model consisted of age group and reproductive variables (age at menarche, history of contraceptive use, and the combined parity and breastfeeding variable). HRT was excluded due to low numbers (only three women in the triple-negative breast cancer group). In the final model, we included all variables from models 1 and 2. An interaction term between HIV status and the combined parity and breastfeeding variable was tested in the final model. Patients were excluded from the models for missing data on wealth index, age at menarche, and parity and breastfeeding history. Included covariates were otherwise complete.

We did sensitivity and subgroup analyses to test the robustness of our main findings among Black women. These analyses were necessary due to the high collinearity between HIV status and Black race in our cohort. We constructed a contingency table that stratified Black women by HIV status to compare reproductive features of the two groups. We repeated the final multivariable logistic regression model in Black women only and made a forest plot to compare these results by year of enrolment and by study site with an I^2 statistic calculated to assess heterogeneity. We also constructed a graph to compare the proportion of triple-negative breast cancer cases among Black women by HIV status across age groups.

Lastly, we evaluated the association of HIV control with breast cancer subtype. Specifically, we stratified women who were HIV-positive by four different HIV-related metrics (detectable HIV viral load, $CD4^+$ T-cell count <200 cells per mm³, history of ART treatment, and duration of HIV infection ≥2 years). We repeated the final multivariable logistic regression analysis four times to evaluate associations of each HIV-related metric with the proportion of triple-negative breast cancer cases, with women who were HIV-negative as the reference. All statistical analyses were done in R (version 4.0.2, released June 22, 2020).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 1, 2015, and Jan 18, 2022, 4122 women enrolled in SABCHO. Of these, we excluded 141 (3·4%) women with unknown breast cancer subtypes, 97 (2·4%) women with unknown HIV status, and one (0·02%) woman with unknown race. Of the

remaining 3883 women included in this analysis, 637 (16·4%) had triple-negative breast cancer (appendix 1 p 5).

Table 1 shows the demographic features of the cohort by triple-negative breast cancer status. The median age at breast cancer diagnosis was 55 years (IQR 45·0–66·0), 3132 (80·7%) women self-identified as Black, 894 (23·0%) women were HIV-positive, and 186 (4·8%) women were HIV-positive and had triple-negative breast cancer. Triple-negative breast cancer accounted for a higher percentage of breast cancer cases among women who were HIV-positive than among women who were HIV-negative (186 [20·8%] of 894 patients who were HIV-positive *vs* 451 [15·1%] of 2989 patients who were HIV negative; p<0·0001) and a higher percentage of breast cancer cases among Black women than among non-Black women (538 [17·2%] of 3132 Black women *vs* 99 [13·2%] of 751 non-Black women; p=0·0079).

Table 2 shows the distribution of reproductive factors by breast cancer subtype. In our cohort, 3608 (92·9%) of 3883 women had been pregnant at least once before enrolment, and the median number of pregnancies was 3·0 (range 0·0–18·0). Among parous women, 3171 (88·6%) of 3579 reported breastfeeding for at least 1 week. Patients with triple-negative breast cancer were more likely to have ever been pregnant than patients with non-triple-negative breast cancer and were more likely to have ever used contraceptives.

The distribution of reproductive factors by HIV status for Black women only can be found in appendix 1 (p 1). The proportion of patients who had ever been pregnant was similar between women with and without HIV (819 [93·9%] of 872 who were HIV-positive *vs* 2129 [94·2%] of 2260 who were HIV-negative; p=0·76), but women who were HIV-positive had fewer full-term pregnancies (mean 2·46 [SD 1·40] *vs* 3·27 [2·21]; p<0·0001). Among parous women, rates of breastfeeding were lower in women with HIV than in women without HIV (691 [85·0%] of 813 women *vs* 1967 [93·1%] of 2113 women; p<0·0001). Compared with women without HIV, a larger proportion of women with HIV were premenopausal (522 [62·3%] of 838 women *vs* 715 [34·1%] of 2096 women; p<0·0001) and reported ever using contraceptives (641 [73·5%] of 872 women *vs* 1340 [59·3%] of 2260; p<0·0001).

Table 3 shows the results of the stepwise multivariable logistic regression analysis of the association of HIV status with triple-negative breast cancer versus non-triple-negative breast cancer in the full cohort. Patients were excluded from the models for missing data on wealth index (n=96), age at menarche (n=261), and parity and breastfeeding history (n=29). In multivariable model 1 (demographic factors), HIV-positive status was associated with an increased proportion of triple-negative breast cancer (adjusted OR 1·38, 95% CI 1·11–1·71). In multivariable model 2 (age and reproductive factors), both parity without breastfeeding (1·77, 1·11–2·88) and parity with breastfeeding (1·50, 1·01–2·32) were associated with an increased proportion of triple-negative breast cancer compared with nulliparity. In the fully adjusted model 3, both HIV-positive status (1·39, 1·12–1·74) and parity without breastfeeding (1·75,

	Non-triple-negative breast cancer (n=3246)	Triple-negative breast cancer (n=637)	Total (n=3883)	p value*
Age at menarche†, years	..	..	..	0·12
<15	1422/3032 (46·9%)	256/590 (43·4%)	1678/3622 (46·3%)	..
≥15	1610/3032 (53·1%)	334/590 (56·6%)	1944/3622 (53·7%)	..
Unknown‡	214	47	261	..
Ever pregnant	..	..	..	0·0065
Yes	3000 (92·4%)	608 (95·4%)	3608 (92·9%)	..
No	246 (7·6%)	29 (4·6%)	275 (7·1%)	..
Number of full-term pregnancies, median (IQR)	3·0 (2·0–4·0)	3·0 (2·0–4·0)	3·0 (2·0–4·0)	0·010§
Range	0·0–18·0	0·0–16·0	0·0–18·0	..
Unknown‡	18	3	21	..
Age at first full-term pregnancy, years	..	..	..	0·011
Nulliparous	246/3202 (7·7%)	29/632 (4·6%)	275/3834 (7·2%)	..
<21	1456/3202 (45·5%)	313/632 (49·5%)	1769/3834 (46·1%)	..
≥21	1500/3202 (46·8%)	290/632 (45·9%)	1790/3834 (46·7%)	..
Unknown‡	44	5	49	..
Parity and breastfeeding history	..	..	..	0·012
Nulliparous	246/3222 (7·6%)	29/632 (4·6%)	275/3854 (7·1%)	..
Parous and did not breastfeed	331/3222 (10·3%)	77/632 (12·2%)	408/3854 (10·6%)	..
Parous and breastfed	2645/3222 (82·1%)	526/632 (83·2%)	3171/3854 (82·3%)	..
Unknown‡	24	5	29	..
Ever used contraceptives¶	..	..	..	0·027
Yes	2010 (61·9%)	424 (66·6%)	2434 (62·7%)	..
No	1236 (38·1%)	213 (33·4%)	1449 (37·3%)	..
Menopausal status	..	..	..	0·72
Premenopausal	1174/2966 (39·6%)	220/571 (38·5%)	1394/3537 (39·4%)	..
Natural menopause	1723/2966 (58·1%)	340/571 (59·5%)	2063/3537 (58·3%)	..
Surgical menopause	69/2966 (2·3%)	11/571 (1·9%)	80/3537 (2·3%)	..
Unknown‡	280	66	346	..
Ever on HRT	..	..	..	0·016
Yes	57/3242 (1·8%)	3/635 (0·5%)	60/3877 (1·5%)	..
No	3185/3242 (98·2%)	632/635 (99·5%)	3817/3877 (98·5%)	..
Unknown‡	4	2	6	..

Data are n (%) unless otherwise stated. HRT=hormone replacement therapy. SABCHO=South African Breast Cancer and HIV Outcomes. *Calculated with Pearson's χ^2 test unless otherwise specified. †Among those who self-reported age at menarche as outside ages 8–24 years, two patients had triple-negative breast cancer and eight patients had other breast cancer subtypes. Among those who reported having gone through menarche but did not report an age, their age at menarche was imputed as 15 years (cohort median); three patients had triple-negative breast cancer and 18 patients had other breast cancer subtypes. ‡Participants with unknown data were not included in analyses. §Calculated with linear model ANOVA. ¶Oral or injectable contraceptives.

Table 2: **Reproductive features of the SABCHO cohort, by breast cancer subtype**

	Model 1 (n=3787)	Model 2 (n=3599)	Model 3 (n=3511)
Age group, years			
<40	0·70 (0·51–0·95)	0·83 (0·61–1·13)	0·76 (0·55–1·03)
40–49	0·98 (0·77–1·26)	1·14 (0·89–1·45)	1·04 (0·80–1·34)
50–59	1 (ref)	1 (ref)	1 (ref)
60–69	1·02 (0·79–1·31)	1·04 (0·80–1·35)	1·10 (0·84–1·44)
≥70	0·74 (0·56–0·99)	0·72 (0·52–0·99)	0·76 (0·54–1·06)
Race			
Black	1·26 (0·96–1·65)	..	1·23 (0·92–1·64)
Non-Black*	1 (ref)	..	1 (ref)
Wealth index†	1·01 (0·94–1·08)	..	1·00 (0·93–1·08)
HIV status			
Positive	1·38 (1·11–1·71)	..	1·39 (1·12–1·74)
Negative	1 (ref)	..	1 (ref)
Age at menarche, years			
<15	..	1 (ref)	1 (ref)
≥15	..	1·14 (0·96–1·37)	1·06 (0·88–1·29)
Parity and breastfeeding history			
Nulliparous	..	1 (ref)	1 (ref)
Parous and did not breastfeed	..	1·77 (1·11–2·88)	1·75 (1·09–2·87)
Parous and breastfed	..	1·50 (1·01–2·32)	1·50 (1·00–2·34)
Ever used contraceptives?			
Yes	..	1·13 (0·92–1·40)	1·14 (0·92–1·41)
No	..	1 (ref)	1 (ref)
Study site			
CHBAH	1 (ref)	..	1 (ref)
CMJAH	1·09 (0·88–1·35)	..	1·08 (0·86–1·35)
Durban	0·93 (0·69–1·25)	..	0·97 (0·71–1·31)
Grey's	1·21 (0·93–1·58)	..	1·27 (0·96–1·67)
Ngwelezana	1·06 (0·53–1·95)	..	1·01 (0·49–1·92)

Data are adjusted odds ratio (95% CI). CHBAH=Chris Hani Baragwanath Academic Hospital. CMJAH=Charlotte Maxeke Johannesburg Academic Hospital. SABCHO=South African Breast Cancer and HIV Outcomes. *In the analysis, non-Black race was self-reported as either White, Coloured, or Asian. †As previously described in published literature, a wealth index was derived via principal component analysis of data from a survey of household possessions and facilities;[19] the wealth index ranges from 1–5, with 5 indicating the greatest wealth. The odds ratio is for each 1 point rise on the wealth index scale.

Table 3: **Multivariable logistic regression models for the SABCHO cohort assessing the association of demographic and reproductive factors with triple-negative breast cancer versus non-triple-negative breast cancer**

1·09–2·87) were associated with an increased proportion of triple-negative breast cancer compared with non-triple-negative breast cancer. There was no statistically significant interaction between HIV status and the combined parity and breastfeeding variable in model 3.

Subgroup analysis of Black women showed that only HIV-positive status remained associated with an increased proportion of triple-negative breast cancer (adjusted OR 1·49, 95% CI 1·18–1·87 in model 3; appendix 1 p 3). Among Black women, triple-negative breast cancer accounted for 183 (21·0%) of 872 breast cancer cases among women who were HIV-positive and 355 (15·7%) of 2260 breast cancer cases among women who were HIV-negative. The absolute percentage of breast cancer cases that were triple-negative was 6·3–6·5% greater among Black women with HIV for all age groups younger than 60 years than Black women without HIV for all age groups younger than 60 years (figure). There was minimal heterogeneity when the association between HIV and the proportion of triple-negative breast cancer cases among Black women was compared by study site (I^2=0·0%) and year of diagnosis (I^2=4·7%; appendix 1 p 6).

Table 4 shows the clinical features of 894 women who were HIV-positive, by breast cancer subtype at the time of enrolment in SABCHO. 121 (13·5%) of these women were diagnosed with HIV at the time of enrolment, 872 (97·5%) self-identified as Black, and 695 (77·7%) were on ART. 216 (46·9%) of 461 women with known data had undetectable HIV viral loads, 729 (91·4%) of 798 had CD4⁺ counts greater than or equal to 200 cells per µL, 606 (68·1%) of 890 women reported duration of HIV infection of 2 years or more, and 581 (95·9%) of these 606 women were on ART. Triple-negative breast cancer accounted for a higher proportion of total breast cancers in women with a duration of HIV infection of at least 2 years than in those with a duration of infection of less than 2 years (139 [22·9%] of 606 women with HIV for ≥2 years *vs* 46 [16·2%] of 284 women with HIV for <2 years; p=0·0209).

When the fully adjusted multivariable logistic regression model was repeated with HIV status stratified by four different HIV-related metrics, an increased proportion of triple-negative breast cancer was observed in women who were HIV-positive with a duration of HIV infection of 2 years or longer (adjusted OR 1·57, 95% CI 1·23–2·00, compared with women who were HIV-negative), women who were HIV-positive and on ART (1·47, 1·16–1·87, compared with women who were HIV-negative), and women who were HIV-positive with CD4⁺ counts of 200 cells per µL or higher (1·30, 1·02–1·65, compared with women who were HIV-negative). Other tested subgroups were not found to be associated with the proportion of triple-negative breast cancer (appendix 1 p 4).

Discussion

Our study found that, among 3883 women diagnosed with breast cancer in South Africa, women who were HIV-positive were more likely to have triple-negative breast cancer than women without HIV (adjusted OR 1·39, 95% CI 1·12–1·74; table 3). The proportion of triple-negative breast cancer cases among women who were HIV-positive was 5·7 percentage points higher than in women who were HIV negative in the whole cohort (table 1) and 6·3–6·5 percentage points higher in the subgroups of Black women younger than 60 years (figure). The association between HIV-positive status and the proportion of triple-negative breast cancer was most prominent among women with a duration of HIV infection of 2 years or longer compared with women who were HIV-negative and in women receiving chronic ART

treatment compared with women who were HIV-negative (appendix 1 p 4).

Our finding that the proportion of triple-negative breast cancer cases in patients with breast cancer and comorbid HIV is higher than in those without HIV is consistent with the findings of a 2020 study of patients with breast cancer in Mozambique (n=210),[20] but differs from the findings of other previous studies that analysed breast cancer subtypes by HIV status.[3,14–17] Of greatest relevance, our findings differ from those of a previous analysis of the SABCHO cohort done in 2019 (n=1016)[3] and a 2013 analysis of patients with breast cancer from Chris Hani Baragwanath Academic Hospital (n=1092),[16] neither of which found an association between HIV and the proportion of triple-negative breast cancer. Our analysis included 3883 women, a sample size almost four times larger than these two previous studies, and therefore has greater statistical power. Specifically, we included 186 women with both triple-negative breast cancer and HIV, whereas the previous analyses included only 38 women[3] and 24 women[16] with both triple-negative breast cancer and HIV. Furthermore, we accounted for potential confounding reproductive factors not included in previous studies, including parity, breastfeeding history, and history of contraceptive use, all of which differed by HIV status, triple-negative breast cancer status, or both. We also adjusted all analyses for age and self-reported race and validated the observed association of HIV with triple-negative breast cancer in the Black subgroup of SABCHO patients. Our results remained consistent within the Black subgroup and had minimal heterogeneity when stratified by year of diagnosis and study site.

This is a case-only analysis that cannot measure the absolute risk of triple-negative breast cancer due to the absence of a control group without a breast cancer diagnosis. This absence makes it challenging to isolate whether the observed increase in the proportion of triple-negative breast cancer among patients with breast cancer and HIV is due to an increased absolute risk of triple-negative breast cancer, or a decreased absolute risk of non-triple-negative breast cancer. Overall rates of breast cancer in South Africa do not differ by HIV status,[9] suggesting that chronic HIV infection in this population could be linked with both an increase in the absolute risk of triple-negative breast cancer and a similar decrease in the absolute risk of non-triple-negative breast cancer (most likely hormone receptor-positive breast cancer).

One mechanism by which HIV status could affect the proportion of breast cancer cases that are triple-negative is by affecting reproductive behaviours associated with breast cancer subtype. Previous studies have shown that parity is associated with an increased risk of triple-negative breast cancer (both absolute risk and relative risk of hormone receptor-positive breast cancer) and that this risk is reduced through breastfeeding.[5–7] This association was present in our cohort, as parous women who did not breastfeed had a higher proportion of triple-negative breast cancer than nulliparous women, while parous women who breastfed did not. We then investigated how HIV status affected rates of parity and breastfeeding. We found similar rates of parity between women with and without HIV and found lower rates of breastfeeding among parous women with HIV compared with parous women without HIV (85·0% *vs* 93·1%, p<0·0001; appendix 1 p 1). This finding suggests that some women who are HIV-positive might not breastfeed out of concern for vertical HIV transmission, which could increase their risk of triple-negative breast cancer. However, there was no statistically significant interaction between HIV status and the combined parity and breastfeeding variable in our final logistic regression model. If the association of HIV with the proportion of triple-negative breast cancer was mediated by parity and breastfeeding alone, we would have expected to observe different associations of HIV by breastfeeding status.

Another mechanism by which HIV could affect breast cancer subtype is through systemic changes in sex hormone concentrations. Women who are HIV-positive have increased rates of amenorrhoea compared with women who are HIV-negative,[21,22] which might decrease their risk of hormone receptor-positive breast cancer through reduced lifetime exposure to sex hormones. A meta-analysis done by Brandão and colleagues[15] found that women who were HIV-positive were less likely than women who were HIV-negative to develop hormone receptor-positive breast cancer, and they proposed hypo-oestrogenism as a mechanism for this relationship. In our cohort, a lower proportion of Black women who were HIV-positive had a BMI greater than 30 kg/m² than Black women who were HIV-negative (41·3% *vs* 56·5%, p<0·0001; appendix 1 p 1), which could contribute to

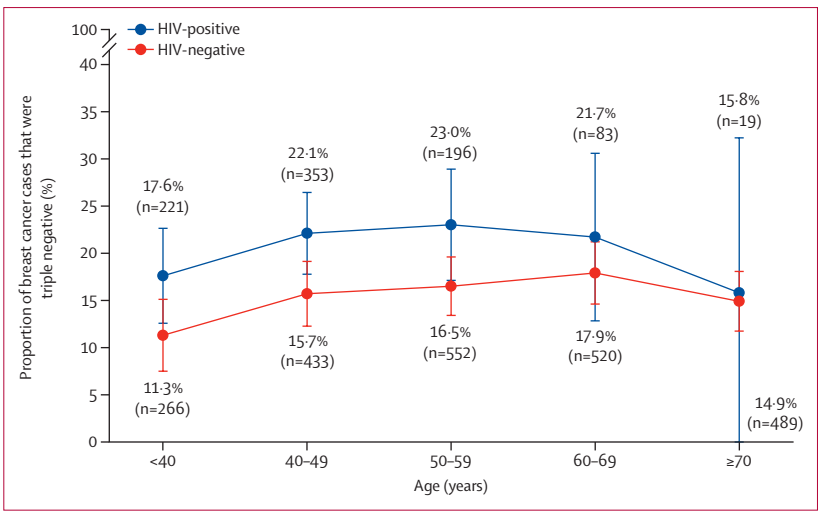


Figure: **Proportion of Black women with breast cancer enrolled in the SABCHO cohort who had triple-negative breast cancer, by age and HIV status**
Error bars show 95% CI.

	Non-triple-negative breast cancer (n=708)	Triple-negative breast cancer (n=186)	Total (n=894)	p value*
Age group, years	..	..	..	0·63
<40	185 (26·1%)	39 (21·0%)	224 (25·1%)	..
40–49	280 (39·5%)	78 (41·9%)	358 (40·0%)	..
50–59	161 (22·7%)	47 (25·3%)	208 (23·3%)	..
60–69	66 (9·3%)	19 (10·2%)	85 (9·5%)	..
≥70	16 (2·3%)	3 (1·6%)	19 (2·1%)	..
Median age (IQR)	45·0 (39·0–53·0)	46·0 (41·0–54·0)	45·0 (39·3–53·0)	0·24†
Race	..	..	..	0·40
Black	689 (97·3%)	183 (98·4%)	872 (97·5%)	..
Non-Black‡	19 (2·7%)	3 (1·6%)	22 (2·5%)	..
Received new HIV diagnosis at time of enrolment	..	..	..	0·2
Yes	101 (14·3%)	20 (10·8%)	121 (13·5%)	..
No	607 (85·7%)	166 (89·2%)	773 (86·5%)	..
Median years since HIV diagnosis§ (IQR)	4·0 (0·0–9·0)	6·0 (2·0–10·0)	4·0 (1·0–9·0)	0·0035†
Range	0·0–28·0	0·0–22·0	0·0–28·0	..
Unknown	3	1	4	..
Years since HIV diagnosis§	..	..	..	0·021
<2 years	238/705 (33·8%)	46/185 (24·9%)	284/890 (31·9%)	..
≥2 years	467/705 (66·2%)	139/185 (75·1%)	606/890 (68·1%)	..
Unknown¶	3	1	4	..
Viral load§				0·51
Detectable	201/373 (53·9%)	44/88 (50·0%)	245/461 (53·1%)	..
Undetectable	172/373 (46·1%)	44/88 (50·0%)	216/461 (46·9%)	..
Unknown¶	335	98	433	..
CD4⁺ cell count§				0·71
<200 cells per µL	54/638 (8·5%)	15/160 (9·4%)	69/798 (8·6%)	..
≥200 cells per µL	584/638 (91·5%)	145/160 (90·6%)	729/798 (91·4%)	..
Unknown¶	70	26	96	..
On antiretroviral therapy				0·14
Yes	543 (76·7%)	152 (81·7%)	695 (77·7%)	..
No	165 (23·3%)	34 (18·3%)	199 (22·3%)	..

Data are n (%) unless otherwise stated. SABCHO=South African Breast Cancer and HIV Outcomes. *Calculated using Pearson's χ^2 test unless otherwise specified. †At the time of study enrollment. ‡In the analysis, non-Black race was self-reported as either White, Coloured, or Asian. §Calculated with linear model ANOVA. ¶Participants with unknown data were not included in analyses.

Table 4: **Demographic and HIV-related features of patients who are HIV-positive in the SABCHO cohort, by breast cancer subtype**

decreased oestrogen concentrations in women who are HIV-positive through reduced peripheral aromatisation of androgens. However, BMI was not associated with breast cancer subtype (table 1).

We can also hypothesise a direct biological interaction between HIV infection and the breast tissue micro-environment that contributes to triple-negative breast cancer oncogenesis. HIV causes chronic immune dysregulation, which is partly alleviated, but not completely reversed, by ART.[11] Compared with other breast cancer subtypes, triple-negative breast cancer has been shown to provoke the greatest anti-tumour response.[23] Therefore, dysregulation of host immune surveillance might preferentially support the oncogenesis of triple-negative breast cancer over non-triple-negative breast cancer among women with HIV. When women who were HIV-positive were stratified by HIV-related metrics, women with a duration of infection greater than or equal to 2 years had an increased proportion of triple-negative breast cancer (compared with women who were HIV-negative), whereas women with a duration of infection of less than 2 years did not. This finding supports a model in which chronic exposure to the HIV immune dysregulated state incrementally increases the likelihood of developing triple-negative breast cancer (appendix 1 p 4). However, 95·9% of women in our cohort with chronic HIV infection (≥2 years) were also on ART, so it is difficult to separate the effects of chronic HIV infection from the effects of chronic ART treatment. Chronic ART exposure might have a direct effect on breast cancer subtype, but this is considered unlikely, given that there is no established biological mechanism to mediate this effect.

Regarding the effect of HIV control on breast cancer subtype, women who were HIV-positive with detectable and undetectable HIV viral loads had nearly identical elevated ORs for triple-negative breast cancer versus non-triple-negative breast cancer compared with women who were HIV-negative, but these results were not statistically significant (appendix 1 p 4). The absence of statistically significant results in both subgroups might be because 402 women who were HIV-positive were excluded from this model for having missing viral load data, in addition to the 21 women who were excluded for missing wealth index, parity or breastfeeding history, or age at first menarche data. Furthermore, women who were HIV-positive with CD4⁺ counts of 200 cells per µL or higher and those with CD4⁺ counts of less than 200 cells per µL both had elevated ORs for triple-negative breast cancer versus non-triple-negative breast cancer (compared with women who were HIV-negative), but this result was only statistically significant among women with CD4⁺ counts of 200 cells per µL or higher. This finding might be due to the low number of women with CD4⁺ counts less than 200 cells per µL (n=64; appendix 1 p 4). These results suggest that the proportion of triple-negative breast cancer cases among women with breast cancer who are HIV-positive is increased regardless of CD4⁺ count and HIV viral load, but future research with larger sample sizes is warranted to better explore these findings.

Our study has multiple strengths and some key limitations. A strength is that our data came from the SABCHO cohort, which has a large patient population drawn from multiple South African public hospitals, many women with both breast cancer and HIV, and detailed data on demographic variables, reproductive history, and HIV control. However, not all factors that might contribute to triple-negative breast cancer pathogenesis are captured in the SABCHO dataset. HIV

viral load and CD4+ counts were measured only at the time of study enrolment. Longitudinal data on HIV-related metrics before enrolment would have been more informative about immune conditions during the period of oncogenesis. Similarly, we cannot say with complete certainty that HIV exposure predated tumour oncogenesis in all cases, given we only have data on HIV status at time of breast cancer diagnosis. However, we have reasonable confidence that HIV exposure predated tumour oncogenesis in most or all cases given the median duration of HIV infection was 4 years. Furthermore, as previously discussed, this is a case-only analysis that cannot measure the absolute risk of triple-negative breast cancer. Future case–control studies with control patients without breast cancer done in regions of high HIV prevalence, such as South Africa, would better delineate whether the absolute risk of triple-negative breast cancer differs by HIV status.

Overall, in this large prospective case-only study conducted in South Africa, we found that patients with breast cancer and comorbid HIV are more likely to have triple-negative breast cancer than patients with breast cancer without HIV, especially among women with chronic HIV infection who are on ART. This association is independent of age, race, and reproductive variables. Future research should study whether this association is mediated by an increase in the absolute risk of triple-negative breast cancer, a decrease in the absolute risk of non-triple-negative breast cancer, or both. Regardless of mechanism, these findings support an emphasis on early breast cancer detection among women with HIV, given the aggressive spread and poor prognosis associated with triple-negative breast cancer. Among women who are HIV-positive, any breast cancer symptom should prompt a full evaluation by a provider with breast cancer expertise, regardless of the woman's age, race, or reproductive history.

Contributors

YSP conceptualised the study. JD, OAA, DSO'N, and WCC curated the data. WCC and MJ verified the data. JD did the formal analysis with supervision by YSP, AIN, and VMcC. JD and YSP wrote the original draft. AIN, JSJ, KDC, MJ, PR, and HC were responsible for study funding acquisition. MJ, HAF, and WCC were responsible for project administration. IB, SRČ, LWS, SN, NM, BP, HC, and PR were responsible for investigation and data acquisition. All authors contributed to review and editing, had full access to all data in the study, and had final responsibility for the decision to submit for publication.

Equitable partnership declaration

The authors of this paper have submitted an equitable partnership declaration (appendix 2). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of *The Lancet Global Health*'s broader goal to decolonise global health.

Declaration of interests

AIN reports a consulting or advisory relationship with Otsuka, United Biosource Corp, Hospira, Value Analytics, Merck, Organon, and GSK; is on the Scientific Advisory Board for EHE Intl; and received research funding from Otsuka. YSP reports ownership interest in Pfizer and a consulting or advisory relationship with BMS and Janssen. PR reports clinical trial funding to their institution from Merck, Roche, Pfizer, GSK, Jansen, AstraZeneca, ImmunityBio, and Amgen. All other authors declare no competing interests.

Data sharing

The datasets generated and analysed during this study are available from the corresponding author upon reasonable request.

Acknowledgments

This study was funded by US National Institutes of Health (NIH) grants (NCI R01CA192627 and R01CA250012) awarded to JSJ, MJ, AIN, and PR; by a University of the Witwatersrand–South African Medical Research Council–University of the Witwatersrand Common Epithelial Cancer Research Centre grant to PR; and in part by the US National Cancer Institute CCSG P30 CA13696. This work was also partly funded by a Conquer Cancer–Janssen Oncology Young Investigator Award awarded to YSP. Any opinions, findings, and conclusions expressed in this material are those of the authors and do not necessarily reflect those of the American Society of Clinical Oncology or Conquer Cancer. JD was funded in part by the Varmus Global Scholars Fund. During this work, DSO'N was a K12 Scholar supported by the National Cancer Institute of the NIH under award number K12CA226330. Where authors are identified as personnel of the International Agency for Research on Cancer, the authors alone are responsible for the views expressed in this Article and they do not necessarily represent the decisions, policy, or views of these organisations.

References

1 International Agency for Research on Cancer, WHO. Global Cancer Observatory: cancer today: South Africa. International Agency for Research on Cancer, 2024. https://gco.iarc.who.int/media/globocan/factsheets/populations/710-south-africa-fact-sheet.pdf (accessed Feb 29, 2024).

2 Yin L, Duan JJ, Bian XW, Yu SC. Triple-negative breast cancer molecular subtyping and treatment progress. *Breast Cancer Res* 2020; **22:** 61.

3 Phakathi B, Cubasch H, Nietz S, et al. Clinico-pathological characteristics among South African women with breast cancer receiving anti-retroviral therapy for HIV. *Breast* 2019; **43:** 123–29.

4 Brewster AM, Chavez-MacGregor M, Brown P. Epidemiology, biology, and treatment of triple-negative breast cancer in women of African ancestry. *Lancet Oncol* 2014; **15:** e625–34.

5 Figueroa JD, Davis Lynn BC, Edusei L, et al. Reproductive factors and risk of breast cancer by tumor subtypes among Ghanaian women: a population-based case-control study. *Int J Cancer* 2020; **147:** 1535–47.

6 Palmer JR, Viscidi E, Troester MA, et al. Parity, lactation, and breast cancer subtypes in African American women: results from the AMBER Consortium. *J Natl Cancer Inst* 2014; **106:** dju237.

7 Sanderson M, Pal T, Beeghly-Fadiel A, et al. A pooled case-only analysis of reproductive risk factors and breast cancer subtype among Black women in the southeastern United States. *Cancer Epidemiol Biomarkers Prev* 2021; **30:** 1416–23.

8 Mabaso M, Makola L, Naidoo I, Mlangeni LL, Jooste S, Simbayi L. HIV prevalence in South Africa through gender and racial lenses: results from the 2012 population-based national household survey. *Int J Equity Health* 2019; **18:** 167.

9 Sitas F, Pacella-Norman R, Carrara H, et al. The spectrum of HIV-1 related cancers in South Africa. *Int J Cancer* 2000; **88:** 489–92.

10 Dubrow R, Silverberg MJ, Park LS, Crothers K, Justice AC. HIV infection, aging, and immune function: implications for cancer risk and prevention. *Curr Opin Oncol* 2012; **24:** 506–16.

11 Lederman MM, Funderburg NT, Sekaly RP, Klatt NR, Hunt PW. Residual immune dysregulation syndrome in treated HIV infection. *Adv Immunol* 2013; **119:** 51–83.

12 Caccuri F, Giordano F, Barone I, et al. HIV-1 matrix protein p17 and its variants promote human triple negative breast cancer cell aggressiveness. *Infect Agent Cancer* 2017; **12:** 49.

13 Savas P, Salgado R, Denkert C, et al. Clinical relevance of host immunity in breast cancer: from TILs to the clinic. *Nat Rev Clin Oncol* 2016; **13:** 228–41.

14 Cubasch H, Joffe M, Hanisch R, et al. Breast cancer characteristics and HIV among 1092 women in Soweto, South Africa. *Breast Cancer Res Treat* 2013; **140:** 177–86.

See **Online** for appendix 2

15 Brandão M, Bruzzone M, Franzoi MA, et al. Impact of HIV infection on baseline characteristics and survival of women with breast cancer. *AIDS* 2021; **35:** 605–18.

16 Bhatia RK, Narasimhamurthy M, Martei YM, et al. Report of clinico-pathological features of breast cancer in HIV-infected and uninfected women in Botswana. *Infect Agent Cancer* 2019; **14:** 28.

17 Chasimpha S, McCormack V, Cubasch H, et al. Disparities in breast cancer survival between women with and without HIV across sub-Saharan Africa (ABC-DO): a prospective, cohort study. *Lancet HIV* 2022; **9:** e160–71.

18 Cubasch H, Ruff P, Joffe M, et al. South African breast cancer and HIV outcomes study: methods and baseline assessment. *J Glob Oncol* 2017; **3:** 114–24.

19 O'Neil DS, Nietz S, Buccimazza I, et al. Neoadjuvant chemotherapy use for nonmetastatic breast cancer at five public South African hospitals and impact on time to initial cancer therapy. *Oncologist* 2019; **24:** 933–44.

20 Brandão M, Guisseve A, Bata G, et al. Breast cancer subtypes: implications for the treatment and survival of patients in Africa – a prospective cohort study from Mozambique. *ESMO Open* 2020; **5:** e000829.

21 King EM, Albert AY, Murray MCM. HIV and amenorrhea: a meta-analysis. *AIDS* 2019; **33:** 483–91.

22 Coburn SB, Dionne-Odom J, Alcaide ML, et al. The association between HIV status, estradiol, and sex hormone binding globulin among premenopausal women in the women's interagency HIV study. *J Womens Health* 2022; **31:** 183–93.

23 Liu Z, Li M, Jiang Z, Wang X. A comprehensive immunologic portrait of triple-negative breast cancer. *Transl Oncol* 2018; **11:** 311–29.