Breast cancer characteristics and HIV among 1,092 women in Soweto, South Africa

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Abstract In the low-income HIV-endemic regions of sub-Saharan Africa, malignancies related to HIV have long been recognized as a major public health problem. However, epithelial malignancies associated with older age, such as breast cancer, are also rising dramatically in those regions. We compared consecutive HIV-positive and -negative black women diagnosed with breast cancer at a large public hospital in Soweto, South Africa, on age, year of diagnosis, stage, grade, and receptor status, and grouped HIV-positive patients by CD4 cell counts. We computed prevalence ratios of the associations of HIV status and CD4 category with stage, grade, receptor status, and among the HIV-positive patients, receipt of ART, controlling for age and year of diagnosis. Of 1,092 patients, 765 were tested for HIV; 151 (19.7 %) tested positive, a prevalence similar to that in the source population. Although, HIV-positive patients were younger than HIV-negative patients (p < 0.001), HIV status was not associated with the tumor characteristics. Thirty-seven women (25.9 %) had CD4 cell counts <200 cells/μl. Patients in that severely immunocompromised group were older than those in the other groups (p = 0.01). This study is the first to analyze the association of HIV with breast cancer in a large sample. Based on similar HIV prevalence in our sample and the population of the hospital’s catchment area, clinicians serving HIV-endemic communities should promote routine HIV testing of younger breast cancer patients and immediate treatment of those who test positive, prior to the initiation of chemotherapy. Research is needed on treatment and outcomes given HIV and low CD4 cell count.

Keywords Breast cancer and HIV · South Africa · Breast cancer and race/ethnicity · HIV and cancer

Introduction

In recent years, breast cancer incidence and mortality rates in Africa have risen rapidly. Women diagnosed with breast cancer in the developing countries generally have a poorer prognosis than those in more developed countries [1].
Among women in sub-Saharan Africa, breast cancer has become the most common malignancy and cause of cancer-related deaths. [2].

Sub-Saharan Africa also has almost 70% of the world’s cases of human immunodeficiency virus (HIV) and acquired immunodeficiency (AIDS) cases; and HIV incidence rates are rising faster among women than among men [3]. HIV has always been associated with certain unusual cancers, especially Kaposi’s sarcoma and non-Hodgkin lymphomas, as well as cervical cancer [4–6]. However, due to the success of anti-retroviral treatment (ART), HIV is changing from a major cause of death among young adults and children to a chronic condition with which the patients may survive into middle age and beyond. That change raises concerns about how HIV and its treatment may affect the risks, characteristics, treatment, and outcomes of the common epithelial cancers of middle- and older-aged adults, such as breast cancer [7, 8].

A few population-based cancer registry-linked studies have been conducted on HIV and breast cancer. Most have found breast cancer incidence rates either no higher or slightly lower among HIV-positive women than among HIV-negative women or women in the general population [8–12]. A study conducted in 1995–1999 in Johannesburg, South Africa, found that 43/687 black women with breast cancer (6.3%) and a similar proportion of controls were HIV-positive [4]. It has even been suggested that HIV may reduce the risk of breast cancer [13]. Postulated mechanisms include HIV-induced impaired proliferation of breast cells, and breast cancer cell apoptosis induced by binding of HIV to specific receptors [13–15]. However, solid evidence that HIV affects breast cancer risk for good or ill is lacking. In addition, very little is known about the association of HIV status with breast tumor subtypes, stage at diagnosis, and tumor grade, especially among the most severely immunocompromised HIV-infected women, those whose CD4 cell counts are less than 200 cells/μl. To determine whether and how HIV status may be relevant to treatment decision making, studies are needed in HIV-endemic countries, where HIV-positive breast cancer patients are most likely to be found.

South Africa is a country in transition, with an ethnically diverse population and features of both developing and industrialized countries. Although, much of its population is very poor, South Africa has several public tertiary care hospitals with facilities that are comparable to those in the industrialized world. Here, we report on the demographic and clinical characteristics of HIV-positive and -negative black women diagnosed with breast cancer in Soweto, South Africa, in 2006–2012.

Methods

Setting and patients

Chris Hani Baragwanath Academic Hospital (CHBAH), one of the largest hospitals in the world, is a public tertiary care institution that serves the largely black and low-income community of greater Soweto, in the southwestern part of Johannesburg, South Africa, and neighboring peri-urban communities, which are home to nearly 3 million people. From the late 1950s to the mid-1970s, only about 20 new cases of breast cancer were diagnosed per year at CHBAH (Professor Charles Isaacson, personal communication). Currently, the hospital’s Batho Pele Breast Unit, a member of the International Breast Centres Network, receives 400–500 patient visits and diagnoses up to 25 new breast cancers per month. The vast majority of patients have never undergone mammographic screening for breast cancer and are symptomatic at diagnosis. Patients receive standard diagnostics and multimodality treatment with surgery, chemotherapy, radiotherapy, and hormonal treatment in keeping with international guidelines. Decision making is monitored by a multidisciplinary team of surgeons, medical oncologists, radiation oncologists, and palliative care physicians.

In 2006, we developed an electronic database of all the patients seen with a diagnosis of breast cancer. As of July 2012, the database included 1,228 patients with invasive breast carcinoma. For the current analysis, we excluded 12 male patients and 124 nonblack (49 white, 46 colored, 22 Asian, and 7 missing ethnicity data) female patients, and included all black female patients diagnosed with histologically confirmed breast cancer from October 2006 through July 2012. The study was approved by the Wits Human Research Ethics Committee (Medical).

Receptor status

As part of the diagnostic workup, estrogen receptor (ER), progesterone receptor (PR), and HER2 status were measured by the National Health Laboratory Service (N HLS) of South Africa (www.nhls.ac.za). Hematoxylin and eosinophil (H&E) staining of 3-μm tissue sections was verified for sufficient numbers of invasive cells and fixation quality. The fully automated immunostainer Ventana Benchmark XT was used for measurement of ER and PR levels by SP1 rabbit monoclonal CONFIRM™ anti-ER 1Ab. Tumors with <1% ER or PR nuclei staining were considered negative; tumors with weak (1–10%), moderate (10–33%), or strong (>33%) staining were considered positive. HER2 was analyzed using Ventana 4B5 rabbit monoclonal PATHWAY® anti-HER2/neu 1Ab. Tumors...
with no, weak, or moderate staining (scores 0, 1+, 2+) were classified as HER2-negative, and those with staining intensity 3+ as positive [16–18].

HIV testing

The prevalence of HIV is high in Soweto (~ 40 % among women in their thirties). Because most patients seen in the breast clinic have never been tested and are likely to need chemotherapy, all were offered HIV testing during their diagnostic workup. HIV-1 and -2 antibodies were detected from patients’ blood samples using either a fourth generation ELISA (Elecsys and Cobas 602, Roche diagnostics, Mannheim, Germany) or a rapid HIV1/2 kit (Determine, Alere Medical Co., Japan). If a positive test was obtained by either method, a confirmatory test was performed using a fourth generation ELISA (Abbott Architect, Wiesbaden, Germany). Among HIV-positive patients, we calculated CD4 cell counts per microliter of blood (cells/µl), by means of a dual-platform, panleucogating technique, using total leukocytes as the common denominator. Cell counts were determined using the Beckmann-Coulter Flow CARE™ 500 Analyzer (Becton–Dickinson Biosciences, San Jose, CA, USA) [19]. Women who tested HIV-positive were referred to the specialist HIV unit so that they could begin ART prior to initiating treatment for their cancer.

Statistical analysis

We categorized the patients as HIV-positive, HIV-negative, or HIV status unknown. We then compared distributions among categories of demographic and clinical characteristics of the HIV-positive and HIV-negative groups, using Chi square tests of the statistical significance of group differences. In addition, we categorized the HIV-positive patients by CD4 cell count categories: ≥500, 200–499, and <200 cells/µl, and compared the distributions of demographic and clinical characteristics of those groups, using Chi square tests or, where necessary, Fisher exact tests of statistical significance. Differences in CD4 count distributions by breast tumor characteristics were also analysed using the nonparametric Kruskal–Wallis test.

Because in this case series, the characteristics of interest were relatively common, we used prevalence ratios (PR) as measures of association [20, 21]. We developed generalized linear models for binary outcomes with robust variance and a log link function to evaluate the associations of dichotomized stage at diagnosis (stages III and IV vs stages I and II), tumor grade (grades 2 and 3 vs grade 1), and ER, PR, HER2, and triple-negative (ER−, PR−, and HER2−) receptor status (positive vs negative) with HIV status (positive vs negative and unknown vs negative), controlling for age and year of diagnosis (continuous). Finally, among HIV-positive women, the associations of CD4 cell count categories with tumor characteristics and prior ART treatment were also evaluated. All the regression models included age at and year of diagnosis.

We also compared the percentages of breast cancer patients who were HIV-positive to those in the general population within age strata. We obtained population age-specific HIV prevalence estimates (%) from the 2008–2010 national antenatal-sentinel HIV prevalence surveys for Gauteng Province (http://www.doh.gov.za/docs/reports/2011/hiv_aids_survey.pdf) for women younger than 45 years, and from the Soweto Women’s Study, a cross-sectional study of 500 women aged 45 years and older, conducted in July 2009 (http://www.anovahealth.co.za/images/uploads/Mental%20Health%20Symposium%20presentation%20-%20Cape%20Town,%20August%202011%20.pdf) for older women. Expected proportions of HIV-positive women in each 5-year age category were compared with observed numbers using the Chi squared test, and age-adjusted risk ratios of the association of HIV with breast cancer were calculated. Among our patients, missingness of data on HIV status was strongly associated with age, and age had a strong inverse association with HIV-positive status. We, therefore, used multiple imputation to estimate the HIV-positive percentage of all breast cancer patients, based on a logistic regression model for the association of HIV with age (in pentads), stage, and ER, PR, and HER2 status.

Results

The CHBAH database included 1,092 black women who were diagnosed with invasive breast carcinoma during the 6-year study period. Of the 765 (70 % of 1,092), whose HIV status was known, 151 (19.7 % of those tested) were HIV-positive.

From 2006–2007 to 2010–2012, the proportion of patients who were tested for HIV increased from 43 to 77 %; but among those tested, the proportion of positives declined from 29 to 18 %. Among those tested for HIV, 35.2 % of patients under age 50 years, 12.1 % of patients aged 50–59 years, and 4 % of patients aged over 60 years were HIV-positive (Table 1).

HIV status in relation to breast cancer characteristics at diagnosis

More than 50 % of the patients were diagnosed in stage III (A–C) or stage IV, and fewer than 10 % were diagnosed with tumors of grade 1; but in bivariate analysis, neither the stage nor the tumor grade at diagnosis was associated with HIV status. Among the patients for whom data were available on molecular subtype, 614/966 (63.6 %) had
Table 1  Demographic and clinical characteristics of black women diagnosed with breast cancer at Chris Hani Baragwanath Academic Hospital, South Africa, 2006–2012, by HIV status

| HIV status | HIV-positive | HIV-negative | Total | p-value |
|------------|--------------|--------------|-------|---------|
|            | N            | %*           | N     | %*     |           |
| Total      | 151          | 19.7**       | 614   | 80.3** | 765       | 100.0**   |
| Age at breast cancer diagnosis | | | | | | <0.001 |
| 25–39      | 58           | 38.4         | 76    | 12.4   | 134       | 17.5      |
| 40–49      | 60           | 39.7         | 141   | 23.0   | 201       | 26.3      |
| 50–59      | 24           | 15.9         | 174   | 28.3   | 198       | 25.9      |
| 60–69      | 8            | 5.3          | 119   | 19.4   | 127       | 16.6      |
| 70–79      | 1            | 0.7          | 78    | 12.7   | 79        | 10.3      |
| 80–103     | 0            | 0.0          | 26    | 4.2    | 26        | 3.4       |
| Year of diagnosis | | | | | | 0.16 |
| 2006–2007  | 18           | 11.9         | 45    | 7.3    | 63        | 8.2       |
| 2008–2009  | 55           | 36.4         | 221   | 36.0   | 276       | 36.1      |
| 2010–2012  | 78           | 51.7         | 348   | 56.7   | 426       | 55.7      |
| Stage at diagnosis | | | | | | 0.98 |
| I          | 7            | 4.6          | 28    | 4.6    | 35        | 4.6       |
| IIA-B      | 62           | 41.1         | 261   | 42.5   | 323       | 42.2      |
| IIIA-C     | 67           | 44.4         | 261   | 42.5   | 328       | 42.9      |
| IV         | 14           | 9.3          | 55    | 9.0    | 69        | 9.0       |
| Missing    | 1            | 0.7          | 9     | 1.5    | 10        | 1.3       |
| Tumor grade | | | | | | 0.60 |
| 1          | 16           | 10.6         | 54    | 8.8    | 70        | 9.2       |
| 2          | 53           | 35.1         | 245   | 39.9   | 298       | 39.0      |
| 3          | 54           | 35.8         | 220   | 35.8   | 274       | 35.8      |
| Missing    | 28           | 18.5         | 95    | 15.5   | 123       | 16.1      |
| ER         | | | | | | 0.57 |
| Positive   | 93           | 61.6         | 357   | 58.1   | 450       | 58.8      |
| Negative   | 46           | 30.5         | 198   | 32.2   | 244       | 31.9      |
| Missing    | 12           | 7.9          | 59    | 9.6    | 71        | 9.3       |
| PR         | | | | | | 0.37 |
| Positive   | 78           | 51.7         | 289   | 47.1   | 367       | 48.0      |
| Negative   | 60           | 39.7         | 264   | 43.0   | 324       | 42.4      |
| Missing    | 13           | 8.6          | 61    | 9.9    | 74        | 9.7       |
| HER2/neu   | | | | | | 0.34 |
| 3+         | 41           | 27.2         | 134   | 21.8   | 175       | 22.9      |
| 2+         | 28           | 18.5         | 108   | 17.6   | 136       | 17.8      |
| 0–1+       | 65           | 43.0         | 295   | 48.0   | 360       | 47.1      |
| Missing    | 17           | 11.3         | 77    | 12.5   | 94        | 12.3      |
| Triple-negative# | | | | | | 0.34 |
| Yes        | 24           | 15.9         | 117   | 19.1   | 141       | 18.4      |
| No         | 112          | 74.2         | 432   | 70.4   | 544       | 71.1      |
| Missing    | 15           | 9.9          | 65    | 10.6   | 80        | 10.5      |
Table 1 continued

| HIV status | HIV-negative | Not tested | Total | p-value |
|------------|--------------|------------|-------|---------|
|            | N            | %*        | N     | %*     | N     | %*    |
| Total      | 614          | 65.2      | 327   | 34.8   | 941   | 100.0** |
| Age at breast cancer diagnosis | | | | | <0.001 |
| 25–39      | 76           | 12.4      | 32    | 9.8    | 108   | 14.1  |
| 40–49      | 141          | 23.0      | 52    | 15.9   | 193   | 25.2  |
| 50–59      | 174          | 28.3      | 80    | 24.5   | 254   | 33.2  |
| 60–69      | 119          | 19.4      | 76    | 23.2   | 195   | 25.5  |
| 70–79      | 78           | 12.7      | 51    | 15.6   | 129   | 16.9  |
| 80–103     | 26           | 4.2       | 36    | 11.0   | 62    | 8.1   |
| Year of diagnosis | | | | | <0.001 |
| 2006–2007  | 45           | 7.3       | 85    | 26.0   | 130   | 17.0  |
| 2008–2009  | 221          | 36.0      | 115   | 35.2   | 336   | 43.9  |
| 2010–2012  | 348          | 56.7      | 127   | 38.8   | 475   | 62.1  |
| Stage at diagnosis | | | | | 0.28 |
| I          | 28           | 4.6       | 17    | 5.2    | 45    | 5.9   |
| IIA-B      | 261          | 42.5      | 121   | 37.0   | 382   | 49.9  |
| IIIA-C     | 261          | 42.5      | 155   | 47.4   | 416   | 54.4  |
| IV         | 55           | 9.0       | 23    | 7.0    | 78    | 10.2  |
| Missing    | 9            | 1.5       | 11    | 3.4    | 20    | 2.6   |
| Tumor grade | | | | | 0.25 |
| 1          | 54           | 8.8       | 22    | 6.7    | 76    | 9.9   |
| 2          | 245          | 39.9      | 111   | 33.9   | 356   | 46.5  |
| 3          | 220          | 35.8      | 103   | 31.5   | 323   | 42.2  |
| Missing    | 95           | 15.5      | 91    | 27.8   | 186   | 24.3  |
| ER         | | | | | 0.260 |
| Positive   | 357          | 58.1      | 164   | 50.2   | 521   | 68.1  |
| Negative   | 198          | 32.2      | 108   | 33.0   | 306   | 40.0  |
| Missing    | 59           | 9.6       | 55    | 16.8   | 114   | 14.9  |
| PR         | | | | | 0.36 |
| Positive   | 289          | 47.1      | 132   | 40.4   | 421   | 55.0  |
| Negative   | 264          | 43.0      | 138   | 42.2   | 402   | 52.5  |
| Missing    | 61           | 9.9       | 57    | 17.4   | 118   | 15.4  |
| HER2/neu   | | | | | 0.55 |
| 3+         | 134          | 21.8      | 70    | 21.4   | 204   | 26.7  |
| 2+         | 108          | 17.6      | 56    | 17.1   | 164   | 21.4  |
| 0–1+       | 295          | 48.0      | 130   | 39.8   | 425   | 55.6  |
| Missing    | 77           | 12.5      | 71    | 21.7   | 148   | 19.3  |
| Triple-negative | | | | | 0.88 |
| Yes        | 117          | 19.1      | 55    | 16.8   | 172   | 22.5  |
| No         | 432          | 70.4      | 209   | 63.9   | 641   | 83.8  |
| Missing    | 65           | 10.6      | 63    | 19.3   | 128   | 16.7  |

* Column percents
** Row percents

Triple-negative is defined as ER−, PR−, and HER2/neu-negative (HER2 negative includes scores 0–2+)

Chi square tests for differences in non-missing proportions between HIV+ and HIV− patients
ER-positive, 499/961 (51.9 %) with PR-positive, and 245/927 (26.4 %) with HER2-positive breast tumors. A total of 196/949 (20.7 %) women were classified as having triple-negative breast cancer. In univariate analysis, molecular subtype was not associated with HIV status (Table 1). In models that included age at and year of diagnosis, HIV status was also not associated with stages III or IV vs stages I and II; grades 2 and 3 vs grade 1; or molecular subtypes (Table 2).

Among HIV-positive women, the median CD4 count was 316 cells/μl (range 7–1,203, interquartile range 196–487). Using clinical cutpoints, 34 (23.8 %) were classified as having a CD4 cell count of ≥500 cells/μl or higher, 72 (50.4 %) had CD4 cell counts between 200 and 499, and 37 (25.9 %) had CD4 cell counts of 200 cells/μl or below, indicative of severe immunosuppression. The patients in that group were older than the other HIV-positive patients (p = 0.01) and had marginally higher stages of breast cancer (p = 0.05), but did not differ from them in other respects (Table 3). With age and year of diagnosis taken into account, CD4 cell counts were not associated with stage at diagnosis; tumor grade; ER, PR, HER2, or triple-negative receptor status; or receipt of ART (Table 4). Adjustment for receipt of ART scarcely changed the point estimates.

Table 2. Associations of breast cancer stage, grade, and molecular subtype with HIV status, controlling for age at and year of diagnosis

| HIV-positive vs HIV-negative | Stage III vs stages I and II | 1.08 | 0.89–1.32 | 1.00 | 1.00–1.01 |
| HIV-negative unknown vs HIV-negative | Stage IV vs stages I and II | 1.04 | 0.60–1.82 | 0.82 | 0.51–1.30 |
| | Grade 2 vs grade 1 | 0.88 | 0.76–1.01 | 1.05 | 0.96–1.15 |
| | Grade 3 vs grade 1 | 0.87 | 0.76–1.01 | 1.03 | 0.93–1.14 |
| | ER-positive vs ER-negative | 1.06 | 0.92–1.23 | 0.98 | 0.87–1.10 |
| | PR-positive vs PR-negative | 1.13 | 0.95–1.35 | 0.98 | 0.84–1.14 |
| | HER2-positive vs HER2-negative | 1.07 | 0.78–1.46 | 1.08 | 0.83–1.40 |
| | Triple-negative vs other | 0.84 | 0.55–1.27 | 0.94 | 0.70–1.27 |

* Prevalence ratios

HIV prevalence in breast cancer patients compared to the general population

Because HIV status was so strongly associated with age, we compared the prevalence of HIV among patients in our database and women in the source population (Soweto/Gauteng Province) within age pentads (Fig. 1). Except in the 40–44 years age group, the 95 % confidence intervals for HIV prevalence among the breast cancer patients included the population proportion. In a model that controlled for age (in pentads), HIV prevalence among our patients did not differ from that in the source population (RR 1.20, p = 0.13).

The 151 HIV-positive patients represented 19.7 % of the 765 tested women, but only 13.8 % of the total sample of 1,092 breast cancer patients because the 327 untested women were older on the average than the tested women. After HIV status was imputed for women with unknown status, taking age, stage, and ER, PR, and HER2 status into account, the estimated HIV prevalence among all 1,092 breast cancer patients was 18.1 %.

Discussion

This study may be the first to evaluate the association of HIV with prognostic factors in a sample of more than 1,000 black breast cancer patients from an African population with high HIV prevalence. Nearly 20 % of the patients were HIV-positive, a proportion and age distribution similar to those of the female population of the Soweto area. Only age at diagnosis was associated with HIV status, and that association was fully explained by the age distribution of HIV in the source population. One-third of patients under age 50 years were HIV-positive. Those findings highlight the need for HIV testing of breast cancer patients, especially young patients, in HIV-endemic populations.

In Johannesburg in 1995–1999, HIV prevalence among both breast cancer patients and controls was 6.3 % [4]. A decade or so later, the prevalence of HIV among both breast cancer patients and the Soweto population was roughly three times higher. If that pattern applies to other HIV-endemic populations, a substantial proportion of breast cancer patients, especially young ones, may be HIV-positive, and HIV status, or at least CD4 cell count, may become an important consideration in breast cancer treatment.

Studies are needed to assess the association of HIV status with access to cancer diagnostic and treatment facilities; adherence to treatment, support or the lack of it for dual-diagnosis patients by families, communities, and health care providers, especially given the special challenges of HIV and cancer treatment. Studies are needed to determine whether cancer treatment interacts with HIV status and treatment, and how HIV status affects survival with cancer, especially among young patients. Our null findings regarding stage, grade, and molecular subtype suggest that HIV does not affect survival, but they require confirmation from follow-up studies.
| CD4 Cell Count | ≥500 cells/μl | 200–499 cells/μl | <200 cells/μl | Missing | Total | p-value** |
|---------------|---------------|------------------|---------------|---------|-------|-----------|
| N            | %  | N  | %  | N  | %  | N  | %  | N  | %  | N  | %  |
| Total        | 151 | 100.0 | 72 | 47.7 | 72 | 47.7 | 37 | 24.5 | 8 | 5.3 | 34 | 22.5 |

| Age at Breast Cancer Diagnosis | N  | %  | N  | %  | N  | %  | N  | %  | N  | %  | N  | %  |
|-------------------------------|----|-----|----|-----|----|-----|----|-----|----|-----|----|-----|
| 25–39                         | 19 | 55.9 | 31 | 43.1 | 6 | 16.2 | 6 | 16.2 | 2 | 25.0 | 37 | 24.5 |
| 40–49                         | 14 | 41.2 | 26 | 36.1 | 19 | 51.4 | 1 | 12.5 | 1 | 12.5 | 37 | 24.5 |
| 50–59                         | 1 | 2.9 | 11 | 15.3 | 9 | 24.3 | 3 | 8.1 | 2 | 25.0 | 8 | 5.3 |
| 60–69                         | 0 | 0.0 | 3 | 4.2 | 3 | 8.1 | 1 | 2.5 | 1 | 2.5 | 2 | 1.3 |
| 70–79                         | 0 | 0.0 | 1 | 1.4 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 0.7 |

| Year of Diagnosis | N  | %  | N  | %  | N  | %  | N  | %  | N  | %  | N  | %  |
|-------------------|----|-----|----|-----|----|-----|----|-----|----|-----|----|-----|
| 2006–2007         | 3 | 8.8 | 10 | 13.9 | 5 | 13.5 | 0 | 0.0 | 0 | 0.0 | 18 | 11.9 |
| 2008–2009         | 12 | 35.3 | 25 | 34.7 | 13 | 35.1 | 5 | 62.5 | 55 | 36.4 |
| 2010–2012         | 19 | 55.9 | 37 | 51.4 | 19 | 51.4 | 3 | 37.5 | 78 | 51.7 |

| Stage | N  | %  | N  | %  | N  | %  | N  | %  | N  | %  | N  | %  |
|-------|----|-----|----|-----|----|-----|----|-----|----|-----|----|-----|
| I     | 3 | 8.8 | 4 | 5.6 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 7 | 4.6 |
| IIA-B | 15 | 44.1 | 30 | 41.7 | 14 | 37.8 | 3 | 37.5 | 62 | 41.1 |
| IIIA-C | 11 | 32.4 | 14 | 37.8 | 19 | 51.4 | 4 | 50.0 | 67 | 44.4 |
| IV    | 4 | 11.8 | 5 | 6.9 | 4 | 10.8 | 1 | 12.5 | 14 | 9.3 |

| Tumor Grade | N  | %  | N  | %  | N  | %  | N  | %  | N  | %  | N  | %  |
|-------------|----|-----|----|-----|----|-----|----|-----|----|-----|----|-----|
| 1           | 5 | 14.7 | 6 | 8.3 | 3 | 8.1 | 2 | 25.0 | 16 | 10.6 |
| 2           | 12 | 35.3 | 28 | 38.9 | 12 | 32.4 | 1 | 12.5 | 53 | 35.1 |
| 3           | 10 | 29.4 | 26 | 36.1 | 14 | 37.8 | 4 | 50.0 | 54 | 35.8 |

| ER | Positive | N  | %  | N  | %  | N  | %  | N  | %  | N  | %  | N  | %  |
|    |          | 23 | 67.7 | 41 | 56.9 | 24 | 64.9 | 5 | 62.5 | 93 | 61.6 |
|    | Negative | 8 | 23.5 | 24 | 33.3 | 11 | 29.7 | 3 | 37.5 | 46 | 30.5 |
|    | Missing  | 3 | 8.8 | 7 | 9.7 | 2 | 5.4 | 0 | 0.0 | 12 | 8.0 |

| PR | Positive | N  | %  | N  | %  | N  | %  | N  | %  | N  | %  | N  | %  |
|    |          | 19 | 55.9 | 35 | 48.6 | 18 | 48.7 | 6 | 75.0 | 78 | 51.7 |
|    | Negative | 12 | 35.3 | 30 | 41.7 | 16 | 43.2 | 2 | 25.0 | 60 | 39.7 |
|    | Missing  | 3 | 8.8 | 7 | 9.7 | 3 | 8.1 | 0 | 0.0 | 13 | 8.6 |

| HER2 | 3+ | N  | %  | N  | %  | N  | %  | N  | %  | N  | %  | N  | %  |
|      | 10 | 29.4 | 20 | 27.8 | 9 | 25.0 | 2 | 25.0 | 41 | 27.2 |
|      | 4 | 11.8 | 13 | 18.1 | 10 | 29.4 | 1 | 12.5 |
| 0/1+ | 16 | 47.1 | 30 | 41.7 | 14 | 41.2 | 5 | 75.0 | 93 | 61.6 |
|      | 4 | 11.8 | 9 | 12.5 | 1 | 12.5 | 1 | 12.5 | 17 | 11.3 |

| Triple-negative | Yes | N  | %  | N  | %  | N  | %  | N  | %  | N  | %  | N  | %  |
|                | 5 | 14.7 | 14 | 19.4 | 4 | 10.8 | 1 | 12.5 | 24 | 15.9 |
|                | 25 | 73.5 | 50 | 69.4 | 30 | 81.1 | 7 | 87.5 | 112 | 74.2 |
|                | 4 | 11.8 | 8 | 11.1 | 3 | 8.1 | 0 | 0.0 | 15 | 9.9 |

| On anti-retroviral treatment | Yes | N  | %  | N  | %  | N  | %  | N  | %  | N  | %  | N  | %  |
|                             | 5 | 14.7 | 11 | 15.3 | 9 | 24.3 | 0 | 0.0 | 25 | 16.6 |
|                             | 29 | 85.3 | 61 | 84.7 | 28 | 75.7 | 8 | 100.0 | 126 | 83.4 |

* Column percents
** Non-parametric Kruskal–Wallis test for differences in non-missing proportions by CD4 cell count group
† Row percents
The similarity in HIV prevalence between breast cancer patients and the Soweto population suggests that HIV may not be related to breast cancer risk [13]. However, we did not attempt to evaluate HIV as a risk factor for breast cancer because we were unable to adjust for potentially confounding factors, such as parity, age at first birth, and body mass index, which are associated with both HIV and breast cancer [22].

We found no association of HIV with stage at diagnosis. In the future, if the facilities that provide care for HIV-positive individuals educate patients about breast cancer, or provide clinical breast examinations as part of their routine care, HIV-positive women may be more likely to be diagnosed with breast cancer at early stages than other women. However, until now, those facilities have found it difficult to provide even cervical screening, the need for which is much more widely accepted in the setting of HIV. In those respects, the HIV clinics do not differ much from the primary care clinics, which provide breast examination only on request at best.

A recent investigation has suggested that anti-HIV medication may affect breast cancer risk either by inhibiting a hypothesized preventive effect of HIV on breast cancer or by causing breast cancer cell apoptosis [23]. We found no association of breast cancer prognostic factors with ART among HIV-positive patients, but only 25 of the 151 patients, including 9 of the 37 severely immunocompromised patients, were receiving ART.

CD4 cell count was associated with age; only one of 34 patients in the high CD4 cell count group was older than 50 (2.9 %), compared with 15 of the 72 in the middle group (20.9 %), and 12 of the 37 severely immunocompromised (32.4 %). The association of age with low CD4 cell count may reflect longer duration of HIV infection.

The treatment of cancer patients with very low CD4 counts presents special problems. Most of the 37 HIV-positive patients with very low counts (62.2 %) were diagnosed in stage III or IV, compared to 32.1 % of other HIV-positive patients ($p = 0.003$). Patients with late stage cancers usually receive aggressive chemotherapy, but without ART cover such treatment may be rapidly fatal for patients with low CD4 cell counts. Giving ART and waiting for the CD4 cell count to rise before providing chemotherapy is also risky. We believe that the safest approach is to initiate chemotherapy after initiating ART. Modifications of standard regimens for patients with the

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two diagnoses have been proposed, but evidence for the safety or efficacy of such modifications, compared to alternatives, is lacking [24, 25]. Clinical studies are needed to address this issue, but they are unlikely to be undertaken in the near future.

A limitation of our study is that nearly 30% of the patients had not been tested for HIV at diagnosis, but only 20% of patients under age 50, who were more likely to be HIV-positive, were untreated. Only one of 105 tested women older than 70 years was HIV-positive; hence, almost all the untreated older women were probably HIV-negative. However, we strongly encourage all patients to be tested prior to treatment, and since 2007, the proportion of untreated patients has declined by 50%.

Another limitation is that more than 10% of patients were missing the data on grade and receptor status. Larger proportions of patients not tested than of patients tested for HIV were missing those data. Missing data is a problem in many other settings, even in more affluent countries, but one of the purposes of the database was to help the team measure up to international standards, and efforts are being made to ensure completeness of record keeping.

Although, the care we provide is comparable to that in tertiary care facilities in more affluent countries, this analysis focuses on patient presentation, not on outcomes. We believe that our patients are similar to those in other low-income urban HIV-endemic populations in Africa and that our findings are therefore generalizable. We are currently extending our database to include long-term follow-up of patients. Other teams of investigators elsewhere in South Africa are also developing databases so as to study HIV patterns in the setting of breast cancer. In the next few years, we hope that these data will shed light on the optimal measure up to international standards, and efforts are being made to ensure completeness of record keeping.

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Conflict of interest The authors declare that they have no conflict of interest.

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