Barriers to early presentation of breast cancer among women in Soweto, South Africa

Maureen Joffe1,2*, Oluwatosin Ayeni1, Shane Anthony Norris1,2, Valerie Ann McCormack3‡, Paul Ruff1,4, Ishani Das5‡, Alfred I. Neugut5,6,7‡, Judith S. Jacobson7‡, Herbert Cubasch1,8

1 Non-Communicable Diseases Research Division, Wits Health Consortium (PTY) Ltd, Johannesburg, South Africa, 2 MRC Developmental Pathways to Health Research Unit, Department of Pediatrics, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa, 3 Section of Environment and Radiation, International Agency for Research on Cancer, Lyon, France, 4 Division of Medical Oncology, Department of Internal Medicine, University of Witwatersrand Faculty of Health Sciences, Johannesburg, South Africa, 5 Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY, United States of America, 6 Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY, United States of America, 7 Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, United States of America, 8 Department of Surgery, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa

* These authors contributed equally to this work.
‡ These authors also contributed equally to this work.

Abstract

Purpose

Reported breast cancer incidence is rising in South Africa, where some women are diagnosed late and have poor outcomes. We studied patient and provider factors associated with clinical stage at diagnosis among women diagnosed at the Chris Hani Baragwanath Academic Hospital in Soweto, Johannesburg in 2015–2016.

Methods

From face-to-face interviewer-administered questionnaires we compared self-reported socioeconomics, demographics, comorbidities, risk factors, personal and health system barriers, and from patient clinical records, clinical staging, receptor subtype, and tumor grade among 499 consecutive women newly diagnosed with advanced stage (III/IV) breast cancer versus those diagnosed early (stage 0/I/II). Logistic regression models were used to identify factors associated with advanced stage at diagnosis.

Results

Among the women, 243 (49%) were diagnosed at early and 256 (51%) at advanced stages. In the multiple logistic regression adjusted model, completion of high school or beyond (odds ratio (OR) 0.59, and greater breast cancer knowledge and awareness (OR 0.86) were associated with lower stage of breast cancer at presentation. Advanced stage was associated with Luminal B (OR 2.25) and triple-negative subtypes (OR 3.17) compared to luminal A, with delays >3 months from first breast symptoms to accessing the health system (OR...
staging and improving survival of breast cancer in South Africa" http://www.cansa.org.za/down-staging-and-improving-survival-of-breast-cancer-in-sa-dr-herbert-cubasch (Dr Cubasch). Dr Norris is supported by the DST-NRF Centre of Excellence in Human Development at the University of the Witwatersrand, Johannesburg, South Africa https://www.wits.ac.za/coe-human. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The Wits Health Consortium (PTY) Ltd provided support in the form of payroll administration of salaries from grant funds for authors M Joffe, O Ayeni and S Norris, but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The specific roles of these authors are articulated in the ‘author contributions’ section.

Competing interests: The commercial affiliation to the Wits Health Consortium (PTY) Ltd (WHC) of authors M Joffe, O Ayeni, S Norris, P Ruff and H Cubasch does not alter our adherence to PLOS ONE policies on sharing data and materials.

Conclusions

Limited patient education, breast cancer knowledge and awareness, and health system inefficiencies were associated with advanced stage at diagnosis. Sustained community and healthcare worker education may down-stage disease and improve cancer outcomes.

Introduction

Breast cancer is the most common cancer among women and a major cause of cancer deaths in women worldwide [1, 2]. Although breast cancer was once considered a disease of affluence, its reported incidence is rising rapidly in low- and middle-income countries (LMICs), such as South Africa (SA). In recent years, with the expanded ARV rollout, SA’s HIV control and life expectancy have dramatically improved, whilst its non-communicable disease burden is growing[1, 3, 4]. An upper middle-income country (UMIC), with an annual per capita Purchasing Power Parity (PPP) gross domestic product of approximately US$13,500[5, 6], SA has a better developed healthcare system than most sub-Saharan African countries. Its private sector facilities are comparable to those of high income countries (HICs), and its public sector facilities, serving approximately 85% of the population, include a number of relatively well equipped and staffed academic hospitals.

The published age-standardized annual breast cancer incidence rate (ASR) per 100,000 is 29.1 among black SA women, much lower than the rates among mixed race, Asian and white SA women (52.9–79.3), and amongst USA black (125.1) and white women (127.7) [1, 7–10]. Yet SA breast cancer mortality rates among socioeconomically disadvantaged patients, although poorly reported, are assumed to be high [11, 12]. This is partly due to more than 70% of patients being diagnosed with advanced stage disease in rural and urban health care settings [3, 13–16]. In the USA, black women also have higher breast cancer-specific mortality rates than do white women [17]. Younger age at presentation and greater proportions of more aggressive breast cancer subtypes are also thought to contribute to those higher mortality rates. [8, 9, 14, 17–21]. Yet Johannesburg and South African National Cancer Registry (SANCR) data reveal that, like USA women, more than 60% of SA women, regardless of race, are diagnosed with estrogen receptor-positive (ER+) tumors [14, 21]. Hence outcomes should improve among SA women if they do not encounter delays in their diagnosis and treatment.

Despite the large proportion of women who present with late stage disease in SA, we observed an encouraging down-staging of invasive breast cancer diagnosed at the Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto, Johannesburg, between 2007 and 2012. The proportion of stage I and II cancers increased over that time interval from approximately 30% to more than 50% [22]. We attributed this improvement to the implementation of an open access clinic and successful breast cancer awareness campaigns. But we still fall well short of the 80–90% proportion of early-stage disease reported for HICs[2]. The personal, societal and health system barriers that impact stage at diagnosis are not well understood in our setting. It is hoped that modifiable factors identified may be addressed in future intervention studies applicable to urban patients treated at CHBAH and to disadvantaged patients from other regions of the country. Prior studies from LMICs and HICs suggest that various patient and health system factors may affect the timeliness of breast cancer diagnosis [4, 23–32]. To
inform future interventional work, we undertook a study of socio-demographic, clinical, lifestyle, and health system factors associated with advanced-stage diagnosis of breast cancer at CHBAH.

**Methods**

**Study population**

CHBAH is a public academic hospital located in Soweto, in the southwestern part of Johannesburg, South Africa. It serves as the referral facility for approximately 3 million people who live within a 60 km radius of the hospital, as well as for patients from farther afield.

In SA’s hierarchical referral system, doctors and nurses at primary care clinics refer patients with breast conditions either directly to an academic tertiary hospital or to a local secondary hospital, which can provide general hospital care and some diagnostic services and can refer patients who need more advanced care to a tertiary hospital. CHBAH has a specialized Surgical Breast Unit where currently 25–35 patients per month are diagnosed with breast cancer.

**Recruitment and data collection**

In this cross-sectional survey, from January 8, 2015, through December 31, 2016, at the CHBAH, 499 consecutive female patients who were 18+ years and newly diagnosed with stage 0-IV breast carcinoma completed an informed, written consent and were enrolled into our study. We had no refusals to participate; therefore our study represents all women who presented at the clinic during this time period. Self-reported socioeconomic and demographic variables were collected, namely date of birth from which age at diagnosis was determined, marital status, highest education level completed, household possession score (determined from home ownership, car ownership, microwave, washing machine, indoor running water, flush toilet inside home with calculations described in the legend to Table 1), employment status and parity (full-term pregnancies). Lifestyle risk factors (BMI, calculated from weight and height measurements, self-reported alcohol consumption, smoking, hypertension, diabetes, and cardiovascular disease) and clinical data (HIV status measured by the ELISA test, intrinsic breast cancer subtypes, grade, and clinical staging) were recorded. Intrinsic breast cancer subtyping included Allred scoring for definition of estrogen and progesterone receptor (ER and PR) status [33]. Luminal A subtypes were defined as ER / PR+ HER2-negative and Ki67 \( \leq 15\% \); Luminal B as ER/ PR+ HER2-positive and/or Ki67 > 15%; HER2-enriched as ER/PR- and HER2- positive; and triple negative as ER/PR- and HER2-negative.

The University of the Witwatersrand Human Research Ethics Committee (HREC) Medical approved the study (M141102, dated January 7, 2015. Clinical data were extracted from the electronic clinical records in the CHBAH Breast Unit and linked to the Barriers to Care questionnaire described below. The anonymized data set used for the analysis is provided as supporting information, S1 Table).

**Barriers to care questionnaire**

The Barriers to Care questionnaire was developed from a literature review on barriers to early-stage presentation of breast cancer among women from LMICs (which referenced validated survey instruments for HICs), considering specific parameters unique to CHBAH. Key themes emerged around awareness of breast cancer and its risk factors[34–39], attitudes toward breast cancer and health-seeking behavior[40–46] and personal and health system barriers to accessing care[47–60]. Two focus group sessions, each comprising 15 former breast cancer patients were undertaken. They reiterated the emergent themes from the literature and supported their
Table 1. Comparison of the socio-demographic, clinical and lifestyle characteristics, knowledge and awareness of breast cancer and health system barriers among patients diagnosed with early and late stage disease at the CHBAH breast clinic.

|                          | Total (N = 499) | Early stage (0-II) (N = 243) | Late stage (III & IV) (N = 256) | ρ- value | Chi square Statistic/DF |
|--------------------------|----------------|-------------------------------|---------------------------------|----------|------------------------|
| **SOCIO-DEMOGRAPHIC CHARACTERISTICS** |                |                               |                                 |          |                        |
| **Age**                  |                |                               |                                 |          |                        |
| <40                      | 69 (13.8)      | 23 (9.4)                      | 46 (18.0)                       | 0.013    | 12.6788                |
| 40–49                    | 124 (24.8)     | 58 (23.9)                     | 66 (25.8)                       | DF = 4   |                        |
| 50–59                    | 120 (24.1)     | 59 (24.3)                     | 61 (23.8)                       |          |                        |
| 60–69                    | 102 (20.4)     | 62 (25.5)                     | 40 (15.6)                       |          |                        |
| 70 and above             | 84 (16.8)      | 41 (16.9)                     | 43 (16.8)                       |          |                        |
| **Marital status**       |                |                               |                                 |          |                        |
| Single                   | 119 (24.0)     | 55 (22.7)                     | 64 (25.2)                       | 0.736    | 0.6133                 |
| Married/co-habiting      | 216 (43.6)     | 105 (43.4)                    | 111 (43.7)                      | DF = 2   |                        |
| Divorced/widowed         | 161 (32.4)     | 82 (33.9)                     | 79 (31.1)                       |          |                        |
| **Level of education**   |                |                               |                                 |          |                        |
| Completion of Informal / Primary | 142 (28.5)     | 56 (23.1)                     | 86 (33.6)                       | 0.010    | 6.6688                 |
| Completion of High school/ any tertiary education | 348 (71.5)     | 186 (76.9)                    | 170 (66.4)                      | DF = 1   |                        |
| **Household socioeconomic status** |            |                               |                                 |          |                        |
| Mean ± S.D.              | 3.71 ± 1.63    | 3.88 ± 1.65                   | 3.54 ± 1.60                     | 0.0226   | Test stat 2.287        |
|                          |                |                               |                                 |          | DF = 497               |
| **Employment status**    |                |                               |                                 |          |                        |
| Unemployed               | 229 (45.9)     | 118 (48.5)                    | 111 (43.4)                      | 0.244    | 2.8184                 |
| Employed                 | 136 (27.2)     | 58 (23.9)                     | 78 (30.5)                       | DF = 2   |                        |
| Retired                  | 134 (26.9)     | 67 (27.6)                     | 67 (26.1)                       |          |                        |
| **Parity**<sup>b</sup> (Mean ± S.D.) | 3.00 ± 1.84 | 2.84 ± 1.68 | 3.15 ± 1.97 | 0.064 | t = -1.8596 DF = 469 |
| **CLINICAL & LIFESTYLE FACTORS** |                |                               |                                 |          |                        |
| **BMI**<sup>b</sup> (Mean ± S.D.) | 31.42 ± 7.85 | 31.77 ± 6.98 | 31.08 ± 8.63 | 0.337 | 0.9645 DF = 468      |
| **Alcohol consumption**  |                |                               |                                 |          |                        |
| Yes                      | 100 (20.0)     | 50 (20.6)                     | 50 (19.5)                       | 0.771    | 0.0849                 |
| No                       | 399 (80.0)     | 193 (79.4)                    | 206 (80.5)                      | DF = 1   |                        |
| **Smoking**              |                |                               |                                 |          |                        |
| Yes                      | 35 (7.0)       | 21 (8.6)                      | 14 (5.5)                        | 0.165    | 1.9247                 |
| No                       | 464 (93.0)     | 222 (91.4)                    | 242 (94.5)                      | DF = 1   |                        |
| **Hypertension**         |                |                               |                                 |          |                        |
| Yes                      | 200 (40.3)     | 113 (46.7)                    | 87 (34.3)                       | 0.005    | 7.9727                 |
| No                       | 296 (59.7)     | 129 (53.3)                    | 167 (65.7)                      | DF = 1   |                        |
| **HIV Status**           |                |                               |                                 |          |                        |
| Positive                 | 113 (22.7)     | 44 (18.9)                     | 69 (28.6)                       | 0.013    | 6.1983                 |
| Negative                 | 361 (72.3)     | 189 (81.1)                    | 172 (71.4)                      | DF = 1   |                        |
| Unknown                  | 25             | 10                            | 15                              |          |                        |
| **Receptor subtype–intrinsic** |          |                               |                                 |          |                        |
| Luminal A                | 54 (10.9)      | 31 (12.9)                     | 23 (9.0)                        | 0.276    | 3.8707                 |
| Luminal B                | 350 (70.6)     | 171 (71.0)                    | 179 (70.2)                      | DF = 3   |                        |
| HER2 enriched            | 33 (6.6)       | 16 (6.6)                      | 17 (6.7)                        |          |                        |

(Continued)
relevance to our Soweto urban setting. Ten research and nursing staff then developed the 24 item questionnaire that covered 8 major domains, namely awareness and knowledge of breast cancer (9 questions); personal hurdles/barriers to seeking help (2 questions); family hurdles (3 questions); community hurdles (1 question); cultural hurdles (2 questions); economic hurdles (4 questions); and health system barriers to care (3 questions). Yes, no and unsure were response options to questions asked and a five point agreement Likert Scale (strongly disagree, disagree, unsure/neutral, agree, strongly agree) was used to measure respondents’ agreement with statements used in the questionnaire (provided as supplementary information, S1 Text).

The knowledge and awareness score (0–9) was calculated from summations of 1 and 0 values assigned respectively for yes and no answers to questions and for correct and incorrect agreements to statements (irrespective of strength of agreement). The participant pathways in the referral health system were probed in detail covering choice of initial consultation, referral within the primary and secondary healthcare facilities, and the number of visits experienced prior to reaching the CHBAH Breast Clinic. We queried time intervals between symptom awareness and visits to healthcare facilities for diagnosis and treatment and between all visits prior to reaching CHBAH, and asked about personal reasons for delays longer than 1 month.

We also probed causes for delays within the referral network. We evaluated the understanding of each question by the research team and former patients and made adjustments for local context and language usage. Finally the reliability of the questionnaire was verified using the test re-test methodology on 36 consenting participants. The questionnaire was repeated and answers compared within 2–4 weeks following the baseline visit. In each case the interview was conducted by the same interviewer who administered the first questionnaire. Scores from the first interview were compared to those from the second interview using Cohen’s kappa coefficient (k). The coefficient ranged from 0.7030 to 1.000 indicating substantial to perfect agreement.

Table 1. (Continued)

|                      | Total | Early stage (0-II) | Late stage (III & IV) | p-value | Chi square Statistic/DF |
|----------------------|-------|--------------------|-----------------------|---------|------------------------|
| N = 499(%) N = 243 (%) N = 256 (%) |       |                    |                       |         |                        |
| TRIPLE NEGATIVE      | 59 (11.9) | 23 (9.5) | 36 (14.1) |       |                        |
| Grade                |        |                    |                       |         |                        |
| Low/intermediate     | 275 (59.0) | 133 (60.2) | 142 (58.0) | 0.626 | 0.2371 DF = 1           |
| High                 | 191 (41.1) | 88 (39.8) | 103 (42.0) |       |                        |
| Unknown              | 33     | 22                | 11                    |         |                        |
| KNOWLEDGE (score 0–9) |       |                    |                       |         |                        |
| Mean ± S.D           | 5.86 ± 1.88 | 6.20 ± 1.73 | 5.53 ± 1.97 | 0.0001 | DF = 497               |
| HEALTH SYSTEM FACTORS |       |                    |                       |         |                        |
| Prior clinical breast examination |   |                     |                       |         |                        |
| None/Self            | 481 (96.4) | 233 (95.9) | 248 (96.9) | 0.553 | 0.3516 DF = 1           |
| Clinician            | 18 (3.6) | 10 (4.1) | 8 (3.1) |       |                        |
| Clinical waiting times as a barrier | |                     |                       |         |                        |
| Yes                  | 42 (8.4) | 23 (9.5) | 19 (7.4) | 0.411 | 0.675 DF = 1           |
| No                   | 457 (1.6) | 220 (90.5) | 237 (92.6) |       |                        |
|                      |         |                    |                       |         |                        |
|                      |         |                    |                       |         |                        |

4HOUSEHOLD SOCIO-ECONOMIC STATUS (possessions) score’ determined from: (Home ownership = 1, Car ownership = 1, Microwave = 1, Washing machine = 1, Indoor running water = 1, Flush toilet inside home = 1. Denominator = 6 (1 for Yes, 0 for No)

5Analyzed as continuous variables DF = Degrees of freedom.

6SELF-REPORTED KNOWLEDGE/ AWARENESS OF BREAST CANCER: 1 was allocated for every correct answer, 0 for wrong answer or don’t know for each of 9 questions probing knowledge of breast cancer and symptoms.

https://doi.org/10.1371/journal.pone.0192071.t001
agreement except for one question with a k of 0.5567 which indicates moderate agreement. (The questionnaire is provided as supplementary information, S1 Text). The survey was completed via one-on-one, face-to-face interviews between participants and a trained, multi-lingual study interviewer in a private room. Interviews were conducted in English and in the mother tongue of participants as required. Patients were grouped by stage at diagnosis as early (0-II) or advanced (III-IV). We compared the patient groups with respect to demographic, socioeconomic and clinical characteristics and responses to the Barriers to Care questionnaire. From the ‘barrier to care’ questionnaire data, we categorized women by time between awareness of a breast symptom and first visit to a health care facility and by the types of health care facilities they visited prior to CHBAH: self-referral directly to CHBAH or after a primary care clinic visit or referral from a primary care clinic to a secondary care hospital before CHBAH. We also grouped patients by the number of visits to each type of facility.

Statistical analysis
We used the Pearson chi squared and Fisher’s exact tests to examine differences in the proportion of early/advanced stage between categorical variables. We computed means and medians for continuous variables and used Student’s t-test and the Wilcoxon rank-sum test to determine differences between groups in means and medians, respectively. To examine associations with advanced stage, we then developed multivariable logistic regression models of factors. We included in the multivariate models variables for which p-values were <0.1 in bivariate analysis. ORs were examined in 4 models by adding in a stepwise fashion, factors of influence (for socio-demographic, clinical and lifestyle, knowledge and awareness, and health system) to examine the association between these factors and advanced presentation of breast cancer. Analysis was performed using Stata version 14 (StataCorp Ltd, Texas, USA).

Results
Of the 499 enrolled women, 243 (48.7%) were diagnosed with early-stage disease (0-II), including 11 (4.5%) with in-situ cancers and 256 (51.3%) with advanced-stage disease (III-IV). Characteristics of the cohort are summarized in Table 1.

Although age overall was not associated with advanced stage at diagnosis, women <40 years had a higher risk of diagnosis at an advanced stage than women >40 years (p = 0.013). Other factors that initially appeared to be associated with advanced-stage disease were no high school education, lower household socio-economic status, higher parity, lower score on self-reported knowledge and awareness of breast cancer, no hypertension, and HIV co-infection. Table 2 describes the association of personal delays and health system factors with advanced-stage diagnosis.

Women who reported a delay of >1 month between identifying breast symptoms and their first visit to the health system were more likely than those who made the first visit sooner to be diagnosed at a late stage (p< 0.001). As shown in Table 3, the two most commonly stated reasons for delays were fear of diagnosis or treatment and failure to recognize that breast symptoms were serious. Other reasons were conflicting commitments, such as caring for sick family members and transport problems.

Most participants (64.7%) referred themselves to CHBAH or were referred directly by a primary care clinic or a private general practitioner, bypassing the secondary hospitals. Among those patients, more than half had only one visit prior to diagnosis, and those with more visits before reaching CHBAH were more likely to be diagnosed at a late stage (p <0.001). Among patients seen at secondary hospitals, more than 80% had at least 3 visits prior to diagnosis and the actual number of visits had no further impact on stage at presentation. Repeat visits within
the referral system appear to have been caused by failure to diagnose and delays with appointments and test results. The details are provided as supporting information S2 Table.

In the bivariate analysis Table 4, those who completed high school/any tertiary education were at lower risk for advanced-stage presentation (OR = 0.60, 95%CI: 0.40–0.88) than those who had informal or only primary school education. For every unit increase in parity there was a borderline higher risk of advanced stage presentation, (OR 1.10, 95%CI: 0.99–1.21).

Those treated for hypertension were found to be at lower risk for advanced stage at diagnosis (OR = 0.59, 95%CI: 0.41–0.85) as were those with greater knowledge and awareness of breast cancer.

Table 2. Descriptive statistics for patients presenting with early compared with late stage breast cancer at CHBAH breast clinic that experienced personal and/or health system delays.

|                      | Total   | Early stage (0–11) | Late stage (III & IV) | p- value | Chi-square Statistic/DF |
|----------------------|---------|--------------------|-----------------------|----------|-------------------------|
| Time to first presentation to HS | N = 499 (%) | N = 243 (%) | N = 256 (%) |          |                          |
| < 1 month            | 307 (61.5) | 173 (71.2) | 134 (52.3) | <0.001   | 22.881                  |
| 1–3 months           | 64 (12.8)  | 30 (12.3)   | 34 (13.3)   | DF = 2   |                          |
| >3 months            | 128 (25.7) | 40 (16.5)   | 88 (34.4)   | DF = 2   |                          |
| Residential distance from CHBAH |          |                |              |          |                          |
| < 10km               | 206 (41.3) | 105 (43.2) | 101 (39.5) | 0.328    | 2.2277                  |
| 10–20km              | 104 (20.8) | 54 (22.2)  | 50 (19.5)   | DF = 2   |                          |
| >20km                | 189 (37.9) | 84 (34.6)  | 105 (41.0)  | DF = 2   |                          |
| Number of HS visits before reaching CHBAH |          |                |              |          |                          |
| 0–1                  | 257 (51.5) | 145 (59.7) | 112 (43.8) | 0.002    | 12.661                  |
| 2                    | 73 (14.6)  | 30 (12.3)  | 43 (16.8)   | DF = 2   |                          |
| ≥3                   | 169 (33.9) | 68 (28.0)  | 101 (39.4)  | DF = 2   |                          |
| Referral mode to CHBAH |        |                |              |          |                          |
| Self + primary-direct | 323 (64.7) | 166 (68.3) | 157 (61.3) | 0.103    | 2.639                   |
| Primary/secondary-indirect | 176 (35.3) | 77 (31.7)  | 99 (38.7)   | DF = 1   |                          |
| Self/primary (direct) | 323 (64.7) | 166 (68.3) | 157 (61.3) | <0.001   | 15.439                  |
| 0–1 visits–self-primary | 251 (77.7) | 143(86.1)  | 108 (68.8)  | DF = 2   |                          |
| 2 visits self/primary | 49 (15.2)  | 18 (10.9)  | 31 (19.7)   | DF = 2   |                          |
| ≥3 visits self/primary | 23 (7.1)   | 5 (3.0)    | 18 (11.5)   | DF = 2   |                          |
| Primary/secondary (indirect) | 176 (35.3) | 77 (31.7)  | 99 (38.7)   | 0.716    | 0.6618                   |
| 0–1 visits primary/secondary | 6 (3.4) | 2 (2.6) | 4 (1.1) | DF = 2 |                          |
| 2 visits primary/secondary | 24 (13.6) | 12 (15.6) | 12 (12.1) | DF = 2 |                          |
| ≥3 visits primary/secondary | 146 (83.0) | 63 (81.8) | 83 (83.8) | DF = 2 |                          |

Table 3. Reasons for personal delays into the health system.

| Reasons for delay | Early stage | Late stage | Total |
|-------------------|-------------|------------|-------|
|                   | N = 243 (%) | N = 256 (%) | N = 499 (%) |
| No delay          | 173         | 136        | 309   |
| Fear of diagnosis | 13          | 20         | 33    |
| Thought it was minor ailment | 56         | 96         | 152   |
| No one to look after the children | 0          | 3          | 3     |
| Worried no money for treatment | 1          | 1          | 2     |
| Total             | 243         | 256        | 499   |

https://doi.org/10.1371/journal.pone.0192071.t003

https://doi.org/10.1371/journal.pone.0192071.t002
Table 4. Bivariate analysis of variables associated with late stage presentation amongst patients diagnosed with breast cancer at the CHBAH Breast Clinic from 2014–2016.

| Variables | Bivariate analysis | OR (95% CI) | P-value* |
|-----------|--------------------|-------------|----------|
| **SOCIO-DEMOGRAPHIC CHARACTERISTICS** | | | |
| **Age** | | | |
| < 40 | | 1.93 (1.05–3.58) | 0.0120 |
| 40–49 | | 1.10 (0.67–1.82) | |
| 50–59 | Reference | | |
| 60–69 | | 0.62 (0.37–1.07) | |
| 70 and above | | 1.01 (0.58–1.77) | |
| **Marital status** | | | |
| Single | | 1.10 (0.70–1.72) | 0.7358 |
| Married/co-habiting | Reference | | |
| Divorced/widowed | | 0.91 (0.61–1.37) | |
| **Level of education** | | Reference | 0.0096 |
| Completion of Informal / Primary | | | |
| Completion of High school/ any tertiary education | | 0.60 (0.40–0.88) | |
| **Household socioeconomic status** | | 0.90 (0.82–0.98) | 0.0214 |
| **Employment status** | | Reference | 0.2433 |
| Unemployed | | | |
| Employed | | 1.43 (0.93–2.19) | |
| Retired | | 1.06 (0.69–1.63) | |
| **Parity** | | 1.10 (0.99–1.21) | 0.0624 |
| **CLINICAL AND LIFESTYLE FACTORS** | | Reference | |
| **BMI** | | 0.99 (0.97–1.01) | 0.3353 |
| **Smoking** | | Reference | |
| No | | | |
| Yes | | 0.61 (0.30–1.23) | 0.164 |
| **Alcohol consumption** | | Reference | |
| No | | | |
| Yes | | 0.94 (0.60–1.45) | 0.7707 |
| **Hypertension** | | Reference | |
| No | | | |
| Yes | | 0.59 (0.41–0.85) | 0.0047 |
| **HIV Status** | | Reference | |
| Negative | | | |
| Positive | | 1.72 (1.12–2.65) | 0.1125 |
| **Intrinsic receptor subtype–IHC** | | Reference | |
| Luminal A | | | |
| Luminal B | | 1.86 (1.10–3.14) | 0.0450 |
| HER2 enriched | | 1.77 (0.77–4.07) | |
| Triple negative | | 2.61 (1.69–5.30) | |
| **KNOWLEDGE/AWARENESS SCORE (0–9)** | | 0.82 (0.74–0.91) | 0.0001 |
| **HEALTH SYSTEM FACTORS** | | Reference | |
| Prior clinical breast examination | | | |
| Clinician | | | |
| None/self | | 1.33 (0.52–3.43) | 0.5531 |
| **Clinic waiting times barrier to attendance** | | | |

(Continued)
cancer (OR = 0.82, 95%CI: 0.74–0.91). Patients aged <40 years (OR = 1.93, 95%CI: 1.05–3.58) and those with luminal B and triple negative breast cancer subtypes (OR = 1.86, 95%CI: 1.10–3.14 and OR = 2.61, 95%CI: 1.69–5.30 respectively) were at higher risk for advanced stage at diagnosis than those with a luminal A subtype. Those who reported having taken >3 months after noting a breast symptom to visit a healthcare facility (OR = 2.84, 95%CI: 1.84–4.39) were also at higher risk for advanced-stage disease at diagnosis than patients who had taken less than one month. Those who had more than one visit prior to reaching CHBAH also were more likely to be diagnosed at an advanced stage than patients who had no more than one visit (mainly those who had self and direct clinic referral to CHBAH).

Associations significant at the bivariate level were further explored in Table 5 in individual and combined multiple logistic regression models 1–4 and 5–7 respectively. Socio-demographic factors (model 1) independently explained 4% of the variance and were shown to influence the likelihood of advanced stage at diagnosis in part by younger age and decreased level of education. Clinical and lifestyle factors (model 2) explained 3% of the variance, with Luminal B and Triple Negative having greater odds of advanced-stage presentation than Luminal A subtype. Greater knowledge and awareness of breast cancer had a lower odds for advanced-presentation (OR 0.82, 95%CI: 0.74–0.91) and explained just over 2% of the variance (model 3). Health system factors (model 4) explained 6% of the variance with patient delays >3 months having more than 3 times greater odds for advanced stage–presentation. In addition patients experiencing >2 referral health system visits had greater than twice the odds for advanced-stage presentation compared with those having 0 visits (self-referrals) and 1 visit (within the primary health system). In the final model with all factors included (model 7), 13% of the variance was explained. Notably, the associations of advanced stage with lower education, tumour subtype, and health system factors were not attenuated upon adjustment; the association with a lower knowledge score was slightly attenuated, whereas associations with

Table 4. (Continued)

| Variables                                      | Bivariate analysis | P-value* |
|------------------------------------------------|-------------------|----------|
| No                                             | OR (95% CI)       |          |
| Yes                                            | 0.77 (0.41–1.45)  | 0.411    |
| Time to first presentation to health system    |                   |          |
| <1 month                                       | Reference         | <0.001   |
| 1–3 months                                     | 1.46 (0.85–2.51)  |          |
| >3 months                                      | 2.84 (1.84–4.39)  |          |
| Residential distance from CHBAH               |                   |          |
| <10km                                          | Reference         | 0.3278   |
| 10–20km                                        | 0.96 (0.6–1.5)    |          |
| >20km                                          | 1.3 (0.9–1.9)     |          |
| Referral HS visits prior to CHBAH              |                   |          |
| 0–1                                            | Reference         | 0.0017   |
| 2                                              | 1.86 (1.10–3.14)  |          |
| ≥3                                             | 1.92 (1.30–2.85)  |          |
| Referral mode to CHBAH                        |                   |          |
| Self + primary–direct route                    | Reference         | 0.1023   |
| Primary/secondary–indirect route               | 1.36 (0.94–1.97)  |          |

*Variables at p<0.1 on bivariate analysis are presented in boldface and were considered in the multiple logistic regression model analysis.

IHC: Immunohistochemistry.

https://doi.org/10.1371/journal.pone.0192071.t004
Table 5. Multiple logistic regression models of factors influencing late stage disease presentation among patients diagnosed with breast cancer at CHBAH Breast Clinic 2014–2016.

| Variables                        | Bivariate analysis OR (95% CI) | Model 1 Sociodemographic (SD) OR (95% CI) | Model 2 Clinical & Lifestyle (CL) OR (95% CI) | Model 3 Knowledge & Awareness (K) OR (95% CI) | Model 4 Health System (H) OR (95% CI) | Model 5 SD +CL OR (95% CI) | Model 6 SD + K OR (95% CI) | Model 7 SD+CL+HS OR (95% CI) |
|----------------------------------|-------------------------------|------------------------------------------|-------------------------------------------|------------------------------------------|-----------------------------------|--------------------------------|------------------------|---------------------------|
| SOCIO-DEMOGRAPHIC                |                               |                                          |                                            |                                          |                                   |                               |                        |                           |
| Age                              |                               |                                          |                                            |                                          |                                   |                               |                        |                           |
| < 40                             | 1.93 (1.05–3.58)              | 2.16 (1.09–4.27)                        | 1.77 (0.84–3.70)                         | 1.81 (0.86–3.83)                      | 1.74 (0.80–3.80)                  |                               |                        |                           |
| 40–49                            | 1.10 (0.67–1.82)              | 1.30 (0.76–2.23)                        | 1.08 (0.60–1.94)                         | 1.10 (0.61–2.00)                      | 1.02 (0.55–1.89)                  |                               |                        |                           |
| 50–59                            | Referent                      | Referent                                 | Referent                                 | Referent                               | Referent                          |                               |                        |                           |
| 60–69                            | 0.62 (0.37–1.07)              | 0.57 (0.32–0.99)                        | 0.66 (0.35–1.24)                         | 0.65 (0.34–1.24)                      | 0.79 (0.40–1.54)                  |                               |                        |                           |
| 70 and above                     | 1.01 (0.58–1.77)              | 0.78 (0.42–1.44)                        | 0.93 (0.47–1.86)                         | 0.90 (0.45–1.81)                      | 1.03 (0.50–2.16)                  |                               |                        |                           |
| Education level                  |                               |                                          |                                            |                                          |                                   |                               |                        |                           |
| Informal/primary                 | Referent                      | Referent                                 | Referent                                 | Referent                               | Referent                          |                               |                        |                           |
| ≥ High school                    | 0.60 (0.40–0.88)              | 0.52 (0.33–0.82)                        | 0.52 (0.32–0.85)                         | 0.57 (0.34–0.95)                      | 0.59 (0.35–1.00)                  |                               |                        |                           |
| Household socioeconomic          | 0.90 (0.82–0.98)              | 0.94 (0.85–1.04)                        | 0.96 (0.84–1.09)                         | 0.99 (0.87–1.13)                      | 0.99 (0.87–1.14)                  |                               |                        |                           |
| Parity                           | 1.10 (0.99–1.21)              | 1.12 (1.00–1.25)                        | 1.11 (0.98–1.26)                         | 1.11 (0.97–1.26)                      | 1.13 (0.98–1.29)                  |                               |                        |                           |
| CLINICAL & LIFESTLE              |                               |                                          |                                            |                                          |                                   |                               |                        |                           |
| HIV status                       |                               |                                          |                                            |                                          |                                   |                               |                        |                           |
| Negative                         | Referent                      | Referent                                 | Referent                                 | Referent                               | Referent                          |                               |                        |                           |
| Positive                         | 1.72 (1.12–2.65)              | 1.48 (0.92–2.36)                        | 1.49 (0.88–2.51)                         | 1.47 (0.87–2.48)                      | 1.53 (0.89–2.65)                  |                               |                        |                           |
| Treated hypertension             |                               |                                          |                                            |                                          |                                   |                               |                        |                           |
| No                               | Referent                      | Referent                                 | Referent                                 | Referent                               | Referent                          |                               |                        |                           |
| Yes                              | 0.59 (0.41–0.85)              | 0.68 (0.46–1.02)                        | 0.69 (0.43–1.10)                         | 0.66 (0.41–1.06)                      | 0.63 (0.38–1.04)                  |                               |                        |                           |
| BMI (continuous)                 | 0.99 (0.97–1.01)              | 1.00 (0.97–1.02)                        | 1.00 (0.97–1.02)                         | 0.99 (0.97–1.02)                      | 1.00 (0.97–1.03)                  |                               |                        |                           |
| Intrinsic receptor subtype       |                               |                                          |                                            |                                          |                                   |                               |                        |                           |
| Luminal A                        | Referent                      | Referent                                 | Referent                                 | Referent                               | Referent                          |                               |                        |                           |
| Luminal B                        | 1.86 (1.10–3.14)              | 1.93 (1.10–3.39)                        | 1.75 (0.96–3.17)                         | 1.80 (0.99–3.29)                      | 2.25 (1.18–4.29)                  |                               |                        |                           |
| HER2-enriched                    | 1.77 (0.77–4.07)              | 1.48 (0.92–2.36)                        | 1.30 (0.51–3.33)                         | 1.34 (0.52–3.45)                      | 1.34 (0.50–3.59)                  |                               |                        |                           |
| Triple negative                  | 2.61 (1.69–5.30)              | 3.17 (1.48–6.80)                        | 2.67 (1.20–5.95)                         | 2.73 (1.21–6.15)                      | 3.17 (1.36–7.43)                  |                               |                        |                           |
| KNOWLEDGE & AWARENESS            |                               |                                          |                                            |                                          |                                   |                               |                        |                           |
| Score (0–9)                      | 0.82 (0.74–0.91)              | 0.82 (0.74–0.91)                        | 0.84 (0.75–0.94)                         | 0.86 (0.76–0.97)                      |                                   |                               |                        |                           |
| HEALTH SYSTEM FACTORS            |                               |                                          |                                            |                                          |                                   |                               |                        |                           |
| Time to 1st visit to health system|                               |                                          |                                            |                                          |                                   |                               |                        |                           |
| < 1 month                        | Referent                      | Referent                                 | Referent                                 | Referent                               | Referent                          |                               |                        |                           |
| 1–3 months                       | 1.46 (0.85–2.51)              | 1.58 (0.91–2.74)                        | 1.58 (0.91–2.74)                         | 1.63 (0.87–3.06)                      |                                   |                               |                        |                           |

Barriers to breast cancer care South Africa

PLOS ONE | https://doi.org/10.1371/journal.pone.0192071 February 2, 2018 10 / 16
household socioeconomic status, parity, HIV, and treated hypertension were no longer significant in mutually adjusted models. Thus, although HIV+ women tended to present at more advanced stages, because they were younger there was some attenuation of this association upon adjustment for either of these factors.

A cluster analysis was undertaken to distinguish group associations of sociodemographic variables with time to breast cancer disease presentation. The analysis was performed on continuous variables, omitting correlating variables, namely age, self-reported parity, self-reported household SES score (0–6) (based on home ownership, car ownership, hot and cold running water in home, flush toilet in house, owning a microwave, owning a washing machine) and the self-reported knowledge score (0–9). Three clusters were generated using the K mean and an ANOVA was performed to identify any statistical differences in the means between the 3 clusters and stage at diagnosis. The results are tabulated in the supporting information S3 Table and reveal no statistical differences between the three groups.

### Discussion

In our cohort of predominantly black women from socioeconomically disadvantaged urban communities around Johannesburg, patients with less than a high school education, those with little awareness or knowledge of breast cancer, those with luminal B and triple negative breast cancer subtypes, those who took more than three months from first recognition of their breast symptoms to visit a health care facility, and those who experienced more than 2 visits within the primary and secondary health system referral network were more likely to have been diagnosed at an advanced stage. We attribute the delay in making the first visit mainly to the two extremes of either patient lack of awareness of symptoms or fear of diagnosis. However, the multiple visits due to healthcare system failure to diagnose or inefficiency in scheduling appointments and retrieving laboratory results were major contributors to diagnostic delays and markedly impacted patient outcomes, especially those with aggressive receptor subtypes. More than 90% of the cohort reported receiving no routine clinical breast examinations during routine visits to women’s health and other clinics prior to experiencing their breast symptoms. Thus clinical breast examination services provided by trained doctors and nurses, though affordable, are not a standard feature of the primary health care system in SA.
Additionally, we found that HIV+ women tended to have more advanced stage. This was in part due to their younger age, but HIV+ women can be reached through their existing contacts with the health system. Education on breast awareness could be included when raising awareness of women’s cancer issues in HIV+ women. Although breast cancer is not a HIV-associated malignancy, as it is a common cancer in women in general, it remains a relevant issue in HIV-affected women too.

According to other studies, lack of knowledge and awareness of breast cancer and symptoms and fear of diagnosis and treatments are widespread and associated with advanced-stage diagnosis in other LMICs. Geographical isolation, inadequate financial resources, a preference for consulting traditional healers linked with cultural and religious beliefs, and a shortage of adequately trained healthcare professionals and facilities to diagnose and treat cancer are also widespread. Most LMICs also have limited cancer prevention and control policies and cancer registries able to monitor incidence and mortality [4, 12, 15, 23, 27, 28, 30, 31, 61].

In HICs, routine cancer screening is available, and healthcare services are well resourced. Yet in the USA, the breast cancer mortality rate is disproportionately high among blacks due to more advanced stage at diagnosis (after controlling for the higher proportion of triple negative subtype). Lack of knowledge of symptoms and risk factors, fear of treatments, higher financial burden of treatments, more lifestyle-associated risk factors and comorbidities, cultural issues, lack of partner support, stigma and taboo, and inferior health care services may all be associated with delays in accessing treatment [2, 24, 30, 32].

Our findings are based on a sample of patients from an urban black community in and around Johannesburg and may therefore have limited generalizability. Our information about delays in care seeking and numbers and types of healthcare visits is based on patient survey responses, rather than administrative data, which may be biased or less accurate. With a near 50% late stage disease in a sample size of 500 women, we had 80% power to detect ORs of 1.66 or larger for exposure prevalence of 50% and an OR of 2.08 or larger for rarer exposure prevalence of 10%. Larger studies will be required to detect smaller ORs. Findings were consistent with other data supporting associations with stage at diagnosis.

Fortunately, many of these factors are modifiable. Partnering with Cancer NGOs in SA, coordinating outreach programs at community and clinic levels to increase knowledge and awareness of breast cancer symptoms and risk factors, allaying fears of diagnosis and treatments, and active navigation of patients through the referral networks would undoubtedly enable more patients to be diagnosed and treated at an early stage. In addition, ongoing education and advisory support for primary and secondary tier doctors and nurses supported by the implementation of efficient referral algorithms would improve breast cancer detection and prevent unnecessary delays within the referral network.

**Conclusion**

Advanced-stage diagnosis of breast cancer among urban SA communities relying on public healthcare services is associated with patient- and health system-related barriers to care. Community and healthcare worker awareness and education programs, swift diagnostic workups and expedited referral processes may overcome these barriers and reduce breast cancer morbidity and mortality.

**Supporting information**

S1 Table.
(XLS)
S2 Table.
(XLSX)

S3 Table.
(DOCX)

S1 Text.
(DOCX)

Acknowledgments
We are grateful to the patients who provided the data for this study and to the team at the CHBAH Batho Pele breast clinic, who have served and continue to serve the patients with skill and devotion.

Author Contributions

Conceptualization: Maureen Joffe, Shane Anthony Norris, Valerie Ann McCormack, Judith S. Jacobson, Herbert Cubasch.

Data curation: Maureen Joffe, Oluwatosin Ayeni.

Formal analysis: Oluwatosin Ayeni, Shane Anthony Norris, Ishani Das.

Funding acquisition: Maureen Joffe, Paul Ruff, Alfred I. Neugut, Judith S. Jacobson.

Investigation: Maureen Joffe, Herbert Cubasch.

Methodology: Maureen Joffe, Shane Anthony Norris, Valerie Ann McCormack, Judith S. Jacobson.

Project administration: Maureen Joffe.

Resources: Maureen Joffe, Alfred I. Neugut, Herbert Cubasch.

Software: Oluwatosin Ayeni.

Supervision: Maureen Joffe, Shane Anthony Norris.

Validation: Maureen Joffe, Oluwatosin Ayeni.

Writing – original draft: Maureen Joffe.

Writing – review & editing: Oluwatosin Ayeni, Shane Anthony Norris, Valerie Ann McCormack, Paul Ruff, Ishani Das, Alfred I. Neugut, Judith S. Jacobson, Herbert Cubasch.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al: Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer Journal international du cancer 2015, 136(5):E359–386. https://doi.org/10.1002/ijc.29210 PMID: 25220842

2. Unger-Saldana K, Miranda A, Zarco-Espinosa G, Mainero-Flatchelous F, Bargalló-Rocha E, Miguel Lázaro-León J: Health system delay and its effect on clinical stage of breast cancer: Multicenter study. Cancer 2015, 121(13):2198–2206. https://doi.org/10.1002/cncr.29331 PMID: 25809536

3. Moodley J, Caimcross L, Naiker T, Momberg M: Understanding pathways to breast cancer diagnosis among women in the Western Cape Province, South Africa: a qualitative study. BMJ open 2016, 6(1):e009905. https://doi.org/10.1136/bmjopen-2015-009905 PMID: 26729392

4. Pace LE, Shulman LN: Breast Cancer in Sub-Saharan Africa: Challenges and Opportunities to Reduce Mortality. Oncologist 2016, 21(6).

5. International Monetary Fund Annual Report 2016https://www.imf.org/external/pubs/ft/ar/.
6. databank.worldbank.org.
7. Cancer in South Africa, Full Report. National Cancer Registry; 2012. http://www.nioh.ac.za/assets/files/NCR_Final_2011_tables(1).pdf.
8. Newman LA: Disparities in breast cancer and African ancestry: a global perspective. The breast journal 2015, 21(2):133–139. https://doi.org/10.1111/tbj.12369 PMID: 25639288
9. Newman LA: Breast cancer disparities: high-risk breast cancer and African ancestry. Surgical oncology clinics of North America 2014, 23(3):579–592. https://doi.org/10.1016/j.soc.2014.03.014 PMID: 24882352
10. Harford JB, Otero IV, Anderson BO, Cazap E, Gradishar WJ, Gralow JR, et al: Problem solving for breast health care delivery in low and middle resource countries (LMCs): a consensus statement from the Breast Health Global Initiative. Breast 2011, 20 Suppl 2:S20–29.
11. Sankaranarayanan R, Swaminathan R, Brenner H, Chen K, Chia KS, Chen-JG, et al: Cancer survival in Africa, Asia, and Central America: a population-based study. The Lancet Oncology 2010, 11(2):165–173. https://doi.org/10.1016/S1470-2045(09)70335-3 PMID: 20051751
12. Yip CH, Buccimazza I, Hartman M, Deo SV, Cheung PS: Improving outcomes in breast cancer for low and middle-income countries. World J Surg 2015, 39(3):686–692. https://doi.org/10.1007/s00268-014-2859-6 PMID: 25398564
13. Edge J, Buccimazza I, Cubasch H, Panieri E: The challenges of managing breast cancer in the developing world—a perspective from sub-Saharan Africa. South African Medical Journal 2014, 104(5):377. PMID: 25295328
14. Dickens C, Duarte R, Zietsman A, Cubasc H, Kellett P, Schuz J, et al: Racial comparison of receptor-defined breast cancer in Southern African women: subtype prevalence and age-incidence analysis of nationwide cancer registry data. Cancer Epidemiology and Prevention Biomarkers 2014; cebp. 0603.2014.
15. Elzawawy A: Breast cancer as a model to improve outcome of cancer care in low- and middle-income countries. World J Surg 2015, 39(3):693–694. https://doi.org/10.1007/s00268-014-2913-4 PMID: 25526922
16. Čačala SR, Giljart J: Factors Relating to Late Presentation of Patients With Breast Cancer in Area 2 KwaZulu-Natal, South Africa. Journal of Global Oncology 2017, 3(5):497–501. https://doi.org/10.1200/JGO.2016.08060 PMID: 29094088
17. Brewster AM, Chavez-MacGregor M, Brown P: Epidemiology, biology, and treatment of triple-negative breast cancer in women of African ancestry. The Lancet Oncology 2014, 15(3):e625–e634. https://doi.org/10.1016/S1470-2045(14)70364-X PMID: 25456381
18. Dietze EC, Sistrunk C, Miranda-Carboni G, O’Regan R, Seewaldt VL: Triple-negative breast cancer in African-American women: disparities versus biology. Nature reviews Cancer 2015, 15(4):248–254. https://doi.org/10.1038/nrc3896 PMID: 25673085
19. Boyle P: Triple-negative breast cancer: epidemiological considerations and recommendations. Annals of oncology: official journal of the European Society for Medical Oncology / ESMO 2012, 23 Suppl 6: vi7–12.
20. McCormack VA, Joffe M, van den Berg E, Broeze N, Silva Idos S, Romieu I, et al: Breast cancer recept or status and stage at diagnosis in over 1,200 consecutive public hospital patients in Soweto, South Africa: a case series. Breast cancer research: BCR 2013, 15(5):RB4. https://doi.org/10.1186/bcr3478 PMID: 24041225
21. Eng A, McCormack V, dos-Santos-Silva I: Receptor-defined subtypes of breast cancer in indigenous populations in Africa: a systematic review and meta-analysis. PLoS Med 2014, 11(9):e1001720. https://doi.org/10.1371/journal.pmed.1001720 PMID: 25202974
22. Murugan N, Dickens C, Pisa P, McCormack V, Joffe M, Jacobson J, et al: Down-staging of breast cancer in the pre-screening era: Experiences from Chris Hani Baragwanath Academic Hospital, Soweto, South Africa. South African Medical Journal 2014, 104(5):380. PMID: 25295329
23. Akuoko CP, Armah E, Sarpong T, Quansah DY, Amankwa I, Boateng D: Barriers to early presentation and diagnosis of breast cancer among African women living in sub-Saharan Africa. PloS one 2017, 12 (2):e0171024. https://doi.org/10.1371/journal.pone.0171024 PMID: 28192444
24. Yedjou CG, Tchounwou PB, Payton M, Miele L, Fonseca DD, Lowe L, et al: Assessing the Racial and Ethnic Disparities in Breast Cancer Mortality in the United States. International journal of environmental research and public health 2017, 14(5):486.
25. Martins T, Hamilton W, Ukoumunne OC: Ethnic inequalities in time to diagnosis of cancer: a systematic review. BMC Fam Pract 2013, 14(197):197.
26. Krok-Schoen JL, Oliveri JM, Paskett ED: Cancer Care Delivery and Women’s Health: The Role of Patient Navigation. Front Oncol 2016, 6:2. https://doi.org/10.3389/fonc.2016.00002 PMID: 26858934
27. Pace LE, Mpunga T, Hategekimana V, Dusengimana J-MV, Habineza H, Bigirimana JB, Mutumbira C, et al: Delays in breast cancer presentation and diagnosis at two rural cancer referral centers in Rwanda. *The oncologist* 2015, 20(7):780–788. https://doi.org/10.1634/theoncologist.2014-0493 PMID: 26032138

28. Brinton LA, Figueroa JD, Awuah B, Yarney J, Wiafe S, Wood SN, et al: Breast cancer in Sub-Saharan Africa: opportunities for prevention. *Breast cancer research and treatment* 2014, 144(3):467–478. https://doi.org/10.1007/s10549-014-2868-z PMID: 24604092

29. Caplan L: Delay in breast cancer: implications for stage at diagnosis and survival. *Frontiers in public health* 2014, 2:87. https://doi.org/10.3389/fpubh.2014.00087 PMID: 25121080

30. Jones CE, Maben J, Jack RH, Davies EA, Forbes LJ, Lucas G, et al: A systematic review of barriers to early presentation and diagnosis with breast cancer among black women. *BMJ Open* 2014, 4(2):e004076. https://doi.org/10.1136/bmjopen-2013-004076 PMID: 24523424

31. Busolo DS, Woodgate RL: Cancer prevention in Africa: a review of the literature. *Global health promotion* 2015, 22(2):31–39. https://doi.org/10.1177/1757975914537094 PMID: 25027971

32. Gerend MA, Pai M: Social determinants of Black-White disparities in breast cancer mortality: a review. *Cancer Epidemiology and Prevention Biomarkers* 2008, 17(11):2913–2923.

33. Harvey JM, Clark GM, Osborne CK, Allred DC: Estrogen Receptor Status by Immunohistochemistry Is Superior to the Ligand-Binding Assay for Predicting Response to Adjuvant Endocrine Therapy in Breast Cancer. *Journal of Clinical Oncology* 1999, 17(5):1474–1474. https://doi.org/10.1200/JCO.1999.17.5.1474 PMID: 10334533

34. Forbes L, Atkins L, Thurnham A, Layburn J, Haste F, Ramirez A: Breast cancer awareness and barriers to symptomatic presentation among women from different ethnic groups in East London. *British journal of cancer* 2011, 105(10):1474–1479. https://doi.org/10.1038/bjc.2011.406 PMID: 21989188

35. Stubbings S, Robb K, Waller J, Ramirez A, Austoker J, Macleod U, et al: Development of a measurement tool to assess public awareness of cancer. *British journal of cancer* 2009, 101 Suppl 2(Suppl 2):S13–17.

36. Bird Y, Banegas MP, Moraros J, King S, Prapsiri S, Thompson B: The impact of family history of breast cancer on knowledge, attitudes, and early detection practices of Mexican women along the Mexico-US border. *Journal of immigrant and minority health* 2011, 13(5):867–875. https://doi.org/10.1007/s10903-010-9418-5 PMID: 21104130

37. Banegas MP, Bird Y, Moraros J, King S, Prapsiri S, Thompson B: Breast cancer knowledge, attitudes, and early detection practices in United States-Mexico border Latinas. *J Women's Health (Larchmt)* 2012, 21(1):101–107.

38. Grunfeld E, Ramirez A, Hunter M, Richards M: Women's knowledge and beliefs regarding breast cancer. *British journal of cancer* 2002, 86(9):1373–1378. https://doi.org/10.1038/sj.bjc.6600260 PMID: 11986766

39. Royak-Schaler R, Cheuvront B, Wilson KR, Williams CM: Addressing women’s breast cancer risk and perceptions of control in medical settings. *J Clin Psychol Med Settings* 1996, 3(3):185–199. https://doi.org/10.1007/BF01993905 PMID: 24226756

40. Talbert PY: The relationship of fear and fatalism with breast cancer screening among a selected target population of African American middle class women. *Journal of Sociobehaviour and Health Science* 2008, 2(1):96–110.

41. Champion VL, Skinner CS, Menon U, Rawl S, Giesler RB, Monahan P, et al: A breast cancer fear scale: psychometric development. *Journal of health psychology* 2004, 9(6):753–762. https://doi.org/10.1177/1359105304045383 PMID: 15367754

42. Champion VL: Revised susceptibility, benefits, and barriers scale for mammography screening. *Research in nursing & health* 1999, 22(4):341–348.

43. Thomas VN, Saleem T, Abraham R: Barriers to effective uptake of cancer screening among Black and minority ethnic groups. *International journal of palliative nursing* 2005, 11(11):562–571. https://doi.org/10.12968/ijpn.2005.11.20096 PMID: 16471043

44. Loerzel VW, Bushy A: Interventions that address cancer health disparities in women. *Family & Community Health* 2005, 28(1):79–89.

45. Powe BD: Fatalism among elderly African Americans: effects on colorectal cancer screening. *Cancer nursing* 1995, 18(5):385–392. PMID: 7585493

46. Shen L, Condit CM, Wright L: The psychometric property and validation of a fatalism scale. *Psychology and Health* 2009, 24(5):597–613. https://doi.org/10.1080/08870440801902535 PMID: 20205014

47. Aday LA, Andersen R: A framework for the study of access to medical care. *Health Serv Res* 1974, 9(3):208–220. PMID: 4436074
48. Krieger N, Smith K, Naishadham D, Hartman C, Barbeau EM: Experiences of discrimination: validity and reliability of a self-report measure for population health research on racism and health. *Social science & medicine* 2005, 61(7):1576–1596.

49. Story H, Love R, Salim R, Roberto A, Krieger J, Ginsburg O: Improving outcomes from breast cancer in a low-income country: lessons from Bangladesh. *International journal of breast cancer* 2011, 2012.

50. Al-Naggar RA, Al-Naggar DH, Bobryshev YV, Chen R, Assabri A: Practice and barriers toward breast self-examination among young Malaysian women. *Asian Pac J Cancer Prev* 2011, 12(5):1173–1178. PMID: 21875261

51. Micklesfield LK, Evans J, Norris SA, Lambert EV, Jennings C, Joffe Y, et al: Dual-energy X-ray absorptiometry and anthropometric estimates of visceral fat in Black and White South African Women. *Obesity* 2010, 18(3):619–624. doi:10.1038/oby.2009.292 PMID: 19763094

52. Wu T-Y, Liu Y-L, Chung S: Improving breast cancer outcomes among women in China: Practices, knowledge, and attitudes related to breast cancer screening. *International journal of breast cancer* 2012, 2012.

53. Facione NC, Giancarlo C, Chan L: Perceived risk and help-seeking behavior for breast cancer: a Chinese-American perspective. *Cancer nursing* 2000, 23(4):258–267. PMID: 10939173

54. Remennick L: The challenge of early breast cancer detection among immigrant and minority women in multicultural societies. *The breast journal* 2006, 12(s1):S103–S110.

55. Arora NK, Johnson P, Gustafson DH, McTavish F, Hawkins RP, Pingree S: Barriers to information access, perceived health competence, and psychosocial health outcomes: test of a mediation model in a breast cancer sample. *Patient education and counseling* 2002, 47(1):37–46. PMID: 12023099

56. Ngo-Metzger Q, Massagli MP, Clarridge BR, Manocchia M, Davis RB, Iezzoni LJ, et al: Linguistic and cultural barriers to care. *J Gen Intern Med* 2003, 18(1):44–52. doi:10.1046/j.1525-1497.2003.20205.x PMID: 12534763

57. Mousa SM, Seifeldin IA, Hablas A, Elbana ES, Soliman AS: Patterns of seeking medical care among Egyptian breast cancer patients: relationship to late-stage presentation. *The Breast* 2011, 20(6):555–561. doi:10.1016/j.breast.2011.07.001 PMID: 21807518

58. Blackman DJ, Masi CM: Racial and ethnic disparities in breast cancer mortality: are we doing enough to address the root causes? *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 2006, 24(14):2170–2178.

59. Guidy JJ, Matthews-Juarez P, Copeland VA: Barriers to breast cancer control for African-American women: the interdependence of culture and psychosocial issues. *Cancer* 2003, 97(1 Suppl):318–323.

60. Smith RA, Caleffi M, Albert US, Chen TH, Duffy SW, Franceschi D, et al: Breast cancer in limited-resource countries: early detection and access to care. *The breast journal* 2006, 12 Suppl 1(s1):S16–26.

61. Yip CH, Taib NA: Challenges in the management of breast cancer in low- and middle-income countries. *Future oncology* 2012, 8(12):1575–1583. doi:10.2217/fon.12.141 PMID: 23231519