Determinants of Delayed Presentation and Advanced-Stage Diagnosis of Breast Cancer in Africa: A Systematic Review and Meta-Analysis

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Abstract

**Background/Objective:** Breast cancer (BC) mortality is exceptionally high in Africa due to late presentation and advanced-stage diagnosis. Previous studies examining barriers to early BC presentation are markedly inconsistent, showing conflicting findings within and between African regions, making resource allocation and designing interventional campaigns challenging. Our objective was to assess the strength or magnitude of the association between determinants/ risk factors and delayed presentation/advanced-stage diagnosis of BC in Africa. **Methods:** Electronic searches in PubMed, AJOL, Google, ResearchGate, ScienceDirect, and PubMed Central found eligible articles between 2000 and 2020. The meta-analytical procedure in Meta-XL used the quality effect model. I-squared \((I^2)\) above 75% indicated high heterogeneity. The summary effect size was the odds ratio with 95% confidence intervals. **Results:** The effect of socio-economic and demographic determinants on delay varies across African regions. Low level of education (1.63, 95% CI 1.01-2.63), and not performing breast self examination (BSE) (13.59, 95% CI 3.33-55.4) were significantly associated with delayed presentation. Younger patients had more significant delays in West Africa (WA, 1.41, 95%CI 1.08-1.85), and the reverse occurred in North Africa (0.68, 95%CI 0.48-0.97). Lack of BC knowledge (1.59, 95% CI 1.29-1.97), not performing BSE, or no history of undergoing clinical breast examination (CBE) (2.45, 95% CI 1.60-3.40), were associated with advanced-stage disease at diagnosis. Older patients had significantly more advanced disease in WA, and the reverse occurred in South Africa. Aggressive molecular BC subtypes [Triple negative (OR 1.62, 95% CI 1.27-2.06) or HER2 positive (1.56, 95% CI 1.10-2.23)] were significant determinants of advanced-stage diagnosis. **Conclusion:** Promoting early presentation and reducing advanced-stage BC throughout Africa should focus on modifiable factors, including providing quality education, improving breast health awareness and BC knowledge, and developing strategies to increase BSE and CBE. Interventions targeting socio-demographic determinants should be context-specific.

**Keywords:** Breast cancer- delay- advanced-stage Africa- meta-analysis

**Introduction**

Cancer of the breast is a disease of public health importance, accounting for more than 2 million new cases, 11.6% of all new cancers, and over 600,000 deaths, 6.6% of all cancer-related mortalities in 2018 (Bray et al., 2018). There is a disproportionate mortality to incidence ratio of breast cancer (BC) in Africa (Bray et al., 2018) due to long delays with presentation intervals longer than six months in most reports (Espina et al., 2017) and over 70% of patients diagnosed with advanced-stage disease (Jedy-Agba et al., 2016b). Consequently, raising the propensity for early help-seeking and lowering the probability of late-stage diagnosis is critical to improving BC outcomes in Africa.

Studies examining barriers to early presentation and early diagnosis of BC in Africa show conflicting associations within and between regions of Africa (Mousa et al., 2011; Ibrahim and Oludara, 2012; Ayoade et al., 2015; Benbakhta et al., 2015; Pace et al., 2015;
Akinkuolie et al., (2016), thus making resource allocation and designing of interventional campaigns challenging. Furthermore, a study of breast cancer-specific survival in the US found that socio-economic determinants were specific to the white race (Agarwal et al., 2017), noting that interventions based on economic status might not influence outcomes among black women. Another study reported that the association between demographics and poor outcomes in black women might be related to tumor biology (Iqbal et al., 2015).

Identifying the most influential risk factors for BC delays and advanced-stage disease presentation will help in designing more effective interventions. Therefore, this meta-analysis aimed to assess the strength of association between the determinants/risk factors and delayed presentation of BC or advanced-stage diagnosis in Africa by comparing the prevalence of the determinants between late and early presenters. Our ultimate goal is to provide data to understand each determinant’s relevance, thus aiding the planning of future campaigns against BC in Africa.

Materials and Methods

This research was conducted according to the MOOSE (meta-analysis of observational studies in epidemiology) guidelines. The need assessment and preliminary literature review [in PubMed, Cochrane library, and Prospero, reference ID CRD42020150932], confirmed there was no similar meta-analysis conducted previously or ongoing. The full literature search was conducted in PubMed.gov from August 19, 2020, to September 3, 2020, using the search terms “delay OR late AND stage AND presentation AND breast cancer Africa.” Hand-search was done on African Journal Online (AJOL), Google, Google Scholar, ScienceDirect, PubMed central, ResearchGate, and Academia. The Snow-balling search was performed in the reference list of original articles and already published systematic reviews. We sent exclusive electronic request messages to authors for full articles not available online or to clarify data.

Article selection and data extraction

Author AO screened articles eligible for full review using the title and abstract. Authors AO and AI independently conducted the full-article review and data extraction using predefined Population, Intervention, Control, Outcome, Time, Study design (PICOTS) criteria shown in Table 1 in the appendix and supplementary file. The authors discussed to resolve any disagreement.

Quality assessment

We adapted the quality assessment variables in the STROBE checklist to define the quality assessment criteria, placing a premium on variables that showed face and content validity of a study primarily designed to describe determinants of late presentation of breast cancer (quality assessment table in Supplementary file). The maximum score was ten, and the minimum was zero.

Statistical analysis

The primary outcome was the odds ratio (OR) of the risk factors in delayed presentation or advanced-stage versus the early-stage presenters. The summary odds ratio (OR) was calculated in the meta-analytical procedure, with a 95% confidence interval for all determinants or risk factors where a minimum of two observations were available, and a simple OR with a 95% confidence interval when only one observation was available. The analysis was reported as a continent-wide result when at least two regions were represented. The meta-analytical procedure was in MetaXL add-in for Microsoft Excel http://www.epigear.com with the quality effect model, using the quality score derived for each study, thus assigning higher weights to studies with better quality scores. I-squared (I2) above 50% indicated moderate heterogeneity and above 75% high heterogeneity. Subgroup analyses and sensitivity analyses were conducted to explain significant heterogeneity.

Results

The search in PubMed found 97 articles. Eighty-one were excluded after the title, abstract, and full-text review (Figure 1). Special requests sent to 4 authors yielded two additional articles (Benbakhta et al., 2015; Rayne et al., 2019) while the other two could not be reached (Mody et al., 2013; Youngblood et al., 2020). Hand-searching and snow-balling yielded 21 more articles.

In total, 38 articles contributed to the quantitative meta-analysis. In twelve articles, 16,347 subjects contributed to the analysis of the determinant of delayed presentation, and in 31 articles, 45,177 subjects contributed to the analysis of advanced-stage determinants. One article was published in French (Benbakhta et al., 2015); all others were English. Sixteen countries across all regions of Africa [Central Africa-CA, East Africa-EA, North Africa-NA, Southern Africa-SNA, West Africa-WA] contributed data; 12 countries contributed data in a single-center study while two contributed data as part of multinational studies (McKenzie et al., 2018; Islami et al., 2015).

Nine of 38 scored seven and above in the quality assessment, while 21 scored five and above (Quality Table, Supplementary file). The rationale in 22 (58%) of included articles was to describe the determinant of delayed presentation or advanced-stage diagnosis. Other articles found during our extensive snow-balling and hand-search were descriptive studies of presentation patterns or tumor biology reporting on determinants of delay or advanced-stage diagnosis. The articles reporting on delay described it as the interval between symptom recognition and first visit to the study center except two that defined delay as the interval between symptom recognition and diagnosis at the study center (Ermiah et al., 2012; Grosse et al., 2018).

Determinants of delayed presentation

Education level was the only socioeconomic variable that influenced delay in the overall analysis; women with lower education had longer delays to presentation (OR 1.63, 95% CI 1.01-2.63) (Table 3). In the age influence
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Figure 1. Flow Chart Diagram of Article Screening

Figure 2a. Forest Plot Showing the Analysis of Molecular Type of Tumor and Risk of Advanced-Stage Diagnosis

Figure 2b.
Table 1. PICOTS Article Screening Criteria

| Participants/Population | Freely available articles reporting on the risk factors linked to advanced-stage presentation or delayed presentation among female breast cancer (BC) patients in Africa. Studies involving more than 5% of male patients were excluded. |
|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Intervention            | Not applicable                                                                                                                                                                                   |
| Control/comparison      | The odds ratio of the determinants or risk factors for Advanced-stage diagnosis or delayed presentation in late presenters (Case) compared to early presenters (Control). Early-stage diagnosis was defined as stage 0, I, or II diagnosis with primary tumor ≤5cm and Advanced-stage diagnosis as stage III or IV disease or with primary tumor >5cm diameter. Based on the predominant pattern of reporting in African literature, early help-seeking was defined as presentation to the study center within three months of symptom recognition, and late help-seeking was defined as presentation after three months of symptom recognition. The absolute counts of risk factor(s) in the late presenters (case) and early presenters (control) had to be published or extractable for a study to be eligible. |
| Outcomes                | Socio-demographic risk factors: Age, marital status, educational status, distance to help care provider Knowledge, awareness, and family history of BC. Pattern of help-seeking: Visiting alternative care first, number of health care providers visited. Breast health behavior: Performing Breast Self-Examination Biologic risk factors: Tumor grade and immunohistochemistry receptor status. The definition /analysis of the determinants: Association with age was analyzed as younger population or older population as defined by the study hence any cut off between 40 and 50 years was acceptable as the emphasis was on the pattern of presentation of the younger compared to the older population age group in the study rather than the exact age defined as young or old. Older age was the reference level Marital status was analyzed as married or unmarried (comprising single, widows, separated or divorced). Married was the reference level. Educational status was analyzed as no education / primary education level versus secondary/tertiary level education. Secondary/tertiary level was the reference level. Being unemployed was compared to being employed, being employed was the reference level. Socio-economic class was analyzed as low vs intermediate / high. Rural dwelling, living remote to study center (>10km away or >1hr drive) was compared to urban dwelling, living close to study center <10km away or <1hr drive) (reference level). Consulting alternative medicine first was compared to consulting orthodox health care provider first (reference level). Seeing more than one Health care provider was compared to seeing only one healthcare provider (reference level). Triple negative status was compared to Hormone receptor positive (luminal A and B) status (reference level) and HER2 positive status was compared to Hormone receptor status (reference level). Classification of determinants The determinants of advanced-stage presentation or delayed presentation were classified as demographic; age, social; including the marital status, educational status, economic indicator; including employment status, and level of income. Awareness and knowledge, breast health behavior and screening practices, the pattern of health-seeking, and the tumor biology comprising tumor grade and molecular receptor status. |
| Time                    | Articles published between January 2010 and August 2020. Articles including data earlier than 2000 were excluded.                                                                                                                                                        |
| Study design            | We included observational studies (prospective, retrospective, and surveys) reporting on risk factors for late-stage diagnosis or delayed presentation of BC in African. Qualitative studies and studies including more than 5% male population were excluded. The language was not an exclusion criterion.                                                                                     |

Determinants of advanced-stage diagnosis

Socio-economic and demographic indicators did not significantly affect advanced-stage diagnosis in the overall analysis. The influence of age, level of education, and marital status varied across the regions. WA’s younger patients had reduced risk, while SA’s younger patients had an increased risk of advanced-stage diagnosis. Unmarried women and women with lower education levels had the more advanced disease in WA (Table 4). In the single study analysis, religion (Muslim vs. Christian) (Jedy-Agba et al., 2017) (OR 1.10, 95% CI 0.54-2.28), or socioeconomic status (low vs. high) (OR 1.22, 95% CI 0.76-1.94), did not significantly affect advanced-stage diagnosis (Table 4).

Women who did not perform breast self-examination (BSE) had 13 times higher odds of delayed presentation (Table 3). BC awareness (OR 1.17, 95% CI 0.52-2.63), family history of BC (OR 2.88, 95% CI 0.50-16.53), absence of a breast mass (OR 2.68, 95% CI 0.26-28.9) or first visiting alternative healthcare practitioners (OR 2.36, 95% CI 0.4-12.18) did not significantly influence delay. A single study analysis for risk of delay among patients with low BC knowledge (Ayoade et al., 2015) (OR 1.61, 95% CI 1.20-2.17) showed a significant association with delay. Other single studies showed that misinterpreting breast cancer symptoms as breast infection (Grosse et al., 2018) (OR 6.11, 95% CI 1.49-25.1) and having a smaller mass (Agodirin et al., 2020), (OR 1.56, 95% CI 1.0-2.43) were associated with delay.
Table 2. Article Characteristics Summarizing the Year, Country, Region, Institution, Design, and Study Level Summary Statistics of Eligible Articles

| First Author | Year | Country       | United Nations Region | Race | Period | Location of hospital                                      | Design | N    | Study level summary statistic | range/mean/median |
|--------------|------|---------------|-----------------------|------|--------|----------------------------------------------------------|--------|------|-------------------------------|-------------------|
| Adly et al (Adly, Hewedi and Mokhtar, 2010) | 2010 | Egypt         | NA                    | NS   | 2007-2009 | University for Science & Technology Hospital & Ain Shams University Hospital |        |     |                               |                   |
| Agbio(Agbo, Khalid and Oboirien et al) | 2014 | Nigeria       | WA                    | NS   | 2007-2011 | Usmanu Dan Fodio Teaching Hospital Sokoto | retro  | 816  | NS                             | 48.2/NS           |
| Agodirin(Agodirin, Olutoke, Rahaman et al, 2017) et al | 2018 | Nigeria       | WA                    | NS   | 2016-2018 | Multicenter | survey | 100  | 26-80/50.5/NS                 |                   |
| Akanbi(Akanbi, Ogunota, Adegbiti et al., 2015) et al | 2015 | Nigeria       | WA                    | NS   | 2012-2014 | NS | cross- | 120  | NS                           |                   |
| Aryudo(Ayrode, Salami, Agbola et al., 2015) et al | 2015 | Nigeria       | WA                    | NS   | 2011-2014 | Olabisi Onabanjo University Teaching Hospital Sagamu | survey | 113  | NS                             | 47.8/NS           |
| Benerbakti(Benbakti, Tari, Benjaifar, Khattabi and Maaroudi, 2015) | 2013 | Morocco       | NA                    | NS   | 2012-2013 | INO Rabat | cross | 200  | 25-82/49.1/                  |                   |
| Brighton(Brinton, Figueroa, Adjei et al., 2017) et al | 2017 | Ghana         | WA                    | NS   | 2008-2009 | Korle Bu Teaching Hospital & Komfo Anokye Kumasi & Peace & Love Kumasi | case   | 1184 | 18-74/NS/NS                   |                   |
| Burson(Burson, Solomon, Ngoma et al., 2010) et al | 2010 | Tanzania      | EA                    | NS   | 2007-2009 | Ocean Road Cancer Institute Dar es Salaam | retro  | 488  | NS                             | 43.4/NS           |
| Cacala(Cacala and Gilart, 2017) | 2017 | South Africa | SNA                   | NS   | 2014 | Grey's Hospital KwaZulu Natal Pieternaritzburg | pros   | 172  | 23-100/56/NS                  |                   |
| Ellima-jedy(Jedy-Agba, McCormack, Adebamowo and Dos Santos-Silva, 2016a) et al | 2017 | Nigeria       | WA                    | NS   | 2014-2016 | Multicenter | pros   | 316  | 24-86/45.4/NS                 |                   |
| Ermiah(Ermiah, Abdalla, Buhmeida et al., 2012) et al | 2012 | Libya         | NA                    | NS   | 2008-2009 | National Oncology Institute Sabratha | survey | 200  | 22-75/45.4/NS                 |                   |
| Errahalli(Ellidrissi Errahalli, Elidrissi Errahalli, Ouazrane et al., 2017) et al | 2017 | Morocco       | NA                    | NS   | 2005-2012 | Hassan II regional oncology center | retro  | 2406 | NS                             | 48.7/NS           |
| Fitzpatrick(Fitzpatrick, Rendi, Kivist, et al., 2019) et al | 2018 | Senegal       | WA                    | NS   | 2001-2016 | Dantec Hospital | retro  | 197  | NS                             | 47/NS             |
| Garmberamiani(Gebremariam, Addisso, Worku et al., 2019) et al | 2019 | Ethiopia      | EA                    | NS   | 2017-2018 | Multicenter | cross | 441  | NS                             | 44.4/NS           |
| Galukande(Galukande, Mirembe and Wabinga, 2014) et al | 2014 | Uganda        | EA                    | NS   | 2008-2011 | Mulago Hospital Kampala | retro  | 201  | 22-87/46.5/45                 |                   |
| Galukande(Galukande, Wabinga and Mirembe, 2015) et al | 2015 | Uganda        | EA                    | NS   | 2004-2012 | National Institute Oncology Sabratha | survey | 200  | 22-75/NS/NS                   |                   |
| Gross-frie(Grosse Frie, Kamate, Traore et al., 2018) et al | 2018 | Mali          | WA                    | NS   | 2016 | University Hospital Bamako | survey  | 64   | NS                             | 45/NS             |
| Gueye et al (Gueye, Gueye, Diallo et al., 2017) | 2017 | Senegal       | WA                    | NS   | 2014 | Aristide Le Dantec Teaching Hospital Dakar | obsr   | 259  | NS                             | 45/NS             |
| Hadda(Hadda, Seif, Tighne et al., 2018) | 2018 | Ethiopia      | WA                    | NS   | 2012-2015 | Oncology Center Tikur Ambessa Specialized Hospital & Paul's Hospital Milennium Medical College | retro  | 114  | 25-75/43/40                   |                   |
| IslamiIslami, Lortet-Tieulent, Okello et al., 2015a) | 2015 | Congo & Ivory Coast | WA                    | NS   | 2008-2009 | Cancer Registry Abidjan Ivory Coast & Brazzaville Congo | retro  | 280  | NS                             | NS/NS/NS          |
| Joffe(Joffe, Ayeni, Norris et al., 2018) et al | 2018 | South Africa | SNA                   | NS   | 2015-2016 | Chris Hani Baragwanath Academic Hospital Hospital Soweto | survey  | 499  | NS                             |                   |
| Kholer(Kholer, Moses, Kreyiak, Liemba and Gopal, 2015) et al | 2015 | Malawi        | EA                    | NS   | 2011-2013 | Kamuzu Central Hospital Lilongwe | retro  | 198  | 12-89/NS/34                   |                   |
| Marcus(Marcus, Lunda and L, 2013) | 2013 | South Africa | SA                    | NS   | 2007-2010 | Sebokeng Hospital, Sedibeng Municipal district, South Gauteng | retro  | 103  | 34-83/59/NS                   |                   |
| McKenzie(McKenzie, Zietsman, Galukande et al., 2018) | 2017 | multicenter | SSA                  | blk  | 2014-2017 | Multicenter  | cross | 1795 | NS                             | 55/NS/NS          |
| Miguel(Miguel, Lopes, Ferreira et al., 2017) Africa | 2017 | Angola        | CA                    | NS   | 2011-2014 | Angola Institute of Cancer Control Luanda & clinica Sagrade esperanca | pros   | 140  | 24-84/47/NS                   |                   |
arriving at the oncology center did not significantly affect the disease stage (>1HCP vs. 1 HCP (OR 1.33, 95% CI 0.92-1.93)). Family history of BC and absence of a breast mass in the initial symptomatology did not significantly influence the disease stage.

Considering non-modifiable factors, triple-negative (OR 1.83, 95% CI 1.39-2.41) or HER2 positive BC (OR 1.73, CI 1.20-2.49) was associated with more advanced stage at diagnosis (Figure 2), whereas tumor grade did not significantly affect the disease stage. In a single study analysis (Rayne et al., 2019), there was no significant association (OR 1.69, 95% CI 0.88-3.27) between black race and advanced-stage diagnosis.

**Discussion**

Downstaging breast cancer is a high priority in Africa, and understanding the determinants of delayed presentation and advanced-stage diagnosis is critical to this endeavor. Our previous meta-analysis ordered the prevalence of perceived risk factors for delayed presentation, from already identified themes, among late presenters only. The current meta-analysis aggregated Africa’s data to compare the socio-economic, demographic, and biologic determinants of delayed presentation or advanced-stage diagnosis between early and late presenters and adds to the existing literature by describing each determinant’s significance. In the overall analysis, low education and not performing BSE increased the risk of delayed presentation significantly. Lack of BC knowledge, not performing BSE/performing BSE increased the risk of delayed presentation significantly. In the overall analysis, low education and not performing BSE/no history of undergoing Clinical Breast Examination and TNBC or HER2 positive BC, significantly increased the risk of advanced-stage diagnosis.

Similar to prior research (Montella et al., 2001), we found an increased risk of delay among younger women in WA. Paradoxically, there was a reduced risk of advanced-stage diagnosis in the same population. The reason for this paradoxical trend is unclear. It might be due to planned behavior underpinned by sociocultural issues, such as fear of diagnosis and treatment, lack of trust in hospital, and unfavorable expectations of treatment outcome (Bish et al., 2005). While older persons might engage in screening and present early due to the perception of a higher risk of cancer (Deeks et al., 2009), they might...
also delay when they underestimate their symptoms (Innos et al., 2013) or when they show altruistic behavior, keeping the information from their relations to prevent them from worrying (Zhang et al., 2019). In contrast, younger persons might delay diagnosis and treatment due to unwanted changes in their bodies.

These regional differences suggest that age-directed messaging might be necessary for different regions. Future research should explore selective messaging that might influence patient subpopulations, such as the cluster of deliberate delayers already identified in Nigeria (Ayoade et al., 2015; Agodirin et al., 2019). Reports show that tailored, individual messaging has potential to improve cancer awareness more than general information (Austoker et al., 2009; Linsell et al., 2009; Campbell et al., 2016), and individual messaging enhances BC knowledge and performance of BSE (Linsel et al., 2009; Campbell et al., 2016).

This study showed a strong association between a low level of education and advanced-stage diagnosis. Similarly, in a population-based study in India, Mathew et al. found a strong association between education and early breast and cervical cancer diagnosis (Mathew et al., 2019). In explaining the association, Jedy-Agba et al., (2017) in Nigeria linked higher education levels to BC knowledge and believing in curability. Additionally, higher education levels might increase the likelihood of comprehending the health campaign messages with terminology that is not representative of local dialects.

The level of education in Africa is transitioning with increasing school attendance, but the quality is lacking. Less than 7 percent of late primary school pupils in Sub-Saharan Africa achieve the appropriate reading proficiency and the majority are unable to comprehend simple written sentences (Sow, 2017). This may result in decreased comprehension of cancer campaign messaging. Females and children in low-income families are particularly disadvantaged (Ali et al., 2008; Kazeem et al., 2010; The Africa-American Institute, 2015), and much can be done by increasing the public spending on education and providing quality education to Africans as an equal right of all, regardless of gender, social or economic status.

Table 3. Summary Estimates of the Odds Ratio of Determinants of Delayed Presentation: Case represents subjects presenting in advanced stages (Stages III and IV), and control represents subjects presenting in early stages (Stages 0, 1 and II).

| Variable (no of articles) | Case (n) | Control (n) | Pooled OR | 95%CI | I-Squared | P-value |
|---------------------------|---------|-------------|-----------|-------|-----------|---------|
| Demographic and social    |          |             |           |       |           |         |
| Age, overall (10)         | Young (764) | Old (1158)   | 1.04      | 0.80-1.41 | 42%       | 0.08    |
| Age, sensitivity (6)      | <40 (477) | >40 (756)    | 1.07      | 0.71-1.63 | 42        | 0.12    |
| Age, WA (4)               | Young (406) | Old (267)    | 1.41      | 1.08-1.85 | 0%        | 0.67    |
| Age, NA (3)               | Young (270) | Old (141)    | 0.68      | 0.48-97  | 0%        | 0.59    |
| Age, SA (2)               | Young (88)  | Old (168)    | 0.92      | 0.35-2.39 | 14        | 0.28    |
| Awareness, overall (3)    | Unaware (194) | Aware (276)  | 1.17      | 0.52-2.63 | 72%       | 0.03    |
| Awareness, WA (2)         | Unaware (136) | Aware (252)  | 1.01      | 0.25-4.07 | 82%       | 0.02    |
| Family history, overall (2) | Negative (373) | Positive (34) | 2.88      | 0.50-16.53 | 77%       | 0.04    |
| Alternative healer, WA (2) | Alternative first (238) | Hospital first (82) | 2.36      | 0.40-12.18 | 49%       | 0.16    |
| BSE overall (2)           | No lump (90) | Lump (268)   | 2.68      | 0.26-28  | 94        | 0.0     |
| Symptomatology, overall (2) | Low (696) | High (931)   | 1.63      | 1.01-2.63 | 63%       | 0.01    |
| Education, overall (8)    | 338      | 131         | 1.26      | 0.76-2.08 | 59%       | 0.06    |
| Education, WA (4)         | 133      | 120         | 2.39      | 1.08-5.29 | 0         | 0.8     |
| Education, NA (2)         | 225      | 137         | 2.98      | 0.98-9.08 | 82%       | 0.02    |
| Economic indicators       |          |             |           |       |           |         |
| Employment status, overall (5) | Unemployed (380) | Employed (389) | 1.2      | 0.5-2.85  | 74%       | 0.01    |
| Employment, WA (2)        | Unemployed (158) | Employed (181) | 0.91      | 0.2-4.13  | 83%       | 0.01    |
| Employment, SA (2)        | 111      | 15          | 1.61      | 0.06-32.5 | 84%       | 0.01    |
| Income, WA (3)            | Low (385) | High (272)  | 1.38      | 0.94-2.04 | 0%        | 0.53    |
| Family history, overall (2) | Negative (373) | Positive (34) | 2.88      | 0.50-16.53 | 77%       | 0.04    |
| Marital status, overall (8) | Unmarried (492) | Married (1003) | 0.93      | 0.60-1.43 | 58%       | 0.02    |
| Marital status, WA (4)    | Unmarried (197) | Married (521) | 0.96      | 0.41-2.27 | 79%       | 0.01    |
| Marital status, NA (2)    | 105      | 48          | 0.92      | 0.58-1.44 | 0%        | 0.79    |
| Marital status, SA (2)    | 160      | 28          | 0.74      | 0.27-2.07 | 45        | 0.18    |
| Location overall (6)      | Rural (473) | Urban (503)  | 1.59      | 0.82-3.07 | 76%       | 0       |
| Location, WA (3)          | Rural (189) | Urban (246)  | 1.51      | 0.91-2.94 | 12%       | 0.32    |
| Location, NA (2)          | Rural (150) | Urban (205)  | 2.09      | 0.28-15.8 | 91%       | 0       |

BSE, Breast Self Examination; NA, Northern Africa; SA, South Africa; WA, West Africa

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Table 4. Summary Estimates of the Odds Ratio of Determinants of Advanced-Stage Presentation: Case represents subjects presenting in advanced stages (Stages III and IV), and control represents subjects presenting in early stages (Stages 0, I and II). Single Study analyses are identified as first author et al.

| Variable (no of articles) | Case (n) | Control (n) | Pooled OR | 95%CI | I-Squared | P-value |
|---------------------------|----------|-------------|-----------|-------|-----------|---------|
| Demographic and social    |          |             |           |       |           |         |
| Age, overall (9)          | Young(1307) | Old (1470)  | 0.54      | 0.23-1.23 | 90%       | 0.01    |
| Age, WA (4)               | 785      | 644         | 0.3       | (0.12-0.73) | 72%       | 0       |
| Age, SA (2)               | 129      | 594         | 1.91      | 1.05-2.73  | 72        | 0       |
| Age, EA (2)               | 194      | 133         | 0.2       | 0.01-4.36  | 92        | 0       |
| Age, Benbakhta et al      | 91       | 103         | 0.54      | 0.31-0.95  |           |         |
| Education, overall (7)    | Low (1645) | High (1929) | 1.26      | 0.89-1.79  | 76%       | 0.01    |
| Education, WA (2)         | 161      | 56          | 2.02      | 1.37-2.99  | 0%        | 0.71    |
| Education, SA (2)         | 267      | 683         | 0.9       | 0.56-1.44  | 48        | 0.16    |
| Marital status, overall (6) |          |             |           |       |           |         |
| Marital status, WA (2)    | 2115     | 2293        | 0.97      | 0.59-1.60  | 87%       | 0.01    |
| Marital status, SA (2)    | 510      | 581         | 1.62      | 1.17-2.25  | 0%        | 0.76    |
| Burson et al              | 59       | 103         | 0.54      | 0.31-0.95  |           |         |
| Location, overall (7)     | Rural (1605) | Urban (2427) | 1.41      | 0.98-2.02  | 58%       | 0.01    |
| Location, WA (4)          | 322      | 1238        | 1.11      | 0.86-1.64  | 0%        | 0.53    |
| Location, EA (2)          | 153      | 76          | 2.9       | 0.49-17.16 | 76%       | 0.04    |
| Location, SA (2)          | 278      | 171         | 2.01      | 0.97-4.17  | 69%       | 0.07    |
| Economic indicator        |          |             |           |       |           |         |
| Employment status, overall (2) | Unemployed (230) | Employed (282) | 1.02      | 0.41-2.57  | 55%       | 0.14    |
| Engagement in screening practices |          |             |           |       |           |         |
| BSE/CBE, overall (3)      | 755      | 254         | 2.45      | 1.6-3.40   | 0%        | 0.53    |
| BSE, WA (2)               | 199      | 142         | 2.03      | 1.20-3.26  | 0%        | 76      |
| Pattern of Help-seeking   |          |             |           |       |           |         |
| Alternative first, WA     | 35       | 336         | 1.44      | 0.41-5.14  |           |         |
| Symptomatology, overall (2) | No lump (49) | Lump (579) | 1.12      | 0.29-4.26  | 63        | 0.1     |
| Number of HCP             | >1 HCP    | IHCp        | 1.02      | 0.41-2.57  | 55%       | 0.14    |
| Overal(2)                 | 238      | 284         |           |       |           |         |
| Delay >3months, overall (8) | 2276      | 1041        | 1.89      | 0.91-3.95  | 86%       | 0       |
| Delay, NA (4)             | 343      | 468         | 2.25      | 1.60-3.16  | 0%        | 0.67    |
| Awareness/Knowledge       |          |             |           |       |           |         |
| Family history, overall (3) | Negative (838) | Positive (156) | 1.2      | 0.64-3.33  | 63%       | 0.07    |
| Awareness, overall (2)    | 384      | 1690        | 2.21      | 1.68-2.92  | 0%        | 0.42    |
| Knowledge of BC, overall (2) | 735      | 1950        | 1.59      | 1.29-1.97  | 8%        | 0.3     |
| Biology                   |          |             |           |       |           |         |
| Grade overall (3)         | high (332) | Medium/low (607) | 1.25      | 0.91-1.71  | 0%        | 0.62    |
| HER2 status, overall (3)  | HER2 positive (370) | Hormone Positive (3897) | 1.73      | 1.20-2.45  | 45        | 0.03    |
| TNBC, overall (3)         | TNBC (1149) | Hormone positive (3897) | 1.83      | 1.39-2.41  | 41%       | 0.05    |

**BC**, Breast Cancer; BSE, Breast Self Examination; CBE, Clinical Breast Examination; HCP, Health Care Provider; NA, Northern Africa; SA, South Africa; WA, West Africa

Our analysis provides evidence in support of BSE as a viable strategy for downstaging BC in Africa. Patients who detect breast masses during BSE are less likely to delay (Dev et al., 2007), perhaps due to selection bias and willingness to take charge of their health, which might also be an element of planned behavior. Performance of BSE/CBE is low in Africa, and previous research found that 10% of inadvertent lump detections were already locally advanced, with an high proportion of those detected early progressing before diagnosis (30% after 30 days delay, and 70% after 90 days delay) (Agodirin et al., 2020). BSE’s effectiveness for downstaging or improving BC survival is controversial (Miller and Baines, 2011; Corbex et al., 2012), especially in places where most patients present early with non-clinically detectable tumors. Nonetheless, increasing performance of BSE and CBE (Miller, 2008; Romanoff et al., 2017) has potential to reduce the prevalence of late-stage disease. Reducing the number of BCs that progress during the interval between detection and diagnosis is of utmost importance. Strategies for this have been demonstrated in Sudan where trained indigenous volunteers screened rural communities...
(Abuidris et al., 2013), and in Ghana where screening targeted micro-communities of BC patients (Bonsu and  
Ncama, 2019).

Reports of prolonged delay of more than three months are prevalent in Africa, ranging up to 70% compared to  
16-17% in Europe and the USA (Innos, Padrík, Valveré, et al., 2013). Breast cancer progression is time-dependent (Fujii et al., 2015; Agodirin et al., 2020); however, the significance of 3 months delay as a predictor of advanced-stage diagnosis was not found in this analysis. The association between delay and advanced stage diagnosis has also not been consistent in African literature; some researchers found an association between long intervals and advanced-stage diagnosis (Brinton et al., 2017) while others did not (Galukande et al., 2014). The conflicting finding might be due to methodological issues as information on delay are collected retrospectively. Also, the impact of delay is usually more clearly demonstrated where most patients present early and with small lesions.

TNBC and HER2 positive BC are non-modifiable factors associated with advanced-stage diagnosis. Prompt diagnosis and access to effective treatment have potential to improve outcomes as the poor survival outcomes in SSA are also a reflection of inadequate and ineffective treatment (McCormack et al., 2020). Accurate pathologic diagnosis, including immunohistochemistry, navigation through the healthcare system, and receipt of of guideline-concordant treatment, including systemic and locoregional therapy, are necessary to improve outcomes in these subgroups.

This is the first meta-analysis to compare the determinants of delayed presentation and advanced stage presentation between early presenters and late presenters using data from Africa. Unfortunately, the small number of studies, the small sample size available for some of the analyzed variables, and inability to assess health systems-related factors limit our results. There was also significant heterogeneity in some of the results. Heterogeneity reduced significantly after the subgroup analysis, meaning some of the differences might be due to regional factors such as cultural, socio-demographic differences, and differences in health care structures.

Our results showed paradoxical relationships between some determinants of delay and advanced-stage diagnosis. In this case, preference should be given to factors associated with advanced-stage diagnosis as they are more consistent than determinants of delay lengths. Furthermore, the disease stage is a stronger and more reliable prognostic indicator of outcome than delay (McCormack et al., 2020).

In conclusion, providing quality education to raise BC knowledge, and increasing the prevalence of breast health awareness, BSE, and CBE are promising targets for reducing delays and downstaging BC throughout Africa. Future interventions addressing social and demographic barriers should implement innovative approaches to identify the context-specific determinants and deliver targeted messaging.

**Author Contribution Statement**

Agodirin, Aremu, Rahman, and Olatoke conceived and designed the study. Agodirin and Aremu collected articles and extracted data. Agodirin analyzed the data. All authors contributed to the interpretation of the data. Agodirin, Akande, Olaogun, and Romanoff contributed to the draft and writeup of the manuscript. All authors contributed to the review and editing of the manuscript, and all authors contributed to the decision to submit the manuscript.

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**Ethical Approval**

This study is exempt from ethical review and approval. It is a meta-analysis aggregating freely available data from published research. The informed consent and all due ethical proceedings were already satisfied by the authors of the individual eligible articles.

**Disclosure**

This article was conceived as individual research; it was not part of any other ongoing or previously conducted research or thesis

**Conflict of Interest**

The authors declare no conflict of interest.

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