Breast Cancer in sub-Saharan Africa: Determinants of Stage at Diagnosis and Diagnostic Delays in Women with Symptomatic Breast Cancer

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Thesis submitted in accordance with the requirements for the degree of

Doctor of Philosophy of the University of London
May 2017

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Funded by The Nigerian Niger Delta Development Commission (NDDC) and the Training Programme in Nigeria for Non-Communicable Diseases Research (TRAPING NCD) from the Fogarty International Centre of the National Institutes of Health, USA.

DECLARATION

I, Elima Jedy-Agba, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that these sources have been indicated in the thesis.

Signed: 

Date: 21/12/2016

ABSTRACT

Background: Breast cancer is the most common female cancer worldwide and in sub-Saharan Africa (SSA). Breast cancer incidence in SSA is relatively low but, as survival from the disease in the region is poor, mortality rates are as high as in high income countries. Late stage at diagnosis, and delays in a woman's journey to a cancer diagnosis, are features known to contribute to poor breast cancer survival rates. There has been little focus on the factors affecting stage at diagnosis and the determinants of diagnostic delays in SSA despite previous studies highlighting the importance of early detection and treatment in breast cancer control.

Aims and Methods: The main objectives of this thesis are: (i) To conduct a systematic review and meta-analysis of stage at breast cancer diagnosis in SSA to examine trends over time and examine possible sources of variation across the region. Random-effects meta-analyses were performed to investigate between-study heterogeneity in percentage of late-stage disease (stage III/IV) breast cancer, and meta-regression analyses were carried out to identify possible sources of variation. Percentages of Black women with late-stage breast cancer in SSA were compared with equivalent estimates for US Black and White women using the Surveillance, Epidemiology and End Results Database. (ii) To design and conduct a study, the Nigerian Integrative Epidemiology of Breast Cancer (NIBBLE) study, (iii) to investigate determinants of late stage at breast cancer diagnosis and diagnostic delays at six tertiary and secondary health facilities in Nigeria. Ordinal logistic regression was used to examine associations of socio-demographic, breast cancer awareness, health care access and clinical factors with the odds of later stage disease. Linear regression analyses were performed to examine the association of these factors with time from noticing symptoms to diagnosis (total delay), and its two main

components: pre-contact delay (i.e. time from symptoms to first contact with any care provider including traditional healers) and post-contact delay (i.e. time from first contact to diagnosis).

Results: (i) Systematic review: 83 studies were eligible representing 26,788 women from 17 SSA countries. There was wide variation in percentage of late stage (median 74.7%, range 30.3-100%, I^2=93.3% p<0.0001). Late stage at diagnosis was notably higher in Black vs non-Black women in SSA and higher for populations from mixed (urban and rural) settings than from urban settings. The percentage of women with late stage breast cancer decreased over time but it was still higher than in US White and Black women 40 years previously. (ii) Findings from NIBBLE: 300 breast cancer patients were recruited, 67.7% with late stage (III/IV) at diagnosis. Multivariate analyses showed lower educational level (odds ratio (OR) 2.35; 95% confidence interval (CI) 1.04, 5.29), not believing in a cure for breast cancer (OR 1.81; 95% CI 1.09, 3.01), Muslim religion (OR 0.46; 95% CI 0.22, 0.94) and living in a rural area (OR 2.18; 95% CI 1.05, 4.51) to be significantly associated with later stage. No associations were found between later stage and age at diagnosis, tumour grade or oestrogen receptor status. Women diagnosed in stages III/IV self-reported, on average, 36% longer total delay times than those in stages I/II. Median (IQR) for pre-, post and total delays were 2.6 (0.6, 8.3), 3.1 (0.79, 8.7) and 7.8 (3.3, 18.7) months, respectively, for all women who presented with suspicious symptoms (n=430). In fully-adjusted analyses, post-contact delays in all women with symptoms were associated with lack of a personal income (OR 1.49; 1.04, 2.00), no previous history of benign breast disease (OR 0.61; 0.42, 0.89) and having 5 or more children (OR 1.88; 95% CI 0.96, 3.67) whilst total delay was inversely associated with presentation at a secondary facility (OR 0.68; 95% CI 0.51, 0.92) and no previous history of benign breast disease (OR 0.64; 0.47, 0.88). Post-contact and total delays were both positively associated with the total number of providers visited before a diagnosis (P for

trend ($P_{t)}$=0.014 and P_t<0.001, respectively). Only 18% of all women with symptoms and 12.4% of the subset with breast cancer were diagnosed within 3 months of noticing a breast symptom.

Conclusions: Although stage at breast cancer diagnosis improved over time in SSA, it is still a common feature. This thesis identified factors amenable to intervention such as breast cancer awareness and health care access, rather than intrinsic tumour characteristics, as the main drivers of late stage at diagnosis in Nigeria. Strategies for early diagnosis of symptomatic breast cancer should be regarded as a major priority in cancer control programmes in SSA.

PREFACE

The thesis for this PhD uses the “research/review papers” format with some chapters in the “book style” format. It therefore includes papers that have been published or submitted to peer-reviewed journals. The chapters that have been published or formatted for publication are preceded by a cover sheet which includes details of the publication, and acknowledges the contributions of other people who are co-authors on the papers. The other chapters not formatted for publication which are written in the “book style format” are preceded by linking material which helps to make the thesis a coherent body of work.

ACKNOWLEDGEMENTS

This work has been made possible because of the amazing support I have received from my supervisors, colleagues, family and friends. First, I would like to thank my supervisors, Prof. Isabel dos Santos Silva and Dr. Valerie McCormack for their guidance and patience; and for sharing their wealth of experience in Epidemiology with me. They provided sound advice, constructive criticisms and helpful comments on data analyses, draft manuscripts and reviewing chapters of my thesis. You both provided stellar supervision! Thank you.

I would also like to thank members of my advisory committee Dr. Bernard Rachet and Prof. Clement Adebamowo. Thank you, Prof. Adebamowo for introducing me to this engaging field of breast cancer research, I remain truly grateful. To my colleagues at IHVN, Eileen, Yinka, Michael and Ayo; thank you all for your encouragement. To my friends in Nigeria, the United Kingdom and the United States; especially my lifelong friend and 'person' Bolaji Sofoluwe, my dear friend Ijeoma Ndukwe, and my colleague at LSHTM; Rachel Brathwaite who provided sound advice, I sincerely appreciate your encouragement. I also thank my Nigerian collaborators, research nurses, volunteers, data manager and research participants for their invaluable contributions towards making this project a success.

Finally, I sincerely appreciate the extraordinary support and steadfastness shown by my dear husband Tim and our wonderful children Jedy, Timmy and Zoe. I do not take for granted the sacrifices we had to make as a family, to enable me actualize this dream, and I remain truly grateful and feel incredibly blessed to have you all by my side. My love and thanks also go to my dear sisters Eudoria Ita and Julie Abaribe and my parents Chief

and Dr. Mrs. Linus E. Okom; for their wise counsel and encouragement. We did it together!

This work was supported by the, Training Programme in Nigeria for Non-Communicable Diseases Research (TRAPING-NCD; Fogarty International Centre of the National Institutes of Health D43TW009106-CA). I also acknowledge the sponsorship of the Nigerian Niger Delta Development Commission (NDDC) and the Cross River State Government of Nigeria.

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ABBREVIATIONS

ADH	Asokoro District Hospital, Abuja, Nigeria
AJCC	American Joint Committee on Cancer
ASR	Age Standardized Incidence Rate
BC	Breast Cancer
BHGI	Breast Health Global Initiative
CT	Computerized Tomography
ER	Oestrogen Receptor
FISH	florescent in situ hybridization
PR	Progesterone Receptor
HER2	Human Epidermal Growth Factor Receptor
H & E	Hematoxylin and Eosin
IHC	Immunohistochemistry
LMICs	Low and Middle Income Countries
LSHTM	London School of Hygiene and Tropical Medicine
MeSH	Medical Subject Heading
MRI	Magnetic Resonance Imaging
NHA	National Hospital, Abuja, Nigeria
NIBBLE	Nigerian Integrative Epidemiology of Breast Cancer Study
NHREC	National Health and Research Ethics Committee
REDCap	Research Electronic Data Capture
SEER	Surveillance Epidemiology and End Results database
SD	Standard Deviation
SSA	Sub-Saharan Africa
TNM	Tumour Node Metastasis
UATH	University of Abuja Teaching Hospital, Gwagwalada, Nigeria
UNTH	University of Nigeria Teaching Hospital, Enugu, Nigeria
USA	United States of America
WGH	Wuse General Hospital, Abuja
WHO	World Health Organization

CHAPTER 1

1.1 BACKGROUND

1.1.1 GLOBAL BURDEN OF BREAST CANCER

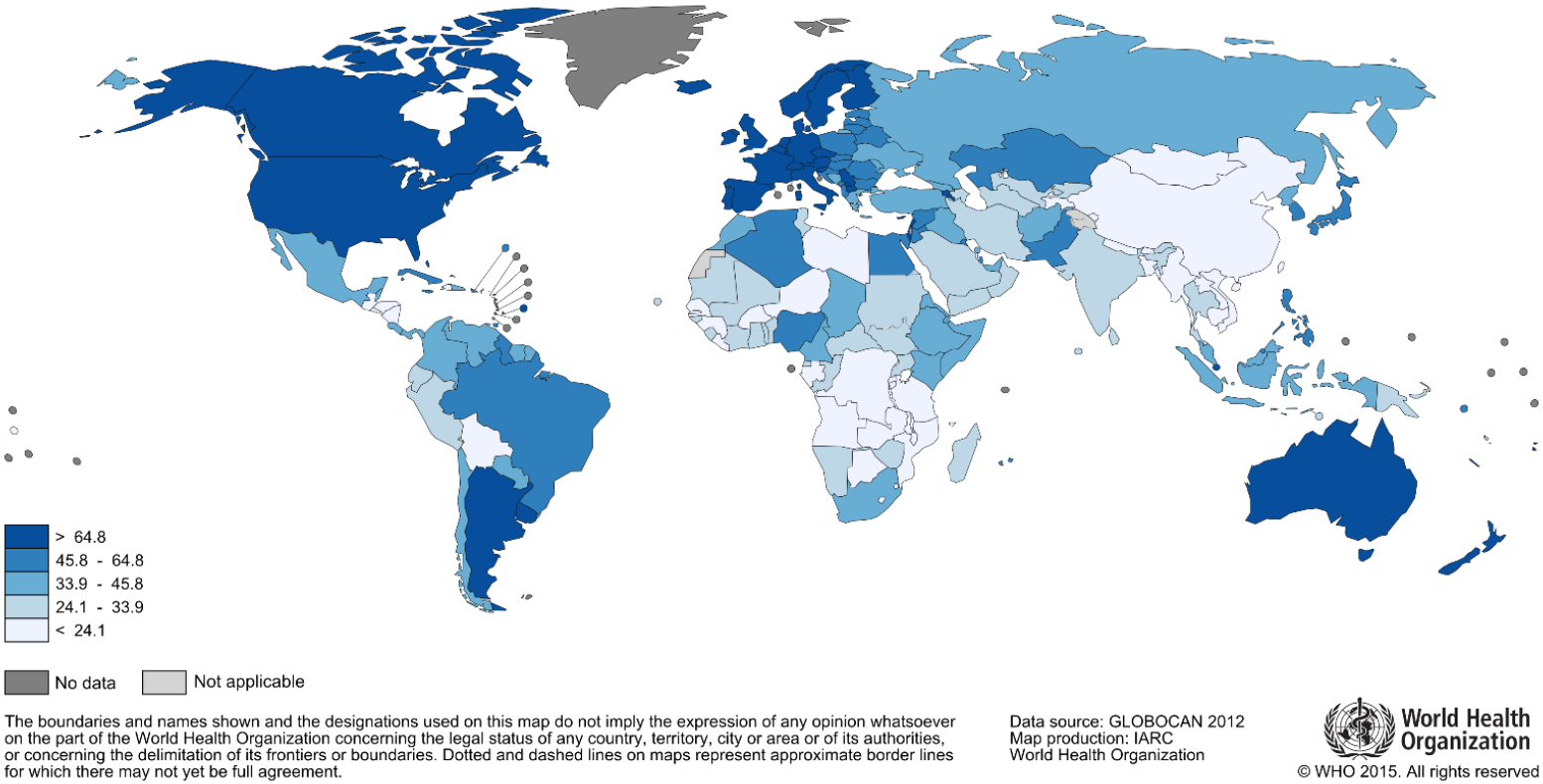
Breast cancer is the most common malignancy among women worldwide and the second most common in both sexes after lung cancer (1). There were an estimated 1.67 million new cases of breast cancer diagnosed in 2012, representing 25% of all cancers worldwide (1). The belief that breast cancer is a disease of the developed world is changing, considering that almost 50% of breast cancer cases and 58% of deaths occur in low and middle income countries (LMICs) (2). Worldwide, the incidence rates of breast cancer vary greatly from low rates of 27 per 100,000 women in Middle Africa to 92 per 100,000 women in Northern America (1) (Figure 1). However, the incidence is rising rapidly throughout LMICs, where it has superseded cervical cancer as the most frequently diagnosed type of cancer (2, 3).

Breast cancer was responsible for 522,000 deaths in 2012, with 62% (324,000) of these deaths occurring in less developed regions of the world (1). Breast cancer mortality rates range from 6 per 100,000 women in Eastern Asia to 20 per 100,000 women in Western Africa(1). There is less regional variation in the breast cancer mortality rates than in the case of incidence (Figure 2) due to differences in terms of access to treatment and survival worldwide. While breast cancer incidence is affected by a demographic transition with a resultant increasing life expectancy and a westernisation of diet and lifestyle, the mortality from breast cancer is affected by early diagnosis, an increasing awareness of the disease and the advances that have been made in breast cancer therapy in many HICs in recent years (4).

1.1.2 BURDEN OF BREAST CANCER IN SUB-SAHARAN AFRICA AND NIGERIA

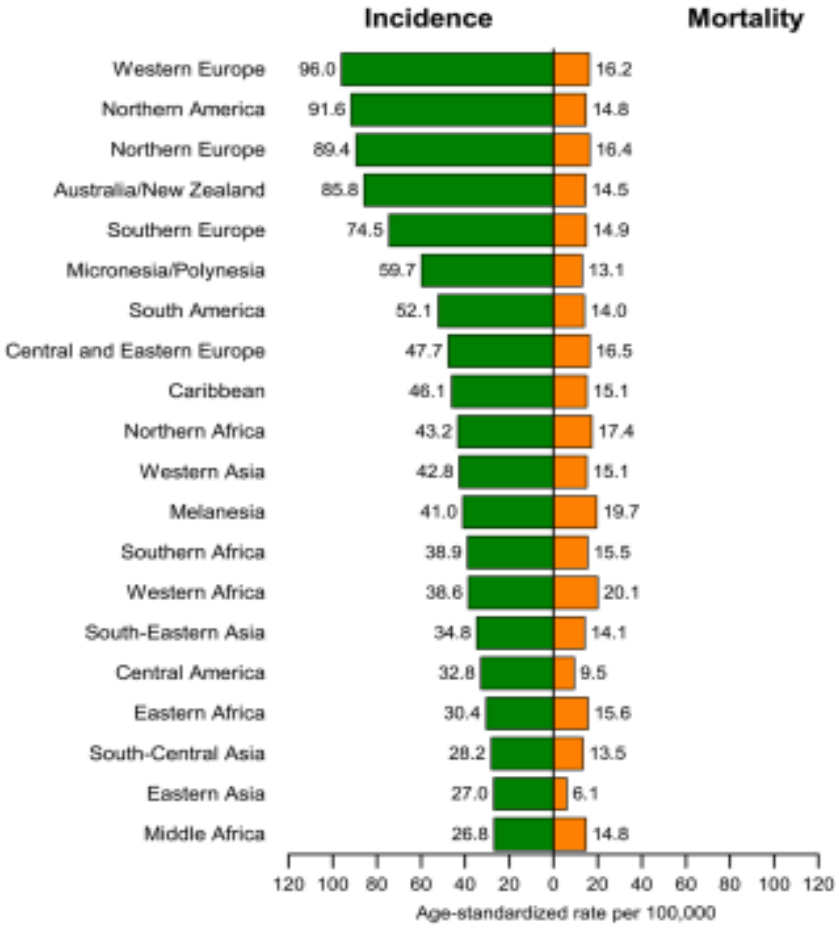
There is a scarcity of high-quality data on the incidence and mortality associated with breast cancer in sub-Saharan Africa (SSA) due to a limited number of population-based cancer registries on the continent (3). However, available estimates indicate that the number of new cases of breast cancer and breast cancer deaths in SSA is increasing(1).

Figure 1: Age standardised incidence rates of breast cancer worldwide per 100,000 women(1)



Nigeria has one of the highest age standardised incidence rates (ASR) of breast cancer in SSA, second only to South Africa and lower than in the case of Europe and North America (2). Breast cancer incidence in Nigeria, although relatively high compared to other SSA countries, is lower than in most developed regions of the world. In 2010, the ASR of breast cancer in the country was 54.3 per 100,000 women. Although much lower than the rate of 111.9 per 100,000 women in Belgium and 92.9 per 100,000 women in the United States (5), it represented a 100% increase in the incidence of breast cancer in the country over the last decade (3). In contrast, Nigeria has the 3rd highest breast cancer mortality rate worldwide (25.9 per 100,000 women) (6) with half of all women diagnosed with breast cancer in the country dying from the disease.

Figure 2: Breast cancer incidence and mortality rates by world region per 100,000 women (7)



1.1.3 FUTURE TRENDS IN BREAST CANCER INCIDENCE IN LMICS

Future trends in breast cancer incidence in LMICs are being driven by two main factors. Firstly, most LMICs are undergoing a demographic transition, which in turn leads to an increasing life expectancy. Consequently, a larger proportion of women are living longer and thus reaching the ages when the incidence of breast cancer is the highest. For example, the female life expectancy in Nigeria was 46 years in 1997, as opposed to 56 years in 2012(8). Although an increase in life expectancy will not lead to an increase in incidence rates, it will nevertheless translate into increases in the absolute number of breast cancer cases occurring in less developed regions of the world. The International Agency for Research on Cancer (IARC) has estimated that these demographic changes alone suggest that the number of breast cancer cases occurring in less developed regions of the world will increase from 882,949 in 2012 to 1,428,133 in 2035, when they will represent over 60% of all breast cancer cases worldwide(1).

Secondly, the trends associated with the incidence of breast cancer in LMICs will be affected by the changes in incidence rates due to adoption of more "westernised" lifestyles. The incidence rates of breast cancer across regions worldwide are essentially a consequence of the distribution of established risk factors for the disease (4). These well-established risk factors affect the risk of disease across all populations regardless of their ethnic/racial background and have been well documented in the literature (9-11). Non-modifiable (intrinsic) and modifiable (extrinsic) risk factors for breast cancer have been identified in many populations. The non-modifiable risk factors include gender, increasing age, race and ethnicity, and a genetic/family predisposition to breast cancer (12, 13). Other risk factors include prolonged exposure to endogenous sex hormones and growth factors, which result from early age at menarche and late menopause, and taller stature (14). The use of exogenous sex hormones (i.e. replacement therapy, oral contraceptives) is also associated with increased risk. Excess weight at post-menopausal

ages also increases the risk of breast cancer, despite the fact that the pre-menopausal high Body Mass Index (BMI) is protective (15). Alcohol consumption and limited physical activity also influence breast cancer risk (15). In contrast, young maternal age at first birth, high parity and breastfeeding reduce breast cancer risk. In Nigeria, similar to other countries in SSA, the demographic transition has resulted in an increasing life expectancy (16), but with changes to increasingly risky reproductive lifestyles characterised by advanced maternal age at first birth, a small number of children and shorter durations of breastfeeding. The adoption of a western lifestyle has been particularly evident in urban areas. According to the 2008 Nigerian Demographic and Health Survey, the general fertility rate in Nigeria is 194 births for every 1,000 women(17). This report highlights the declining fertility rate over the past 20 years and significant rural vs. urban disparities with rural areas and Northern Nigeria recording higher fertility rates(17). The changing patterns of child birth, breastfeeding, dietary factors, excess body weight, and use of exogenous hormones have been identified by other authors as some of the driving forces in the changes noted in the breast cancer incidence rates worldwide (4).

1.2 BREAST CANCER CONTROL IN HICS AND OPPORTUNITIES FOR LMICS

Breast cancer control constitutes a public health approach aimed at reducing the burden of breast cancer in populations worldwide, particularly in those characterised by high incidence and mortality from breast cancer. There are three components to breast cancer control. These include the primary, secondary and tertiary prevention of breast cancer (18). In many HICs, the governments through national cancer control programmes along with non-governmental organisations through breast cancer outreach and early detection activities incorporate evidence-based and cost-effective interventions that are spread across these three categories of breast cancer prevention.

1.2.1 Primary Prevention

The aim of primary prevention is to reduce the incidence of breast cancer by controlling the exposure to established risk factors for breast cancer. However, many of the well-established risk factors for breast cancer (e.g. reproductive-related factors, such as advanced maternal age at first birth, low parity and short duration of breastfeeding) are not amenable to change in modern societies. Thus, primary prevention strategies for breast cancer have been restricted to established modifiable risk factors such as post-menopausal excess weight, lack of physical activity, alcohol intake, use of exogenous hormones (i.e. oral contraceptives and hormone therapy) and exposure to ionizing radiation. Regular physical activity, maintenance of a healthy body weight and reductions in the alcohol intake are important components of the primary prevention strategy against a large number of non-communicable diseases including many other types of cancer apart from breast cancer, cardio-vascular disorders and diabetes.

For a small proportion of women who are at high risk of breast cancer (e.g. those with a strong family history) chemoprevention is also recommended (19).

Chemoprevention has been recommended by the United States Preventive Services Task Force, whereby it was suggested that asymptomatic women aged 35 years and above without a prior diagnosis of cancer should be informed about medications such as tamoxifen and raloxifene, which can reduce their risk for the disease (19).

Primary prevention, whilst important in cancer control, is unlikely to prevent the majority of breast cancers, therefore, early detection seeking to improve the outcomes and survival from this disease remains the cornerstone of breast cancer control (20).

1.2.2 Secondary Prevention

In secondary prevention, the goal is to either detect asymptomatic breast cancer by means of mammographic screening or to detect symptomatic breast cancer at an early stage

through early detection when treatment is more effective and, hence, more likely to lead to reductions in mortality.

Breast cancer mammographic screening

The primary aim of a breast cancer screening programme is to reduce disease mortality. Globally, mammography is the most common screening method for the detection of asymptomatic breast cancer and is an important component of the secondary prevention strategy in many HICs. The World Health Organization (WHO), the American Cancer Society and a wide range of other public health organisations recommend population-based mammography screening in the case of HICs. In the United Kingdom and many other high-income countries, population-based mammographic screening programmes have been implemented. The age groups targeted by such programmes vary from country to country but in general they range from the early/mid-40s to the late 60s/early 70s.

The introduction of a breast cancer screening programme in some populations has led to increases in the proportion of cancers diagnosed at an earlier stage (21) , improvements in the survival rates from the disease and, ultimately, reductions in breast cancer mortality. However, there has been some controversy recently, regarding the relative benefits and harms of breast cancer screening in HICs. An Independent UK Panel on Breast Cancer Screening concluded that screening reduces breast cancer mortality by about 20% but that it was associated with some degree of over-diagnosis, as well as other harms (e.g. false-positives, false-negatives, exposure to ionizing radiation) (22). These findings were broadly supported by a subsequent review by the International Agency for Research on Cancer (IARC) (23).

Population-based mammographic screening is not feasible in LMICs (24). Health systems in LMICs face a myriad of challenges including a lack of resources and a poor infrastructural capacity that is currently unable to support population-based breast cancer

screening programmes. Factors such as a younger population with a shorter life expectancy and more prevalent competing causes of mortality could reduce the benefits of such programmes in LMICs. Furthermore, breast cancer screening programmes in LMICs cannot be rigorously evaluated given the current state of the health facilities and the limited number of care providers (25). In Nigeria and other SSA countries, the lack of proper health infrastructure and the limited access to health care services impedes the successful implementation of a population-wide breast cancer screening programme. Even where opportunistic breast cancer screening programmes exist in certain SSA settings, their effect may be limited because women lack basic knowledge of the disease and are therefore unaware of the benefits entailed by these screening programmes (26). Over the past two decades, there has been a significant improvement in the stage at diagnosis of breast cancer in some African settings despite the lack of population-based or opportunistic breast cancer screening programmes in the region (27). However, more than 60% of the patients diagnosed with breast cancer still present late in Nigeria. Therefore, early detection strategies that have been successfully implemented in several LMICs, such as India (28), Malaysia (29), South Africa (30), Tanzania (31) and Sudan (32), where the stage at diagnosis has improved over time can be reproduced in other settings that lack screening programmes.

Early detection of symptomatic breast cancer

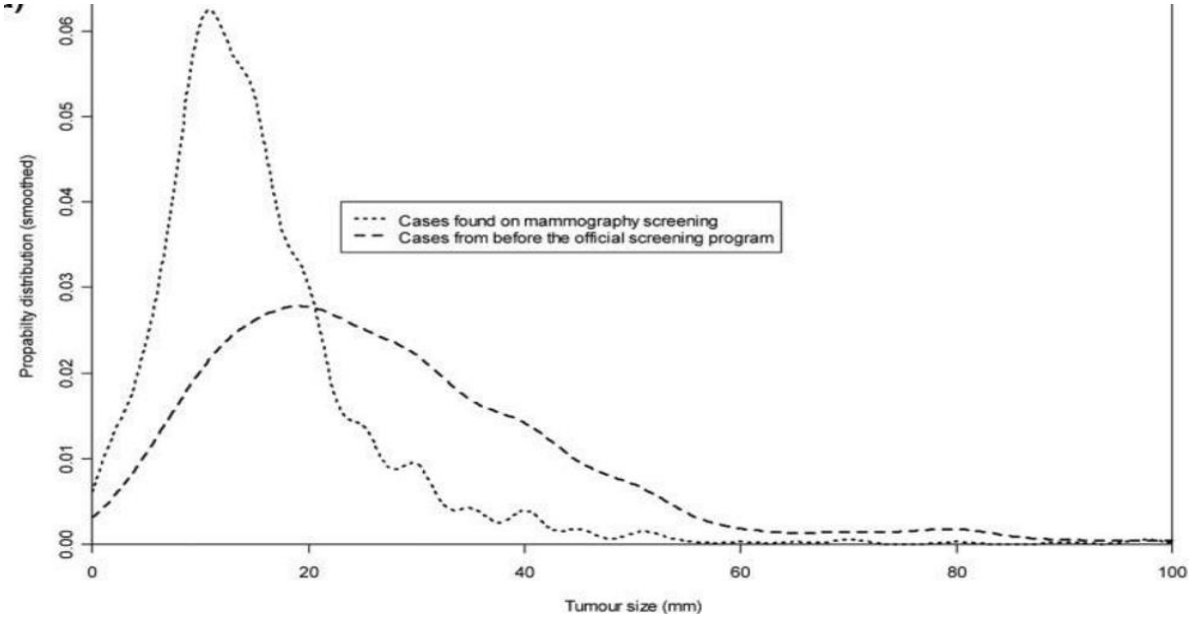
Many initial breast cancers are asymptomatic. Therefore, a lack of population-wide screening programmes may contribute to the late stage diagnosis in many African countries (33). In settings where mammographic screening is widely unavailable, the main methods used in the secondary prevention of breast cancer are self-breast examination (SBE) and clinical breast examination (CBE). A consequence thereof is that most breast lumps are identified only when they become palpable, which in most cases measure >2 cm in diameter(34). In a Norwegian study using breast tumour growth

models, it was estimated that on average tumours in women grow 10-20 mm every 1.7 years, increasing with age (35). The authors also reported larger tumour sizes, prior to the onset of screening (35) (Figure 3). The average tumour size recorded among US women aged 50-60 years and <40 years is 1.4 cm and 1.9 cm respectively (36). These tumour sizes are in sharp contrast with those found in the SSA countries, where the average tumour size ranges from 3-13 cm(37, 38). This therefore indicates the need for public health interventions to promote awareness and encourage downwards stage migration in the absence of mammographic screenings in the region.

Although some authors have questioned the effectiveness of SBE and CBE in reducing the stage at diagnosis (39), a recent review by IARC reports sufficient evidence suggesting that CBE shifts the stage distribution of breast cancers towards a lower stage, though there is limited evidence indicating that CBE reduces breast cancer mortality (23). However, both SBE and CBE contribute to increasing the awareness about breast cancer in the population, particularly in LMICs where the general knowledge about breast cancer and its symptoms is limited. The Breast Health Global Initiative recommends CBE as a diagnostic tool and a necessary resource for both HICs and LMICs (40, 41). Furthermore, the findings from a large randomised controlled trial in India suggest that CBE can be used as a method to stage migrate breast cancer downwards, and if combined with effective treatment, it can improve breast cancer survival (42).

In the USA, prior to the onset of the breast cancer screening in 1973, improvements in the breast cancer survival rates were largely due to breast education programmes and the detection of palpable breast cancers by means of SBE or CBE (43). These findings, together with the tumour size distributions found in SSA, which are much larger than those in the pre-screening era in Norway, thus suggest that the breast cancer outcomes in developing countries can be improved in a more rapid manner by means of early detection and migration to a lower stage at diagnosis, rather than by screening mammography (44).

Figure 3: Distribution of tumour sizes of the cases found on screening and before the onset of the mammographic screening programme in Norway (35).



1.2.3 Tertiary Prevention

Tertiary prevention involves the treatment of women with breast cancer with the purpose of improving the quality of life, disease specific outcomes and survival. This often includes breast surgery, radiotherapy, systemic therapy and palliative care (41). For breast cancer survivors, support groups and rehabilitation programmes are key components of the tertiary prevention strategy in HICs. In LMICs, the most common treatment method for breast cancer is surgery. However, in cases where women present at late stages, the tumour may be inoperable (45). Although radiotherapy is an important component of any cancer control programme, the access to radiotherapy machines is often limited or non-existent in many LMICS. A recent review by Abdel-Wahab and colleagues revealed that out of 52 African countries, only 23 provided radiotherapy services (46). Out of the 277 radiotherapy machines available in the African continent in 2010, 60% of these were concentrated in South Africa and Egypt with over 198 million people in the neighbouring regions having no access to radiotherapy (46). The access to cancer drugs for systemic therapy is often limited in LMICs. Conducting a laboratory assessment for oestrogen,

progesterone and the human epidermal growth factor receptor 2 (HER2), though required prior to the initiation of the hormonal treatment, is expensive and often unavailable in many low-resource settings. Therefore, in LMICs where the resources may be limited to effectively incorporate tertiary prevention programmes, the impact of primary and secondary prevention would be significantly important in improving outcomes and survival.

1.3 BREAST CANCER SURVIVAL IN SUB-SAHARAN AFRICA

As mentioned above, the ultimate goal of a breast cancer control programme is to reduce mortality from this disease. However, in order to achieve this, such programmes must lead to improvements in breast cancer survival. Survival is significantly influenced by the stage at diagnosis of breast cancer. In Uganda, the 5-year survival rate for women diagnosed in a tertiary hospital in Kampala was 100% for those in the early stages (I/II) and 51.8% for those in the late stages (III/IV) (47) (Figure 4) (the staging classification is discussed in section 1.6). Previous studies conducted on breast cancer survival in SSA report low survival estimates, particularly in women diagnosed at late stages (Table 1). The incidence of breast cancer in Uganda is 27.5 per 100,000 women, constituting only 30% of the overall breast cancer incidence in the USA which is 92.9 per 100,000 women(1). However, the probability that a Ugandan woman would die from breast cancer is much higher than in the case of her counterpart in a western country owing to the differences in the available treatment and survival (48).

An advanced stage at diagnosis has been widely reported to significantly affect breast cancer survival worldwide (49) and in SSA (Table 1), and further research into the factors that predict the late stage at diagnosis is needed in SSA. Potential determinants of the late stage at diagnosis and, hence, breast cancer survival include factors that affect the tumour

growth rate – e.g. age at diagnosis and tumour morphology, grade, and hormone receptor status – as well as delays in breast cancer diagnosis.

Figure 4: Probability of dying from breast cancer by stage at diagnosis (47)

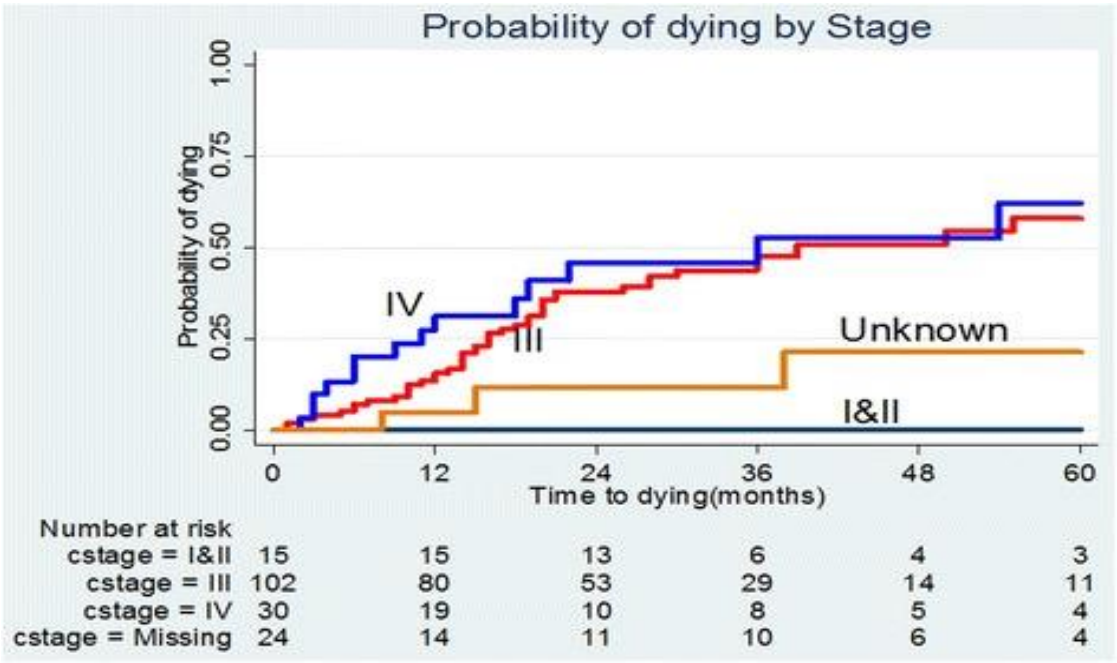


Table 1: Published studies showing breast cancer survival estimates in SSA

Author, year of publication [ref no.]	Country	Setting	Sample size (n) /Study design	Mean age at diagnosis	Year of diagnosis	Late stage % (III/IV)	Survival time (years)	Survival (%) Early Vs Late
			Population-based studies					
Coleman, 2008 (50)	Africa-Algeria	NR	P	NR	2008	NR	5	45
Sankaranarayanan, 2011 (51)	Uganda	NR	P	NR	1993-1997	NR	5	36
	Zimbabwe	NR	P	NR	1993-1997	NR	5	47
	Gambia	NR	P	NR	1993-1997	NR	5	10
			Hospital-based studies					
Anyanwu, 2000 (52)	Nnewi, Nigeria	1 tertiary and 2 secondary hospitals	78 (R)	44	NK	56	2.6	50
Gakwaya, 2008 (53) Early/Late	Uganda	Tertiary	297 (R)	45	1996-2000	77	5	74/39
Kene, 2010 (54)	Zaria, Nigeria	Tertiary	99 (R)	44.5	2001-2005	62.1	3	70
Arowolo, 2010 (55)	Ife, Nigeria	Tertiary	62 (R)	49.1	NR	100	1, 2, 5	66.7, 42.9, 11.9

Author, year of publication [ref no.]	Country	Setting	Sample size (n) /Study design	Mean age at diagnosis	Year of diagnosis	Late stage % (III/IV)	Survival time (years)	Survival (%) Early Vs Late
Popoola, 2012 (56)	Lagos, Nigeria	Tertiary	176 (R)	50.5	2005-2011	65.3	5	26
Kantelhardt, 2012 (57) Early/Late	Ethiopia	Tertiary	1303 (P)	43	2005-2010	74.7	5	78/38
Galukande, 2015 (47) Early/Late	Uganda	Tertiary	262 (P)	45	2004-2007 & 2010-2012	89.5	5	100/51.8

SSA: sub-Saharan Africa; NK: not known; P: prospective; R: retrospective; Early: sages I/II; Late stages III/IV

1.4 STAGE AT DIAGNOSIS OF BREAST CANCER

1.4.1 TNM CLASSIFICATION

Breast cancer has been categorised into four stages (I, II, III and IV) by the American Joint Committee on Cancer (AJCC), using the tumour, node, metastasis (TNM) system(58). This categorisation takes into account the size of the primary tumour (T), the lymph node involvement (N) and the absence or presence of metastases (M), which are all important prognostic indicators in breast cancer.

Tumour Size (T)

Tumour size (T) is an important component of the stage at diagnosis and a strong predictor of survival (59). Tumours with a small size are associated with a better prognosis. In stage 1, T measures less than 2 centimetres (cm) in diameter, in stage II, T = 2-5 cm in size, in stage III T >5 cm in diameter, whereas stage IV involves a tumour of any size with extension to the skin or chest wall.

Table 2: Breast cancer staging by T, N, M grouping (AJCC) 7th Edition (58)

Anatomic Stage/Prognostic Groups			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Regional lymph node involvement (N)

Breast cancer can spread through the lymphatic vessels to the lymph nodes. Therefore, the regional lymph node involvement is an important component of the TNM staging. If the lymph nodes cannot be assessed, the result is reported as NX; if there is no regional lymph node involvement, the result is N0; if there is involvement of the ipsilateral lymph

node, it is N1; if the lymph nodes are fixed to each other or to other structures, N2; if there is involvement of the ipsilateral internal mammary lymph node(s), it is reported as N3 (Table 2).

Metastases (M)

The absence (M0) or presence of metastases (M1) to distant body organs forms the (M) component of the TNM staging (Table 2). In cases where metastases cannot be assessed, the result is reported as (MX).

The various combinations of T, N and M to give stages I, II, III and IV are shown in Table 2. Stages I and II are usually referred to as "early stage" breast cancer and stages III and IV as "late stage" breast cancer.

1.4.2 LATE STAGE DIAGNOSIS OF BREAST CANCER IN SSA AND NIGERIA

The stage at diagnosis is one of the most important prognostic factors associated with breast cancer (52, 54). The situation in SSA and Nigeria is similar to that in many other developing regions where a late stage diagnosis is usually the more common outcome (60-62). In HICs, such as the United States and the United Kingdom, reductions in mortality from breast cancer prior to the introduction of a population-wide screening programme suggest that an earlier stage at diagnosis, which can be achieved through improved breast cancer awareness, is crucial in obtaining favourable outcomes in the management of breast cancer patients (4). Breast cancer awareness and knowledge of the benefits associated with early stage at diagnosis are poor in most SSA countries (63). There is a lack of awareness among the public and health care professionals of the need for early detection of breast cancer in SSA (64) and consequently, advanced stage at diagnosis remains a common feature in the region (61, 65). Studies from western countries have reported ethnic disparities in the stage at diagnosis, with minority groups

presenting at later stages (66, 67). However, there is little empirical evidence of the drivers of late stage diagnosis in SSA.

The stage at diagnosis is an important predictor of treatment options and breast cancer survival. Studies have reported a survival advantage (disease free and overall survival) in early stage (I and II) over late stage (II and III) breast cancer patients (54). Identifying the factors that predict late stage diagnosis is crucial to the development of strategies to stage migrate breast cancer downwards in SSA settings. Breast cancer stage migration can result in improved survival rates among the breast cancer patients in SSA. As many risk factors for breast cancer are not amenable to change, as discussed in section 1.4.1, reductions in breast cancer mortality can be mainly achieved through early diagnosis and treatment. Consequently, many have advocated the need for more research into the factors responsible for the late stage at diagnosis in SSA populations (68).

1.5 DIAGNOSTIC DELAYS IN BREAST CANCER

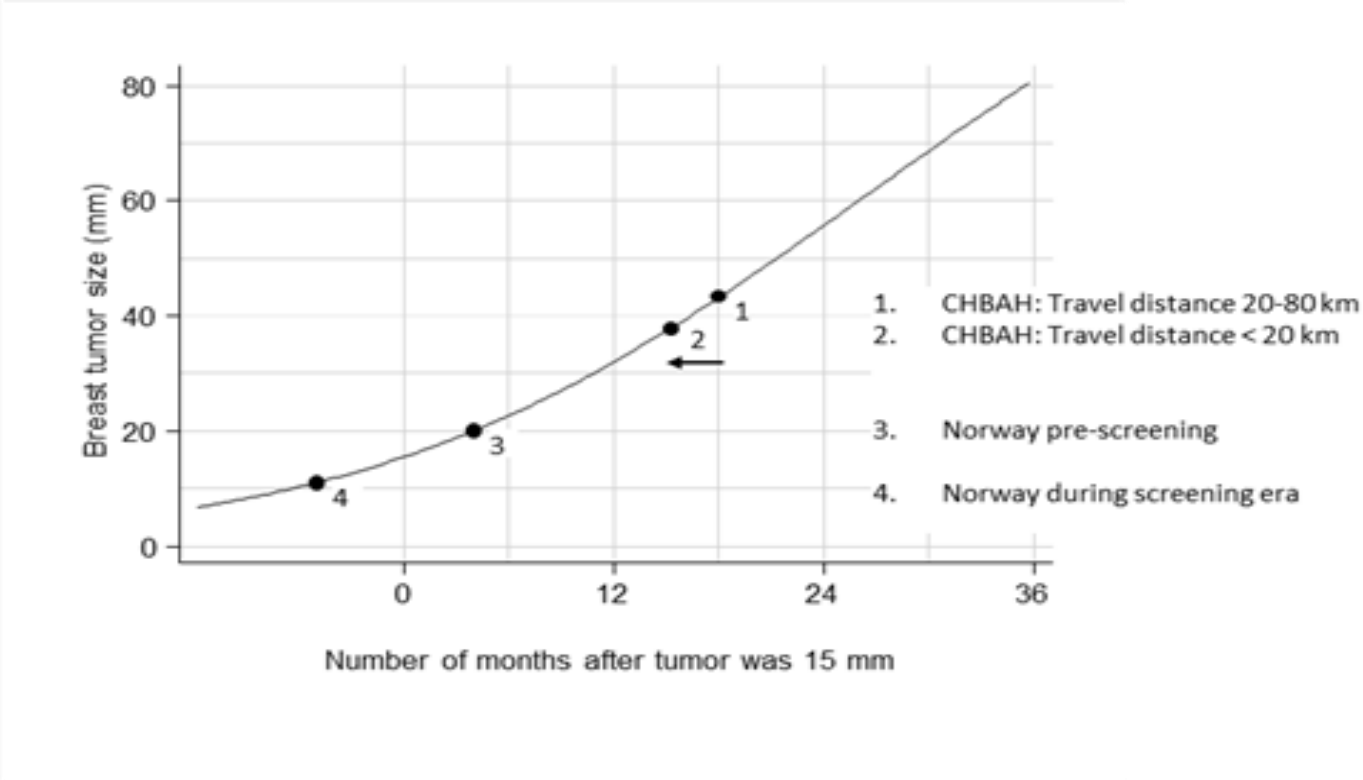
Delays in a woman's journey from her first reported symptom to a diagnosis of breast cancer can significantly affect the stage at diagnosis and survival (69). Longer waiting periods prior to a breast cancer diagnosis and the initiation of therapy are of prognostic concern, as these delays can lead to stage progression and death from breast cancer (69). Delays in breast cancer have been described in the context of *total delay*, *patient delay* and *provider delay*. Total delay has been defined as the time from the symptom discovery to the diagnosis or the start of treatment for breast cancer (70). This time period has been further categorised into two main intervals of *patient delay* and *provider or system delay* (69). Patient delay has been described in the literature as the time from the first reported symptoms to the presentation at a care provider, while provider delay is the time from the presentation at the care provider to a confirmed diagnosis of breast cancer (69). In HICs, the time from when a woman discovers a breast cancer symptom to her presentation and

subsequent diagnosis is significantly shorter than in many LMICs. In a London breast clinic, the median patient delay was 13 days, whereas the median system delay was 18 days (71). Poum *et al.* from Thailand also reported a median patient delay of 12 days and a system delay of 21 days (72), similar to the reports from Canada (73), France (74), Germany (75) and the United States (76). In Mexico, the self-reported patient delay was only 10 days, similar to findings in HICs. However, the system delay was much longer at 5 months due to patients having to visit multiple care providers before a definitive diagnosis was made, in line with findings from other LMICs (70). The short delay intervals in HICs are in sharp contrast with the SSA setting. In South Africa, the median patient delay reported by Moodley *et al.* was 164 days and the median system delay was 92 days (77). In Rwanda, the median patient and system delays were both 150 days (78). Similar long delays have been reported in Nigeria (60) and Uganda (79). In HICs, less than 20% of women report a total delay of over 3 months (72), which is comparable to the findings in Germany (75). In contrast, 70% of the breast cancer patients in Nigeria reported a total delay greater than 3 months (60).

A relationship between delayed diagnosis of breast cancer and more advanced clinical stage has been highlighted in studies conducted in other settings including Mexico (70), Thailand (72) and Germany (75), and in a SSA country, namely Rwanda (78). These findings suggest that the efforts to promote shorter intervals from the first reported symptoms to the presentation and diagnosis in LMICs could have a substantial impact on disease stage and survival (78). A delayed diagnosis is also associated with an increasing tumour size and longer travel distance to a diagnostic health facility. In Figure 5 below, the expected growth curves were generated based on the observed delay to diagnosis and the tumour sizes from the review by Weedon-Fekjær *et al.* (35), and the travel distance to a health facility as reported in South Africa by Dickens *et al.* (80). In the South African study, a more advanced stage at diagnosis at the Chris Hani Baragwanath Academic

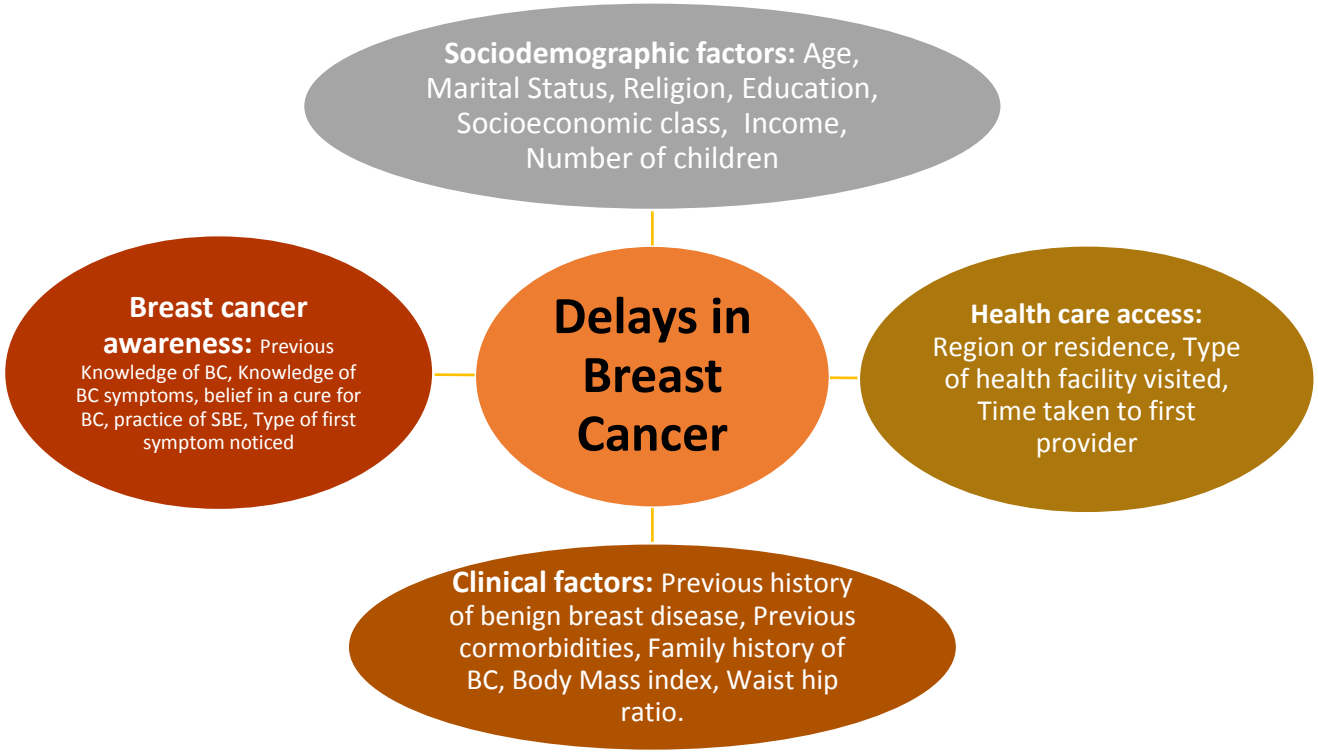
Hospital, Johannesburg (Soweto) South Africa (CHBAH) was reported in patients who lived further away from the facility. The authors speculated that the delays to diagnosis in women who lived further away from the facility could contribute to the later stage at diagnosis reported in this population.

Figure 5: Tumour growth curve model based on the tumour sizes reported in the review by Weedon-Fekjær, 2008 (35) and the travel distance reported by Dickens, 2014 (80) in South Africa.



Patient and system delays have been described extensively in the literature from high income countries, but only a limited number of studies in SSA have been published on this topic (60, 78, 81). It is critical that the reasons for the delay are properly investigated and that interventions seeking to address these issues are developed in SSA. The conceptual framework below (Figure 6) shows the various factors that may contribute to the delays in a woman's journey from her first reported symptom to a diagnosis of breast cancer. These factors have been grouped into sociodemographic, breast cancer awareness, health care access and clinical factors.

Figure 6: Conceptual framework showing the determinants of diagnostic delays in women with breast cancer



BC: Breast Cancer, SBE: Self-Breast Examination

Sociodemographic factors

Lower educational levels, younger age at diagnosis and single status are some of the sociodemographic factors that have been identified as being significantly associated with diagnostic delays in women with breast cancer in Nigeria (82). Other authors have identified women with older age, lower income and low socioeconomic class more likely to present late (75).

Breast cancer awareness factors

Previous knowledge of breast cancer and awareness of breast cancer symptoms and the treatment thereof might be significant determinants in relation to diagnostic delays in women with breast symptoms. Previous studies have identified a lack of breast cancer awareness (among women and health care professionals) (60), poor knowledge of breast cancer symptoms and poor screening practices as some of the factors associated with diagnostic delays (83).

Health care access factors

A lack of clear referral channels from primary to secondary or tertiary health facilities notably results in prolonging the time from when symptoms are initially noticed to when a diagnosis is made and the treatment is offered, which imposes health system related barriers on the diagnosis and treatment of breast cancer (41). Some studies have reported region of residence and urban vs. rural differences in relation to the diagnostic delays in breast cancer. In Mexico, although a short patient delay of 10 days was reported, whereas a long system delay of 5 months (150 days) was observed and the authors speculated that this delay may be due to patients typically receiving care from different practitioners and different facilities, which often prolongs the health care system navigation process (70).

Clinical factors

The role of clinical factors such as a previous history of benign breast disease, the presence or absence of co-morbidities, family history of breast cancer, body mass index (BMI) and waist hip ratio have not been properly described in the SSA setting. The focus of the previous studies investigating the delays in the diagnosis of breast cancer in SSA has been on sociodemographic and health care access factors and not on clinical factors. The extent to which clinical factors contribute to these delays is therefore unclear. In the case of women with a previous history of comorbidities, such as hypertension or diabetes, who are in constant contact with the health care system for regular checks and follow-ups, it is not known whether being in close contact with the health care system renders them less likely to delay than others or whether women with a previous history of benign breast disease are less likely to delay given their previous contact and ability to navigate the health care system.

1.6 PROBLEM STATEMENT, RESEARCH QUESTIONS AND OBJECTIVES

The stage at breast cancer diagnosis significantly affects breast cancer survival in SSA. Therefore, there is a need to investigate the factors that influence stage and diagnostic delays in the region. As presented above, there is evidence suggesting that breast cancer in SSA is often characterised by an advanced stage at diagnosis and delays from the first reported symptom to diagnosis in majority of women with symptoms (60, 61, 78). There also appears to be a consensus suggesting that interventions in the region should target factors that have been reportedly associated with a later stage at diagnosis. However, there is a dearth of literature on the determinants of later stage at diagnosis and diagnostic delays in SSA, particularly in West Africa and Nigeria. As such, the new knowledge provided in this study will serve as a first step towards developing interventions aimed at achieving a downward stage migration in the region.

The main focus of this PhD thesis was to investigate the determinants of stage at diagnosis and the delays to diagnosis in women with breast cancer in SSA and to identify the factors that may be amenable to intervention in order to reduce late stage diagnosis of breast cancer, and to improve survival and reduce mortality from BC in SSA.

The main objectives of this PhD thesis were:

1. To carry out a systematic review of stage at diagnosis of breast cancer in sub-Saharan Africa to: (i) identify possible sources of variation across SSA and (ii) compare the percentage of late stage of breast cancer diagnosis in SSA with black and white populations in the United States (US) using Surveillance, Epidemiology, and End Results (SEER) data.
2. To design and implement a multicentre case-control study referred to as the Nigerian Integrative Epidemiology of Breast Cancer Study (NIBBLE), at six government hospitals in Nigeria.
3. To conduct a case-only analysis within the framework of NIBBLE, to identify the sociodemographic, breast cancer awareness, health care access and clinical determinants of (i) stage at diagnosis of breast cancer; and (ii) a woman's journey from the first reported symptom to the diagnosis of breast cancer, and of any delays, in Nigerian women with breast cancer.

1.7 OUTLINE OF THE THESIS

This thesis incorporates published and recently submitted journal papers and other chapters linked by supporting material. There are six chapters in this thesis. Following the introduction, and five other chapters which are described in detail below, the references and appendices are presented.

Chapter 2: In this chapter, the published literature on stage at diagnosis of breast cancer in SSA is systematically reviewed in order to provide the overall context for the thesis (objective 1). The factors associated with late stage diagnosis in SSA are investigated and the results are subsequently presented. A comparison of stage at diagnosis is made between the studies conducted in SSA and those in white and black populations in the United States. This chapter follows the conventions that govern research paper writing and is titled, "Stage at Diagnosis of Breast Cancer in Sub-Saharan Africa: A Systematic Review and Meta-Analysis".

Chapter 3: This chapter provides an overview of the methods used to design and implement a multi-centre study in Nigeria (objective 2). The study setting, study population, data collection process and field work are described. The parent study - The Nigerian Integrative Epidemiology of Breast Cancer Study (NIBBLE), within the framework of which this PhD study was conducted, and the six study sites in Nigeria are described in detail.

Chapter 4: The fourth chapter follows the conventions that govern research paper writing, is written in research paper style and is titled: "Determinants of the Stage at Diagnosis of Breast Cancer in Nigerian Women: Sociodemographic, Breast Cancer Awareness, Health Care Access and Clinical Factors" This chapter addresses objective 3(i).

Chapter 5: The fifth chapter addresses objective 3(ii) and describes the determinants of delays to diagnosis in Nigerian women and a woman's journey from her first reported symptom to a diagnosis of breast cancer. In this chapter, the factors contributing to diagnostic delays in Nigerian women are identified and presented.

Chapter 6: This chapter collates the major findings of the thesis to provide a critical assessment of the factors that affect the stage at diagnosis of breast cancer and the diagnostic delays in SSA women. In chapter six, the previously known findings on these topics will be discussed and how this thesis contributes to the existing body of knowledge. The strengths and limitations of this thesis are highlighted, the implications for future research and policy are discussed and further recommendations are made for future research.

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PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A- Student Details

Student	Elima Jedy-Agba
Principal Supervisor	Prof. Isabel dos-Santos Silva
Thesis Title	Breast Cancer in sub-Saharan Africa: Determinants of Stage at Diagnosis and Diagnostic Delays in Women with Symptomatic Breast Cancer

If the Research Paper has previously been published, please complete Section B, if not please move to Section C

SECTION B- Paper already published

Where was the work published?	The Lancet Global Health		
When was the work published?	December 2016		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	Not applicable		
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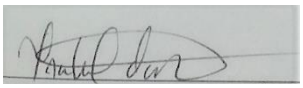
SECTION D- Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I extracted data from all eligible studies in the review, analysed data, drafted the manuscript, and made subsequent revisions to the manuscript

Student Signature:  **Date: 30/12/2016**

Supervisor Signature:  **Date: 21/12/2016**

CHAPTER 2

2.1 RESEARCH PAPER 1: STAGE AT DIAGNOSIS OF BREAST CANCER IN SUB-SAHARAN AFRICA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: Breast cancer incidence rates in sub-Saharan Africa (SSA) are relatively low but, as survival from the disease in the region is poor, mortality rates are as high as in high-incidence countries. Stage at diagnosis is a major contributing factor to poor survival from breast cancer. We conducted the first systematic review and meta-analysis on stage at diagnosis of breast cancer in SSA to examine trends over time, and investigate sources of variations across the region.

Methods: A search was conducted in MEDLINE, EMBASE, Africa-Wide Information and Web of Knowledge to identify studies on breast cancer stage at diagnosis in SSA women published before 1st January 2014. Random-effects meta-analyses were performed to investigate between-study heterogeneity in percentage of late stage breast cancer (stage III/IV), and meta-regression analyses to identify potential sources of variation. Percentages of late stage breast cancer in SSA were compared with similar estimates for US Blacks and Whites derived from the Surveillance, Epidemiology, and End Results database.

Findings: Eighty-three studies, representing 26788 women from 17 SSA countries, were included. There was wide between-study heterogeneity in the percentage of late stage (median 74·7%, range: 30·3%, 100%; I^2=98·3%, P<0·001). Percentage of late stage was lower for Southern African non-Blacks (absolute difference (AD) relative to Western African Blacks=-18·1%; 95% CI: -28·2%, -8·0%), but higher for populations from mixed (urban and rural) rather than urban settings (AD=13·2%, 95% CI: 5·7%, 20·7% in analysis restricted to Blacks). Percentage of late stage in Blacks decreased over time (AD for years ≥2000 vs. <1980: -10·5%, 95% CI: -19·3%, -1·6%) but, around 2010, it was still higher than it was in US Whites and Blacks four decades previously.

Interpretation: Strategies for early diagnosis of breast cancer should be regarded as a major priority by cancer control programmes in SSA.

RESEARCH IN CONTEXT

Evidence before this study

The number of new diagnoses of breast cancer in sub-Saharan Africa (SSA) is expected to rise rapidly due to population aging and changes in the prevalence of risk factors. As survival from breast cancer in the region is poor, despite relatively low incidence rates, mortality rates from this disease are as high as those in western countries. Stage at diagnosis is a main determinant of survival from breast cancer. Previous studies have reported a wide variation in stage at diagnosis of breast cancer across SSA, but none has examined trends in stage at diagnosis over time or investigated potential sources of variations across the region. We searched four databases – MEDLINE, EMBASE, Web of Knowledge and Africa-Wide Information – using a combination of keywords and MESH terms (detailed in Appendix 3) to identify all studies published in any language before the 1st January 2014 which reported on stage at diagnosis of primary invasive breast cancer in women in SSA. Studies which focused only on a particular stage (e.g. metastatic breast cancer only), reviews and conference proceedings were excluded. A total of 83 eligible papers were identified (as detailed in Figure 1), comprising a total of 24213 staged patients. Random effects models revealed wide between-study heterogeneity in the percentage of late stage (stages III/IV): median 74·7%, range: 30·3 to 100%; I^2=98·3%, P<0·001. Meta-regression analyses showed that percentage of late stage was lower for Southern African non-Black women and, among Black women, higher for women residing in areas that included rural settings than in urban only settings. Percentage of late stage in SSA Black women decreased over time. Nevertheless, a comparison with data from the US Surveillance, Epidemiology, and End Results database

showed that the percentage of late stage in SAA Black women around 2010 was still higher than it was in US White and Black women in the 1970s.

Added value of this study

This systematic review provides the most comprehensive synthesis to date of the available evidence on stage at diagnosis of breast cancer in SSA. The review showed that the large majority of patients in SSA were diagnosed at a late stage (stages III/IV). There was, however, a wide range of estimates across the region; the reasons for this were unclear. Percentage late stage was, as expected, higher in Black than non-Black women; however, among Black women there were no clear differences by region or type of health facility, except that it was lower in urban settings. The review also highlighted the paucity of published data on breast cancer stage from certain parts of the region, e.g. from Middle Africa.

Implications of all the available evidence

Although some improvements in stage at diagnosis of breast cancer in sub-Saharan Africa have occurred over the last few decades, in many settings, very advanced disease is still prevalent at diagnosis. Nevertheless, within the region, public-sector settings exist with a much improved stage profile, indicating that stage migration is achievable in such settings, i.e. in the absence of organised screening. To prevent avoidable deaths from this potentially good prognosis cancer, breast cancer control measures require a strong emphasis on early diagnosis and treatment. Earlier diagnosis primarily concerns a time window with symptomatic disease; thus efforts to promote early presentation and faster referrals, diagnosis and treatment need strengthening.

INTRODUCTION

Breast cancer incidence is highest in high-income countries (HICs) but it has been rising in low and middle income countries (LMICs).(84, 85) Survival from breast cancer is poorer in LMICs, and because of their large populations, most deaths from this cancer now occur in less developed parts of the world. In 2012, about 53% of all newly diagnosed cases of breast cancer, and about 58% of deaths from this disease, occurred in LMICs.(1) Breast cancer incidence in LMICs is likely to increase further in forthcoming decades as a result of population ageing and increased adoption of Western lifestyles.(84, 85)

Breast cancer incidence in Sub-Saharan Africa (SSA) is among the lowest in the world (estimated age-standardized rates (ASR) ranging from 27/100000 in Middle Africa to 39/100000 in South Africa regions). However, mortality from this cancer is as high as in high-incidence countries (estimated ASR range from 15/100000 in Middle Africa to 20/100000 in Western Africa)(86), higher than in North America (ASR=14.8/100000) which has a much higher breast cancer incidence (ASR=91.6/100000).(86)

Stage at diagnosis is a major determinant of survival from breast cancer, with early stage disease being associated with a better prognosis compared to late stage disease(49), a pattern present in SSA settings.(57, 87-89) Earlier stage at diagnosis, combined with therapeutic advances, was a major contributor to the sharp reductions in breast cancer mortality over recent decades in most HICs.(49) In contrast, the majority of breast cancer patients in SSA present with late stage disease, thought to be due to low levels of awareness, lack of early detection programme and poor facilities for accurate and timely diagnosis and treatment.(87, 90-98) Variations in stage of breast cancer at diagnosis across SSA, and over time in some of its settings(30), have been previously reported in

individual settings(47, 87, 89, 90, 94) but, to our knowledge, have not been examined systematically across SSA.

In this study, we systematically review the published literature on stage at diagnosis of breast cancer in SSA, examine trends over time, and investigate possible sources of between-study heterogeneity which may help to identify appropriate approaches for down-staging this disease in the region.

METHODS

Literature search and study inclusion

A study protocol (Appendix 1), based on the PRISMA guidelines (Appendix 2), was developed. Four databases – MEDLINE, EMBASE, Web of Knowledge and Africa-Wide Information (AWI) (https://www.ebscohost.com/academic/africa-wide-information) – were searched to identify all studies published before 1st January 2014 which reported on stage at diagnosis of primary invasive breast cancer in women in SSA. The United Nations classification (99) was used to define SSA countries and to group them according to region (i.e. Southern, Eastern, Western and Middle Africa). An initial keyword search, and subsequent searches based on Medical Subject Headings (MeSH), were performed using various combinations of "breast cancer*" or "breast neoplasm*" or "breast carcinoma*" or "breast sarcoma*" or "breast tumour*" or "breast tumour*" or "breast malignanc*" AND "Stage" or "presentation" or "grade" or "clinical features" or "clinical findings" AND "Africa" (Appendix 3). No restrictions were imposed on the ethnicity/race of women, whether conducted in public/private settings, age at diagnosis, or language of the publication.

We identified 675 articles and reviewed in a two-step process (Figure 1). The first step consisted of a title and abstract review to identify those that were deemed potentially eligible for inclusion. This review was done by one of three authors (EJA, IdSS or VM)

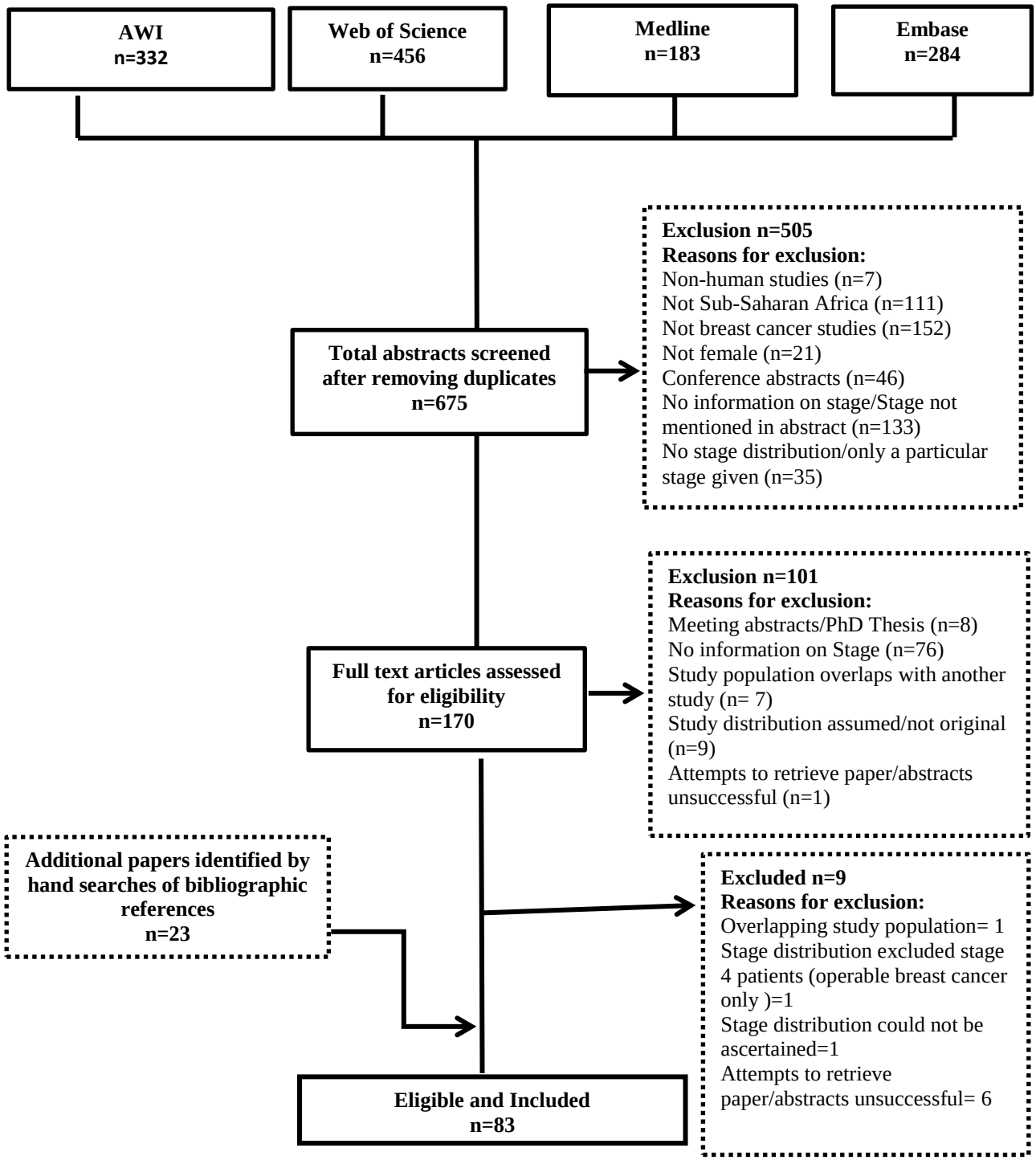
to exclude: duplicate publications; articles from North Africa (i.e. Algeria, Egypt, Libya, Morocco, Sudan, Tunisia, and Western Sahara)(99); those which did not focus on breast cancer (e.g. studies of 'all cancers'), did not include women with breast cancer (e.g. surveys on awareness), did not provide information on stage (e.g. pathology series, papers on screening), or focused exclusively on male breast cancer. Articles that restricted inclusion to a particular stage (e.g. metastatic breast cancer) were also excluded. Reviews and conference proceedings were not included, but their references were cross-checked for completeness. Studies that included both female and male breast cancer patients were included, even if they did not provide enough information to allow the exclusion of male patients because men typically represented <2% of all study subjects. A random sample of 50% of the total abstracts was independently reviewed by one of the other two reviewers; this showed no disagreements on which papers to select for full text review. A total of 170 articles were considered as potentially relevant, and the full text retrieved for all of these except six which could not be traced through institutional libraries or direct contact with the authors (the latter attempts proved futile). The sample sizes of two(100),(101) of the untraceable six studies were 47 and 120 according to Edmund et *al*.(102)

Data Extraction and quality appraisal

In the second step, all 164 full-text articles were reviewed to confirm eligibility and, if eligible, data extraction was performed. EJA assessed all articles for eligibility and abstracted the data, using an adapted version of a pretested data entry e-form.(103) All articles were independently reviewed by one of the other two reviewers (IdSS or VM). For each eligible paper, data were extracted on the numbers of patients who presented in stages I, II, III and IV at diagnosis, or at early (I/II) and late (III/IV) stages if only this combined information was provided, country, study design, study population and type of clinical setting (e.g. primary, secondary, or tertiary clinical facility; population-based

cancer registry; public/private/mixed patients), years when breast cancer patients were diagnosed, race, average age at time of diagnosis (mean or median; if only age categories were reported the mean age was estimated from the mid-point and the reported numbers in each category), and methods and classification used to ascertain stage.

Figure 1. Flow diagram describing study identification, screening and eligibility



Footnote: Many studies could fit into more than one exclusion category; these were allocated to the first eligible category in the order listed in the Figure.

Time at diagnosis in the original papers was either the time at clinical or pathological diagnosis. If a study provided numbers for each specific American Joint Committee Cancer Tumour Node Metastases (TNM) category (e.g. T2, N0, M0; Chapter 1, Table 2) we used these to derive numbers in each one of the four stages. For three studies(104-106) we obtained estimates that differed from those published because T3N1M0 tumours in the original publications were classified as stage II, but they should be stage III according to the 7th edition of the American Joint Committee on Cancer Breast Cancer Staging Manual.(107) Four studies(108-111) provided information on the tumour (T1-T4) only and, for these, T3/T4 was taken as a proxy for stages III/IV. Whenever available, we extracted data on menopausal status, tumour's characteristics (e.g. histology, size, grade, receptor status) and time from first symptoms to diagnosis. Disagreements between extractors were discussed and a consensus reached. Most of the papers with missing information were from studies conducted several decades ago, hence no attempt was made to contact their authors as it is unlikely that the required information could still be retrieved. If there were multiple papers for the same study period, setting and author, the paper with the most information on tumour stage was selected for inclusion.

The quality of the papers included in the review was assessed by two independent reviewers. An adapted version of the standardized quality assessment criteria developed by Eng *et al.*(103) was used to assess the potential for selection and information bias as well as the availability of data on key variables (e.g. age and year at diagnosis, tumour grade) (Appendix 4). A quality score ranging from 0 (low) to 28 (high quality) was given to each paper.

Data analysis

The primary outcome was percentage (p_{34}) of breast cancer diagnosed at late stages (stages III/IV), defined as $p_{34}=n_{34}/n$, where n_{34} is the number of women who presented at

stages 3 or 4 and *n* is the number of women with known stage information. The suite of *metan* and *metaprop* commands from Stata version 13 (StataCorp, Texas) were used to graphically display population-specific late stage percentages and to estimate pooled percentages using random effect models. The *metaprop* command was specifically designed to model binary data, thereby allowing for proportions near boundaries (i.e. in this instance near 100% late stage). Between-population heterogeneity was assessed using I^2-statistic and the *P*-value for heterogeneity (Cochrane's *Q* statistic). To examine potential sources of heterogeneity population-specific estimates were stratified by relevant clinico-epidemiological variables, and meta-regression analyses were conducted to identify independent correlates of percentage late stage disease. Study-level determinants of late stage are expressed as *absolute* differences (AD) in the percentage of patients with late stage (p_{34}). Analyses were conducted among all study populations (Black and non-Black) and among Black populations only (non-Black populations, which were all from South Africa, were excluded from the latter analysis owing to their known privileged access to health care). The potential for small study bias was assessed using Funnel plots and the Egger test.(112)

To compare late stage breast cancer in SSA with corresponding figures for Whites and Blacks in the US, relevant data were extracted from the Surveillance, Epidemiology, and End Results (SEER) database, which includes information on all incident female cases of invasive primary breast cancer from nine US population-based cancer registries for two time periods: 1973-2002 and 1998-2011.(113) The SEER database provided numbers of incident in situ, localised, regional and distant (metastatic) breast cancer cases as well as numbers with unknown or missing stage. No age restrictions were imposed on the data. The SEER summary staging classification was used to estimate the percentage of patients with regional or distant disease, as a proxy for stages III/IV, out of those with known stage.

RESULTS

Characteristics of eligible studies

The full-text review identified 83 eligible papers (Figure 1) from 17 sub-Saharan African countries comprising late-stage estimates for 91 distinct study populations as five studies provided separate estimates for different subsets of participants (i.e. for pregnant/lactating (PL) and non-pregnant/lactating (NPL) women(114) or different racial groups(93, 115),(116),(117)). The characteristics of the included studies are summarised in Table 1; study-specific details and references are given in Table 2. They comprised 26788 breast cancer patients, with sample sizes ranging from 12 to 2346 (median: 141; -Table 1). Stage information was available for 24213 (90·4%) patients. Thirty-six studies (43.4%), comprising 8407 staged patients, were from Nigeria and 16 studies (19.3%), comprising 10182 staged patients, were from South Africa. Thirty-five (42·2%) were consecutive case series; the remaining were convenience case series, i.e. patients seen in pathology or radiotherapy departments only or studies where not all eligible patients that reported at the surgery/oncology clinics were included (Table 1). The average age at diagnosis was <45 years in 33.7% of studies, between 45-49 years in 43.4% and >49 years in 19.2%. Age was not reported in only 3 (3.6%) studies as shown in Table 1. The mean year of diagnosis ranged from 1960 to 2011, being 2000 or later for 39·8% of the studies.

Table 1. Summary characteristics of 83 studies included in the systematic review.

Variable	No. of studies	No. study populations [a]	No. of breast cancer patients	Breast cancer patients with known stage	
				N	%
TOTAL	83	91	26788	24213	90·4
Race					
Black [b]	75	76	18805	16669	88.6
Non-Black [c]	8	15	7983	7544	94·5
Region/Country					
Western Africa	48	49			
Nigeria	36	37	8623	8407	97·5
Benin	2	2	204	204	100
Ghana	5	5	1969	1191	60·5
Mali	2	2	324	324	100
Other [d]	3	3	797	719	90·2
Eastern/Middle Africa	19	19			
Tanzania	5	5	1 310	1151	87·7
Kenya	2	2	287	157	54·7
Ethiopia	3	3	1267	841	66·4
Madagascar	2	2	289	233	80·6
Uganda	3	3	562	502	89·3
Other [e]	4	4	445	302	67·9
Southern Africa	16	23			
South Africa	16	23	10711	10182	95·1
Study design					
Convenience case series	48	55	10780	9788	90·8
Consecutive case series	35	36	16008	14425	90·1
Study population					
Urban	27	34	15571	14208	91·2
Mixed (rural/urban)	56	57	11217	10005	89·2
Type of health facility					

Variable	No. of studies	No. study populations [a]	No. of breast cancer patients	Breast cancer patients with known stage	
				N	%
	9	12	1639	1503	91·7
Tertiary/Secondary/Primary [f]					
Tertiary	72	77	24742	22399	90·5
NR	2	2	407	311	76·4
Age at diagnosis (years) [g]					
< 45	28	29	5475	4840	88·4
≥ 45 to <50	36	37	7882	7218	91·6
≥ 50	16	22	11056	9841	89·0
NR	3	3	2375	2314	97·4
Year of diagnosis [h]					
< 1980	11	16	3971	3782	95·2
1980-1999	32	34	11125	10737	96·5
≥2000	33	33	8648	6733	77·8
NR	7	8	3044	2961	97·3
Staging methods					
Clinical and imaging	25	26	10416	9516	91·4
Clinical only	10	10	975	967	99·2
NR	48	55	15397	13730	89·2
Staging classification					
TNM	50	57	20388	18048	88·5
Manchester	11	11	1436	1426	99·3
NR	22	23	4964	4739	95·5
Study quality scores [i]					
≥23 (higher quality)	12	12	4067	3569	87·8
22-20	26	27	6181	5721	92·6
19-17	31	38	14541	13327	91·7
<17 (lower quality)	14	14	1999	1596	79·8

NR: Information not reported in the original paper; TNM: Tumour, lymph Node and Metastasis staging system

[a] Five studies provided separate estimates for different subsets of participants (i.e. for pregnant/lactating (PL) and non-pregnant/lactating (NPL) women(114) or different ethnic groups.(93, 115-117)

[b] Includes seven Southern African studies which reported estimates for Black women only(93, 115-120); one Southern African study(30) which presented only an overall (all ethnic groups combined) estimate but reported that >80% of their study population was Black; nine studies from Western and Eastern Africa which were conducted exclusively among Black women (87, 110, 111, 121-126) as well as the remaining 58 studies from these two regions which did not report on race but were assumed to have been conducted in

predominantly Black women (i.e. >80% Black; see webappendix-Table 1), corresponding to 76 study population groups as one Nigerian study(114) presented separate estimates for pregnant/lactating (PL) and non-pregnant/non-lactating (NPL) women (see webappendix-Table 1).

[c] Includes 15 Southern African study population groups: four studies(127, 128) (95, 129) which did not report on race but were assumed to be predominantly non-Black, four studies(109, 130-132) which present only overall estimates but reported an ethnically mixed population with ≤80% being Black, and four multi-ethnic studies(93, 115-117) which together reported separate estimates for seven non-Black population groups (see Table 2).

[d] Includes one study from Guinea (total no. of cases/total no. cases with known stage: 178/124), one from Niger (146/146) and one from Senegal (473/449).

[e] Includes one study from Rwanda (total no. of cases/total no. cases with known stage: 145/7), one from Zimbabwe (84/79), one from Eritrea (82/82) and one from Zaire (now Democratic Republic of Congo, 134/134).

[f] All studies which recruited participants from secondary and primary health centers also included a tertiary center.

[g] Mean or median age at breast cancer diagnosis. If only age categories were reported mean or median age was estimated from the mid-point and the reported number in each age category. The three studies in the NR category did not provide sufficient information to allow their allocation into one of the three age categories: Ajekigbe 1991[71] reported that 50.8% of the participants were aged <50 years; Amir 1997[72] reported that 90% of the participants were aged <50 years; and Pegoraro 1980(109) reported that 50% were between ages 45-64 years (Table 2).

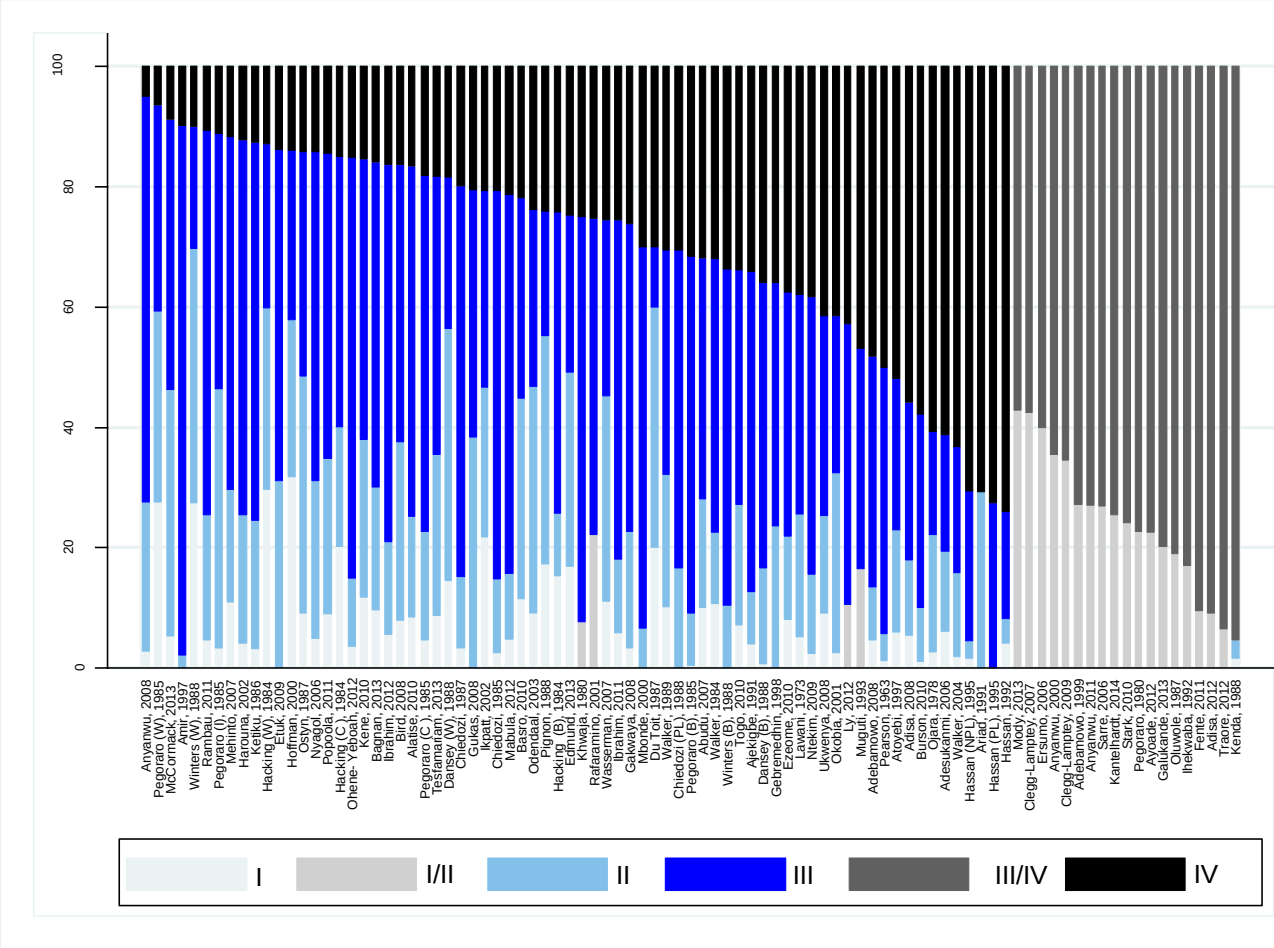
[h] Middle year of the time interval during which patient recruitment took place.

[i] Categories represent fourths of the overall score distribution (Appendix).

Stage at diagnosis and sources of between-study heterogeneity

There was wide variation in the distribution of stage at diagnosis in SSA. For instance, among studies that provided stage IV specific estimates, the percentage of women diagnosed with stage IV breast cancer ranged from 4%(65) to 70%(114) (Figure 2a). Consequently, there was wide between-population heterogeneity (I^2=98·3%; P<0·0001) in the percentage of late stage (III/IV) (median 74·7%; range: 30·3%-100%), with 64·8% study populations yielding an estimate >70% (Figure 2b).

Figure 2a: Breast cancer stage at diagnosis: (a) study-specific distribution of stages I, II, III and IV (133)



Footnote: B: Blacks; C: Coloured: I: Indian; NPL: Non-pregnant/non-lactating women; PL: Pregnant/lactating women SP: study population; W: Whites. Study-specific references given in webappendix-Table 1. In four studies (Ly 2012(108) Muguti 1993(111), Pegoraro 1980(109) and Rafaramino 2001(110), percentage of T3/T4 was used as a proxy for percentage stage III/IV. In Ly 2012(108), Muguti 1993(111) and Rafaramino 2001(110), the percentage with metastases (M1) was given and this was taken to be the percentage of stage IV in figure 1a. Race as defined in Table 1 and Table 2.

Region and race

Nine studies from Western and Eastern Africa were conducted exclusively among Black women(87, 110, 111, 121-126); the remaining 58 did not report on race but their populations were assumed to have the racial composition of their countries' population and, hence, to comprise predominantly (≥80%) Black women. Studies from South Africa included exclusively(118-120) or predominantly (≥80%) Black(30); or predominantly

(≥80%)(95, 109, 127-132) non-Black women (i.e. White, Indian or Coloured women); or provided separate estimates for Black and non-Black women(93, 115-117) (Table 2).

South African Black women presented much later than their non-Black counterparts, but with marked between-population heterogeneity within each racial stratum (I^2>97% for both; Figure 3). Four South African studies examined racial differences (Figure 4), consistently showing higher percentage of late stage for Blacks (range: 74%-91%) than Whites (30-44%), with Indian and Coloured women having intermediate values, even when all the participants were diagnosed at the same facility. However, these were not adjusted for socio-economic status owing to lack of information from the original publications.

Figure 2b: Study-specific percentage of late stage disease (III/IV) ranked by increasing magnitude(133)

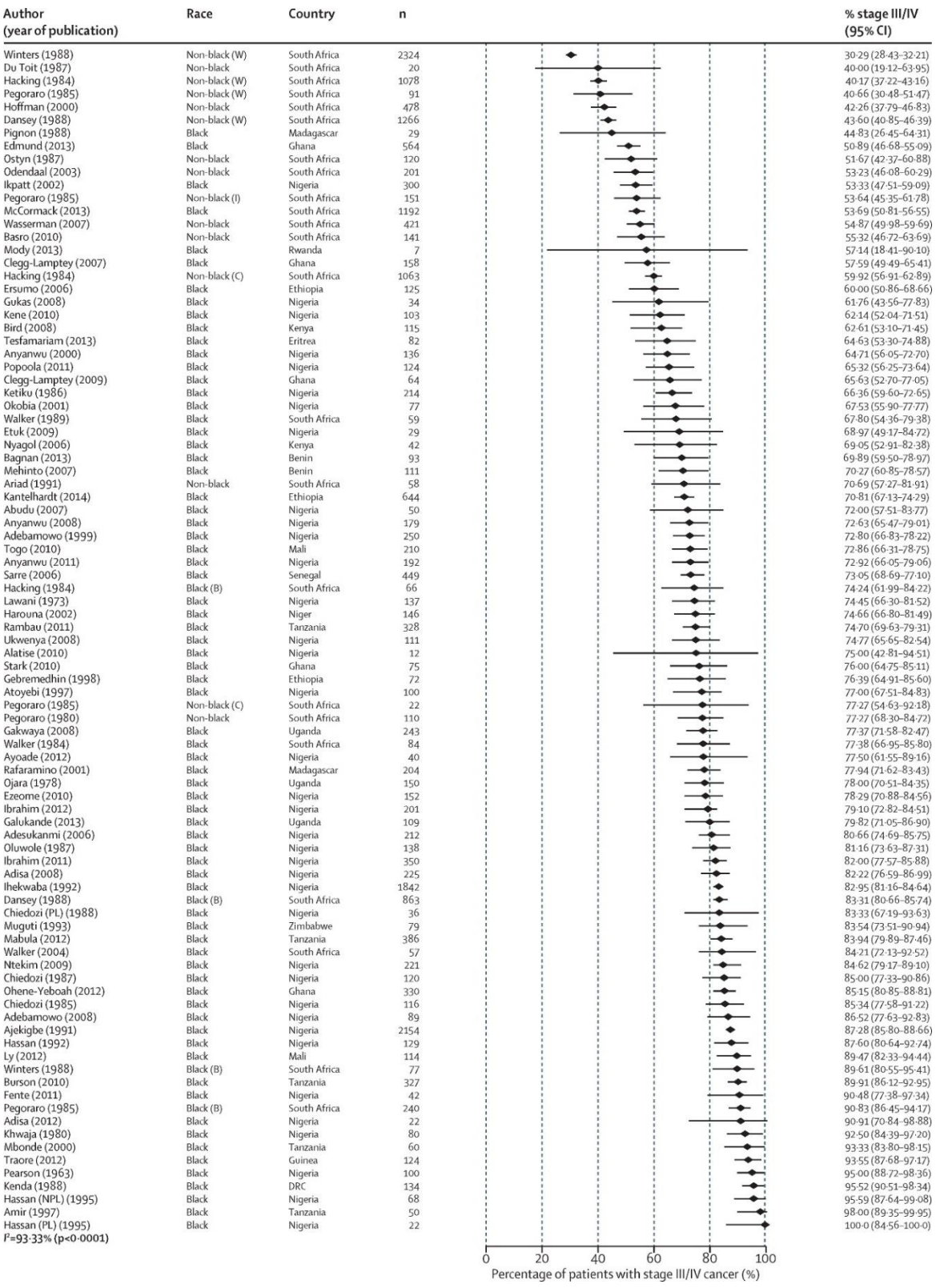


Figure 3: Study-specific percentage of late stage disease (III/IV) ranked by region of SSA(133)

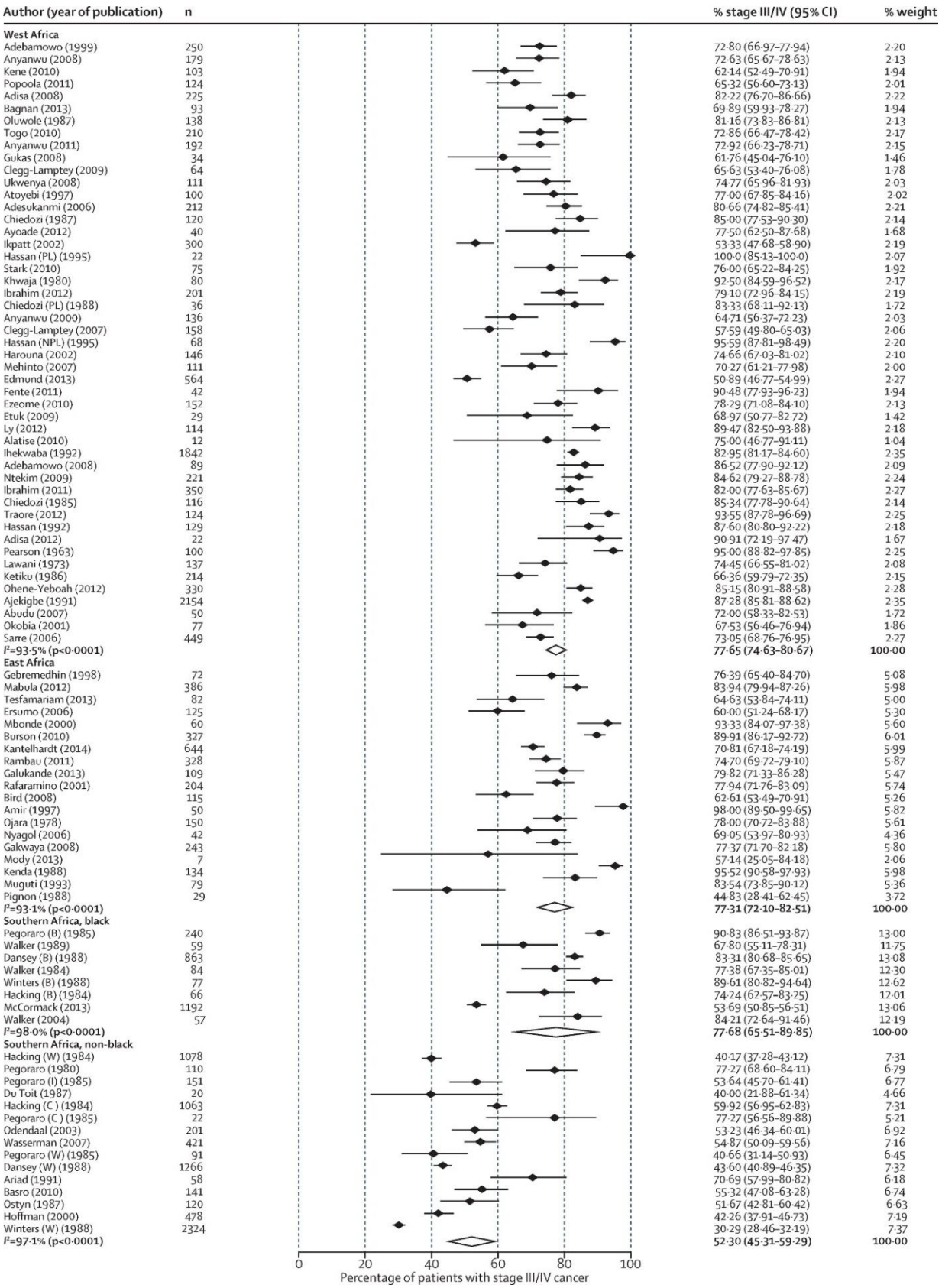
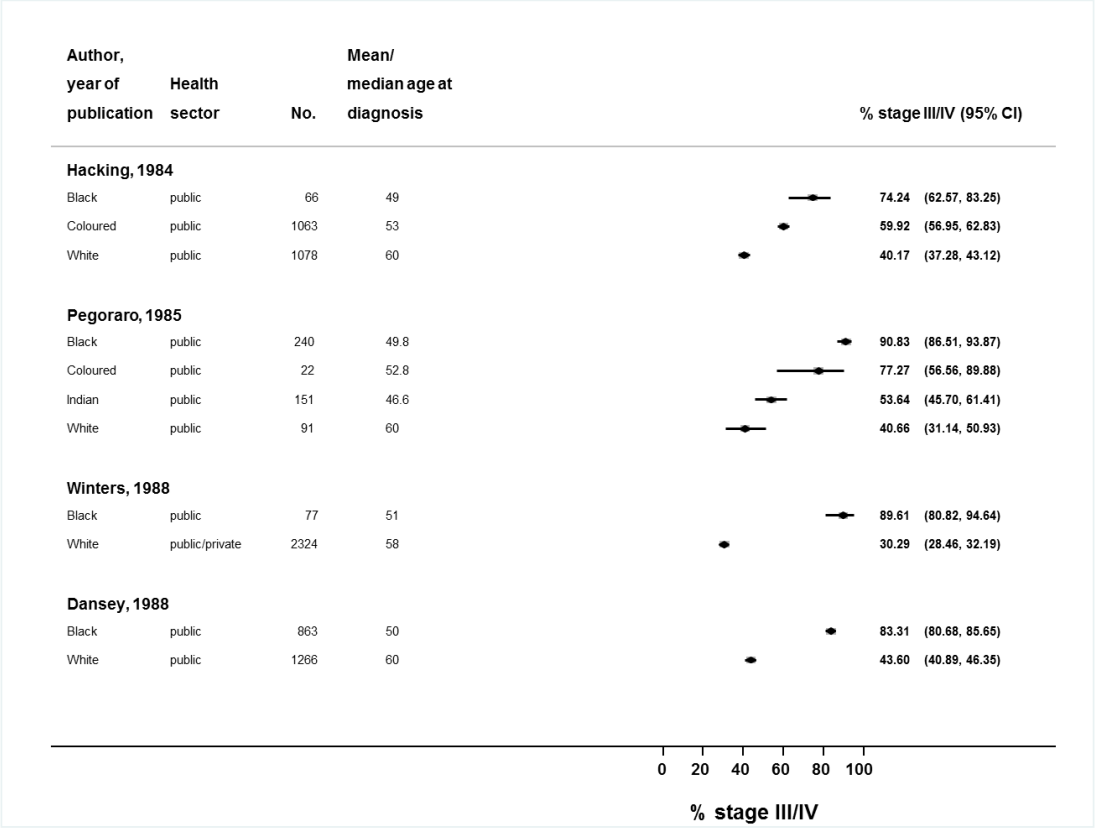


Figure 4: Study-specific percentage late stage breast cancer at diagnosis in multi-racial South African studies



Fully-adjusted meta-regression analysis (adjusting for region/race, study design, setting, facility type, age and year of diagnosis) confirmed the racial differential with percentage of late stage being 18.1% lower (95% CI: -28·2%, -8·0%) for South African non-Blacks than for Blacks in Western Africa. In contrast, analysis restricted to Blacks revealed no difference in late stage between the three SSA regions (Table 3).

Study design and setting

After adjustment for region/race there were no differences in late stage disease between consecutive or convenience case series, or by type of health facility (Table 3). Studies conducted in mixed urban/rural populations had an excess percentage of late stage disease than those conducted in urban populations, and this finding remained significant in the fully adjusted model (AD=12·9%; 95% CI: 5·5%, 20·3%) and in analysis restricted to Blacks (AD=13·2%; 5·7%, 20·7%) (Table 3).

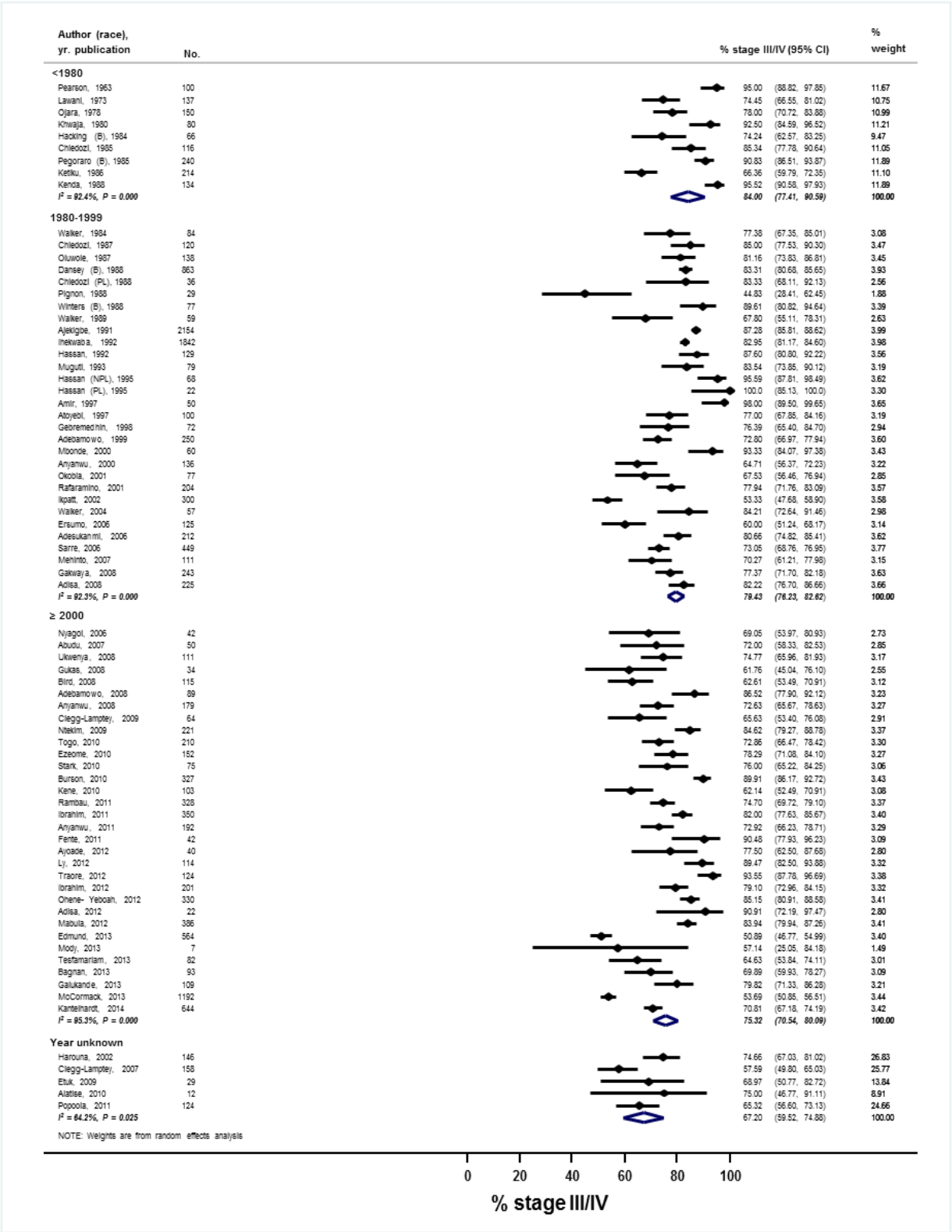
Age and year of diagnosis

Women aged ≥50 years had a lower percentage of late stage disease than those aged <45 years (AD=-13·2%; 95% CI -21·2%, -5·3%), but most studies of older women comprise predominantly South African non-Blacks. Consequently, the age difference attenuated markedly upon adjustment for region and race, and disappeared in analysis restricted to Blacks (Table 2). There was a slight improvement in stage at diagnosis over time (Figure 5). In the fully-adjusted meta-regression model, percentage of late stage disease was lower in Blacks diagnosed since 2000 compared to those diagnosed prior to 1980 (AD=-10·5%; 95% CI: -19·3%, -1·6%; Table 2). In analysis restricted to Blacks, percentage late stage was lower in studies that did not report on year of diagnosis than studies published prior to 1980, but this finding was not statistically significant (Table 2); as the years of publication of these studies ranged from 2002 to 2011, it is likely that patients recruited into these studies would have been diagnosed in recent years.

Staging approach

The TNM or the Manchester staging classification (Table 2) were used in the majority of studies, but this information was missing in 21 studies (Table 1). There were no clear differences in percentage of late stage disease between studies that reported the staging classification used and those which did not, or between those conducted in facilities where there was access to imaging methods (e.g. x-rays) – either routinely or in clinically suspicious cases – and those performed without access to imaging (Table 2).

Figure 5: Study-specific percentage of late stage (III/IV) breast cancer at diagnosis by calendar year at diagnosis(133)



Footnote: B: Blacks; C: Coloured: I: Indian; NPL: Non-pregnant/non-lactating women; PL: Pregnant/lactating women SP: study population; W: Whites. Study-specific references given in webappendix-Table 1.

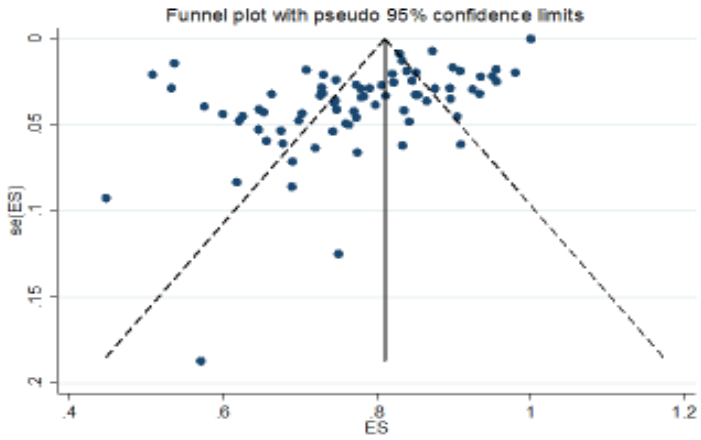
Correlation of stage with tumour characteristics

Few studies reported on tumour characteristics or duration of symptoms (Table 4) Among studies of Black populations that reported on these characteristics, late stage at diagnosis was positively associated with mean tumour size (Pearson correlation coefficient (r)=0.63, P=0.004, based on data from 19 studies), but not with self-reported mean duration of symptoms (r=-0.14, P=0.42, 35 studies) or with percentages of tumours classified as being invasive ductal carcinomas (r=0.09; P=0.50, 53 studies), oestrogen receptor (ER)-positive (r=-0.03, P=0.91, 15 studies) or grade 3 (r=0.21, P=0.26, 32 studies).

Study Quality and Study Small Bias

The median study quality score was 19·5 (inter-quartile range: 17·5-21·5), with no evidence of regional or racial differences. There was also no variation in the percentage of late stage breast cancer by study quality (Table 2). The funnel plot (Figure 6) and the value of the Egger's test for small study bias (P=0.01) were difficult to interpret due to the marked between-population heterogeneity.

Figure 6: Funnel plot assessing small study bias

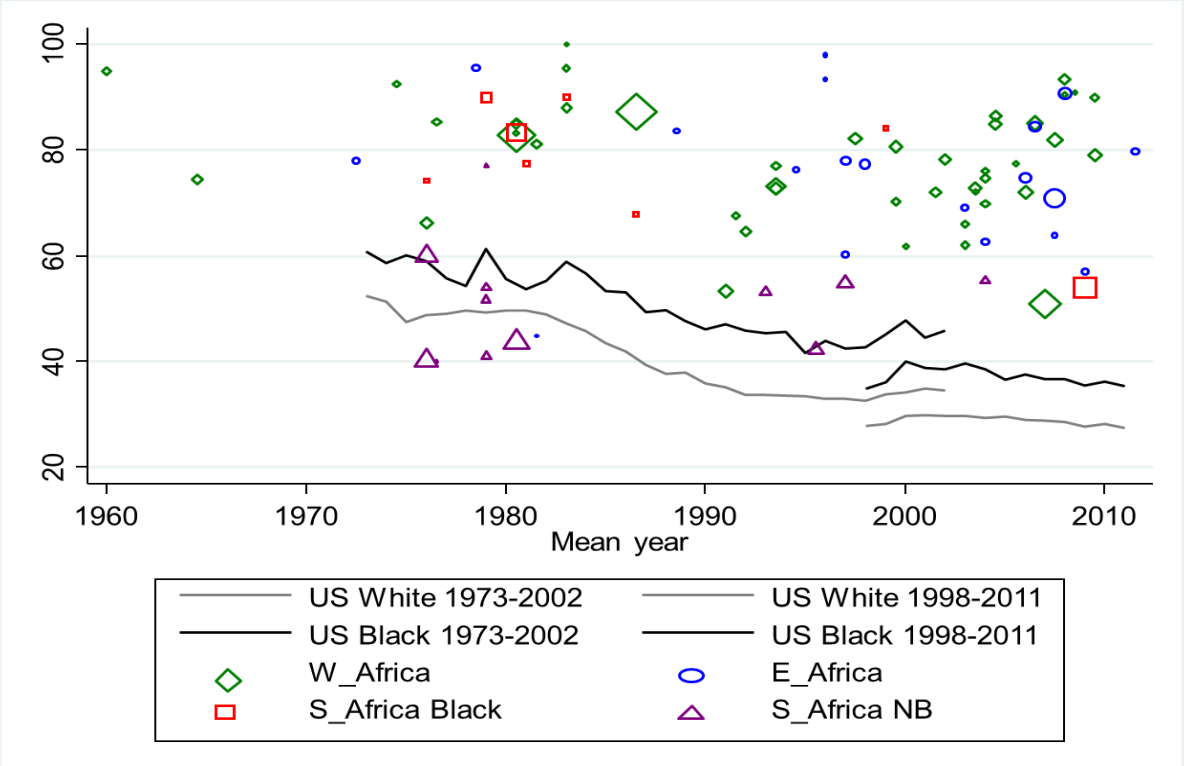


Comparison with US SEER data

The proportion of late stage breast cancer at diagnosis declined markedly in the US between 1973 and 2011: from 50% to 27% among Whites, and from 60% to 32% among Blacks (Figure 7). In contrast, the large majority of study-specific estimates of late stage disease among SSA Blacks remained well above 60% from the 1970s to 2012, albeit with some indication of a slight downward trend in some settings in more recent years (Figure 7). Notably, the proportion of late stage disease in SSA Blacks in the most recent study years (around 2010) was still higher than in US Black women 40 years previously. Among Southern African women, the proportion of late stage disease remained unchanged for non-Blacks but appeared to have declined somewhat among Blacks. Remarkably, only two studies were conducted after 2000 in the whole Southern African region, both in South Africa: one in non-Blacks(95) and one in Blacks.(30) In contrast, the number of

studies from Eastern and Western Africa published after 2000 was higher than in previous decades, although the majority had relatively small sample sizes.

Figure 7: Trends in stage of breast cancer at diagnosis in Black and non-Black populations in SSA, 1960-2011, and in Black and White women in the US for two time periods, 1973-2002 and 1988-2011.(133)



Footnote: * The SSA estimates correspond to percentage of stage III/IV breast cancer patients at diagnosis, with the size of the point estimate symbols being proportional to the size of the study. The US estimates represent percentage of breast cancer patients with regional or distant disease (as a proxy for stages III/IV) out of all patients with known stage in the Surveillance Epidemiology End Results (SEER) database (see Data Analysis section); the SEER summary staging classification was used for both time periods 1973-2002 (based on 365,695 and 31,781 breast cancer cases in US Whites and US Blacks, respectively) and 1998-2011 (based on 780,137 and 96,526 breast cancer cases in US Whites and US Blacks, respectively). The discontinuity between the two time series was due to a change in staging classification as detailed in http://seer.cancer.gov/seerstat/variables/seer/yr1973_2009/lrd_stage/index.html.

DISCUSSION

This is the first systematic review of stage at diagnosis of breast cancer in SSA. It compiled data from 83 studies comprising 24213 staged patients. The findings highlight two main issues. First, they demonstrate the paucity of data on one of the most important clinical prognostic markers of breast cancer in this region. Specifically, no published data from Middle Africa were identified, and those from Southern Africa were restricted to

one country (South Africa), with only two studies (one among Blacks and another among non-Blacks) having been conducted after 2000. Furthermore, no study presented data from population-based cancer registries. Secondly, the findings demonstrate that the large majority of patients in SSA (77% across all Black study populations) were diagnosed at stages III/IV. Whilst this overall situation may seem grave, the presence of public-sector SSA settings with a better stage profile needs to be highlighted as those settings reveal that progress in down-staging breast cancer can be made within the public sector setting where mammography is often unavailable. However, the reasons for the marked between-population heterogeneity, present even in analyses restricted to Blacks, are not entirely clear – with no distinct patterns defining the better settings. Late stage was, as expected, more frequent in Blacks than non-Blacks; however, among Blacks there were no clear differences in the percentage of late stage by region or type of health facility, except that it was lower in urban settings. There was evidence of down-staging of breast cancer over time among Blacks diagnosed after 2000, consistent with the within-study downward trend in late stage at diagnosis described by one of the studies in this review – McCormack *et al.* reported a decrease in the frequency of stage III/IV in South Africa from 66% in 2006-7 to 46% in 2010-2012.(30)

We did not find a strong association between age at diagnosis and late stage in Blacks. Most patients were aged 35-49 years at diagnosis, i.e. approximately 10 to 15 years earlier than in developed countries.(134) This likely reflects the much younger age structure of the SSA population, consequent to higher fertility and shorter life expectancy, and the lower prevalence of risk factors in older generations rather than any inherent biological differences in disease aggressiveness between Blacks and Whites. Consistent with this interpretation is the fact that, at a study level, late stage was not correlated with tumour grade perhaps indicating that the former is not entirely a consequence of Blacks experiencing a biologically more aggressive form of disease – indeed a recent review

suggests that ER-positive disease constitutes two-thirds of tumours in SSA Blacks.(103) Late stage disease was, however, positively correlated with mean tumour size, as expected given that tumour size is used to derive stage, consistent with delays in access to health care.

Increased breast cancer awareness and improvements in healthcare over time have been paralleled by decreases in tumour size and down-staging of breast cancer in other LMICs.(135, 136) However, studies have reported a low level of breast cancer awareness among the general population and health care professionals in SSA.(77, 137) This significantly contributes to the late stage at diagnosis seen in SSA.(138, 139) Other barriers to access, such as distance to health care facility, also play a role in this region.(80)

Most studies used the TNM or the Manchester staging classifications, but only a quarter reported on the staging methods used. Of these, the majority relied on both clinical and imaging methods but a few relied on clinical-only methods. Although the latter approach leads to under-staging,(140) most women in settings where imaging procedures are unavailable or unaffordable(141) are likely to have presented at advanced stages when clinical methods may suffice. This is consistent with our finding of no differences in late stage disease according to whether staging methods were reported and, if reported, by type used.

There was no correlation, at a study level, between percentage of late stage and average self-reported duration of symptoms (i.e. time between onset of symptoms and diagnosis). It is unclear the extent to which this ecological-level association reflects a similar lack of association at an individual level. Women may not recognise symptoms due to poor breast cancer awareness(142, 143), or they may not accurately remember the dates they first noticed symptoms. Nevertheless, average duration with symptoms were between 8 and

12 months in most studies (Table 4), indicating that for the most part advanced stage at diagnosis may be a result of delayed diagnosis. Hence, a large window exists in which delays to diagnosis can be shortened.

The frequency of late stage at diagnosis among SSA Black women remained higher than among US Whites and Blacks from over the 1970-2010 period, including during the pre-mammography screening era (in the US, screening began in 1976(144)). This illustrates that, through the more rapid diagnosis of palpable clinical disease, considerable improvements can still be made before expensive systems for the detection of pre-clinical disease are warranted. In SSA, where mammography is often unavailable or unaffordable, down-staging through breast cancer awareness and improved access to diagnostic facilities, not mammographic screening, is urgently required.

Strengths and limitations

Major strengths of this review include the detailed and inclusive search strategy (e.g. including non-English publications); the large sample size (>24000) of women with breast cancer in the region; and the use of standard methodology for study identification, and data extraction and synthesis. There were also limitations. The representativeness of the review might have been compromised by several factors. Firstly, it comprised studies from only 17 out of 49 SSA countries, albeit together they represent 71% of the total population in the region, with the majority of the studies being based on convenience samples of patients. Secondly, by definition, the large numbers of breast cancer patients in the region who never reach a health care facility could not be included. Dickens et al.(80) showed that distance to a tertiary care facility was a major determinant of access to diagnosis even within a relatively small geographical area (i.e. Soweto in Johannesburg, South Africa). As the patients in the review are, by definition, those who reach a health facility, predominantly a tertiary centre, they may not be a representative

sample of the generality of breast cancer patients in SSA. Thirdly, some participants might have contributed to more than one study; to minimize this, whenever papers from the same institution and recruitment period were identified we included the paper that had the more comprehensive information on stage at diagnosis. Fourthly, six potentially eligible papers could not be retrieved; the sample sizes for two of these papers are known to be small, and therefore it is unlikely that their exclusion would have significantly affected our findings. Finally, the lack of information on staging methods and procedures in many studies as well as the lack of standardisation in staging procedures between studies, and possibly even within studies, might have obscured some of the findings. Staging is affected by neo-adjuvant chemotherapy but this treatment is not available in most SSA settings(145); it was mentioned in only two papers in this review(95, 146) being unclear whether staging was ascertained before or after its administration.

Implications

This review demonstrates that the percentage of late stage breast cancer at diagnosis in SSA Black populations around 2010 was higher than it was in US White and US Black populations four decades previously. Cancer control strategies in the region should target early detection and diagnosis as one essential component of the strategy to improve survival from breast cancer. In most settings, 8-12 months symptoms duration shows that there is a considerable delay and thus a considerable time window in which to realistically achieve this. Population-level interventions for down-staging of breast cancer have been shown to be successful in Tanzania(31), similarly to what has been observed in other LMICs, e.g. Malaysia(29). Indeed, several SSA studies have shown improved survival rates in women diagnosed at earlier stages(47, 88), demonstrating that early-diagnosis coupled with timely and appropriate treatment can prevent deaths from this disease.

Role of the funding source

No specific funding was received for this study. EJA, VM and IdSS had full access to all the data and the corresponding author had the final responsibility for the decision to submit for publication. We acknowledge the Training Programme in Nigeria for Non-Communicable Diseases Research (TRAPING-NCD; Fogarty International Center of the National Institutes of Health D43TW009106-CA) for providing funding support for EJA's PhD research work at the London School of Hygiene and Tropical Medicine. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Fogarty International Center of the National Institutes of Health

Conflict of interest

We declare that we have no conflicts of interest

Authors' contributions

EJA extracted data, analysed data, drafted the manuscript and made subsequent revisions to the manuscript; IDS had the idea for the study, extracted data, supervised data extraction and analysis and revised the manuscript; CA provided critical revisions to the manuscript; VM had the idea for the study, extracted data, analysed data and provided critical revisions to the paper. All authors read and approved the final draft.

Table 2. Characteristics of the study populations included in the systematic review, by SSA region

First author, year of publication [ref no.]	Country	Race		Hospital/clinic, location	Study design	Sample size females (males)	No. of patients with known stage	Staging classification / edition (yr)	Joint TNM distribution given (Y/N)	Criteria used to define late stage	Staging methods	Percent stage III/IV	Year of diagnosis	Mean/ Median age at diagnosis (males where given)	Study quality score
		As reported in the original publication	As assigned in the present review [a]												
West Africa															
Abudu, 2007(147)	Nigeria	NR	Black	Olabisi Onabajo University Teaching Hospital, Shagamu	OCS	50	50	Manchester (NK)	N	Manchester Stage III and IV	NR	72	2003-2004	47·5	18·5
Adebamowo, 1999(121)	Nigeria	Black	Black	University College Hospital, Ibadan	CCS	250	250	Manchester (NK)	N	Manchester Stage III and IV	NR	72·8	1992-1995	43	16·5
Adebamowo, 2008(148)	Nigeria	NR	Black	University College Hospital, Ibadan	CCS	192	89	TNM (NK)	Y	**Stage IIIA** T0 N2 M0 T1 N2 M0 T2 N2 M0 T3 N1 M0 T3 N2 M0 **Stage IIIB** T4 N0 M0 T4 N1 M0 T4 N2 M0 Stage IIIC Any T N3M0 **Stage IV** Any T Any N M1	NR	86·5	2004-2005	48·8	19·5
Adesunkanmi, 2006(149)	Nigeria	NR	Black	Obafemi Awolowo University Teaching Hospital, Ife	CCS	211 (+1)	212	Manchester (NK)	N	Stage III & IV	NR	80·6	1996-2003	48	22·5
Adisa, 2008(150)	Nigeria	NR	Black	Obafemi Awolowo University Teaching Hospital, Ife	OCS	219 (+6)	225	TNM (NK)	N	Stages III & IV	NR	82·2	1993-2002	48	15·5
Adisa, 2012(151)	Nigeria	NR	Black	Abia State University Teaching Hospital, Abia	CCS	22	22	NR	-	Stages III & IV	NR	90·9	2008-2009	47	20·5
Ajekigbe, 1991(152)	Nigeria	NR	Black	Lagos University Teaching Hospital, Lagos	CCS	2154	2154	TNM (NK)	N	Stages III & IV	NR	87·3	1984-1989	50·8% <50 yrs	17·5
Alatise, 2010(104)	Nigeria	NR	Black	Surgery Clinic Obafemi Awolowo University Teaching Hospital, Ife	OCS	12	12	TNM (NK)	Y	Stages III & IV	NR	75	NR	50	17·5
Anyanwu, 2000(153)	Nigeria	NR	Black	University of Nigeria Teaching Hospital, Enugu; Iyi-Enu Hospital, Onitsha; Nnamdi Azikiwe University Teaching	CCS	134 (+2)	136	Manchester (2008)	N	Stages III & IV	C & I (occasional Imaging, likely	64	1987-1997	44·3	25·5

First author, year of publication [ref no.]	Country	Race		Hospital/clinic, location	Study design	Sample size females (males)	No. of patients with known stage	Staging classification / edition (yr)	Joint TNM distribution given (Y/N)	Criteria used to define late stage	Staging methods	Percent stage III/IV	Year of diagnosis	Mean/ Median age at diagnosis (males where given)	Study quality score
		As reported in the original publication	As assigned in the present review [a]												
				Hospital, Nnewi; Ace Specialist Hospital, Onitsha							under-staged)				
Anyanwu, 2008(65)	Nigeria	NR	Black	Nnamdi Azikiwe University Teaching Hospital, Nnewi; Ace Specialist Hospital, Onitsha	CCS	179	179	NR	-	NR	C & I (Occasional imaging, likely understaged)	72	1998-2005	46·9	22·5
Anyanwu, 2011(154)	Nigeria	NR	Black	Nnamdi Azikiwe University Teaching Hospital, Nnewi; & Ace Specialist Hospital, Onitsha	CCS	273 (+2)	196	NR	-	Stages III & IV	C & I	72	2004-2008	45·2	21·5
Atoyebi, 1997(155)	Nigeria	NR	Black	Lagos University Teaching Hospital, Lagos	CCS	99 (+1)	100	Manchester (NK)	N	Stages III & IV	NR	77	1992-1995	45·8	19·5
Ayoade, 2012(156)	Nigeria	NR	Black	Olabisi Onabanjo University Teaching Hospital, Shagamu	CCS	44	40	TNM	Y	Stage III & IV T3N1M0,T4N1Mx & T4N2M1	NR	77·5	2005-2006	47	18·5
Bagnan, 2013(157)	Benin	NR	Black	Hopital de la Mere et de l'enfant-Lagune Cotonou & Clinique Universitaire de gynécologie et d'obstétrique, Cotonou	CCS	93	93	NR	-	Stages III and IV	NR	69·9	2000-2008	34·2	15·5
Chiedozi, 1985(122)	Nigeria	Black	Black	University of Benin Teaching Hospital, Benin	CCS	116	116	TNM (1985)	N	Stages III & IV	C	85·3	1974-1979	42·4	20·5
Chiedozi, 1987(158)	Nigeria	NR	Black	University of Benin Teaching Hospital, Benin	CCS	120	120	TNM (1973)	N	Stages III & IV	NR	85	1978-1983	44·8	22·5
Chiedozi (PL[b]), 1988(159)	Nigeria	NR	Black	University of Benin Teaching Hospital, Benin	CCS	36	36	TNM (1988)	N	Stages III & IV	C	83·4	1977-1984	28·3	22·5
Clegg-Lamptey, 2007(160)	Ghana	NR	Black	Korle Bu Teaching Hospital, Kumasi	CCS	156 (+2)	158	TNM (2002)	N	Stages III & IV	C & I	57·6	NR	48·1	21·5
Clegg-Lamptey, 2009(146)	Ghana	NR	Black	Korle bu Teaching Hospital, Accra	OCS	64	64	NR	-	Stages III & IV	NR	66	2001-2005	51	14·5
Edmund, 2013(102)	Ghana	NR	Black	Dept. Of Pathology, University of Ghana Medical School, Accra	CCS	1342	564	TNM (2013)	Y	Stages III & IV	NR	50·9	2005-2009	50·3	16·5
Etuk, 2009(161)	Nigeria	NR	Black	Lagos University Teaching Hospital &	OCS	29	29	NR	-	Stages III & IV	NR	68·9	NR	47·2	16·5

First author, year of publication [ref no.]	Country	Race		Hospital/clinic, location	Study design	Sample size females (males)	No. of patients with known stage	Staging classification / edition (yr)	Joint TNM distribution given (Y/N)	Criteria used to define late stage	Staging methods	Percent stage III/IV	Year of diagnosis	Mean/ Median age at diagnosis (males where given)	Study quality score
		As reported in the original publication	As assigned in the present review [a]												
				Lagos State University Teaching Hospital (LASUTH).Lagos											
Ezeome, 2010(98)	Nigeria	NR	Black	University of Nigeria Teaching Hospital, Enugu	CCS	162 (+2)	152	NR	-	Stages III & IV	NR	78·3	1999-2005	45·7	20·5
Fente, 2011(162)	Nigeria	NR	Black	Niger Delta University Teaching Hospital, Okolobiri	OCS	42	42	TNM & Manchester (UICC 1960)	N	Stage IV (Manchester)	NR	90·5	2007-2009	40	16·5
Gukas, 2008(163)	Nigeria	NR	Black	Jos University Teaching Hospital, Jos	OCS	34	34	TNM (2008)	Y	Stages III & IV	C	61·8	1999-2001	45	21·5
Harouna, 2002(164)	Niger	NR	Black	General Surgery Unit, Issaka Gazoby's Maternity Hospital, Niamey	CCS	146	146	TNM (2002)	Y	Stages III & IV	C & I	74·7	NR	41·1	22·5
Hassan, 1992(165)	Nigeria	NR	Black	Ahmadu Bello University Teaching Hospital, Zaria	CCS	129	129	TNM (1979)	Y	Stages III & IV	C	88	1977-1989	38	21·5
Hassan (PL), 1995(114)	Nigeria	NR	Black	Ahmadu Bello Univeristy Teaching Hospital, Shika	OCS	25	22	TNM (1979)	N	Stages III & IV	NR	100	1977-1989	34	19·5
Hassan (NPL), 1995(114)	Nigeria	NR	Black	Ahmadu Bello University Teaching Hospital, Shika	OCS	70	68	TNM (1979)	N	Stages III & IV	NR	95·5	1977-1989	37	19·5
Ibrahim, 2011(166)	Nigeria	NR	Black	Lagos State University Teaching Hospital, Lagos	CCS	344 (+6)	350	TNM (2002)	Y	Stages III & IV	C & I	82	2006-2009	48·9	25·5
Ibrahim, 2012(167)	Nigeria	NR	Black	Lagos State University Teaching Hospital, Lagos	CCS	201	201	NR	-	Stages III & IV	C	79·1	2009-2010	49·8	22·5
Ihekwaba, 1992(123)	Nigeria	Black	Black	University College Hospital, Ibadan	CCS	1842	1842	TNM (1992)	Y	Stage III (T2/T3 N2M0) and Stage IV (T2-4N2M1)	C & I	82·8	1971-1990	48	18·5
Ikpatt, 2002(168)	Nigeria	NR	Black	University of Calabar Teaching Hospital, Calabar	OCS	300	300	TNM (1997)	N	Stages III & IV	C & I	53·3	1983-1999	42·7	25·5
Kene, 2010(87)	Nigeria	Black	Black	Ahmadu Bello University Teaching Hospital, Shika (near Zaria)	OCS	99 (+4)	103	Manchester	N	Stages III & IV	NR	62·1	2001-2005	44·5	18·5
Ketiku, 1986(169)	Nigeria	NR	Black	Lagos State University Teaching Hospital, Lagos	OCS	214	188	NR	-	Stages III & IV	C & I	66·3	1971-1981	45·1	19·5
Khwaja, 1980(170)	Nigeria	NR	Black	Ahmadu Bello University Teaching Hospital, Shika	CCS	73 (+7)	80	NR	-	Stages III & IV	C	82·5	1972-1977	42	19·5
Lawani, 1973(171)	Nigeria	NR	Black	University College Hospital, Ibadan	CCS	169	137	Manchester	N	Stages III & IV	C	74·5	1961-1968	43·5	24·5

First author, year of publication [ref no.]	Country	Race		Hospital/clinic, location	Study design	Sample size females (males)	No. of patients with known stage	Staging classification / edition (yr)	Joint TNM distribution given (Y/N)	Criteria used to define late stage	Staging methods	Percent stage III/IV	Year of diagnosis	Mean/ Median age at diagnosis (males where given)	Study quality score
		As reported in the original publication	As assigned in the present review [a]												
Ly, 2012(108)	Mali	NR	Black	Hopital du Point G, Bamako University Hospital, Bamako	CCS	114	114	TNM (NK)	N	T3 & T4	C & I	90	2008-2011	46	23·5
Mehinto, 2007(105)	Benin	NR	Black	Centre National Hospitalier et Universite Hubert K. Maka de Cotonou, Cotonou	OCS	111	111	TNM (UICC 1987)	Y	**Stage III** T3N1M0 T4N1M1 T4N2M1 **Stage IV** T4N1M2	NR (but metastatic sites listed)	70·3	1994-2005	48·5	18·5
Ntekim, 2009(96)	Nigeria	NR	Black	University College Hospital, Ibadan	OCS	221	221	NR	-	NR	NR	85	2003-2006	35·0 [c]	17·5
Ohene-Yeboah, 2012(140)	Ghana	NR	Black	Komfo Anokye Teaching Hospital, Kumasi	CCS	325 (+5)	330	TNM (AJCC 2002)	Y	**Stage IIIA** T2N2M0 T3N1M0 T3N2M0 Total **Stage IIIB** T4N1M0 T4N2M0 Total **Stage IIIC** Any TN3Mx **Stage VI** M1	C & I (no bone scans done; likely most patients were under-staged)	85·2	2004-2009	49·1	24·5
Oluwole, 1987(172)	Nigeria	NR	Black	University of Ife, Ile-Ife	CCS	138 (+1)	138	NR	-	Stages III & IV	NR	81·2	1977-1986	42	15·5
Okobia, 2001(91)	Nigeria	NR	Black	University of Benin Teaching Hospital, Benin	OCS	75 (+2)	77	Manchester	N	Stages III & IV	C (mostly late stage)	67·5	1987-1996	43·8	19·5
Pearson, 1963(92)	Nigeria	NR	Black	University College Hospital, Ibadan	CCS	99 (+1)	100	Manchester	N	Stages III & IV	NR	95	1957-1963	44·9	19·5
Popoola, 2011(56)	Nigeria	NR	Black	Lagos State University Teaching Hospital, Lagos	CCS	129	124	TNM (NK)	N	Stages III & IV	NR	65·3	NR	50·5	19·5
Sarre, 2006(173)	Senegal	NR	Black	Hospital Principal de Dakar, Dakar	OCS	473	449	TNM (NK)	Y	T4N1M & T3N1M0	NR	73·1	1986-2001	42·5	18·5
Stark, 2010(37)	Ghana	NR	Black	Komfe Anokye Teaching Hospital, Kumasi	OCS	75	75	NR	-	Stages III & IV	C	76	2007-2008	48	17·5
Togo, 2010(174)	Mali	NR	Black	Teaching Hospital of Gabriel Toure & Mother and Children Hospital Luxembourg, Bamako	OCS	205 (+5)	210	TNM (NK)	Y	NR	NR (but metastatic sites listed)	72·9	1999-2008	47·4	19·5

First author, year of publication [ref no.]	Country	Race		Hospital/clinic, location	Study design	Sample size females (males)	No. of patients with known stage	Staging classification / edition (yr)	Joint TNM distribution given (Y/N)	Criteria used to define late stage	Staging methods	Percent stage III/IV	Year of diagnosis	Mean/ Median age at diagnosis (males where given)	Study quality score
		As reported in the original publication	As assigned in the present review [a]												
Traore, 2012(175)	Guinea	NR	Black	Surgical Oncology Unit, Donka University Hospital, Conakry	CCS	178 (+6)	124	NR	-	Loco-regional involvement & Metastatic	C & I (skeletal x-ray, chest x-ray, US scans)	93·5	2007-2009	48	16·5
Ukwenya, 2008(176)	Nigeria	NR	Black	Ahmadu Bello University Teaching Hospital, Kaduna	CCS	111	111	Manchester (NK)	N	Stages III & IV	NR	74·7	2003-2005	43·8	20·5
East Africa															
Amir, 1997(62)	Tanzania	NR	Black	Muhimbili Medical Centre, Dar Es Salaam	CCS	50	50	TNM (NK)	Y	**Stage IIIA** T3N0M0,T1N2M0, T3N2M0 **Stage IIIB** T3N3M0 T4N1MO, T4N2MO **Stage IV** M1	C & I (rays, abdominal US, bone scans)	98	1996-1996	90% < 50years	25·5
Bird, 2008(177)	Kenya	NR	Black	Africa Inland Church Kijabe Hospital, Kijabe	CCS	125 (+4)	115	NR	-	NR	C & I (No bone scans performed so patients might have been under-staged)	62·6	2001-2007	48	21·5
Burson, 2010(178)	Tanzania	NR	Black	Muhimbili National Hospital and Ocean Road Cancer Institute, Dar es Salaam	OCS	474 (+14)	356	TNM (2002)	N	Stages III & IV	NR	90·7	2007-2009	43·4	16·5
Ersumo, 2006(124)	Ethiopia	Black	Black	Tikur Anbessa Hospital Addis Ababa	OCS	112 (+13)	125	TNM (1992)	N	Stages III & IV	C & I	60·2	1995-1999	42·4	18·5
Gakwaya, 2008(89)	Uganda	NR	Black	Mulago Hospital, Kampala	CCS	285 (+12)	243	TNM (AJCC, 2002)	N	Stages IIIA, IIIIB, IIIC & IV	NR	77·4	1996-2000	47	18·5
Galukande, 2013(179)	Uganda	NR	Black	Mulago Hospital, Kampala; Makarere University Teaching Hospital; & Ugandan Cancer Institute, Kampala	CCS	113	109	NR	-	Stages III & IV	NR	79·8	2011-2012	46·7	20·5

First author, year of publication [ref no.]	Country	Race		Hospital/clinic, location	Study design	Sample size females (males)	No. of patients with known stage	Staging classification / edition (yr)	Joint TNM distribution given (Y/N)	Criteria used to define late stage	Staging methods	Percent stage III/IV	Year of diagnosis	Mean/ Median age at diagnosis (males where given)	Study quality score
		As reported in the original publication	As assigned in the present review [a]												
Gebremedhin, 1998(94)	Ethiopia	NR	Black	Tikur Anbessa Hospital, Addis Ababa	CCS	62 (+10)	72	NR	-	Stages III & IV	NR	76·4	1992-1997	41·8 (52·1)	21·5
Kantelhardt, 2014(88)	Ethiopia	NR	Black	Addis Ababa University Radiotherapy Center, Addis Ababa	OCS	1070	644	TNM (AJCC 7th Edition 2010)	N	Stage III & IV [d]	C & I (Chest x-ray and abdominal US)	74·7	2005-2010	43	26
Kenda, 1988(180)	Zaire (Democratic Republic of Congo)	NR	Black	Kinshasa University Hospital, Kinshasa	CCS	134	134	TNM (NK)	N	Stages III & IV	NR	95·6	1974-1983	47	17·5
Mabula, 2012(90)	Tanzania	NR	Black	Bugando Medical centre, Mwanza	CCS	376 (+8)	384	TNM (AJCC 2012)	N	Stages III & IV	C & I	84·4	2002-2011	45	18·5
Mbonde, 2000(181)	Tanzania	NR	Black	Muhimbili Medical Center, Dar Es Salaam	OCS	60	60	TNM (NK)	N	Stages III & IV	NR	93·3	1995-1997	52	22·5
Mody, 2013(182)	Rwanda	NR	Black	Butare University Teaching Hospital; Kigali University Teaching Hospital; Kigali & King Faisal Hospital, Kigali	CCS	141 (+4)	7	TNM (2013)	N	NR	NR	57	2007-2011	48·5	13·5
Muguti, 1993(111)	Zimbabwe	Black (B) 100%	Black	Mpilo Central Hospital, Bulawayo	CCS	82 (+2)	79	TNM (NK)	N	T3 and T4 tumours	C & I	83·5	1987-1990	50	24·5
Nyagol, 2006(183)	Kenya	NR	Black	Pathology Department Nairobi Hospital, Nairobi	CCS	158	42	TNM (2006)	N	Stages IIIA, IIIB & IV	NR	69·1	2002-2004	47	20·5
Ojara, 1978(125)	Uganda	Black	Black	Mulago Hospital, Kampala	CCS	152	150	M (1978)	N	Stage III & IV	NR	78	1970-1975	35	21·5
Pignon, 1988(126)	Madagascar	Black	Black	The island's only cancer hospital, Antananarivo	CCS	30	29	TNM (1988)	N	NR	NR	44·8	1977-1986	30·7 [e]	20·5
Rafaramino, 2001(110)	Madagascar	Black	Black	The island's only cancer hospital, Antananarivo	CCS	259	204	TNM (1998)	N	T3 & T4 tumours	C & I	77·9	1996-1998	48·5	22·5
Rambau, 2011(184)	Tanzania	NR	Black	Bugando Medical centre, Mwanza	OCS	328	328	TNM (AJCC 2011)	N	Stages III & IV	NR	74·7	2002-2010	47·8	18·5
Tesfamariam, 2013(185)	Eritrea	NR	Black	Orotta Medical Surgical National Referral Hospital, Asmara; Halibet Hospital, Asmara & Sembel Hospital, Asmara	OCS	77 (+5)	82	TNM (WHO classification of tumours 2003)	N	Stages III & IV	C & I (Imaging in 29% of patients)	64	2007-2008	48·4	22·5
Southern Africa															

First author, year of publication [ref no.]	Country	Race		Hospital/clinic, location	Study design	Sample size females (males)	No. of patients with known stage	Staging classification / edition (yr)	Joint TNM distribution given (Y/N)	Criteria used to define late stage	Staging methods	Percent stage III/IV	Year of diagnosis	Mean/ Median age at diagnosis (males where given)	Study quality score
		As reported in the original publication	As assigned in the present review [a]												
Ariad, 1991(186)	South Africa	NR	Non-Black	Johannesburg Hospital, Johannesburg	OCS	58	58	NR	-	Stages III & IV	C & I	70·7	NR	45·5	20·5
Basro, 2010(95)	South Africa	NR	Non-Black	Tertiary Hospital and private breast health center in South Africa	OCS	141	139	TNM (AJCC 2002)	N	Stage III (locally advanced) & Stage IV (metastatic disease)	NR	55·3	2000-2008	31 [f]	19·5
Dansey, 1988(115)	South Africa	White: 60.5%	Non-Black	Johannesburg and Hilbrow Hospitals, Johannesburg	CCS	1351	1267	TNM (AJCC 1983)	N	**Stage 3:** T3 and T4 & any N; any T & N3; **Stage 4:** any T & any N & M1	C & I	43·6	1976-1985	60	22·5
		Black: 39.5%	Black	Johannesburg and Hilbrow Hospitals, Johannesburg	CCS	882	863	TNM (AJCC 1983)	N	**Stage 3:** T3 and T4 & N, any T & N3; **Stage 4:** any T any N & MI	C & I	83·3	1976-1985	50	22·5
DuToit, 1988(132)	South Africa	White: 45% Black: 55%	Non-Black	Bloemfontein Academic Hospital, Bloemfontein	CCS	20	20	TNM (AJCC 1988)	N	Stages III & IV	NR	40	1971-1982	53·6	17·5
Hacking, 1984(116)	South Africa	White: 49%	Non-Black	Groote Schuur Hospital, Cape Town	OCS	1085	1078 [g]	TNM (1978) & Manchester	Y	T3-4, N0-3,M0 & T1-4,N0-3, M1	NR	40·2	1971-1981	60	17·5
		Coloured: 48%	Non-Black	Groote Schuur Hospital, Cape Town	OCS	1063	1063 [g]	TNM (1978) & Manchester	Y	T3-4, N0-3,M0 & T1-4,N0-3, M1	NR	59·9	1971-1981	53	17·5
		Black: 3%	Black	Groote Schuur Hospital, Cape Town	OCS	66	66 [g]	TNM (1978) & Manchester	Y	T3-4, N0-3,M0 & T1-4,N0-3, M1	NR	74·2	1971-1981	49	17·5
Hoffman, 2000(130)	South Africa	Black: 15%; Coloured: 85%	Non-Black	2 Tertiary Hospitals in Cape Town	PB	485	478	TNM (1992)	N	Stages III & IV (advanced breast cancer)	NR	42·2	1994-1997	59% < 45 years	19·5
McCormack, 2013(30)	South Africa	Black: 90.3%; White: 4.1%, Coloured: 3.8% & Asian: 1.8%	Black	Chris Hani Baragwanath Academic Hospital (CHBAH) [h]	CCS	1216	1192	TNM & Manchester	N	Stages III & IV	C & I	54	2006-2012	55·3	25·5
Odendaal, 2003(187)	South Africa	NR	Non-Black	NR	OCS	236	201	TNM (1988)	Y	Stage III & T4b N0-1 lesions only	C & I	53·2 [i]	1990-1996	79 [j]	25·5
Ostyn, 1987(131)	South Africa	Mostly Coloured or Indian	Non-Black	Coronation Hospital, Johannesburg	OCS	156	120	TNM (1979)	N	Stages III & IV	NR	51·7	1974-1984	52·1	16·5

First author, year of publication [ref no.]	Country	Race		Hospital/clinic, location	Study design	Sample size females (males)	No. of patients with known stage	Staging classification / edition (yr)	Joint TNM distribution given (Y/N)	Criteria used to define late stage	Staging methods	Percent stage III/IV	Year of diagnosis	Mean/ Median age at diagnosis (males where given)	Study quality score
		As reported in the original publication	As assigned in the present review [a]												
Pegoraro, 1980(109)	South Africa	Whites: 23%, Indians: 35% Blacks: 42%	Non-Black	NR	OCS	167 (+4)	110	TNM (1980)	N	T3 & T4	NR	77·2	NR	50% were between 45-64 years	14·5
Pegoraro, 1985(117)	South Africa	White: 31%	Non-Black	University of Natal Teaching Hospital & all major hospitals, Durban	OCS	197	91	TNM (AJCC 1983)	N	Stages III & IV	NR	41	1975-1983	60	19·5
		Indian: 26%	Non-Black	University of Natal Teaching Hospital & all major hospitals, Durban	OCS	168	151	TNM (AJCC 1983)	N	Stages III & IV	NR	54	1975-1983	46·6	19·5
		Coloured: 4%	Non-Black	University of Natal Teaching Hospital & all major hospitals, Durban	OCS	23	22	TNM (AJCC 1983)	N	Stages III & IV	NR	77	1975-1983	52·8	19·5
		Black: 39%	Black	University of Natal Teaching Hospital & all major hospitals, Durban	OCS	252	240	TNM (AJCC 1983)	N	Stages III & IV	NR	90	1975-1983	49·8	19·5
Walker, 1984(118)	South Africa	Black: 100%	Black	Baragwanath Hospital, Johannesburg	CCS	96	84	NR	-	NR	NR	77·5	1980-1982	51·7	17·5
Walker, 1989(120)	South Africa	Black 100%	Black	Baragwanath Hospital, Johannesburg	CCS	65	59	NR	-	Stages III & IV	NR	67	1986-1987	52·5	
Walker, 2004(119)	South Africa	Black: 100%	Black	King Edward the VIII Hospital, Durban	CCS	57	57	NR	-	Stages III & IV	NR	84·2	1999-1999	54·1	12·5
Wasserman, 2007(127)	South Africa	NR	Non-Black	Tygerberg Hospital, Tygerberg	OCS	483	421 [j]	TNM (6th edition)	Y	Stages III & IV	NR	(14) 54·8 [k]	1990-2004	77·3 [l]	20·5
Winters, 1988(93)	South Africa	White: 96%	Non-Black	NR [m]	OCS	2346	2324	NR	-	NR	NR	30	NR	58	19·5
		Black: 4%	Black	Baragwanath Hospital, Johannesburg	OCS	94	77	NR	-	NR	NR	90	1980-1986	51	20·5

C: Clinical methods; CCS: Consecutive case series; I: Imaging methods; M: Manchester staging classification; NPL: Non-pregnant/non-lactating women; NR: Not reported in the original publication; OCS: Opportunistic (convenience) case series; PBS: Population-based study; PL: Pregnant/lactating women; TNM: Tumour Node Metastases.

[a] As defined in Table 1.

[b] This study included a group of PL and a group of NPL, but the latter was not included in the review because NPL women were matched the PL women on stage at diagnosis.

[c] This study included women aged ≤40 years only.

[d] Information in supplementary material used to calculate number in Stage IV.
[e] This study included women aged ≤35 years only.
[f] This study included women aged ≤35 years only.
[g] Numbers of women by stage and race were not given; hence, approximate numbers were inferred from the data shown in table 1 and figure 1 of the original publication.
[h] Chris Hani Baragwanath Academic Hospital Johannesburg was previously the Baragwanath Hospital Johannesburg.
[i] The authors included stages I to III and early stage IV cancers in their study but provided stage information on the patients excluded and we included these in the calculation of % late stage in our review.
[j] This was a study of elderly breast cancer patients aged ≥70 years with T1-T3 and small localised T4N0-1 tumours.
[k] The authors gave stage distribution for the included patients (n=188) with % stage III as 14% in table 5 of the paper, however, the stage of distribution of excluded patients (n=233) was also given in the text, so a total of 421 patients were used to derive % III/IV (54.8%).
[l] This study included women aged ≥70 years only.
[m] The authors stated that their series of Black patients was compared with a similar unpublished study of White women but did not provide details on how the latter were recruited.

Table 3. Sources of between-population heterogeneity in the percentage of late stage breast cancer (stages III/IV) of breast cancer from meta-regression analyses

	No. BC cases	All study populations (Black & non-Black)						Black populations only			
		Unadjusted analysis		Region & race adjusted analysis		Fully-adjusted analysis [a]		Unadjusted Analysis		Fully-adjusted analysis [b]	
Variable		**Absolute difference (%)**	**95% CI**	**Absolute difference (%)**	**95% CI**	**Absolute difference (%)**	**95% CI**	**Absolute difference (%)**	**95% CI**	**Absolute difference (%)**	**95% CI**
Region/Race [c]											
West Africa/Black	10845	0 (ref)		0 (ref)		0 (ref)		0 (ref)		0 (ref)	
East Africa/Black	3186	-0·2	(-6·8, 6·4)	-	-	-3·0	(-9·2, 3·2)	-0·2	(-6·6, 6·3)	-3·3	(-9·5, 2·9)
Southern Africa / Black	2638	0·1	(-9·0, 9·3)	-	-	8·6	(-2·0, 19·1)	0·1	(-8·9, 9·1)	5·8	(-5·9, 17·5)
Southern Africa / Non-Black	7544	-25·5	(-32·6, -18·3)	-	-	-18·1	(-28·2, -8·0)	-	-	-	-
Study Design											
Consecutive case series	14425	0 (ref)		0 (ref)		0 (ref)		0 (ref)		0 (ref)	
Convenience case series	9788	-6·5	(-12·9, -0·4)	-0·6	(-6·1, 4·9)	-2·0	(-7·1, 3·1)	-2·2	(-7·9, 3·6)	-2·6	(-8·0, 2·8)
Study Setting											
Urban	14208	0 (ref)		0 (ref)		0 (ref)		0 (ref)		0 (ref)	
Mixed (urban/rural)	10005	16·3	(10·6, 22·0)	10·7	(3·4, 17·9)	12·9	(5·5, 20·3)	7·7	(1·7, 13·7)	13·2	(5·7, 20·7)
Facility Type											
Tertiary	22399	0 (ref)		0 (ref)		0 (ref)		0 (ref)		0 (ref)	
Tertiary/Secondary/Primary	1503	-3·7	(-13·2, 5·8)	-1·2	(-8·8, 6·4)	-1·9	(-9·1, 5·4)	-3·2	(-11·5, 5·1)	-1·4	(-9·5, 6·6)
NR	311	-8·8	(-30·5, 12·9)	14·8	(-3·4, 32·9)	10·1	(-0·8, 28·3)	-	-	-	-
Age at Diagnosis (yrs) [d]											
<45	4840	0 (ref)		0 (ref)		0 (ref)		0 (ref)		0 (ref)	
≥ 45 to <50	7218	0·8	(-6·0, 7·8)	0·3	(-5·5, 6·0)	3·9	(-2·0, 9·9)	-0·3	(-6·2, 5·6)	3·9	(-2·3, 10·1)
≥ 50	9841	-13·2	(-21·2, -5·3)	-6·2	(-14·4, 2·0)	-1·7	(-9·9, 6·4)	-3·9	(-12·0, 4·1)	1·8	(-8·9, 12·4)
NR	2314	12·0	(-4·4, 28·5)	17·4	(3·8, 31·1)	20·6	(6·4, 34·8)	14·6	(-1·3, 30·6)	20·4	(4·8, 36·1)

Year of Diagnosis [e]											
<1980	3782	0 (ref)	-	0 (ref)		0 (ref)		0 (ref)		0 (ref)	
1980-1999	10737	4·8	(-4·3, 13·9)	-3·0	(-10·6, 4·6)	-5·2	(-12·6, 2·2)	-4.7	(-13·1, 3·7)	-6·8	(-15·5, 1·9)
≥2000	6733	4·3	(-5·0, 13·5)	-6·2	(-14·2, 1·8)	-8·5	(-16·1, -1·0)	-8.4	(-16·8, -0·1)	-10·5	(-19·3, -1·6)
NR	2961	-6·5	(-19·9, 6·9)	-7·3	(-18·2, 3·6)	-8·5	(-19·0, 2·1)	-16.5	(-29·7, -3·3)	-12·5	(-26·9, 1·8)
Staging Methods											
Clinical & Imaging	9516	0 (ref)	-	0 (ref)		0 (ref)		0 (ref)		0 (ref)	
Clinical only	967	5·0	(-6·4, 16·4)	2·3	(-7·0, 11·6)	-1·4	(-10·4, 7·6)	3·0	(-5·9, 11·9)	-1·3	(-10·3, 7·8)
NR	13730	0·2	(-7·1, 7·4)	3·0	(-2·7, 8·8)	3·2	(-2·3, 8·7)	4·0	(-1·9, 10·0)	4·1	(-1·7, 9·8)
Staging classification											
TNM	18048	0 (ref)	-	0 (ref)	-	-	-	-	-	-	
Manchester	1426	2·4	(-7·6, 12·5)	-3·7	(-12·1, 4·6)	-	-	-	-	-	-
NR	4739	3·1	(-4·5, 10·7)	-0·8	(-7·0, 5·5)	-	-	-	-	-	
Study quality scores [f]											
≥23 (highest quality)	3569	0 (ref)	-	0 (ref)	-						
22-20	5721	-2·1	(-12·7, 8·5)	-0·1	(-8·5, 8·3)	-	-	-	-	-	-
19-17	13327	-1·1	(-11·2, 9·0)	2·1	(-5·9, 10·1)	-	-	-	-	-	-
<17 (lowest quality)	1596	0·7	(-11·5, 12·9)	2·9	(-6·9, 12·6)	-	-	-	-	-	-

BC: breast cancer; CI: confidence interval; NR: not reported in the original publication; ref: reference category; TNM: Tumour, lymph Node and Metastasis staging system

[a] Adjusted for all other variables in the Table except for staging classification and study quality because of concerns of over-adjustment.

[b] Adjusted for all other variables in the Table except region/race, staging classification and study quality

[c] The study population was classified as Black if ≥80% of the participants were Black (see webappendix-Table 1 and Figure 3b).

[d] Mean or median age at breast cancer diagnosis (see footnote g of Table 1 for details).

[e] Taken as the middle year of the period during which patient recruitment took place.

[f] Categories defined using fourths of the overall score distribution. Analyses were not further adjusted for the other variables in the table because most of them were integrated into the study quality scores (see webappendix-Text 4).

Table 4: Late stage (III/IV) breast cancer at diagnosis, self-reported duration of symptoms, and tumour characteristics (size, grade, ER positivity and histology), by study population in SSA [a, b]

First author, year (race) [c]	% Late stage (III/IV) at diagnosis	Mean/median duration of symptoms (months)	Mean/median tumour size (cm)	% ER-positive tumours	% grade 3 tumours	Histology (% ductal NST)
West Africa						
Abudu, 2007 (B)	72	-	-	-	62	92
Adebamowo, 2008 (B)	86·5	-	-	65·1	15·6	82·3
Adesunkanmi, 2006 (B)	80·6	11·2	-	-	-	90
Adisa, 2012 (B)	90·9	-	-	24	100	53 [d]
Alatise, 2010 (B)	75·0	-	8·5	-	91·7	100
Anyanwu, 2000 (B)	64·0	4·5	-	-	-	73
Anyanwu, 2008 (B)	72·0	3·5	-	-	-	80
Anyanwu, 2011 (B)	72·0	52% >6 months	-	-	-	85·5
Atoyebi, 1997 (B)	77·0	13·3	-	-	-	94
Ayoade, 2012 (B)	77·5	6·7	-	-	-	-
Bagnan, 2013 (B)	69·9	-	-	-	-	33·3 [e]
Chiedozi, 1985 (B)	85·3	-	-	-	50	19 [f]
Chiedozi, 1987 (B)	85.0	-	-	-	50	-
Chiedozi, 1988 (B, PL)	83·4	6	-	-	55·6	-
Clegg-Lamptey, 2007 (B)	57·6	10	7	-	-	85·8
Edmund, 2013 (B)	50·9	7·5	4·5	-	28·9	91·6
Ezeome, 2010 (B)	78·3	2	-	-	-	-
Fente, 2011 (B)	90·5	-	-	-	-	54·7 [g]
Gukas, 2008 (B)	61·8	-	-	26·5	70·6	97
Harouna, 2002 (B)	74·7	8·8	-	-	-	-
Hassan, 1992 (B)	88·0	9·3	10	-	-	85
Hassan, 1995 (B, PL)	100	10	8	-	-	72
Hassan, 1995 (B, NPL)	95·5	9	8	-	-	70·5
Ibrahim, 2011 (B)	82·0	10·8	-	-	-	93
Ibrahim, 2012 (B)	79·1	12·1	-	-	-	-
Ihekwaba, 1992 (B)	82·8	10·9	6·5	-	-	49·2 [h]
Ikpatt, 2002 (B)	53·3	-	4·8	-	45·7	84
Kene, 2010 (B)	62·1	-				82·5
Ketiku, 1986 (B)	66·3	-	-	-	-	33·6 [i]
Khwaja, 1980 (B)	92·5	11	-	-	90·9	82·5
Lawani, 1973 (B)	74·5	9	-	-	31	53·8 [j]
Ly, 2012 (B)	90·0	-	90% >5	39	78	94
Mehinto, 2007 (B)	70·3 [k]	-	-	-	38·9	86·4
Ntekim, 2009 (B)	85	-	-	-	-	95
Ohene-Yeboah, 2012 (B)	85·2	13·8	-	47·1	53·7	82·1
Okobia, 2001 (B)	67·5	9	-	-	-	66·8
Oluwole, 1987 (B)	81·2	-	-	-	-	30·2 [l]
Pearson, 1963 (B)	95·0	6	9·7	-	80	-
Sarre, 2006 (B)	73·1	9	-	-	45·6	89·9
Stark, 2010 (B)	76·0	-	3·2	24	76	66·7
Togo, 2010 (B)	72·9	17·8	-	58·1	-	57·4 [m]
Traore, 2012 (B)	93·5	-	-	30·7	-	73·8

Ukwenya, 2008 (B)	74·7	9	-	-	-	-
East Africa						
Amir, 1997 (B)	98	-	-	-	-	100
Bird, 2008 (B)	62·6	12	6·8	24	50	90
Burson, 2010 (B)	90·7	17·2	69·1% ≥5	50·8	-	85·5
Ersumo, 2006 (B)	60·2	11·5	60% >5	-	-	77·6
Gakwaya, 2008 (B)	77·4	-	-	-	58	76
Galukande, 2013 (B)	79·8	-	-	47	65·2	93·8
Gebremedhin, 1998 (B)	76·4	12	6·5	-	-	85·2
Kantelhardt, 2014 (B)	71	-	5	-	24·8	79·2
Kenda, 1988 (B)	95·6	-	-	-	26·5	68·9
Mabula, 2012 (B)	84·4	11·4	6	-	63·8	91·7
Mbonde, 2000 (B)	93·3	11	8	33·3	46·6	78·3
Mody, 2013 (B)	57	11·2	-	-	-	-
Muguti, 1993 (B)	83·5	7	8	-	-	-
Nyagol, 2006 (B)	69·1	-	4·5	37·3	66	92·4
Pignon, 1988 (B)	44·8	14·1	-	-	60	0 [n]
Rafaramino, 2001 (B)	77·9	9·4	-	-	56·5	55·6 [o]
Rambau 2011 (B)	74·7	-	5·5	-	56·4	91·5
Tesfamariam, 2013 (B)	64	34·8	-	-	-	82
South Africa						
Ariad, 1991 (NB)	70·7	-	-	40·7	-	84·5
Basro, 2010 (NB)	55·3	-	79% ≥2	67·8	46·7	92·9
Du Toit, 1988 (NB)	40	-	-	-	-	85 [p]
McCormack, 2013 (B)	54	-	-	64·9	42·3	80
Odendaal, 2003 (NB)	53·2	-	4	-	11·2	73
Ostyn, 1987 (NB)	51·7	-	-	-	-	67
Pegoraro, 1980 (NB)	77·2	-	7·5	52·7	-	-
Pegoraro, 1985 (B)	90	-	7·5	-	71	-
Pegoraro, 1985 (NB, I)	54	-	5	-	72	-
Pegoraro, 1985 (NB, W)	41	-	3·5	-	47	-
Winters, 1988 (B)	90	-	-	55	27	90
Winters, 1988 (NB, W)	30	-	-	65	-	-
No. of study populations with available information [a]						
All (Black & non-Black)	73 [b]	36	27	19	36	58
Black only	64	36	22	15	32	53

- Information not provided in the original publication; B: Black women; I: Indian women; NST: invasive intra-ductal carcinoma; NB: Non-Black women; NPL: Non-pregnant and non-lactating women; PL: Non-pregnant and non-lactating women; SSA: sub-Saharan Africa; W: White women

[a] Some studies have more than one study population (i.e. PL and NPL women; multiple racial groups) – see Table 1 (footnote a).

[b] Restricted to study populations with information on stage at presentation and at least one of the other variables shown in this Table.

[c] Reference numbers as in webappendix-Table 1. Race as defined in Table 1 (footnote b) and webappendix-Table 1.

[d] The authors reported that 53% of the tumours were invasive ductal carcinoma, not otherwise specified (NST), 18% invasive lobular carcinoma (ILC), 18% a mix of NST and ILC, and 12% other subtypes.

[e] Other histological subtypes not reported.

[f] Other histological subtypes included anaplastic carcinoma (50%), scirrhous carcinoma (28.4%), Paget's disease (1.7%), and mucoid carcinoma (0.9%).

[g] Other histological subtypes comprised undifferentiated (19.1%), lobular carcinoma (12%), papillary (7.4%), others (6.9%).
[h] Other histological types included infiltrating anaplastic carcinoma (33.3%), medullary carcinoma (5.9%), lobular carcinoma (2.8%), papillary carcinoma (2.3%), mucinous carcinoma (1.5%), others (5%).
[i] Other histological subtypes comprised anaplastic carcinoma (22.9%), scirrhous carcinoma (8.9%), adenocarcinoma (7.5%), medullary carcinoma (4.2%), mixed carcinoma (3.7%), colloid carcinoma (2.8%), comedo carcinoma (2.8%) and other subtypes (13.6%).
[j] The most common subtypes reported were adenocarcinoma 33.7%, and other subtypes 12.5%
[k] The authors used the UICC 1987 TNM classification (33rd Edition). Stage reclassified using the AJCC TNM classification 7th Edition
[l] Other histological subtypes were poorly differentiated adenocarcinoma (33.8%), anaplastic carcinoma (9.4%), inflammatory carcinoma (7.9%), and others (18.7%).
[m] Other histological subtypes comprised infiltrating lobular carcinoma (21.4%), medullary carcinoma (3.3%), and others (17.9%)
[n] Most common subtypes were adenocarcinoma not otherwise specified (31.3%), intraductal carcinoma (6.3%), atypical carcinoma (28.1%), and others (34.4%).
[o] Other histological subtypes included adenocarcinoma (31.7%), mucinous carcinoma (3.5%), infiltrating lobular carcinoma (2.3%),and others (6.9%).
[p] All patients in this study had Paget's disease of the breast; histologically, they were all ductal carcinomas but three were intra-ductal.

CHAPTER 3

Study protocol and data collection methods

This chapter describes the study designed and implemented in order to investigate objectives 3 (i) and (ii) of this PhD thesis, which were to identify the sociodemographic, breast cancer awareness, health care access and clinical determinants of (i) stage at diagnosis of breast cancer; and (ii) a woman's journey from the first reported symptom to the diagnosis of breast cancer, and of any delays, in Nigerian women with breast cancer. The study protocol will be described (study design, setting, sample size determination, case definition and study sites for the Nigerian Integrative Epidemiology of Breast Cancer Study, i.e. the parent study within the framework of which my PhD study was conducted) and subsequently the study coordination, recruitment process and challenges will be discussed, including methods used in data collection, entry and analysis. An overview of the methods is later provided in subsequent chapters 4 and 5.

3.1. STUDY PROTOCOL

3.1.1. Study Design

This PhD research study was conducted within a larger multi-centre case-control study exploring the breast cancer associations with dietary, genetic and epigenetic factors – *The Nigerian Integrative Epidemiology of Breast Cancer Study* referred to as the 'NIBBLE study.' Its case-control design is supported by the fact that breast cancer is a relatively rare disease among Nigerian women with an ASR of 54.3 per 100,000 women (3), for which a case-control study is considered efficient. All eligible women (see section 3.1.3, box 1) who presented breast symptoms suggestive of breast cancer during the study period (January 2014-July 2016) were approached and invited to participate.

This design was chosen in order to achieve the aim of identifying the determinants of stage at diagnosis of breast cancer and diagnostic delays in Nigerian women with breast cancer.

3.1.2. Study Setting

The NIBBLE study was conducted in six government hospitals in Nigeria (five hospitals in the capital, Abuja, and one hospital in Enugu, located about 400 km from Abuja). Nigeria is Africa's most populous country, with a population of approximately 182.2 million people in 2015(188). The country is home to 50% of the West African population and represents 20% of the entire population on the African continent. It is Africa's most diverse economy with a Gross Domestic Product of $481.1 billion(188) a total health expenditure of 3.7%(8). It is located in the Gulf of Guinea and shares boundaries with the Republics of Cameroun, Benin, Chad and Niger. The average life expectancy at birth in females is 56 years, having increased by five years over the last decade(8). The country is divided into six geopolitical zones for ease of administration. However, an easier identification is provided by the country's North and South distinction with large

variations in the socio-economic indicators across Northern and Southern Nigeria (189, 190). The majority of the study sites were located in Abuja, the capital city of Nigeria, which has a predominantly younger and working-class population compared with Enugu(191). In Abuja, only 10.7% of the female population is aged $\geq$ 40 years compared to 20.5% in Enugu (Table 1).

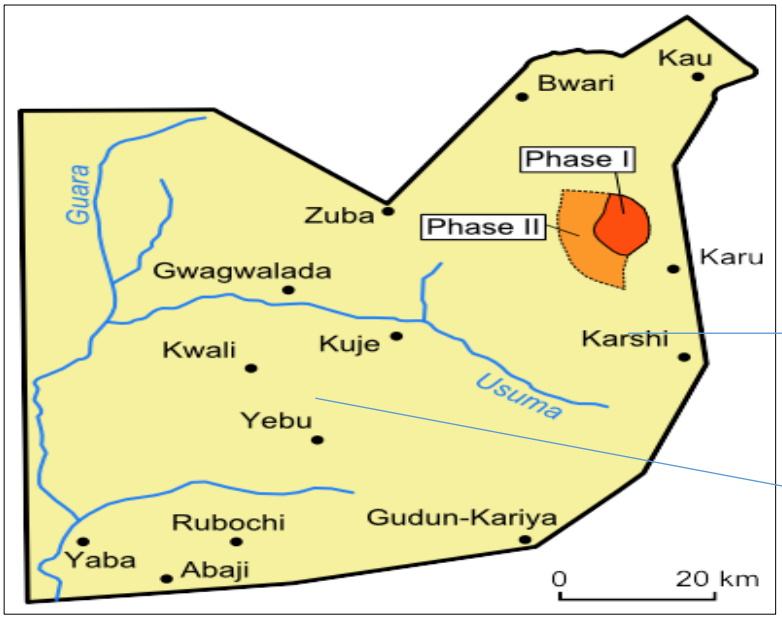
Figure 1: (a) Map of Nigeria showing the study locations (b) Map of Abuja showing 5 study sites in Abuja

FIVE ABUJA SITES (North-Central Nigeria)

- NHA
- UATH
- ADH
- GH
- WGH

ONE ENUGU SITE (South-Eastern Nigeria)

- UNTH



Four sites located in Abuja AMAC Phase 1.

NHA

ADH

GH

WGH

UATH

Table 1: Differences between the city profiles of Abuja and Enugu State (191)

Description	Abuja	Enugu
Location	North-central	South-eastern
Predominant Religion	Mixed: Islam and Christianity	Christianity
Type of City	Urban	Predominantly rural
Predominant Ethnic Groups	Indigenous inhabitants are Gwari, but due to the large influx of people from all over the country, a wide range of ethnic groups can be found in Abuja.	Igbos
Predominant Occupation	Government employees in public ministries, working class population	Trading, farming
Total Population	1,406,239	3,257,298
Total Female Population	673,067	1,671,795
Total Female Population > 40 years	72,081	343,322

3.1.3. Case Definition

All newly diagnosed cases of breast cancer during the study period (January 2014-June 2016) in each of the six participating hospitals, and with no previous history of cancer, were considered eligible to be recruited into the study. All participating hospitals routinely perform breast tissue biopsies for all new cases. However, in advanced cases

where a histological confirmation was not possible, these women were also included in the study.

***Inclusion Criteria**:*

1. All newly diagnosed cases of breast cancer seen at any of the participating hospitals during the period of study (i.e. January 2014- June 2016)
2. No previous diagnosis of any cancer
3. Women aged 18 years and above
4. Must provide written informed consent

Box 1. Eligibility criteria for study participants

Pregnant women were not excluded as this study did not interfere with the standard care provided by these hospitals.

3.1.4. Study Sites

This was a multi-centre study conducted at 6 government hospitals in Nigeria that offer diagnostic services, care, and treatment for breast cancer patients. These six centres were selected partly due to logistic reasons (e.g. five in the capital city of Abuja) and partly to represent different types of hospitals, including tertiary and secondary centres with differences in the availability of diagnostic and treatment facilities, and catchment populations: one centre in Southern Nigeria, four within the capital city and one on the outskirts of Abuja catering to a less urbanised population (e.g. with varying levels of urbanisation). A description of each of the study sites and the services offered is provided below:

<u>University of Nigeria Teaching Hospital Enugu (UNTH)</u>

The UNTH is a large tertiary hospital located in south-eastern Nigeria and a major referral centre for breast cancer patients from south-eastern Nigeria. The hospital was founded in

1966 and has a capacity of 500 beds and 29 specialist surgeons. The UNTH provides chemotherapy and surgery services and has a dedicated oncology department. The hospital has a radiotherapy machine which is currently non-functional. The UNTH predominantly caters to the urban city of Enugu and the poorer surrounding cities with predominantly rural populations, but receives breast cancer patients who are referred from smaller institutions across the southern part of Nigeria (Figure 2).

Figure 2: The University of Nigeria, Nsukka (UNTH, Enugu) the only study site outside Abuja located 400 km from Abuja, Nigeria

National Hospital Abuja (NHA)

The NHA is a renowned tertiary hospital and referral centre located in Abuja, the capital city of Nigeria. This 200-bedded hospital was founded in 1999, initially as a hospital for women and children only, but extended its services to the entire population in 2003. The hospital has recently undergone expansion to a current capacity size of 407 beds. The NHA is one of the best equipped tertiary health care centres in Nigeria, with facilities for diagnostic and therapeutic services for breast cancer including magnetic resonance imaging (MRI), computerised tomography scans, and radiotherapy/oncology and nuclear

medicine departments. Its radiotherapy department is equipped with a linear accelerator, SLI Philips simulator and brachytherapy machines. The hospital provides surgery, chemo-therapy and radiotherapy services to patients referred from various facilities all over the country (Figure 3).

Figure 3: The National Hospital Abuja, a tertiary hospital located in Abuja, Nigeria

University of Abuja Teaching Hospital Gwagwalada (UATH)

The UATH is a teaching hospital currently affiliated with the University of Abuja, located in Gwagwalada, approximately 60 km from the Abuja city centre (Figure 4). This tertiary health care facility has a training programme for medical students and resident doctors and is equipped with 350 beds. It primarily caters to the rural populations on the outskirts of the capital city and provides chemotherapy, surgery, and palliative care services for breast cancer patients. For radiotherapy, patients are referred to the National Hospital Abuja.

Figure 4: The University of Abuja Teaching Hospital, Gwagwalada located on the outskirts of Abuja city.

Asokoro District Hospital (ADH)

This is a general hospital located in the capital city of Abuja. This secondary level facility has 149 beds and is located within close proximity of the National Hospital Abuja. The hospital caters to both urban and rural populations from the surrounding suburbs near the city of Abuja. The hospital provides surgery services only and patients are often referred to the National Hospital Abuja for chemotherapy and radiotherapy (Figure 5).

Figure 5: Asokoro District Hospital, one of the secondary centres located in Abuja, Nigeria

Garki Hospital (GH)

This secondary level facility is located in Abuja, and caters mainly to the people of Abuja and its surrounding suburbs. The GH also receives referrals from general hospitals located in the poorer surrounding states such as the states of Niger, Nassarawa and Kaduna. The GH became a public–private partnership (PPP) between the Federal Government and a private hospital, the Nisa Premier Hospital in 2007 in a bid to upgrade the facility and the types of medical services provided. The hospital has 127 beds and is only equipped with surgery facilities (Figure 6). Patients are referred to the oncology unit of the National Hospital Abuja or to private centres in the state of Lagos for post-surgical treatment and management.

Figure 6: Garki Hospital, a secondary level facility located in Abuja, Nigeria

Wuse General Hospital (WGH)

This is a secondary level health facility located in the Phase 1 district of Abuja and the smallest of all the sites included in this study. The hospital is equipped with 110 beds and has a surgery department that manages breast cancer patients. Patients consulted at the WGH following surgery are subsequently referred to the National Hospital Abuja for further management.

3.2. COORDINATION OF THE STUDY

I took part in each phase of this study from conception to the planning and subsequent field execution in Nigeria (Figure 7). This work included the request for ethical approval from all study sites, the design of study materials including two questionnaires, a clinical report form and a laboratory form for breast tissue sample monitoring. This study was overseen by my supervisor, co-supervisor and a member of my Advisory Committee to whom I provided regular progress reports on the recruitment and operational challenges encountered in the field. I worked with 8 field staff members, including one research

interviewer at each of the six participating sites, a data manager for the parent study and one laboratory assistant who received samples in the laboratory, recorded all the samples received and stored them for analysis purposes. Initial fortnightly meetings, which later became monthly meetings after six months when the field staff members had become conversant with the project, were held with the field staff to monitor recruitment rates and address logistic challenges. Prior to the commencement of the study, a 2-day training exercise was held with the field staff where they were introduced to the study aims and objectives, use of study materials including nexus tablets for data collection and data entry into the database specifically developed for the study (Figures 8 & 9). Other aspects of the training addressed the topics of research methodology, research ethics and confidentiality. Following the training of the field staff, an initial meeting was held with the site collaborators (surgeons) by the principal investigator of the parent study and myself to discuss the aims of the study, the recruitment expectations and the publication authorship. After this initial meeting, two weekly visits were made to the study sites for the first six months to assess the interview process undertaken by the field staff with the purpose of addressing individual site logistic peculiarities and challenges (Figures 10, 11, 12 & 13). Weekly recruitment updates were provided to my supervisors, any existing challenges were discussed and the methods seeking to address them were formulated and implemented. As per the LSHTM requirements applicable in the case of PhD research conducted overseas, my PhD supervisors, Prof. Isabel dos Santos Silva and Dr. Valerie McCormack also visited Nigeria in October 2014 in order to monitor the progress being made during the fieldwork in Nigeria and to offer advice in relation to the challenges encountered and how these could be overcome (Figure 11).

Figure 7: Study planning and implementation

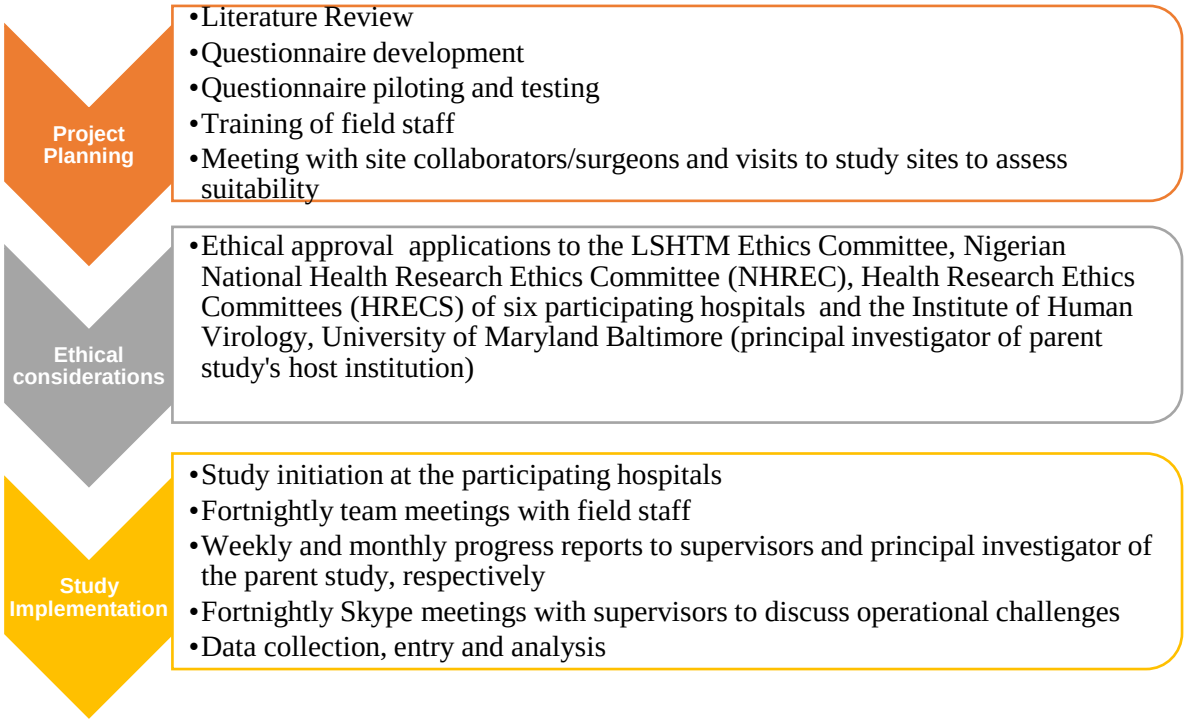


Figure 8: NIBBLE study initiation training workshop for research assistants (October 2013, Abuja, Nigeria)

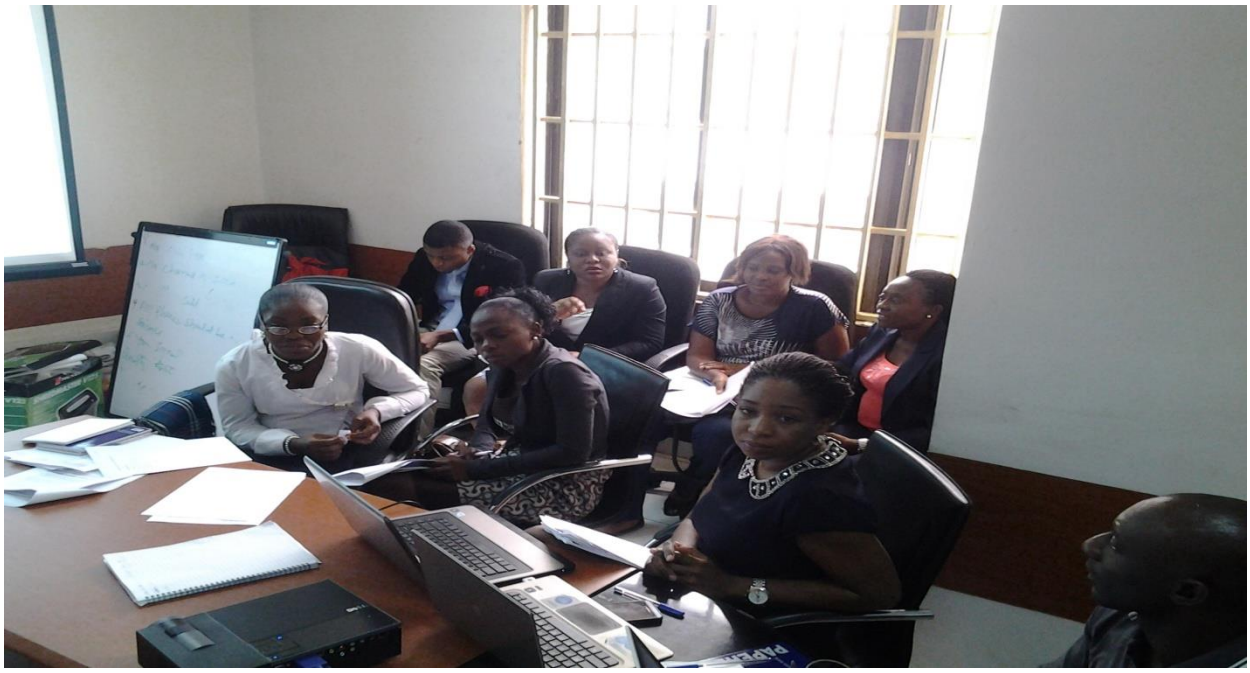


Figure 9: NIBBLE study initiation training workshop on how to take anthropometric measurements (October 2013, Abuja, Nigeria)

Figure 10: During a site visit to the UNTH Enugu site, observing Mr. Kenneth Oruka (research assistant), recruit a participant with breast symptoms into the study at the UNTH Enugu study site in June 2014

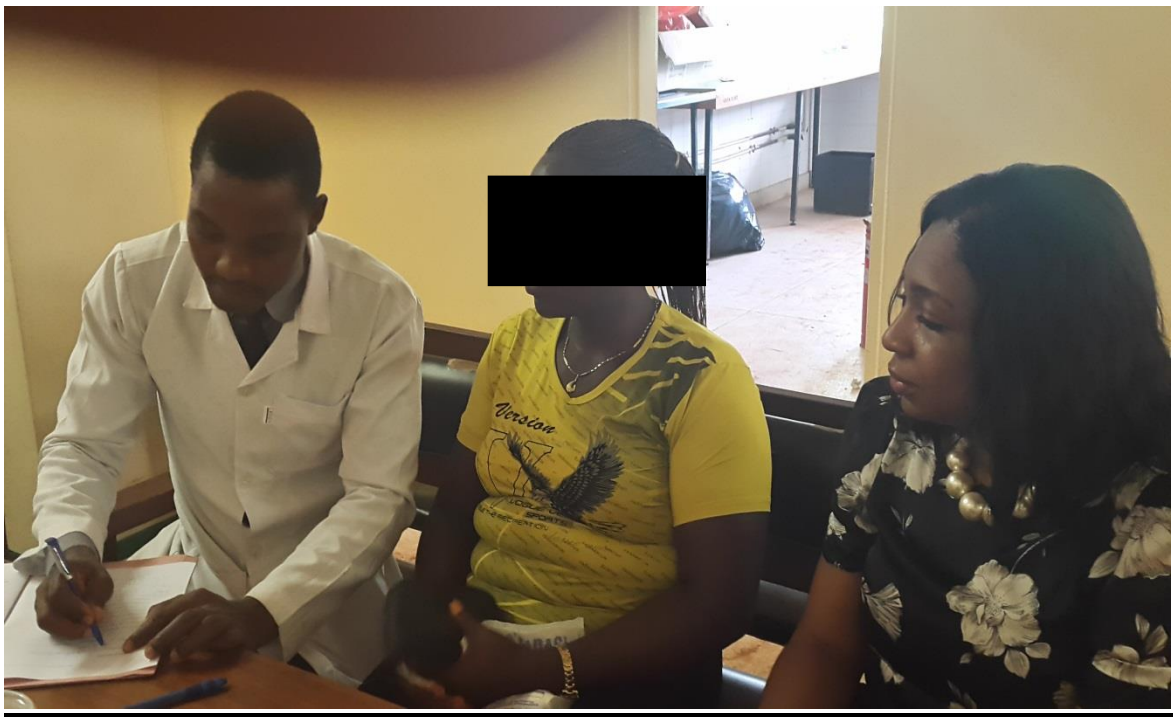
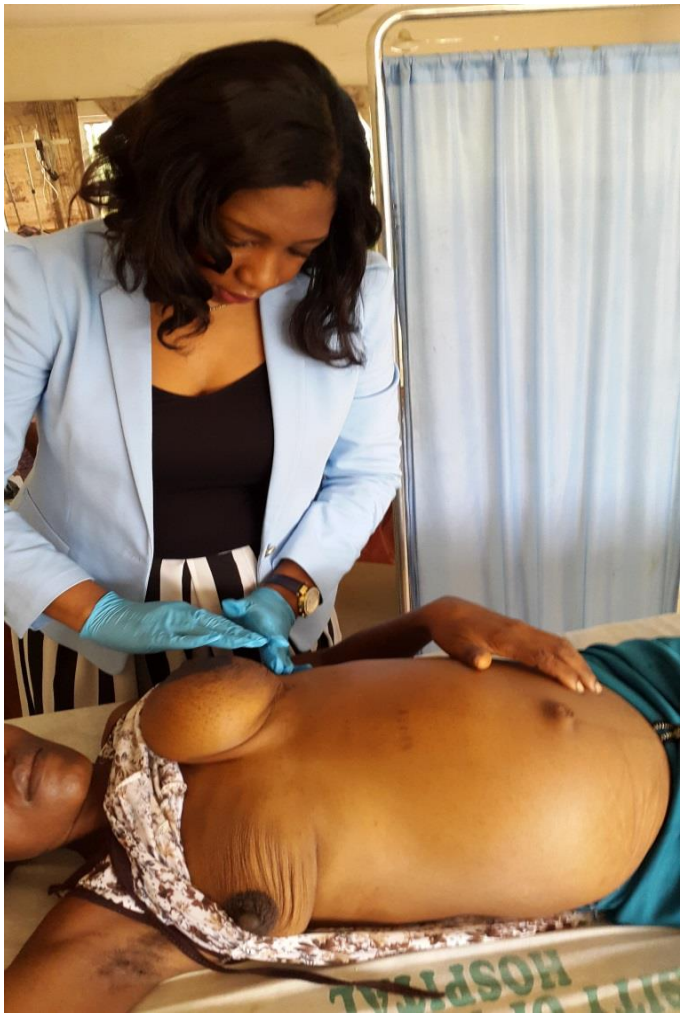


Figure 11: Visit to the Surgical Outpatients Department (SOPD) of the Asokoro District Hospital with Prof. Isabel dos Santos Silva and Dr. Valerie McCormack

Figure 12: Participant with advanced stage (IV) breast cancer recruited into the study during a site visit to Garki Hospital, Abuja, Nigeria

Figure 13: A 38-year old participant diagnosed with stage IV breast cancer. Patient had a breast lump for a period of 8 months, measuring 8 cm in the widest diameter with matted lymph nodes in the axilla, overlying skin changes and metastases to the liver. In the picture above, the patient was being examined during enrolment by Elima Jedy-Agba during a site visit to UNTH, Enugu in June 2014



3.3. DATA COLLECTION

Study Questionnaires and Data Collection Forms

Participants with symptoms consistent with a possible diagnosis of breast cancer were interviewed during their first visit at any of the six participating hospitals to ensure that all eligible patients would be recruited even if they never returned to the hospital for a diagnostic confirmation or treatment. Data were collected for many women prior to the

diagnostic confirmation using interviewer-administered structured questionnaires specifically developed and piloted for this study. The clarity and appropriateness of the questions were assessed during the pilot study. I developed, pretested and piloted all the questionnaires and clinical data forms used in the NIBBLE study. (excluding the food frequency questionnaire, because it was not relevant to my PhD study). A detailed description of each of these forms is provided below:

Upon enrolment, a questionnaire that focused on patient navigation and diagnosis delays (Appendix 6) was administered. This questionnaire was divided into 6 sections which focused on (a) the patient's knowledge, attitudes, and practices towards breast cancer (14 questions), (b) breast symptoms (8 questions), (c) the patient navigation pathway (66 questions, including contact details of the first 6 care providers), (d) local health services (5 questions), (e) the patient's perception of family/community support; (8 questions) and (f) the hurdles encountered when seeking help for a breast condition (2 questions). Detailed information on the patient's navigation from when the symptoms were first noticed to when the patient sought help from any care provider (orthodox or traditional) to a subsequent diagnosis and treatment was collected in the 3rd section of the questionnaire. Information was collected on the first 6 providers visited and information on additional providers, where applicable, was collected on additional forms. During the development of the questionnaire, it had been reported that breast cancer patients in SSA contacted on average 4-6 care providers before a diagnosis was made (78).

A second questionnaire developed for the parent NIBBLE study, which focused on the risk factors for breast cancer (Appendix 6), was also administered. The questionnaire was divided into 7 sections: (a) background information, (b) determination of household wealth, (c) reproductive history, (d) medical history, (e) lifestyle factors, (f) family history and (g) anthropometric and blood pressure measurements. In this 61-item questionnaire,

information was collected on sociodemographic variables such as age, religion, marital status, educational level, occupation, and on items used to depict the socioeconomic status such as house ownership, ownership of goods, toilet and cooking facilities. The questionnaire also included questions on reproductive and other risk factors for breast cancer including the age at menarche and, if applicable, menopause, use of hormonal contraceptives, total number of pregnancies and live births, family history of cancer, smoking and alcohol intake.

A clinical data form (Appendix 6) was completed by the research assistants when the results of the breast tissue biopsies were received. The information collected on this form included the patients histology result, stage at diagnosis, tumour grade, morphology, and the treatment(s) received.

As part of the parent study, a food-frequency questionnaire was also administered to participants during recruitment, but the information collected using this questionnaire was not used in the analyses for my thesis and is therefore not described in detail herein.

Anonymised information on non-responders, including age and socioeconomic status, was collected using a non-responder's form. Descriptive analyses were performed to compare this group of women with those who participated in the study. The reasons associated with their refusal to participate were also documented. In the case of the participants who dropped out of the study before the interview was completed, the reasons for dropping out of the study were documented.

3.3.1. Pre-testing Questionnaires

After developing the questionnaires and the forms used in the study, I pre-tested the questionnaires on 7 women who sought care at the surgical out-patients department (SOPD) at the National Hospital Abuja and who were 18 years of age or above. This pretesting was undertaken to check that the questions would work as intended, to identify

any issues in terms of clarity, and to question the sequence and the response choices offered. In addition to pre-testing the questionnaire on women who sought care at the SOPD, the questionnaire was pre-tested with colleagues at the research department of the Institute of Human Virology Nigeria who previously served as research coordinators on several studies in order to receive feedback on potential difficulties that might not have been revealed in a pre-test conducted with the respondents. Based on the feedback collected during pre-testing, I identified that the questionnaires took on average 90 minutes to complete, which some respondents considered too long, and received some comments on how to re-word some questions before piloting the questionnaire.

3.3.2. Questionnaire Piloting

The pilot study was conducted in order to ensure that the questionnaire developed could effectively collect the information required, and to ensure that the range of responses used were adequate and could generate accurate information. Following the pre-testing stage, a revised instrument was then piloted on the women who presented with breast symptoms at the Asokoro District Hospital and the University of Abuja Teaching Hospital, Gwagwalada. The pilot study was conducted over a period of 2 months from November - December 2013. The trained research assistants interviewed 14 women in total, with 7 consecutively attending patients who sought care at the SOPD of each hospital. The two hospitals were selected in order to ensure that the pilot was conducted at a secondary (ADH) and tertiary (UATH) hospital. Following the pilot study, I explored the participants' views in terms of the wording, content, and format of the questionnaire. The pilot study revealed that the questionnaire was easy to understand, the questions followed in a logical sequence and the responses offered were sufficient in order to elicit responses from the participants. Respondents on average visited 3 providers before a diagnosis was made and no women visited more than 6 care providers in total. Secondly, some respondents had a difficult time remembering the exact date when a first symptom was

noticed or when they visited a previous care provider and as a result, these questions had to be modified in order to allow for a more open-ended response. The feedback received during the pilot study was used in an iterative process in order to develop a modified and final version of the questionnaire.

The study questionnaires were administered in English, the common language spoken in Nigeria. All research assistants were fluent in English language and the predominant local language(s). For participants who could not speak English or the predominant local language, a staff member at the clinic who could speak the participants' language was commissioned to translate on the spot with the research assistant recording the interview. A note was made on the questionnaire on whether a translator was used.

3.3.3. Tumour Staging

Breast cancer staging formed a significant component of my PhD study. Therefore, in order to accurately stage the women, a physical breast examination was performed at the time of enrolment by the surgeons. The size of the tumour was measured and the lymph nodes were assessed during the clinical examination. Mammography, chest x-rays, abdominal ultrasound scans and a bone scan were performed in order to check for metastases. The staging of the breast tumours was classified into stages I, II, III, IV based on the tumour, node, and the metastases (TNM) staging classification of the American Joint Committee on Cancer 7th Edition(58). The TNM staging is described extensively in Chapter 1, Table 2.

3.4. SAMPLE SIZE DETERMINATION

In order to calculate the sample size, information was obtained from each of the collaborating hospitals on the number of the newly diagnosed cases of breast cancer per year. This information is presented below:

Table 2: Expected number of the newly-diagnosed breast cancer cases per year by study site

S/No	Study Site	Expected Number of Cases per year
1	University of Nigeria Teaching Hospital, Enugu (UNTH)	100
2	National Hospital Abuja	100
3	University of Abuja Teaching Hospital, Gwagwalada (UATH)	75
4	Garki Hospital Abuja (GH)	50
5	Asokoro District Hospital (ADH)	75
6	Wuse General Hospital (WGH)	25
	Total Expected	425

The expected number of new cases reportedly seen at these hospitals over the course of one year was estimated to be 425. Assuming a 10% (n=43) exclusion (i.e. ineligible, refusal to participate, or too ill to partake), 382 women were expected to be recruited in 1 year, and 764 over a 2-year period.

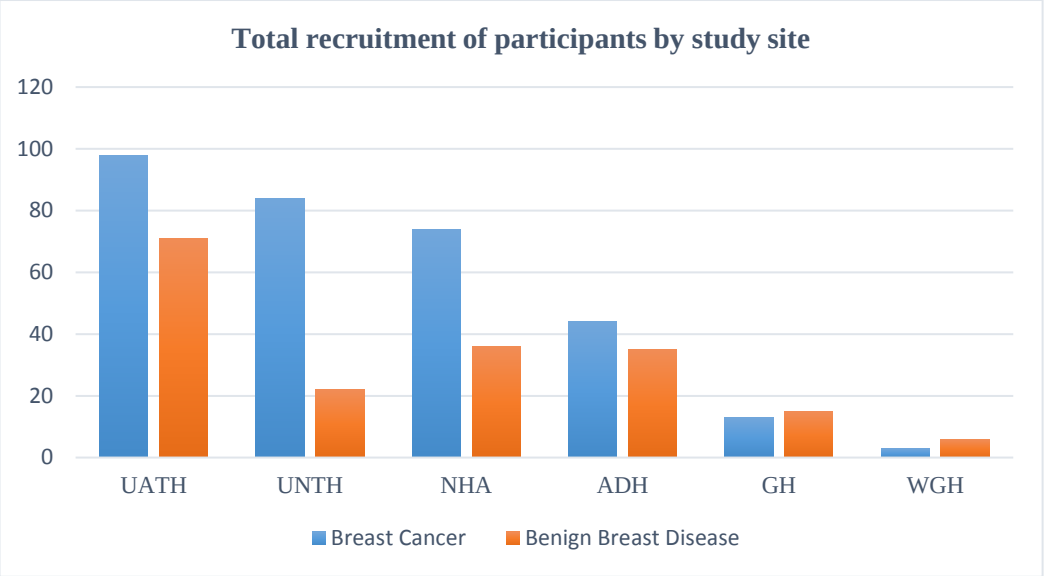
At the planning stage, the sample size calculations for the proposed study were made for 2-year survival estimates, as this was supposed to be the main outcome of interest of my PhD studies. Survival from breast cancer is poor in Nigeria with over half of the patients dying in the first two years after diagnosis. The anticipated sample size would be large enough to provide precise estimates of the survival rates (+/10%) for up to two years following breast cancer diagnosis and will have a power rate greater than 80% in terms of identifying the major determinants of survival (HR≥2). For example, focusing on the differences in survival dictated by the stage at presentation and comparing the 2-year fatality rate between the cases with an early stage (I and II) vs. a late stage (stages III and IV) at presentation - a study of 700 breast cancer cases will have 80% power to detect a hazard ratio (HR) as high as or higher than 2.0, assuming a 5% significance level, with 35% of the cases being diagnosed at stages I-II (unexposed group) and a 2-year fatality rate of 10% among early stage women.

The anticipated sample size would also be large enough to ensure that the study would be well powered to examine the determinants of late stage at diagnosis and diagnostic delays. For instance, the study will have 80% power to detect, at a 5% significance level, an odds ratio as low as or lower than 0.70 in the percentage of the late stage diagnosis between women with a high vs. low educational level assuming that the proportion of women with a low educational level (unexposed group) was 65%.

3.5. RECRUITMENT PERIOD AND TARGETS

The recruitment targets were determined based on the required sample size and the total number of breast cancer cases reportedly seen at each of the participating hospitals on an annual basis. Prior to the commencement of the study the site collaborators assessed the clinic registers at their hospitals and provided an approximate number of patients expected to be recruited monthly (Table 2). Based on this, I anticipated that the recruitment of breast cancer patients in this study would be influenced by the number of eligible breast cancer patients seen at the surgical and oncology clinics (where available) at each of the individual sites accounting for a refusal rate of 10%. I set a monthly recruitment target of 32 cases/month for the six participating sites and assigned numbers that were proportionate to the total number reported by the collaborators as the expected number of breast cancer patients per year (8 cases from the UNTH and NHA, 6 cases from the UATH and ADH and, 2 cases from GH and 2 cases from the WGH). The total recruitment by study site is shown in Figure 14. The numbers recruited were lower than expected and more details in relation thereto are provided in section 3.6 below.

Figure 14: Total recruitment by study site of all women who presented with breast cancer and benign breast disease symptoms from January 2014 to July 2016



3.6 . RECRUITMENT CHALLENGES

I encountered several challenges with the recruitment and implementation of this study in Nigeria. There were long periods of strike action by health professionals in Nigeria, which adversely affected recruitment. The Nigerian Medical Association went on strike in July 2014 until the end of September of the same year. During this period, the recruitment was at a standstill and most patients who were admitted in the hospitals were discharged and asked to seek care at private facilities. A few months after the strike by the Nigerian Medical Association was called off, the Joint Health Sector Unions (JOHESU) which are constituted by nurses and other support staff went on strike between November 2014 and February 2015. Following these events, there have been several other periods of intermittent strike actions throughout the duration of the study that adversely affected recruitment. Secondly, as part of the parent study, the research assistants had to complete a food frequency questionnaire in addition to the two questionnaires administered on the patients. This increased the participants' waiting time and some participants withdrew halfway through the interviews expressing anxiety about time and

other commitments. Thirdly, the study required the collection of breast tissue samples which constitutes standard practice as part of the management of the breast cancer patients at all the participating hospitals. However, for the parent study, additional blood and stool samples were required, which in turn increased the time required to recruit the participants. There were also some additional logistic challenges associated with the transportation of samples from the UNTH Enugu site to the laboratory of the Institute of Human Virology in Abuja, in terms of processing and ensuring that the breast tissue samples were received in Abuja within 72 hours of collection as per the study protocol. Another important challenge was the high turn-over of research assistants working on this study. Considering that most of the research assistants working on this study were employed on a contract basis, a few resigned from their jobs during the study in favour of permanent or better-paying jobs elsewhere. As a result, new research assistants had to be employed and trained, often with intermittent periods during which no research assistants were present at some of the sites. Finally, the recruitment outcomes from Garki Hospital and the Wuse General Hospital were much lower than expected and both sites had to be discontinued one year into recruitment. This may have been due to the proximity of both hospitals to the National Hospital Abuja (NHA), a tertiary centre that is better equipped to manage cancer patients. Although, this study initially included a survival component which was the basis of the initial sample size calculation used in this study, it was no longer feasible to conduct a survival study within the framework of my PhD study owing to the challenges discussed above. Nevertheless, the target sample size was not attained. However, despite this drawback, the study was well powered to find the determinants of stage at diagnosis and diagnostic delays in Nigerian women with breast cancer. A high response rate of 94.3% was recorded and with no differences being identified between respondents and non-respondents, as discussed in section 3.10 below.

The survival analysis was initially meant to be a component of my PhD study, hence the use of the 2-year survival as the outcome in the original sample size calculations performed at the planning stage. However, considering that the final sample size was smaller than originally anticipated and that delays were experienced with patient recruitment due to reasons outside my control, a 2-year patient follow-up became unfeasible due to the time constraints of my PhD study.

3.7. HISTOLOGY, TUMOUR GRADE AND IMMUNOHISTOCHEMISTRY ANALYSES

All breast tumour samples were transported to the laboratory of the Institute of Human Virology Nigeria (IHVN) and to the bio-repository in Abuja where specially qualified immunohistochemistry (IHC) staff members analysed the tissue samples. A common protocol for the collection, storage, processing, and transport of tumour specimens was used in this study (Appendix 7). IHC staining was used in order to assess the prevalence of different molecular subtypes of breast cancer. All participants underwent a core needle biopsy at presentation using a Bard Magnum core needle and biopsy gun. This method was preferred to excisional or incisional biopsies in order to ensure adequate fixation. Three cores were taken: one for routine Haematoxylin and Eosin (H & E) to confirm the diagnosis of invasive breast cancer, a second core for IHC subtyping, and a third to be archived (frozen) for use in instances where the first or second slides were not properly stained.

As soon as the samples were collected they were stored on ice and immediately transported to the laboratory. Once the samples were received in the laboratory, the laboratory assistant immediately fixed the tissue in a 10% neutral buffered formalin solution with a fixation period averaging 18 hours. A sample custody form was implemented which detailed the time allocated to each step from collection to fixation. This was particularly useful in order to identify any deviations from the study protocol.

The H and E slides were prepared in order to confirm the diagnosis of invasive cancer. The IHC staining was done using the 1D5 clone for anti-ER, PR-2C5 for anti-PR and Z4881 for anti-HER2. The staining results were evaluated for the presence of a positive reaction, pattern of staining and intensity of reaction. All slides were graded in a standard fashion into 0, 1+, 2+, 3+, and <1% positivity values, as recently recommended by the American Society of Clinical Oncology/College of American Pathologist guideline recommendations, which constituted the cut-off point for negative staining characteristics (192). For the determination of the HER2/neu status, fluorescent in situ hybridization (FISH), which has been described as the gold standard for detecting the HER2/neu status was used (193).

The IHC analysis was performed in batches and a standard operating manual was followed by the laboratory personnel in order to ensure that the processing of the samples in different batches was done in a similar manner in order to reduce the inter-batch variability. The batches included a random sample of 5% duplicate specimens with laboratory staff and the consultant pathologist (slide reviewer) being unaware of the duplicates in order to assess the within- and between-batch variability. To minimise the between-observer variability, slides from all six participating hospitals were read by the same pathologist who was blinded to the clinical history of the participants.

3.7.1. Tumour grade

The pathologist graded tumours as well-differentiated (grade 1), moderately differentiated (grade 2) and poorly differentiated (grade 3) using the Scarff-Bloom-Richardson grading system (194).

3.8. DATA ENTRY

The research assistants entered the data into a database using the REDCap online platform, designed by an experienced data manager working on the parent study (Figure

15). REDCap is a secure, web-based application used for data entry in clinical and translational research studies (195). The major advantages of using REDCap are that it is easy to use, enables data protection, improves efficiency by making it possible to undertake double data entry and has in-built validation checks which enhance the accuracy of the data. Data was initially collected on the field using paper questionnaires and was subsequently entered into the database using Google Nexus tablets. Data entry was performed online and all the research assistants were trained on data entry techniques using REDCap (Figure 16), and provided with internet modems (dongles) with monthly subscription to the internet. Once the data was entered by the research assistants into the database, it immediately became available online and I could remotely access the data, monitor recruitment, and perform quality checks on the data.

Figure 15: REDCap database designed for data entry into the NIBBLE study

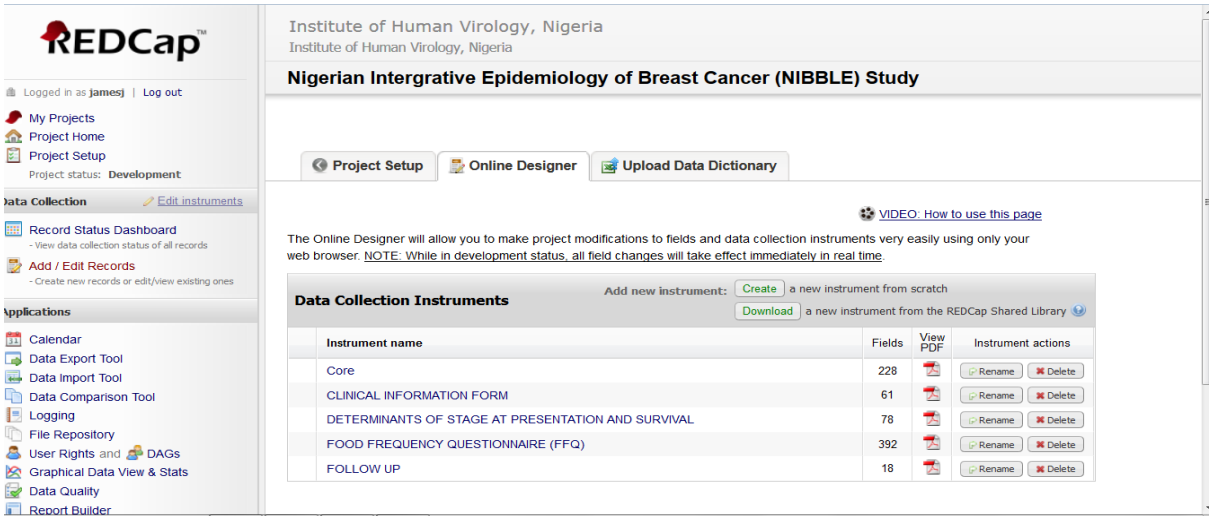


Figure 16: Training session for the research team on data entry and management using REDCap in Abuja, Nigeria

3.9 . DATA ANALYSES

The methods used in data analyses are described in detail in the relevant analytical chapters (4 and 5) of this thesis.

3.10. CONSIDERATION OF BIAS IN MY PHD CASE-ONLY STUDIES

Selection bias is a major potential bias of my case-only studies. However, clear case definitions and strict inclusion and exclusion criteria for the selection of cases were defined in this study, rendering the selection bias less likely. To further reduce the selection bias, which could have arisen from missed cases of patients who will only come to the clinic for their first visit and never return, the patients involved in all suspicious cases of breast cancer, including those which were later proved to be benign cases, were interviewed upon first contact and a biopsy sample was subsequently received and analysed. In cases where they turned out to be benign lesions, we analysed them separately whenever appropriate (see Chapter 5). The participation rate for the breast cancer cases was high (94.3%). Patients who were eligible, but declined to participate did

not differ from those who participated in the study by age, nor were they more critically ill than the respondents. Nevertheless, many women with breast cancer in Nigeria, as in many other SSA settings, may never be known to the health system (e.g. if they only seek traditional or spiritual healers) or may be known but never referred to a secondary or a tertiary health hospital for diagnosis and treatment. Despite these caveats, the present case series should be representative of the breast cancer cases diagnosed in Abuja and Enugu. Furthermore, although a lack of representativeness may affect the external validity of the study findings and the generalisability thereof, it should not compromise its internal validity.

Information bias in the study was reduced by minimising observer variability by training the field staff/research assistants (mostly nurses) on interviewing the patients and taking measurements. A detailed and structured pre-tested and piloted questionnaire was administered prior to the confirmation of the breast cancer diagnosis, and quality assurance checks were conducted fortnightly on the completed questionnaires. During the interviews, in cases where participants forgot important dates, the field staff asked questions about significant personal events to help the participants remember the dates. Secondly, in order to reduce the number of errors associated with data entry, an online data management tool was used (195), which incorporated in-built logical checks and data entry into the REDCap database. This was further reviewed by the data manager as an additional level of quality control.

In order to minimise confounding, we attempted to collect high-quality data on a large number of variables, which had been formerly identified in previous studies as being independent determinants of late stage and/or delays in the breast cancer diagnosis. Nevertheless, as this is an observational study, one can never exclude the possibility that the reported exposure-outcome associations might have been distorted because of residual confounding or confounding by unmeasured variables.

3:11. ETHICAL CONSIDERATIONS

Prior to the commencement of the study, the study protocol and questionnaires were submitted to the LSHTM ethics committee, the University of Maryland Baltimore Institutional Biosafety Committee (institution of the principal investigator of the parent study), the National Health Research Ethics Committee of Nigeria (NHREC) and the health research ethics committees of the six participating institutions to obtain ethical approvals. After several institutions inquired about the administrative management and the funding methods of the study, the approval was granted.

Patients were adequately informed about the study and provided with the opportunity to ask questions about various aspects of the study. All participants were required to give written informed consent and were asked for consent prior to having their biological samples stored and used for future studies as part of the parent study. The informed consent form is included in Appendix 8. Each participant was given a unique study identification number which was used across all questionnaires, blood and stool samples, and breast tissue biopsies and to link clinical data with the laboratory data. Paper questionnaires were stored in accordance with the standard operating practices at the Institute of Human Virology, Nigeria.

All the information collected was treated as confidential. All Google Nexus tablets used for data entry were password protected. Participant names were excluded from all analyses and electronic information was not sent via email but through a secure password protected shared drive.

3.12. RESEARCH COSTS AND FUNDING

This study was funded as part of a training grant by the Fogarty International Centre of the National Institutes of Health (FIC/NIH D43TW009106), referred to as the ‘Training Programme in Nigeria for Non-Communicable Disease Research’ (TRAPING). The grant

covered monthly stipends for the research assistants and laboratory assistants and further research costs including the purchase of reagents for IHC and histology, Bard Magnum biopsy guns and needles, nexus tablets for data entry and payment for the pathologist review of the histology slides.

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A- Student Details

Student	Elima Jedy-Agba
Principal Supervisor	Prof. Isabel dos-Santos Silva
Thesis Title	Breast Cancer in sub-Saharan Africa: Determinants of Stage at Diagnosis and Diagnostic Delays in Women with Symptomatic Breast Cancer

If the Research Paper has previously been published, please complete Section B, if not please move to Section C

SECTION B- Paper already published

Where was the work published?	Cancer Causes and Control		
When was the work published?	April 2017		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	Not applicable		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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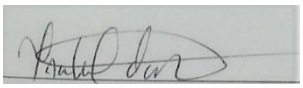
SECTION D- Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I had the idea for the study, contributed to the study design and implementation, analysed the data, drafted the manuscript and made subsequent revisions to the manuscript;

Student Signature:  **Date: 30/12/2016**

Supervisor Signature:  **Date: 30/12/2016**

CHAPTER 4

4.1 RESEARCH PAPER 2: DETERMINANTS OF STAGE AT DIAGNOSIS OF BREAST CANCER IN NIGERIAN WOMEN: SOCIODEMOGRAPHIC, BREAST CANCER AWARENESS, HEALTH CARE ACCESS, AND CLINICAL FACTORS

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Key words: breast cancer, stage, stage at diagnosis, awareness, Nigeria

ABSTRACT

Purpose: Late stage at diagnosis is a common feature of breast cancer in Sub-Saharan Africa (SSA), contributing to poor survival rates. Understanding its determinants is key to preventing deaths from this cancer in SSA.

Methods: Within the Nigerian Integrative Epidemiology of Breast Cancer Study (NIBBLE) multicentre case-control study on breast cancer, we studied factors affecting stage at diagnosis of cases, i.e. women diagnosed with histologically confirmed invasive breast cancer between January 2014 and July 2016 at six secondary and tertiary hospitals in Nigeria. Stage was assessed using clinical and imaging methods. Ordinal logistic regression was used to examine associations of socio-demographic, breast cancer awareness, health access and clinical factors with odds of later stage (I, II, III or IV) at diagnosis.

Results: A total of 316 women were included, with a mean age (SD) of 45.4 (11.4) years. Of these, 94.9% had stage information: 5 (1.7%), 92 (30.7%), 157 (52.4%), and 46 (15.3%) were diagnosed at stages I, II, III and IV respectively. In multivariate analyses, lower educational level (odds ratio (OR) 2.35, 95% confidence interval (CI): 1.04, 5.29), not believing in a cure for breast cancer (1.81: 1.09, 3.01), and living in a rural area (2.18: 1.05, 4.51) were strongly associated with later stage, whilst age at diagnosis, tumour grade and oestrogen receptor status were not. Being Muslim (Vs Christian) was associated with lower odds of later stage disease (0.46: 0.22, 0.94).

Conclusion: Our findings suggest that factors that are amenable to intervention concerning breast cancer awareness and health care access, rather than intrinsic tumour characteristics, are the strongest determinants of stage at diagnosis in Nigerian women.

INTRODUCTION

Breast cancer is the most common cancer in women worldwide and in Nigeria. Breast cancer incidence in Nigeria (estimated age-standardised incidence rate (ASR)=50.5 per 100,000) in 2012 was only half that in the United States (US) (ASR=92.9 per 100,000), but estimates of mortality rates from this cancer were higher in this West African country than in the US (25.9 vs 14.9 per 100,000, respectively)(18), reflecting poorer survival.(5)

One of the most important prognostic factors for breast cancer is stage at diagnosis, and has been shown to be relevant in the African setting.(54, 88, 196) However, in contrast with breast cancer diagnosed in developed countries, stage at diagnosis of breast cancer in Nigeria, as in the rest of sub-Saharan Africa (SSA), has been widely reported to be late.(54, 60, 133) Women are typically symptomatic at presentation as there are no organised, and little opportunistic, pre-clinical early detection. Moreover, presentation in majority of women is not in the early symptomatic stages, rather at advanced stage when regional spread and metastases are not uncommon. Although breast cancer survival data in Nigeria are limited, available data support poor survival from this disease in women who present late.(52, 54)

Recognizing the importance of early detection and treatment in breast cancer control, an increasing body of research is examining factors associated with late stage at diagnosis, particularly in settings where stage has persistently remained late over decades and tumour size at presentation (mean 5-8 cm) is far beyond that of a palpable tumour (2 cm).(133) In SSA, later stage at diagnosis of breast cancer has been linked to various factors such as low educational level(139), rural region of residence,(197) lack of medical aid/insurance(197) and poor health care access,(60) e.g. long distance to health provider(80). These factors would translate into delays in the time to diagnosis. On the other hand, clinical factors(198), e.g. young age, poorly differentiated tumour grade(199),

and negative hormone receptor status(199), may contribute to advanced stage as a result of a more rapid tumour growth rate. A significant number of papers that have investigated factors associated with stage at diagnosis have been reported from studies in western countries and a few other SSA countries, but has been less well studied in Nigeria. Of particular relevance to the African setting, the extent to which the younger age at diagnosis distribution and the small excess of more aggressive tumour subtypes(103) contribute to later stage diagnosis remains unknown.

In our study, we examined the role of socio-demographic, breast cancer awareness, access to health care and clinical factors on stage at diagnosis of breast cancer among women seeking care at tertiary and secondary health institutions in Nigeria as a first step to identify which of these factors may be amenable to intervention in the Nigerian setting.

METHODS

Study Design and Setting

This study was conducted within the Nigerian Integrative Epidemiology of Breast Cancer Study (NIBBLE), an on-going multicentre case-control study which began recruitment in January 2014 at six government hospitals in Nigeria: five located in the capital city of Abuja (population 1.4 million) (191) comprising two tertiary hospitals (National Hospital and University of Abuja Teaching Hospital Gwagwalada) and three secondary hospitals (Asokoro District Hospital, Garki Hospital and Wuse General Hospital) - and one further tertiary hospital site (University of Nigeria Teaching Hospital) located 400 km south in Enugu, South-Eastern Nigeria, with a population size of 3.3 million(191). The three large tertiary hospitals serve as major referral centres for cancer patients across Nigeria and all have facilities for chemotherapy, with one - the National Hospital Abuja - being one of four government hospitals in the country that currently also offer radiotherapy. The present analysis was restricted to NIBBLE cases, i.e. women newly-diagnosed with primary invasive breast cancer at the six participating hospitals between January 2014 and July 2016.

Ethical approval was obtained for NIBBLE from the National Health Research Ethics Committee of Nigeria, health research ethics committees in each participating hospital, and institutional ethics committees at the University of Maryland Baltimore (US) and the London School of Hygiene and Tropical Medicine (UK). The study was carried out in compliance with the Nigerian National Code for Health Research Ethics and the Declaration of Helsinki. Written informed consent was obtained from all participants in the study.

Subject recruitment and interviewing

Participants were recruited at the surgical outpatient departments (SOPD) and the oncology departments in two of the participating hospitals (i.e. the National Hospital Abuja and the University of Nigeria Teaching Hospital, Enugu) and only at the SOPDs at the remaining four. All newly-diagnosed patients with a primary invasive breast cancer aged 18 years and over were eligible regardless of their ethnicity or language. Potentially eligible patients were identified at their first visit by the surgeon, oncologist, or research nurse, informed about the study, and invited to participate prior to histological confirmation. Overall, 94.3% consented for whom a confidential structured face-to-face interview was conducted by a trained research nurse in English (70.6%), a predominant Nigerian language (20.6%) or other local language (8.8%) as per the patient's preference. Information was collected on socio-demographic variables, lifestyle, comorbidities, awareness of breast cancer causes and symptoms and health care access (Tables 1 and 2). The research nurse also performed measurements, using a standard protocol, of the patient's height, weight, and waist and hip circumferences, from which body mass index (BMI, weight (kg)/height^2 (m^2)) and waist-hip ratio (WHR) measures were calculated. For these anthropometric measurements, participants were asked to remove shoes, heavy outer garments, hair ornaments and head scarves.

We adapted the scoring method previously used by Mena *et al.*(200) to generate scores for knowledge of breast cancer causes (based on 8 items; Table 1) and symptoms (based on 7 items; Table 1). For both domains, a woman was given a score of 2 for a correct answer, 1 if not sure/did not know and 0 for the wrong answer to each of its items. The total score for each domain was calculated as the sum of its item-specific scores and then categorised as poor, fair and good knowledge as described in Table 1 (footnotes a and b).

Tumour staging and pathology

Physical breast examination was performed at the time of enrolment by surgeons. Participants were asked to undergo mammography, chest-x-rays, abdominal ultrasound, and a bone scan to check for metastases. These tests are routinely recommended and majority of patients undergo them. Lymph node involvement was assessed on clinical examination at the time of presentation; no information was recorded on possible re-assessment during surgery. Thereafter, the study assigned tumour stage according to the tumour, node, metastasis (TNM) classification (American Joint Committee of Cancer 7th Edition TNM classification) into stages I, II, III and IV.

Most patients underwent a core needle biopsy for histological confirmation, the results of which were retrieved from pathologists' reports within two weeks of a biopsy. Data were extracted on tumour characteristics (e.g. laterality, size, morphology, grade, receptor status). Tumours were graded as 1, 2 and 3 using the Scarf-Bloom-Richardson system.(194) Immunohistochemistry staining was used to assess oestrogen receptor (ER) status. A <1% positivity was the cut-off point for negative staining characteristics.(192)

Statistical analyses

Ordinal logistic regression models were used to identify correlates of later stage at diagnosis, i.e. assuming a common odds ratio (OR) for the binary outcomes: stage IV v I/II/III, IV/III vs I/II and IV/III/II vs I). Age at diagnosis was regarded as *a priori* confounder and thus examined alone and included in all models. Age-adjusted models were initially fit separately to each group of variables: socio-demographic, breast cancer awareness, health care access and clinical. Subsequent models assessed the extent to which: (i) associations between socio-demographic variables and later stage at breast cancer diagnosis were mediated by breast cancer awareness or health care access factors; and (ii) associations between breast cancer awareness and health care access variables

with later stage at breast cancer diagnosis were confounded by socio-demographic variables. Finally, a fully-adjusted model was fitted to identify independent correlates of later stage at breast cancer diagnosis. This model included age at diagnosis, and the two most strongly found to be associated with later stage at breast cancer diagnosis within each group in the age-adjusted models. Variables found to be associated with others already included in the model were excluded (e.g. hospital type was excluded because it was defined by region of residence in Enugu). Data analyses were performed using Stata14.1 (Stata Corporation, College Station, Texas, USA).

Principal Component Analyses (PCA) was applied, as previously described by Filmer and Pritchett(201), to generate a single summary index of a woman's socio-economic status on the basis of her household assets. The variables included in the PCA were all binary variables (Y/N), e.g. for owning your home, living in an apartment, house or duplex, drinking water from outside, well, borehole, piped or bottled, various types of cooking fuel, having a separate room for cooking, type of toilet used and ownership of certain household goods including a car, refrigerator, bicycle, electric fan, television, and motorcycle. The first component in the PCA was used, as it explained most of the variation, to generate wealth scores and categories of low (lowest 40% of the score distribution), middle (middle 40%) and high (highest 20%) socio-economic class.

Participants with WHR >1.2 or <0.6 and those with a BMI<10 kg/m^2 or >50 kg/m^2 were regarded as outliers and therefore excluded from analyses involving these variables.

RESULTS

Participants' characteristics

In all, 316 eligible participants were recruited into the study, but sufficient information to derive stage at diagnosis was available for only 300 (94.9%) women. Of these, five (1.7%) were diagnosed at stage I, 92 (30.7%) in stage II, 157 (52.4%) in stage III and 46 (15.3%) in stage IV. The characteristics of the study participants are summarized in Tables 1 and 2. The mean (SD) age at breast cancer diagnosis was 45.4 (11.4) years in all women. The majority (81%) were recruited in a tertiary hospital, 67.2% of these in Abuja. The commonest first breast cancer symptom noticed by the women was a breast lump (Table 1). Median (interquartile range) self-reported time from symptom to diagnosis was 8.25 (4.24-18.5) months. In all, 46 (14.6%) breast cancer patients were found to have metastases at the time of diagnosis, including to the lung (n=17, 36.9%), liver (n=9, 19.6%), bone (n=5, 10.9%), brain (n=2, 4.3%) and site unknown (n=13, 28.3%).

Table 1: Socio-demographic characteristics of women with breast cancer, by stage at diagnosis

Characteristics		**Early BC (Stages I & II) N (%) [a]**	**Late BC (Stages III & IV) N (%) [a]**
Socio-demographic	**Total no. of women**	97 (32.3)	203 (67.7)
Age at BC diagnosis (years)	Mean age (SD)	42.6 (11.5)	46.4 (11.7)
Marital status	Married	71 (33.6)	140 (66.4)
Educational level	None	5 (12.2)	36 (87.8)
	Primary/Secondary	33 (29.2)	80 (70.8)
	Tertiary/Post graduate (PG)	59 (41.3)	84 (58.7)
	Not reported	0 (0)	3 (100)
Religion	Christianity	80 (30.7)	181 (69.3)
	Islam	17 (47.2)	19 (52.8)
	Not reported	0 (0)	3 (100)
Do you have a personal income?	Yes	23 (25.6)	67 (74.4)
	No	74 (35.2)	136 (64.8)
Socioeconomic class	Low	37 (27.2)	99 (72.8)
(using household data)	Middle	38 (36.5)	66 (63.5)
	High	22 (36.7)	38 (63.3)
Lifestyle	No. of ever smokers (%)	1 (50.0)	1 (50.0)
	No. drinkers (%) (1 measure/day)	10 (21.7)	36 (78.3)
	(2-5 measures/day)	1 (6.7)	14 (93.3)
Breast Cancer Awareness			
Ever heard of BC	No	8 (16.3)	41 (83.7)
	Yes	88 (36.1)	156 (63.9)
	Don't Know/Not reported	1 (33.3)	2 (66.7)
Knowledge of BC causes [b]	Poor	57 (28.5)	143 (71.5)
	Fair	25 (40.9)	36 (59.1)
	Good	15 (38.5)	24 (61.5)
Knowledge of BC symptoms [c]	Poor	48 (28.4)	121 (71.6)
	Fair	30 (33.3)	60 (66.7)
	Good	19 (46.3)	22 (53.7)
Belief in cure for BC	No	26 (22.2)	91 (77.8)
	Yes	71 (39.9)	107 (60.1)
	Don't know	0 (0)	5 (100.0)
Practice of BSE	No	37 (25.0)	111 (75.0)
	Yes	53 (41.1)	76 (58.9)
	Never heard of / Unknown	7 (30.4)	16 (69.6)
First BC symptom	Breast Lump	86 (33.0)	175 (67.0)
	Other Symptom [d]	11 (28.2)	28 (71.8)
Health Care Access			
Region of residence	North-Central (Abuja)	85 (37.6)	141 (62.4)
	South-Eastern (Enugu)	12 (16.2)	62 (83.8)
Diagnostic hospital type [e]	Tertiary	68 (28.1)	174 (71.9)
	Secondary	29 (50.0)	29 (50.0)
Travel time taken to diagnostic hospital	< 1 hour	66 (36.1)	117 (63.9)
	1 - < 2	15 (33.3)	30 (66.7)

Characteristics		Early BC (Stages I & II) N (%) [a]	Late BC (Stages III & IV) N (%) [a]
	>=2	5 (22.7)	17 (77.3)
	Not reported	11 (22.0)	39 (78.0)

BC: breast cancer; BSE: breast self-examination; HCP: health care provider including traditional and spiritual healers; SD: standard deviation;

[a] Unless otherwise specified

[b] A score was assigned to each one of 8 items on BC causes: 2 to the correct answer, 1 to not sure/certain and 0 to the wrong answer. The 8 items included (i) lifestyle, (ii) not breastfeeding, (iii) getting older, (iv) family history of BC, (v) if cancer is caused by a curse, (vi) an insect bite, (vii) injury to the breast or if (viii) it is contagious. The sum of the 8 item-specific scores was then grouped into 3 categories of poor (score 0-8), fair (9-11) and good knowledge (12-16).

[c] Scores 0, 1 and 2 were assigned as above to 7 common BC symptoms: (i) breast lumps, (ii) breast pain, (iii) change in the size or shape of the breast, (iv) dimpling of the skin or a wound to the breast, (v) fluid coming from the nipple in a woman not breastfeeding, (vi) swelling in the armpit and (vii) change in the shape of the nipple. The sum of the 7 item-specific scores was then grouped into poor (0-7), fair (8-11) and good knowledge of symptoms (12-14).[d] Other symptoms included swelling underarm, nipple discharge and change in shape or size of breast.

[e] Recruitment numbers for tertiary hospitals were: National Hospital Abuja- 70, University of Abuja Teaching Hospital Gwagwalada - 98, University of Nigeria Teaching Hospital, Enugu - 74; for secondary hospitals: Asokoro District Hospital - 44, Garki Hospital - 11 and Wuse General Hospital - 3)

Table 2: Clinical characteristics of women with breast cancer by stage at diagnosis

Clinical characteristics	**Categories**	**Early BC (Stages I/II) (row %)**	**Late BC (Stages III/ IV) (row %)**
Total		97 (32.3)	203 (67.7)
Co-morbidities [a]			
Previous HTN or diabetes	Yes	29 (36.7)	50 (63.3)
Previous history of BBD	Yes	18 (43.9)	23 (56.1)
Family history of BC	Yes	7 (26.9)	19 (73.1)
Other Clinical characteristics			
BMI (kg/m^2)	< 25 (Normal weight)	22 (24.4)	68 (75.6)
	25-29 (Overweight)	38 (38.4)	61 (61.6)
	>30 (Obese)	36 (35.6)	65 (64.4)
	Unknown	1 (10.0)	9 (90.0)
WHR	<0.80 (low)	15 (48.4)	16 (51.6)
	0.8-0.85 (moderate)	15 (27.8)	39 (72.2)
	>0.85 (high)	67 (32.2)	141(67.8)
	Unknown	0 (0)	7 (100)
Tumour laterality	Left breast	42 (29.2)	102 (70.8)
	Right breast	52 (34.7)	98 (65.3)
	Other (underarm)	3 (50.0)	3 (50.0)
Morphology	NST/IDC	85 (34.3)	163 (65.7)
	Medullary	7 (26.9)	19 (73.1)
	Others (lobular, mucinous)	5 (21.7)	18 (78.3)
	Unknown	0 (0)	3 (100)
Stage at BC diagnosis	I	5 (100)	-
	II	92 (100)	-
	III	-	157 (100)
	IV	-	46 (100)

Tumour grade (n=250) [b]	Well differentiated	20 (38.5)	32 (61.5)
	Moderately differentiated	55 (34.4)	105 (65.6)
	Poorly differentiated	6 (23.1)	20 (76.9)
Oestrogen receptor status (n=220) [c]	Positive	32 (34.0)	62 (66.0)
	Negative	45 (39.5)	69 (60.5)

HTN: hypertension; BBD: benign breast diseases; BC: breast cancer; BMI: body mass index; WHR: waist-hip ratio;
NST: Not Otherwise Specified; IDC: invasive ductal carcinoma.
[a] Number missing or unreported 7 or less in smoking, alcohol, hypertension, BBD and family history of BC categories.
[b]There were 250 women with information on tumour grade, 12 patients with missing information on stage have been excluded.
[c]There were 220 women with information on oestrogen receptor status, 12 patients with missing information on stage were excluded.

Socio-demographic characteristics and later stage at diagnosis

There was no association between age and the odds of later stage at diagnosis (p for linear trend (p_t)=0.16; Table 3). After adjusting for age, there was positive trend in the odds of later stage with lower educational level (p_t=0.002), with women with no formal education having 2.75 (95% CI 1.37, 5.52; p=0.004) times the odds of being diagnosed at a later stage relative to those with tertiary or higher education (Table 3; Figure 1a). Higher educational level was associated with having ever heard about breast cancer (p<0.001) and with believing in a cure for this disease (p<0.001), but the trend in the odds of later stage with educational level persisted, albeit attenuated, upon further adjustment for these two breast cancer awareness variables (p=0.02; Figure 1b). Similarly, the association between educational level and the odds of later stage at diagnosis persisted after further adjustment for health care access variables (i.e. region of residence, type of hospital and travelling time to diagnostic hospital) (Figure 2b).

Muslim women were less likely to be diagnosed at later stages than Christian women (age-adjusted OR=0.46; 95% CI 0.24, 0.90; p=0.02), with this association strengthened slightly after further adjustment for educational level (OR=0.38; 95% CI 0.19, 0.75; p=0.005). Further adjustment for breast cancer awareness or health care access variables did not change, however, the magnitude of the ORs (Figures 1 and 2).

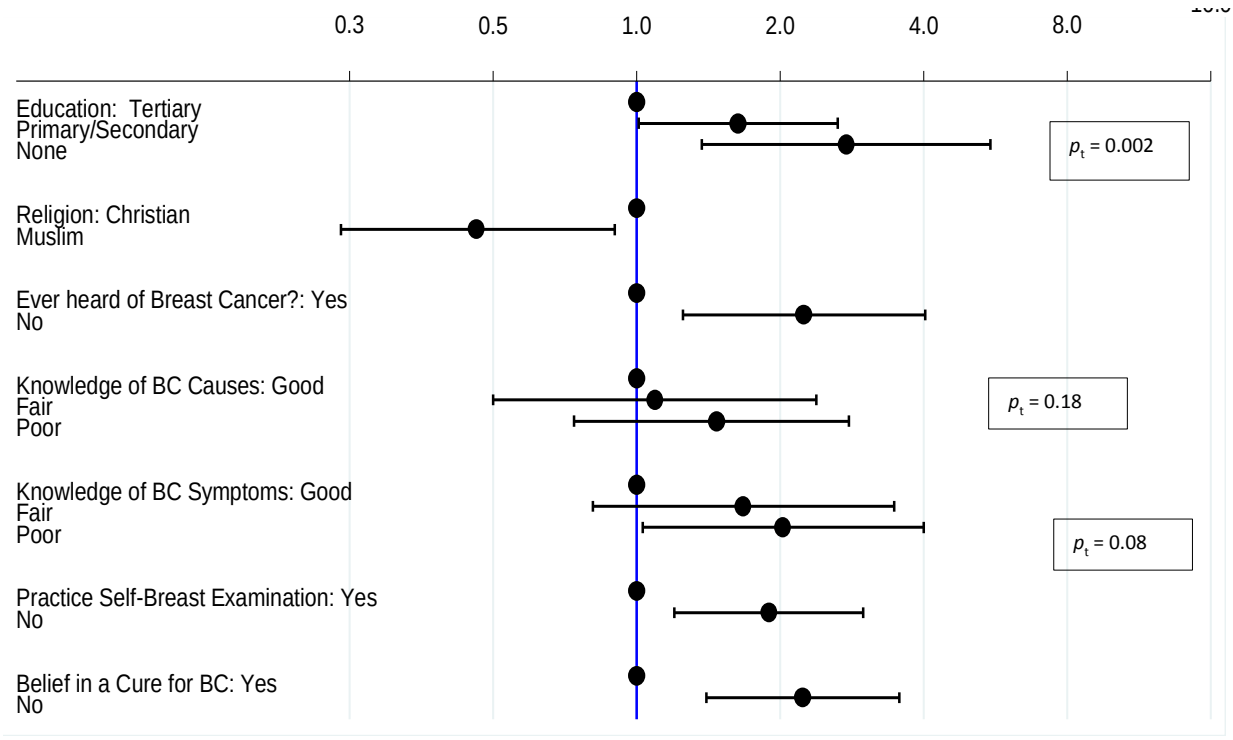
The age-adjusted analyses showed no associations between later stage at breast cancer diagnosis and a woman's marital status, self-reported personal income, or socioeconomic status (Table 3). There was also no association between later stage and self-reported alcohol consumption. Only 2 out of the 316 women in our study were ever smokers so the role of this lifestyle variable could not be assessed.

Breast cancer awareness and later stage at diagnosis

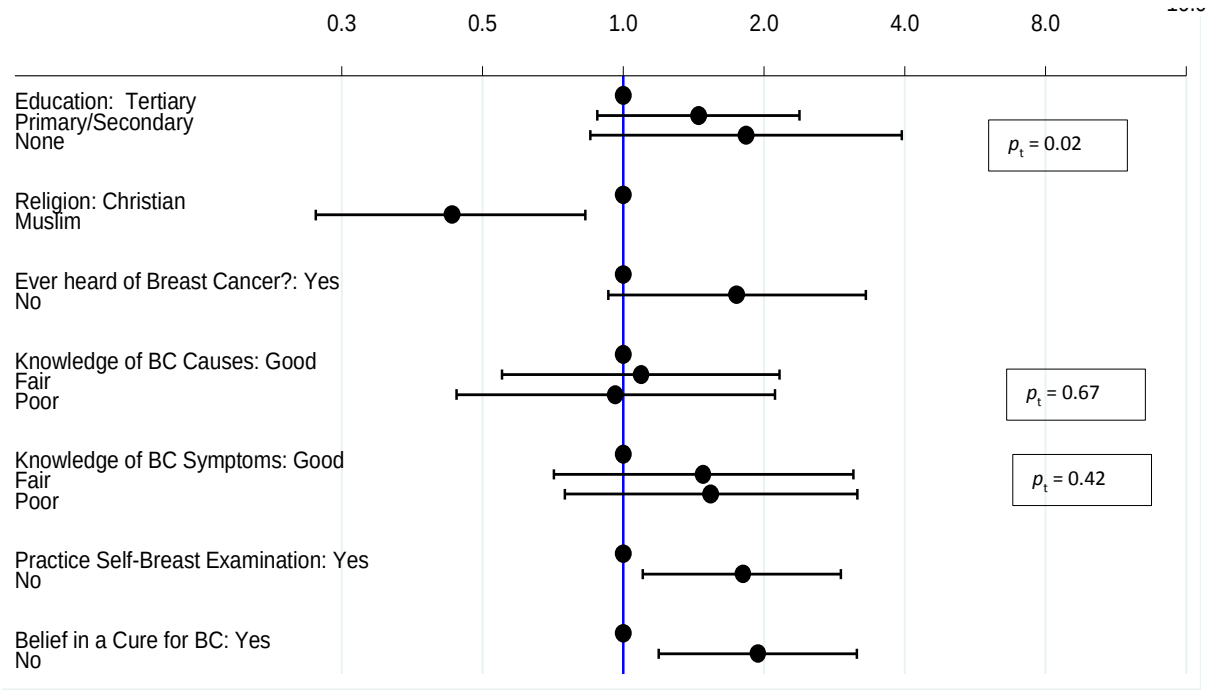
Overall, 80.4% women had ever heard of breast cancer, but few displayed good knowledge of its causes (12.6%) or symptoms (13%) (Table 1). Only 59.5% of women believed in a cure or treatment for breast cancer, and only 42.4% of women practised breast self-examination (BSE). After adjustment for age, never having heard of breast cancer was significantly associated with an increased odds of later stage (OR=2.24; 95% CI 1.25, 4.03; p=0.01; Figure 1a). Women who did not believe in a breast cancer cure (OR=2.23; 95% CI 1.40, 3.56; p=0.001) and those who did not practice BSE (OR=1.89; 95% CI 1.20, 2.99; p=0.01) were also more likely to be diagnosed at a later stage (Figure 1a). These associations were slightly attenuated upon further adjustment for a woman's educational level and religion.

In contrast, there were no clear trends in the odds of later stage with knowledge of breast cancer causes or symptoms either in age-adjusted analyses or in those further adjusted for educational level and religion (Figure 1).

Figure 1: Odds of later stage at breast cancer diagnosis by: (a) a woman's educational level, religion and breast cancer awareness adjusting for age; and (b) a woman's educational level and religion adjusting for age and breast cancer awareness, and by breast cancer awareness variables adjusting for age, educational level and religion.



p*t*= p-value for linear trend; BC: breast cancer

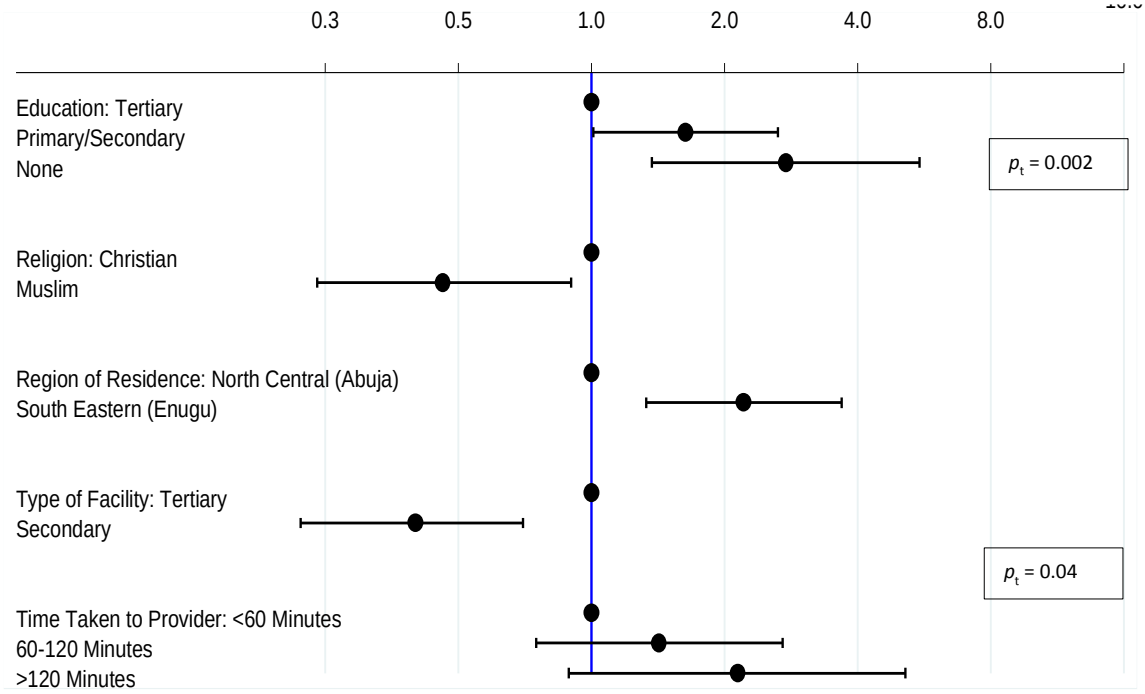


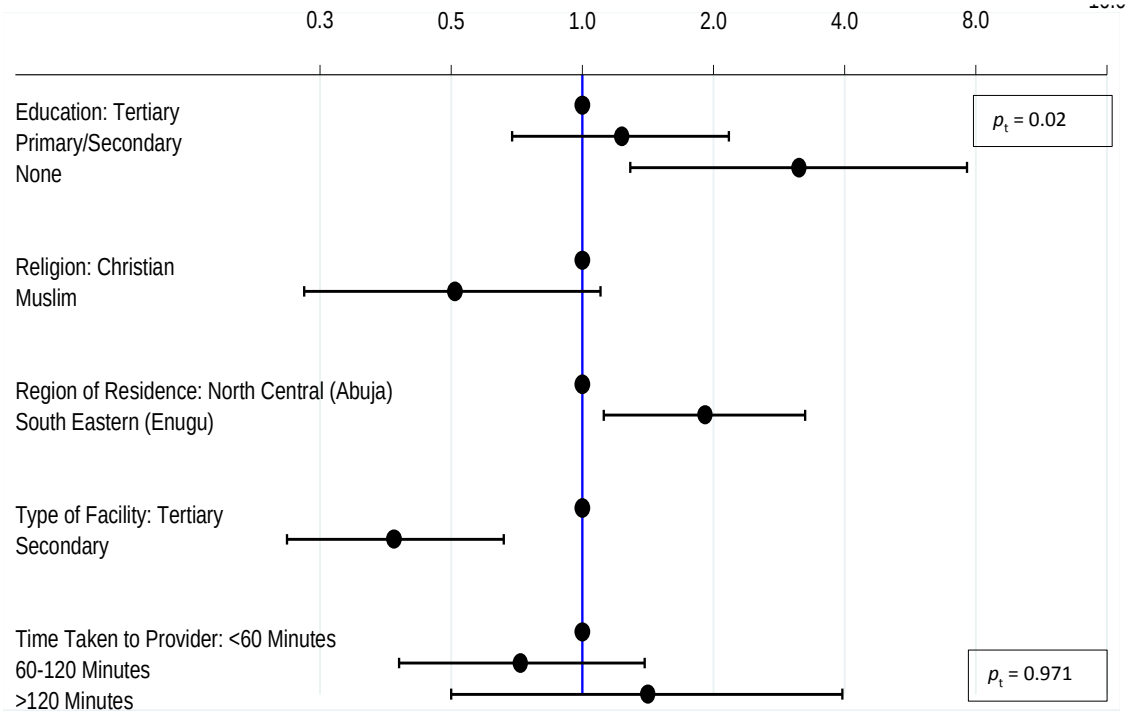
p*t*: p-value for linear trend; BC: breast cancer

Access to health care and later stage at diagnosis

The proportion of participants with later stage was higher at the three tertiary hospitals (National Hospital Abuja: 62.3% (43/69); University of Abuja Teaching Hospital Gwagwalada: 69.4% (68/98); and University of Nigeria Teaching Hospital, Enugu: 83.8% (62/74)) than at the three secondary care hospitals in Abuja (50.8% (30/59)). These associations persisted after further adjustment for educational level and religion (Table 3; Figure 2a). In age-adjusted analysis, the odds of later stage were positively associated with the amount of travel time taken by the woman to reach the first healthcare provider she visited (p_t=0.04; Table 3 and Figure 2a), but this trend was no longer significant upon further adjustment for educational level and religion (p_t=0.97; Figure 2b).

Figure 2: Odds of later stage at breast cancer diagnosis by: (a) a woman's educational level, religion and health care access adjusting for age; and (b) a woman's educational level and religion adjusting for age and health care access, and by health care access variables adjusting for age, educational level and religion.





p*t*: p-value for linear trend; BC: breast cancer

Clinical factors and later stage breast cancer diagnosis

Invasive ductal carcinoma (non-otherwise specified (NST)) was the commonest morphological type (83.2%). Information on tumour grade was available for 79.1% women, with 10.8% of these being poorly differentiated (Table 2). ER status was known for 69.6% women, with 45.2% of these being ER-positive overall. X% of ER positive and y% of ER negative tumours were diagnosed at stages III/IV (Table 2), but age-adjusted analyses revealed no associations between later stage at breast cancer diagnosis and tumour grade, morphology, or ER (Table 3). There were also no clear trends in the odds of later stage with BMI or WHR at diagnosis, and no evidence of associations of later stage with a positive family history of breast cancer or with having ever been diagnosed with diabetes, hypertension, or benign breast disorders (Tables 3 and 4).

Table 3: Age-adjusted associations between socio-demographic, breast cancer awareness, health care access and clinical variables with odds of later stage breast cancer estimated using ordinal logistic regression

Socio-demographic characteristics		**Age adjusted OR (95% CI)**	**p value**
Age at BC diagnosis (years)	<40	1	
	40-49	1.44 (0.85, 2.42)	0.18
	50-59	1.76 (0.94, 3.28)	0.08
	≥60	1.44 (0.69, 3.01)	0.33 (p_t = 0.16)
Marital Status	Married	1	
	Unmarried	1.31 (0.77, 2.23)	0.32
Educational level	Tertiary/PG	1	
	Primary/Secondary	1.63 (1.01, 2.64)	0.045
	None	2.75 (1.37, 5.52)	0.004 (p_t =0.002)
Religion	Christian	1	
	Muslim	0.46 (0.24, 0.90)	0.02
Do you have a personal income?	Yes	1	
	No	1.21 (0.74, 1.99)	0.45
Socio-economic class	High	1	
	Middle	0.99 (0.53, 1.84)	0.97
	Low	1.43 (0.79, 2.60)	0.24 (p_t = 0.15)
Breast Cancer Awareness			
Ever heard of BC	Yes	1	
	No	2.24 (1.25, 4.03)	0.01
Knowledge of BC causes	Good	1	
	Fair	1.09 (0.50, 2.38)	0.82
	Poor	1.47 (0.74, 2.79)	0.29 (p_t = 0.18)
Knowledge of BC symptoms	Good	1	
	Fair	1.67 (0.81, 3.47)	0.17
	Poor	2.02 (1.03,4.00)	0.04 (p_t = 0.08)
Practise of BSE	Yes	1	
	No	1.89 (1.20, 2.99)	0.01
Belief in a cure for BC	Yes	1	
	No	2.23 (1.40, 3.56)	0.001
Health Care Access			
Region of residence	North-Central (Abuja)	1	
	South-Eastern (Enugu)	2.21 (1.33, 3.68)	0.002
Diagnostic hospital type	Tertiary	1	
	Secondary	0.40 (0.22, 0.70)	0.001
Travel time taken to diagnostic hospital (hrs)	<1	1	
	1 - <2	1.42 (0.75, 2.71)	0.28
	≥ 2	2.14 (0.89, 5.13)	0.09 (pt =0.04)
Clinical Characteristics			

Socio-demographic characteristics		Age adjusted OR (95% CI)	p value
Previous HTN or diabetes	Yes	1	
	No	1.40 (0.81, 2.42)	0.22
Previous history of BBD	Yes	1	
	No	1.46 (0.77, 2.77)	0.25
Family History of BC	Yes	1	
	No	1.07 (0.49, 2.34)	0.86
BMI (kg/m^2)	< 25 (Normal weight)	1	
	25-29 (Overweight)	0.55 (0.32, 0.95)	0.03
	≥30 (Obese)	0.66 (0.38, 1.14)	0.14
	Unknown	1.45 (0.40, 5.18)	0.57 (*p*t =0.41)
WHR	<0.80 (low)	1	
	0.8-0.85 (moderate)	2.80 (1.18, 6.68)	0.02
	>0.85 (high)	2.20 (1.06, 4.60)	0.04 (*p*t =0.098)
Tumour grade	Well differentiated	1	
	Moderately differentiated	0.93 (0.50, 1.72)	0.82
	Poorly differentiated	1.42 (0.58, 3.49)	0.44
	Unknown	1.56 (0.76, 3.23)	0.23 (*pt* =0.09)
Oestrogen receptor status	Positive	1	
	Negative	1.18 (0.70, 2.01)	0.531

BC: breast cancer; BSE: breast self-examination; HCP: health care provider including traditional and spiritual healers; HTN: hypertension; BBD: benign breast disease; BMI: body mass index; WHR: waist-hip ratio; PG: post graduate; OR: odds ratio; CI: confidence interval; p_t: p-value for linear trend

Fully-adjusted model

A woman's educational level, religion, region of residence and belief in a cure for breast cancer were identified as being independent correlates of later stage at breast cancer diagnosis in the fully-adjusted model (Table 4). Notably, the association of lower educational level with the odds of later stage persisted in the fully-adjusted model, albeit with a slightly weakened trend (p_t=0.033). The association of later stage with religion, though slightly attenuated when region of residence was included in the model, reflecting the fact that a higher percentage of Muslims resided in the North-Central than in the South-East region, also remained significant in the fully adjusted model (OR=0.46;95% CI 0.22, 0.94; p=0.033). This association also held when restricted to women diagnosed in Abuja (OR=0.42; 95% CI 0.20, 0.88; p=0.02). The association of belief in a breast cancer cure with later stage, which was slightly attenuated upon adjustment for

educational level and religion (Figure 1), was little affected with further adjustment for the other variables included in the fully-adjusted model (OR 1.81; 95% CI 1.09, 3.01; *p*=0.022). In contrast, the association between having ever heard of breast cancer and later stage, which was weakened upon adjustment for educational level and religion (Figure 1), was further attenuated in the fully-adjusted analysis and no longer significant (Table 4).

Table 4: Fully-adjusted model showing associations between predictor variables and late stage breast cancer

Variable	Categories	Age adjusted OR (95% CI)	p value	Fully-adjusted [a] OR (95% CI)	p value
Age at BC Diagnosis (years)	<40	1		1	
	40-49	1.44 (0.85, 2.43)	0.18	1.53 (0.87, 2.68)	0.139
	50-59	1.76 (0.94, 3.29)	0.08	1.63 (0.84, 3.18)	0.149
	≥60	1.44 (0.69, 3.02)	0.33	0.89 (0.38, 2.08)	0.789
	p_t		0.16		0.86
Educational level	Tertiary/PG	1		1	
	Primary/Secondary	1.63 (1.01, 2.64)	0.045	1.48 (0.89, 2.47)	0.133
	None	2.75 (1.37, 5.52)	0.004	2.35 (1.04, 5.29)	0.039
	p_t		0.002		0.033
Religion	Christian	1		1	
	Muslim	0.46 (0.24, 0.90)	0.02	0.46 (0.22, 0.94)	0.033
Region of residence	North-Central (Abuja)	1		1	
	South-Eastern (Enugu)	2.21 (1.33, 3.68)	0.002	2.18 (1.05, 4.51)	0.037
Travel time taken to diagnostic hospital	<1	1		1	
	1 - <2	1.42 (0.75, 2.71)	0.28	1.45 (0.72, 2.93)	0.300
	≥ 2	2.14 (0.89, 5.13)	0.09	1.50 (0.59, 3.83)	0.396
	p_t		0.04		0.786
Ever heard of BC	Yes	1		1	
	No	2.24 (1.25, 4.03)	0.01	1.57 (0.80, 3.09)	0.189
Belief in cure for BC	Yes	1		1	
	No	2.23 (1.40, 3.56)	0.001	1.81 (1.09, 3.01)	0.022
WHR	<0.80 (low)	1		1	

	0.8-0.85 (moderate)	2.80 (1.18, 6.68)	0.02	2.22 (0.88, 5.60)	0.093
	>0.85 (high)	2.20 (1.06, 4.60)	0.04	1.75 (0.84, 4.16)	0.166
	p_t		0.10		0.154
Tumour grade	Well Differentiated	1		1	
	Moderately Differentiated	0.93 (0.50, 1.72)	0.82	0.86 (0.45, 1.65)	0.647
	Poorly Differentiated	1.42 (0.58, 3.49)	0.44	1.27 (0.50, 3.27)	0.616
	Unknown	1.56 (0.76, 3.23)	0.23	1.09 (0.49, 2.42)	0.828
	p_t		0.09		0.85

BC: breast cancer; HCP: health care provider including traditional and spiritual healers; WHR: waist hip ratio; pt: p-value for linear trend; PG: post-graduate; p_t: p-value for linear trend; OR: odds ratio; CI: confidence interval;
[a] Mutually-adjusted for all the other variables in the table.

DISCUSSION

In this study, we examined the relationship between socio-demographic, breast cancer awareness, access to health care and clinical factors with late stage diagnosis of breast cancer at six tertiary and secondary level hospitals in two distinct regions of Nigeria. The findings showed that 67.7% women were diagnosed at late (III/IV) stages. The study identified lower educational level, being Christian, poor breast cancer awareness and poor health care access as being independent correlates of later stage at breast cancer diagnosis in Nigeria. In contrast, clinical and tumour features were not found to be related to stage at breast cancer diagnosis.

This study is unique being the first multi-centre study to investigate socio-demographic, breast cancer awareness, health care access and clinical determinants of late stage diagnosis of breast cancer in two different regions in Nigeria. As the study was hospital-based, breast cancer cases that do not reach a secondary or tertiary health facility to be diagnosed could not be included. However, the majority of breast cancer cases in Nigeria are diagnosed at tertiary health facilities where facilities for diagnosis and treatment are available and given our high response rate of ~95%, it is highly likely that our findings are a true representation of the all breast cancer cases diagnosed histologically in the cities included. The mean age at breast cancer diagnosis was similar to that reported by other studies conducted in Nigeria(60, 202) and other SSA countries.(145, 179) Although some authors have associated younger age at diagnosis with later stage at presentation,(203) others have found the reverse.(199) We did not find an association between age at diagnosis and stage.

Breast cancer awareness is low in most African countries.(63) Most women in our study had heard about breast cancer, but only a few had good knowledge of its causes or symptoms, in line with the findings reported by other Nigerian studies.(204, 205) Women

in our study who did not practice BSE had higher odds of presenting later than women who did. Other authors have reported an association between education and practise of BSE.(206) While BSE has not been shown to be effective in early detection of breast cancer, the awareness it generates may prove useful in low-resource settings.(207)

Access to health care is an important determinant of stage at diagnosis. Previous authors have reported variations in late stage breast cancer by region of residence.(208) Residing in areas with poorer access to health care, or taking longer time to travel for care, may increase the likelihood of a late stage diagnosis.(208) Women diagnosed in Enugu had greater odds of later stage than those diagnosed in Abuja, perhaps reflecting differences in access to health care between the two cities. Abuja is a more affluent city with many secondary and tertiary health care facilities within easy reach whereas in Enugu participants had to travel long distances, often from rural areas, to get to the participating hospital which is located on the outskirts of the city. In addition, with the high prevalence of private practice and the frequent strike action in government hospitals, it is possible that only those who could not afford private care sought care at the participating hospital. High percentages of late stage at diagnosis have also been reported from other studies in South-Eastern and Western regions of Nigeria which cater to a predominantly more rural population than Abuja.(60, 202, 209) In other similar settings, less developed areas reportedly have more advanced stage at diagnosis than the cities.(203) We also found stage at diagnosis to be significantly better in secondary level facilities than at tertiary centres, perhaps because women may first present at secondary facilities, which may delay their presentation at tertiary hospitals, but more research is needed to confirm this.

Level of education was a strong determinant of stage at diagnosis in our study. Women with no education had significantly higher odds of later stage disease than women with tertiary education. Several studies in Nigeria(139), other SSA countries(78) and other

developing countries (e.g. Brazil(203)) as well as multi-ethnic studies in the US(134) have associated lack of education with later stage diagnosis of breast cancer. Educational level was also positively correlated with knowledge of breast cancer symptoms in our study similar to findings by Marcu *et al.* in the United Kingdom.(210) Interestingly, the association of educational level did not appear to be fully mediated by differences in breast cancer awareness or health care access, but the variables examined here may be too crude to fully capture these domains. Nevertheless, this finding has important implications for the development of educational interventions that can potentially improve the stage at diagnosis of breast in developing countries.

We found no associations between tumour characteristics and later stage at breast cancer diagnosis. Obesity has been identified as a strong risk factor for late stage diagnosis in breast cancer.(211) However, in our study there was no association between BMI, or WHR, and later stage. As factors associated with later breast cancer stage were not related to the tumour biology, but to woman's characteristics, they must act through increasing the time from onset of symptomatic disease to diagnosis at a health care facility. There are reports from other SSA settings of long patient-level and system delays which could result in considerable change in stage.(78) We observed a long delay from time of a woman noticing the first breast cancer symptoms to diagnosis at the recruiting hospitals, in line with previous reports of 12.1 months in Nigeria(82) and 10 months in Ghana.(160) Racial disparities have also been documented in the US with African-Americans reporting longer delays from first contact to diagnosis and from diagnosis to breast cancer treatment than Whites and significantly more advanced stage at diagnosis.(67)

In this study, Muslim women were diagnosed at earlier stages than Christian women. This finding contrasts with previous studies that have reported less breast cancer early detection practices among Muslim women. We speculate that the Muslim women in this

study may belong to a higher socio-economic class than the Christian women, therefore may have the financial ability to seek care more readily. Secondly, Muslim women may be less likely to work outside the home and therefore would have the time to seek help once a breast symptom is felt without having to obtain permission from employers to get medical care. However, more research is needed to confirm this.

In SSA, ensuring early diagnosis and treatment of symptomatic women is crucial for stage-migration of the disease and, hence, achieve better outcomes. In our study, breast cancer awareness and poor access to health care were identified as independent determinants of later stage at diagnosis in Nigeria. Most of these factors are amenable to change by awareness creation, educational and behavioural change interventions to diagnose breast cancer at earlier stages. Stage migration interventions have proven to be successful and cost effective in several low- and middle-income countries such as India(28), Malaysia(29), South Africa(30), Tanzania(31) and Sudan(32) following educational interventions, and need to be followed by appropriate treatment. In Sudan, the implementation of a cancer awareness and breast examination intervention program using trained local volunteers improved the early detection of breast abnormalities in women in rural communities.(32) In Tanzania, late stage diagnosis (stages III/IV) was reduced by 51% over three years after trained health personnel delivered an educational intervention that focused on the signs and symptoms of cancer, and subsequently screened women by clinical examinations and taking pictures of suspicious lesions.(31) More research is needed to characterise delays and factors associated with diagnostic delays in Nigeria, as well as in other SSA populations(160), as such knowledge is crucial to the development of context appropriate breast cancer control programs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest disclosed.

Author Contributions

EJA had the idea for the study, contributed to the study design, implementation and data analysis, drafted the manuscript and made subsequent revisions to the manuscript; VM had the idea for the study, supervised data analyses and provided critical revisions to the manuscript; OO, WB, MY, TY, EE, MA, IS, EM, IA, and BA contributed to data collection, data quality and approved the final draft; SNA contributed to the study design, data quality and manuscript revision; IDS supervised data analyses and provided critical revisions to the manuscript; CA had the idea for the study design, obtained funding, supervised data analyses and provided critical revisions to the manuscript. All authors read and approved the final draft.

Acknowledgements

The project described was supported by the Training Program in Nigeria for Non-Communicable Diseases Research (TRAPING NCD) grant number FIC/NIH D43TW009106 from the Fogarty International Centre. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Fogarty International Centre or the National Institutes of Health.

CHAPTER 5

Determinants of Diagnostic Delays in Nigerian Women with Breast Cancer

It has been widely established that diagnostic delays (delays in terms of breast cancer presentation and diagnosis) significantly contribute to the late stage diagnosis of breast cancer (69). In the previous chapter, it was reported that the majority of Nigerian women are diagnosed with breast cancer at late stages (III & IV). However, little is understood about a woman's journey to a breast cancer diagnosis, and why diagnostic delays occur in Nigerian women. This study was conducted to identify the extent and determinants of delays in women diagnosed with breast cancer and the impact of these delays on the stage of the disease. The sociodemographic, breast cancer awareness, health care access and clinical factors that may contribute to diagnostic delays in Nigerian women were examined. Finally, the self-reported reasons that were formerly identified to deter the early presentation and diagnosis in Nigerian women are presented.

5.1. INTRODUCTION

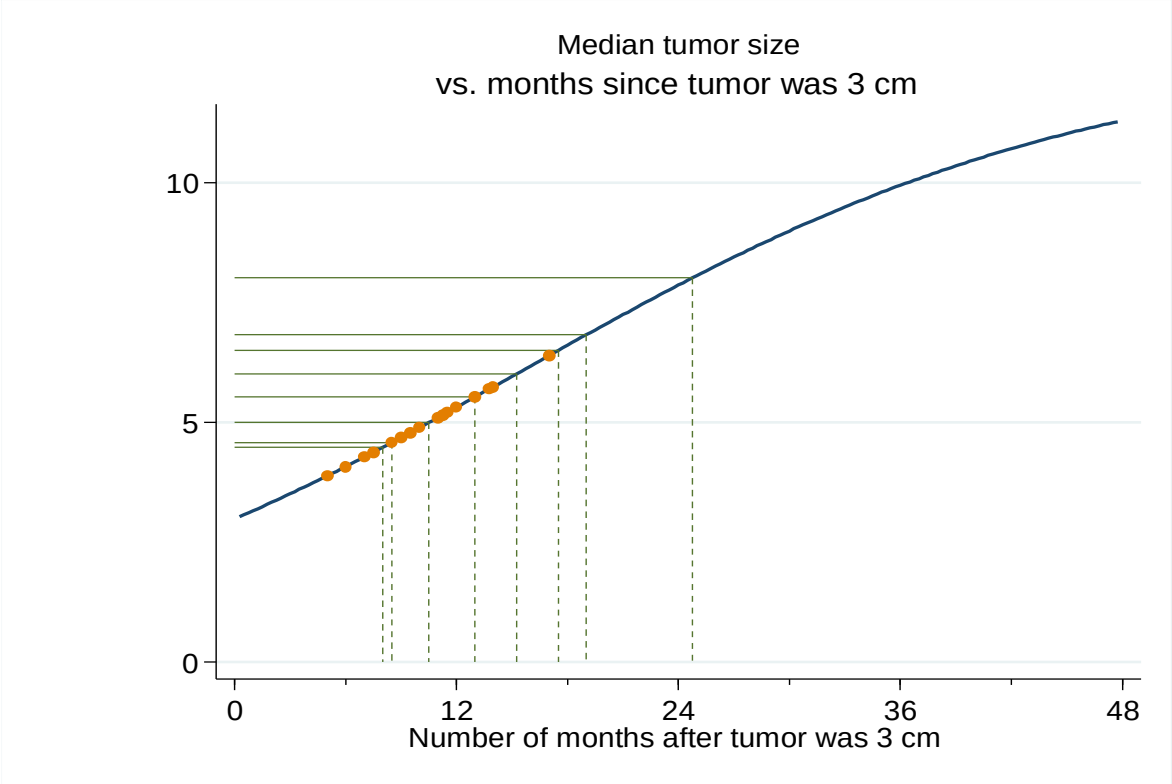
5.1.1. Background

Breast cancer in SSA is often characterised by late presentation, an advanced stage of the disease at diagnosis, and a younger demographic than in the case of HICs (63). Research into the delays in terms of breast cancer presentation and diagnosis is crucial for cancer control because of the increasing evidence demonstrating an association between the time from the onset of the symptoms to the diagnosis and stage of the disease, and in turn to its impact on breast cancer survival (212). A delayed period of time prior to diagnosis has been identified as a significant contributor to the late stage diagnosis in Nigeria and other developing countries (69). Although screening programmes for breast cancer have been introduced in many HICs, this is not the case in most SSA countries, where a cancer diagnosis is usually made after the onset of symptoms and not by means of screening. With the tumour growth already causing symptoms, any additional delays can significantly worsen cancer outcomes, and therefore an early diagnosis of symptomatic breast cancer is crucial (75). The findings collated from a meta-analysis of 87 studies indicated that women who begin treatment 3-6 months after noticing breast cancer related symptoms have poorer chances of survival than women who wait < 3 months only (213). Longer waiting times or delays prior to diagnosis could lead to disease progression or treatment complications in women with breast cancer (69).

The severity of the late stage at breast cancer diagnosis reported in the previous chapter (67.7% stage III/IV), i.e. with 14% having a tumour size greater than 2 cm and 38% greater than 5 cm, indicates that the tumours are not only detected at the symptomatic stage, but that, on average, they are detected sometime after they become palpable (around 2 cm). Reducing this pre-diagnostic symptomatic period would lead to an early stage at diagnosis and the potential of improved survival rates, but first the drivers of this

period need to be understood. Using the established tumour growth model curve by Weedon-Fekjaer *et al*. (35) a range of median tumour sizes reported in the systematic review presented in Chapter 2 were plotted against the average number of months since the tumour measured 3 cm and was hence definitely palpable (Figure 1). This figure suggests that women with larger tumour sizes were more likely to experience delays in seeking help after the tumour had become palpable at 3 cm (Figure 1). Targeting and shortening the pre-diagnosis symptomatic window is the action required for early diagnosis in the SSA setting.

Figure 1: Relationship between tumour size and delays in diagnosis as predicted by the tumour growth model developed by Weedon-Fekjaer *et al*. (35)



5.2 BREAST CANCER DELAY: DEFINITION AND CLASSIFICATION

5.2.1 Total Delay in Breast Cancer

The total delay in breast cancer was first described by Pack and Gallo in 1938(214). With reference to breast cancer, total delay has been defined as the time lapsed from the

discovery of symptoms, which are constituted by a breast lump in the majority of women (215), to the start of breast cancer treatment (70). This time-period has been divided into two main intervals of patient delay and provider or system delay. Delays could occur at different stages of the pathway from when a woman first notices a symptom to her presentation to a health care provider (patient delay) and from the initial presentation to the diagnosis and commencement of treatment (provider delay) (69). Longer total delay exerts a negative influence on breast cancer survival, as it is associated with an advanced stage at diagnosis and poor prognosis (216). A previous study by Richards *et al.* conducted in London, United Kingdom in 1999 (217), estimated that approximately one third of the women experiencing symptoms of breast cancer, delayed seeking help for at least 3 months, whereas approximately a quarter of these women will delayed seeking care for a period of 6 months or longer (218). In Nigeria, Ezeome et al. reported a delay of > 3 months in over 70% of patients (60).

5.2.2 Patient or Pre-contact Delay

In 2014, Lee Caplan defined patient delay as a delay in seeking medical attention after noticing a potential breast cancer symptom (69). Others have defined patient delay as a time interval of over 3 months between symptom detection and the first medical consultation (6). There is substantial evidence to suggest that in women with breast cancer, patient delay exceeding 3 months is associated with late stage diagnosis and poorer chances of survival (219, 220). Nevertheless, this has not been previously studied in the Nigerian population.

5.2.3 Provider or Post-contact Delay

Provider delay, defined as the time from the first medical consultation to the beginning of the definitive treatment, has been further divided by some authors into diagnosis delay;

namely the time between the first medical consultation and the cancer diagnosis, and treatment delay; or the time between diagnosis and the beginning of treatment (221).

However, the terms pre-contact and post-contact are preferred and will be used throughout this study. This is because the terms 'patient' and 'provider delay' assume that the responsibility for the first interval (time from when a symptom is first noticed to presentation at a care provider) is attributed entirely to the patient, whereas the responsibility for the second interval (time from first medical consultation to the beginning of definitive treatment) is attributed to the provider. Such mutually exclusive definitions are not appropriate in settings wherein there is no universal access to health care, as in the case of the SSA settings. For instance, a woman who has sought the assistance of a care provider and has been diagnosed with breast cancer may experience delays in returning for treatment following the initial consultation due to issues such as financial constraints, preference for unorthodox treatments (e.g. by traditional and spiritual healers), or a lack of belief in a cure for breast cancer. Therefore, delays after the first visit to a care provider should not be exclusively assigned to factors related to health care providers, as the factors affecting a woman's decision to delay treatment may also play a substantial role. Similarly, a woman may delay a visit to the first care provider after noticing a breast symptom because there may be an industrial strike action and the hospitals within easy access of her residence may be closed. In this case, some element of the delay may be assigned to the health system.

5.2.4 Factors Associated with Delays in the Breast Cancer Diagnosis

There is a scarcity of information related to the delays occurring between symptom recognition and breast cancer diagnosis in women with symptomatic breast cancer in SSA. A search of the literature for studies of delayed presentation in breast cancer

returned 22 results, with the duration of the total delay ranging from 2 to 13.3 months(133). However, only 5 of these previous studies (60, 81, 82, 139, 222) included relevant information on the factors associated with diagnostic delays in Nigerian women. These studies have suggested that cultural beliefs, fear of a breast cancer diagnosis and use of alternate medical practitioners, such as pharmacists and traditional healers, contribute to the aforementioned delays. However, none of these studies have examined the specific factors related to these delays in detail or reported on the magnitude of the impact that these factors have on the time to presentation and diagnosis. In some SSA countries, traditional healers represent an accessible, easily available and less expensive health care resource. Patients widely seek traditional treatment due to widespread beliefs in the efficacy of traditional and spiritual medicine (223). In Zimbabwe, the government legitimised traditional medicine in 1980 and this facilitated the collaborative work between traditional healers and the ministry of health. In Nigeria, in a study of 162 patients with breast cancer, 17.5% visited a traditional healer before seeking orthodox care (60).

In other sub-Saharan African countries, older age, a lower educational level and the distance to the health care providers have been associated with considerable diagnosis delays (78). In developed countries, an ethnic minority and low socio-economic status, along with younger age have been associated with treatment delays (224). Others have reported older age, symptoms other than breast lumps, fear of treatment and pregnancy/post pregnancy anxiety as contributing factors (225, 226). In Nigeria, with very few studies conducted on this topic, the strength of the current evidence in the country is inadequate to develop appropriate context-specific strategies to shorten the delays in women who are diagnosed with breast cancer. One major limitation of the previous studies is that they relied on hospital records, which may not have been obtained

in a standardised manner. Additionally, the reasons why women delay in seeking care are often not well documented in many LMICs, including Nigeria (63).

5.3 ACCESS TO HEALTH CARE SERVICES

Delay and Access to Health Care Services in the Nigerian Context

The aforementioned definitions of delays in cancer treatment commencement constitute useful conceptual and analytical tools in many settings, but their definitions have been largely modelled on western health care systems, and often on the basis of countries where national public health systems are in place. In these contexts, the patient and provider delays can be partitioned because after the first provider contact, the healthcare system had an opportunity to cater for appropriate referral and the responsibility to guide the patient to the next diagnostic or treatment stage. However, in Nigeria, the pathway to cancer diagnosis and treatment is complex, as it is often the case in many LMICs (77). Several studies have reported that the time to diagnosis may be influenced by health care access and utilisation in many settings (77). Limited access to health care has been shown to contribute to diagnostic delays and disparities in breast cancer outcomes in many populations (227). However, this has not been fully explored in the Nigerian setting. In Nigeria, although the health care sector is largely driven by the public sector (66%), there is a substantial private sector that also provides health care to the population (228) with heterogeneity in the type and quality of the services provided in both sectors. The provision of health care in the country is the function of the 3 governmental tiers, namely the federal, state and local government (229). The primary health care (PHC) system is the first level of care and it is managed by the local government institutions. The state ministries of health and private medical practitioners provide support to the PHC system. Patients from the PHC are often referred to the secondary health care system that provides

the first level of specialist intervention offering laboratory and diagnostic services. The tertiary health care system is driven by the university teaching hospitals and specialist hospitals that provide care and treatment for breast cancer patients (229). Prior to the advancement of orthodox medicine, and in spite of the hierarchical health care system, traditional medicine which was the widely recognised health care system in the past, is still practised in many SSA countries and in Nigeria (230). In this study, we will consider the health care service to include both orthodox and unorthodox care providers, including traditional healers. Financial implications are also a major consideration for women who access healthcare in Nigeria, with a very small proportion of the Nigerian population covered by health insurance (228). Even in cases where health insurance is available, cancer treatment is often not included in the package provided. It is possible that these challenges experienced in terms of accessing health care may partially contribute to diagnostic delays in the country.

While a reasonably small element of delay is inherently inevitable in cancer diagnostic pathways (231), it is likely for the delay identified in the case of a significant number to be largely preventable. Preventing diagnostic delays involves primarily identifying the factors that contribute to the delays in the Nigerian setting and using these as a foundation in the development of strategies seeking to reduce diagnostic delays in Nigerian women.

5.4 METHODS

Study Design and Setting

Starting from January 2014, within the framework of an ongoing multicentre case control study of breast cancer in Nigeria, namely the Nigerian Integrative Epidemiology of Breast Cancer Study (NIBBLE), potential cases were women aged ≥18 years who presented with symptoms highly suggestive of primary breast cancer at the surgical outpatient departments (SOPD) of six government hospitals in Nigeria and the oncology departments of two of these hospitals (NHA and UNTH). These women were subsequently found to have either malignant breast carcinoma or benign breast lesions. The present analysis was initially conducted on all women who presented with symptoms highly suggestive of primary breast cancer and was then restricted to those who were subsequently confirmed to have a newly-diagnosed primary invasive breast cancer. The controls in the NIBBLE study did not contribute to the analyses shown in this chapter. A detailed description of the study sites and setting and of the methodology used is provided in Chapter 3 of this thesis.

Participant Recruitment

A face-to-face interview with each eligible woman was conducted by a trained research nurse at each of the study sites. Three pre-tested and piloted structured questionnaires were used in order to collect information on various sociodemographic (e.g. age, marital status, religion, educational level, socioeconomic class and number of children), breast cancer awareness (e.g. previous knowledge of breast cancer, knowledge of treatment/cure for breast cancer, knowledge of breast cancer and symptoms), health care access (e.g. region of residence, type of facility where a diagnosis was made, time taken from the first symptom to the first provider, number of health care providers visited before a diagnosis was made) and clinical variables (e.g. previous history of benign breast disease, family

history of breast cancer, previously diagnosed hypertension or diabetes, body mass index, waist hip ratio and the stage at breast cancer diagnosis) and on the patient's journey from the first symptom, and health care providers visited to their eventual presentation and diagnosis at the recruiting hospital. Information on the symptom duration was collected and patients were asked to provide reasons for the delays where applicable. All measurements were performed using a standardised protocol.

Written informed consent was sought and received from all participants. Ethical approval for the study was obtained from the health research ethics committees (HRECS) at each study site, the National Health Research Ethics Committee Nigeria (NHREC), the University of Maryland Baltimore and the London School of Hygiene and Tropical Medicine.

Statistical Analyses

Outcome Variables in Delay Analyses

Patient delay (pre-contact delay) was defined as the number of months from the first reported symptom to the patient's first presentation to any care provider. Post-contact delay was defined as time in months from the presentation at the first care provider to diagnosis. Total delay in this study was defined as the time (in months) from the first reported symptom to the diagnosis at the recruiting hospital, i.e. pre-contact and post-contact delays combined. When patients were unable to provide a date for when their first symptoms were noticed, they were asked to provide a month and a year. If the month was provided, the estimated date was the midpoint of the month – or in other words the 15th of that month. If they only provided information on the year when the symptom was noticed, the estimated date was the last day of the middle month of that year, namely June 30th of that year. Previous studies have classified delay into "no delay" and "delay" using a cut-off period of 1 month (83) or 3 months (82). In our study, patient delay was defined

using the term “pre-contact delay” i.e. the delay prior to the first contact with the first care provider and was classified into “no delay” if it took less than 3 months from the onset of symptoms to the presentation to a care provider or “delay” if it took $\geq$ 3 months. Care providers in this instance were orthodox (private or public hospitals, pharmacies, community clinics and private general practitioners) or unorthodox (traditional healers, churches and pastors). A time-period of < 3 months was classified as “no delay”, whereas a period of $\geq$ 3 months was classified as “delay”. We further categorised women with delay into 3 groups of 3 to < 6 months, 6 months to < 12 months, and $\geq$ 12 months. Despite the cut-off period of 1 or 3 months used in order to classify delays in previous studies, the factors associated with breast cancer delay have been reportedly similar (71).

In women with breast cancer, the clinical stage of the patients was determined using the tumour node metastasis classification of the AJCC staging system (as described in Chapter 1). Patients were classified into stages I, II, III and IV with stages I/II being defined as early stage breast cancer and stages III/IV being defined as late stage breast cancer.

Information on the total number of providers visited by the women was reported. We categorised women into 3 groups, namely women who had visited 1, 2 or $\geq$ 3 providers before a diagnosis was made at the recruiting hospital. The type of the health facility visited was also recorded. Detailed information on whether a woman visited a private GP, public or private hospital, community health centre/clinic sister or nurse, or other providers such as traditional healers, chemists or churches was also collected. These were then categorised into three groups designated as “private clinic/hospital” (including private GP), “public clinic/hospital”, and “others”, with the latter encompassing traditional healers, churches, community health centres and clinic sisters due to the small numbers in this group.

Regression Analysis

Delay (post-contact and total) were first examined as explanatory variables and their relationship to late stage at diagnosis was studied. Logistic regression was used to estimate the odds ratio for late (stages III/IV) versus early stages (stages I/II).

Thereafter, pre-contact, post-contact and total delays were analysed as the outcome, with each constituting continuous variables in each case. Normal errors linear regression models were used in this instance. Initial boxplots and histograms were created for the continuous variable in order to identify potential outliers, check the plausibility of the delay times and prepare the data for analysis (Appendix 8: Figure 1). As the temporal distribution from the onset of symptoms to the final diagnosis was not normally distributed, this outcome was log transformed before modelling it as the outcome (Appendix 8: Figures 2 - 4). Beta coefficients represent the differences in the log delay times. As a result the exponentiated beta coefficients and their 95% CIs are presented as they provide a more meaningful comparison, namely the ratio of the geometric mean delay time associated with the comparison in question. Two linear regression models were implemented in order to examine the association of each of the factors (e.g. sociodemographic, breast cancer awareness, health care access and clinical factors) with the delay (pre-contact, post-contact and total) – first in all women presenting breast cancer symptoms and then restricting the examination to the women with a confirmed breast cancer diagnosis. Then in the fully adjusted models including the number of women presenting with breast symptoms and the ones diagnosed with breast cancer, a stepwise variable selection was performed to include variables that were significant at the 0.1 level from both initial linear regression models. Two variables, namely the stage at diagnosis in women with breast cancer and the number of providers visited, though significant at the 0.1 level were not included in the fully adjusted models as these were regarded as

consequences of the delay (stage) or part of the same pathway, and thus highly correlated (number of providers).

5.5 RESULTS

Participant Characteristics

There were 512 women who presented with breast symptoms and were recruited into the Nigerian Integrative Epidemiology of Breast Cancer Study (NIBBLE). Among these, 430 (84%) had information in relation to the date of first symptom, the date of first contact and the date of diagnosis and were subsequently included in this study. Some, 266/430 (61.9%) had histologically confirmed breast cancer. The characteristics of the study participants are presented in Tables 1 and 2. The majority of the women who presented with symptoms were married (73.2%), Christian (86.5%), had tertiary education (51.9%) and a personal income (70.5%). The median (IQR) number of children per woman was 3 (1-5). Overall, 82.6% had previous knowledge of breast cancer, 78.6% resided in Abuja, and 16.3% had a previous history of benign breast disease. On average, women visited 2 (1-3) median (IQR) care providers, including the hospital where the recruitment took place and where a breast cancer diagnosis was confirmed. The mean (SD) patient age was 44.4 (11.8) in all women and 45.2 (11.3) in the women with breast cancer. In the case of all women with suspicious symptoms, the median (IQR) pre-contact delay, post-contact delay and total delay were 2.6 (0.6-8.3), 3.1 (0.8-8.7) and 7.8 (3.3-18.7) months, respectively. In women with breast cancer, these were 3.0 (0.8-8.5), 3.5 (0.8-8.3) and 7.6 (3.9-18.2) months, respectively. The diagnostic journey of 80 randomly selected women from the onset of the first symptoms to the visits to the care providers is shown in Figure 2 and suggests that a large number of women delay in seeking care (patient or pre-contact delay), with a similar proportion of women being delayed by the health care system (provider or post contact delay) (Figure 3). Only 18.1% of all women with symptoms and 12.4% of the subset with breast cancer sought care within 3 months of noticing a breast symptom (Table 2).

Delay and Stage at Diagnosis Using Logistic Regression

On average, women diagnosed in stages III/IV self-reported 36% longer total delay times than those in stages I/II. In the unadjusted analysis, when compared with the delays of < 3 months, both post-contact and total delays showed a significant trend suggestive of late stage disease, p_t= 0.028 and p_t=0.004 for post-contact and total delays, respectively (Figure 4).

Table 1: Characteristics of the study population of women presenting with breast symptoms in Nigeria

Characteristics		**All Women with Breast Symptoms N (%)**	**Subset of women with Breast Cancer N (%)**
Sociodemographic	**Total no. of women** [a]	430 (100)	266 (100)
Age at diagnosis (years)	Mean age (SD)	44.4 (11.8)	45.2 (11.3)
Marital status	Married	315 (73.2)	194 (72.9)
Religion	Christianity	372 (86.5)	234 (87.9)
	Islam	55 (12.8)	32 (12.1)
Education	None	58 (13.5)	40 (15.0)
	Primary/Secondary	148 (34.4)	99 (37.2)
	Tertiary/Post-graduate	223 (51.9)	127 (47.8)
Socioeconomic class	Low	182 (42.3)	124 (46.6)
(using household data)	Middle	173 (40.2)	93 (35.0)
	High	75 (17.5)	49 (18.4)
Do you have a personal income?	Yes	303 (70.5)	187 (70.3)
	No	127 (29.5)	79 (29.7)
Number of children	None	26 (6.0)	19 (7.1)
	1-2	110 (25.6)	62 (23.3)
	3-4	119 (27.7)	82 (30.9)
	$\geq$ 5	113 (26.2)	70 (26.3)
	Not reported	62 (14.5)	33 (12.4)
Breast cancer awareness			
Ever heard of breast cancer	Yes	355 (82.6)	219 (82.3)

Characteristics		All Women with Breast Symptoms N (%)	Subset of women with Breast Cancer N (%)
	No	74 (17.2)	47 (17.7)
Knowledge of BC symptoms [b]	Poor	225 (52.3)	145 (54.5)
	Fair	143 (33.3)	85 (32.0)
	Good	62 (14.4)	36 (13.5)
Belief in a cure for BC	Yes	248 (57.7)	157 (59.0)
	No	177 (41.7)	107 (40.2)
	Don't know	5 (0.6)	2 (0.8)
Practise SBE	Yes	194 (45.2)	116 (43.6)
	No	210 (48.8)	135 (50.8)
	Never heard of / Unknown	26 (6.0)	15 (5.6)
First symptom	Breast lump	381 (88.6)	233 (87.6)
	Other symptom *	49 (11.4)	33 (12.4)
Health care access			
Region of residence	North Central (Abuja)	338 (78.6)	192 (72.2)
	South East (Enugu)	92 (21.4)	74 (27.8)
Type of health facility where the diagnosis was made	Tertiary	330 (76.7)	216 (81.2)
	Secondary	100 (23.3)	50 (18.8)
Journey time taken to first provider	< 1 hour	263 (61.2)	152 (57.1)
	1 hour - < 2 hours	61 (14.2)	39 (14.7)
	>= 2 hours	27 (6.3)	18 (6.8)
	Not reported	79 (18.3)	57 (21.4)
Clinical			
Previous benign breast disease (BBD)	Yes	70 (16.3)	44 (16.5)
Previously diagnosed HTN or diabetes	Yes	101 (23.5)	70 (26.3)
Family history of BC	Yes	36 (8.4)	22 (8.3)

Characteristics		All Women with Breast Symptoms N (%)	Subset of women with Breast Cancer N (%)
BMI	< 25 (normal weight)	131 (30.4)	78 (29.3)
	25-29 (overweight)	134 (31.2)	91 (34.2)
	> 30 (obese)	150 (34.9)	89 (33.5)
WHR	< 0.80 (low)	52 (12.1)	25 (9.4)
	0.8-0.85 (moderate)	79 (18.4)	49 (18.4)
	> 0.85 (high)	286 (66.5)	187 (70.3)

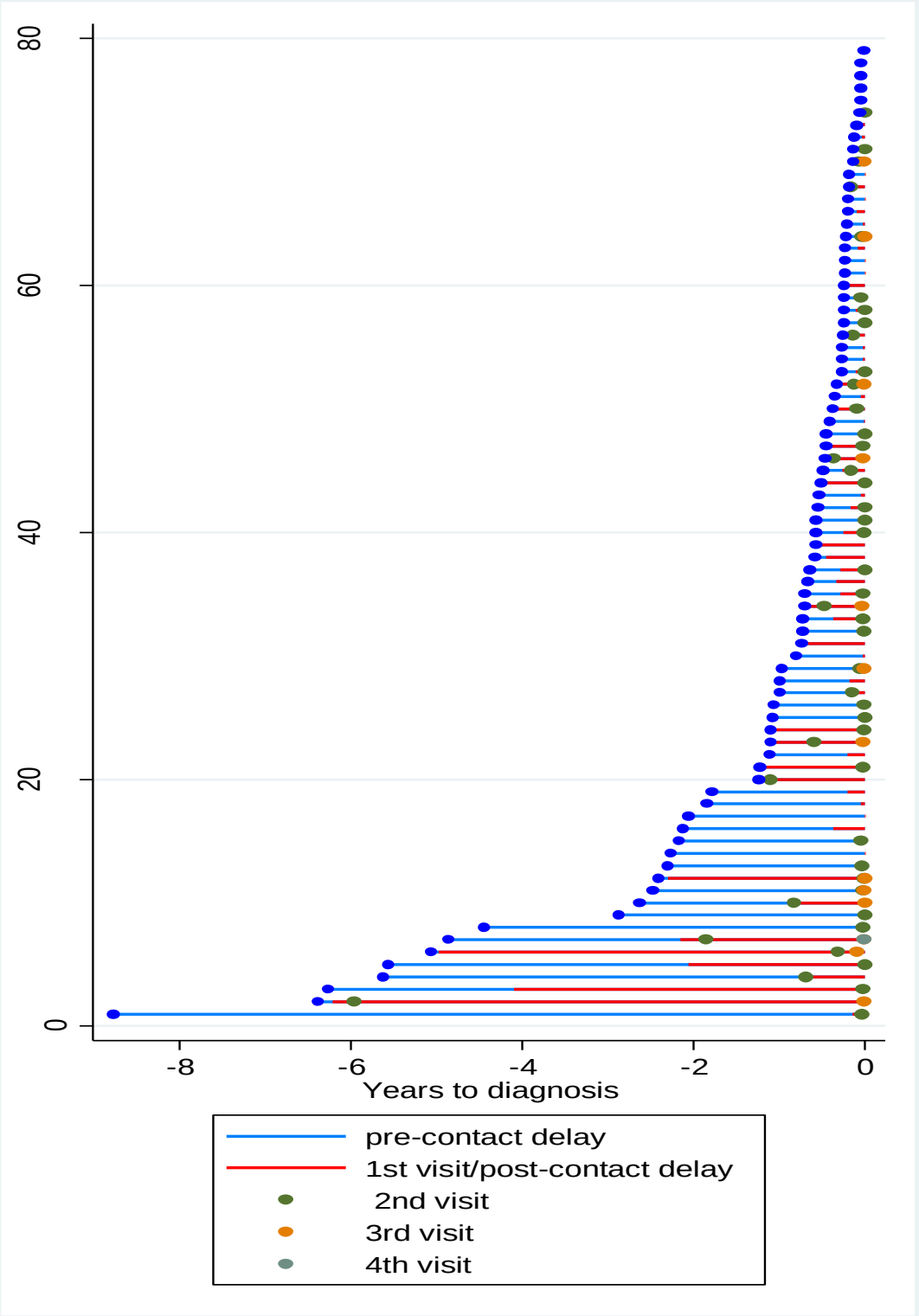
[a]All women: Unknown religion = 3 (0.7%), Unknown education = 1 (0.3%) Unknown knowledge of BC = 1 (0.2%), Unknown BBD = 4 (1.0%) Unknown BMI = 15 (3.5%) Unknown WHR = 13 (3%)
Breast cancer: Unknown BBD = 1 (0.4%), Unknown BMI = 8 (3.0%) Unknown WHR = 5 (1.9%)
*Other symptoms included underarm swelling, nipple discharge and change in the breast shape or size.

Table 2: Description of the outcome variables - time to diagnosis, number and type of providers visited and stage at diagnosis in Nigerian women

Variables	Description		All women with breast symptoms N (%)	Women with breast cancer only N (%)
Total number of women			430 (100)	266 (100)
Months to diagnosis	Months from first symptom to presentation* (Pre-contact delay)	Median (IQR)	2.6 (0.6-8.3)	3.0 (0.8-8.5)
	Months from presentation to diagnosis (Post-contact delay)	Median (IQR)	3.1 (0.79-8.7)	3.5 (0.8-8.3)
	Months from first symptom to diagnosis (Total delay)	Median (IQR)	7.8 (3.3-18.7)	7.6 (3.9- 18.2)
No. of providers contacted [a]	1		142 (33.0)	83 (31.2)
	2		193 (44.8)	121 (45.5)
	3		70 (16.3)	44 (16.5)
	4		16 (3.7)	13 (4.9)
	5		5 (1.2)	4 (1.5)
	6		2 (0.5)	1 (0.4)
First provider contacted	Private clinic/Hospital		130 (30.2)	85 (32.0)
	Public clinic/Hospital		265 (61.6)	158 (59.4)
	Others [b]		31 (7.2)	21 (7.9)
Total delay categories	< 3 months		78 (18.1)	33 (12.4)
	3-< 6 months		80 (18.6)	56 (21.0)
	6-< 12		93 (21.6)	68 (25.6)
	12-< 18		64 (15.0)	41 (15.4)
	>= 18		115 (26.7)	68 (25.6)
Stage at diagnosis (n=255)	I/II		-	79 (31.0)
	III/IV		-	176 (69.0)

[a] All women: Unknown number of providers = 2 (0.5%) Unknown first provider = 4 (1.0%),
BC: Breast cancer: Unknown first provider = 2 (0.7%),
[b] Others for all women with breast symptoms = 31, (Traditional healer - 2, Church/pastor-3, Chemist/pharmacist - 14, Community-based worker - 8 & Other hospital staff - 4) Others for women with breast cancer = 21 (Traditional healer - 1, Church/pastor - 3, Chemist/pharmacist - 8, Community-based worker - 6 & Other hospital staff - 3)
*Presentation at any care provider

Figure 2: Pre- and post-contact diagnostic journey of 80 randomly selected women from the onset of the first symptoms to the first 4 visits to care providers



Time 0: Time at breast cancer diagnosis

5.5.1 FACTORS ASSOCIATED WITH PRE- AND POST-CONTACT DELAYS

Pre-contact delay

In the unadjusted analysis in women with breast cancer, no factors associated with pre-contact delays were identified (results not shown). In the fully adjusted analysis, only one factor, i.e. having 3-4 children compared to having none (OR 2.25; 95% CI 1.01, 5.03; p=0.048) was associated with delays in women with breast cancer. No factors associated with pre-contact delays in all women with symptoms were identified in the unadjusted and fully adjusted analyses.

Post-contact delay

In all women with breast symptoms, increasing age (pt=0.024), a lower educational level (pt=0.023), having 5 or more children (p=0.042), no personal income (OR 1.38; 95% CI 1.00, 1.90; p=0.047) and an increasing number of providers visited (pt<0.001) were positively associated with post-contact delays in the unadjusted analysis, while the presentation at a secondary facility and having no previous history of benign breast disease (OR 0.45; 95% CI 1.01, 5.03; p=0.001) were inversely associated (Table 3). Patient knowledge of breast cancer symptoms was borderline significant (Table 3). In the fully adjusted analysis, the effect of having no personal income was amplified and no previous history of BBD remained significant (Table 4). The effect of a lower educational level on post-contact delays was no longer significant when knowledge of breast cancer symptoms was introduced into the model.

In the unadjusted analysis for women with breast cancer, a lower educational level (pt=0.044), an increasing number of providers visited (pt=0.014) and the region of residence (OR 1.54; 95% CI 1.01, 2.36; p=0.047) were positively associated with post-contact delays. Not having a personal income was borderline significant (OR 1.47; 95% CI 0.98, 2.22; p=0.064). The type of health facility visited (i.e. secondary) was inversely

associated with post-contact delays, whereas women with no previous history of benign breast disease were more likely to delay treatment (Table 3). In the fully adjusted analysis, only personal income and a previous history of BBD remained significantly associated with post-contact delays (Table 4). The effect of education was weakened, but still remained significant when the income variable was included in the model. However, it was further attenuated when knowledge of symptoms was introduced into the model. The effect of the region of residence on delays was no longer significant when the type of facility visited was included in the model (Table 4).

Table 3: Factors associated with post-contact delays – unadjusted model

Characteristics	**Categories**	**All women with breast symptoms Unadjusted model Ratio (95% CI)**	***P* value**	**Women with breast cancer only Unadjusted model Ratio (95% CI)**	***P* value**
Sociodemographic					
Age at diagnosis	< 40	1		1	
	40-49	1.12 (0.80, 1.58)	0.509	1.03 (0.67, 1.62)	0.862
	50-59	1.28 (0.85, 1.95)	0.240	1.01 (0.58, 1.75)	0.982
	> 60	1.71 (0.99, 3.06)	0.069	1.77 (0.85, 3.68)	0.128
	P for trend per 10 years		0.024		0.131
Marital status	Married	1		1	
	Single	1.18 (0.84, 1.65)	0.329	1.35 (0.87, 2.09)	0.176
Religion	Christian	1		1	
	Muslim	0.88 (0.55, 1.40)	0.594	0.85 (0.46, 1.56)	0.595
Socioeconomic class	High	1		1	
	Middle	0.92 (0.59, 1.42)	0.710	0.72 (0.42, 1.23)	0.227
	Low	1.03 (0.66, 1.58)	0.910	0.87 (0.51, 1.46)	0.589
	P for trend		0.750		0.829
Educational level attained	Tertiary/Postgraduate	1		1	
	Primary/Secondary	0.97 (0.70, 1.34)	0.852	1.05 (0.70, 1.59)	0.803
	None	1.72 (1.09, 2.71)	0.019	1.83 (1.03, 3.26)	0.039
	P for trend		0.023		0.044
Personal income	Yes	1		1	
	No	1.38 (1.00, 1.90)	0.047	1.47 (0.98, 2.22)	0.064
Total number of children	None	1		1	

Characteristics	Categories	All women with breast symptoms Unadjusted model Ratio (95% CI)	*P* value	Women with breast cancer only Unadjusted model Ratio (95% CI)	*P* value
	1-2	0.90 (0.47, 1.72)	0.747	1.09 (0.51, 2.38)	0.808
	3-4	1.03 (0.54, 1.96)	0.932	0.94 (0.45, 1.98)	0.876
	5 or >	1.9 (01.02, 3.71)	0.042	1.90 (0.89, 4.05)	0.094
	P for trend		0.110		0.343
Breast cancer awareness					
Ever heard of breast cancer	Yes	1		1	
	No	1.15 (0.77, 1.71)	0.495	1.16 (0.68, 1.99)	0.572
Practise SBE	Yes	1		1	
	No	1.08 (0.79, 1.47)	0.627	1.10 (0.75, 1.64)	0.609
	Never heard of SBE	0.98 (0.51, 1.87)	0.944	0.83 (0.36, 1.89)	0.652
Knowledge of BC symptoms	Good	1		1	
	Fair	1.25 (0.79, 1.98)	0.337	1.23 (0.79, 1.93)	0.361
	Poor	1.51 (0.98,2.33)	0.063	1.38 (0.89, 2.11)	0.142
	P for trend		0.060		0.176
Belief in a cure for BC	Yes	1		1	
	No	1.22 (0.90, 1.65)	0.192	1.18 (0.89, 1.57)	0.243
First symptom	Breast lump	1		1	
	Other symptom	0.83 (0.52, 1.32)	0.434	0.80 (0.45, 1.44)	0.464
Health care access					
Region of residence	North Central (Abuja)	1		1	
	South East (Enugu)	1.39 (0.96, 2.01)	0.084	1.54 (1.01, 2.36)	0.047
Facility type	Tertiary	1		1	
	Secondary	0.69 (0.48, 0.99)	0.045	0.69 (0.42, 1.13)	0.140
Time taken to first provider	< 1 hour	1		1	
	≥ 1 hour-< 2 hours	0.84 (0.55, 1.28)	0.411	0.76 (0.50, 1.14)	0.176
	≥ 2 hours	1.06 (0.56, 2.00)	0.848	0.79 (0.45, 1.38)	0.408
	P for trend		0.771		0.182
No. of providers visited before diagnosis	1	1		1	
	2	1.41 (0.95, 2.10)	0.088	1.27 (0.91, 1.77)	0.165
	>= 3	2.25 (1.45, 3.49)	<0.001	1.63 (1.10, 2.41)	0.014
	P for trend		<0.001		0.014
Clinical					

Characteristics	**Categories**	**All women with breast symptoms Unadjusted model Ratio (95% CI)**	***P* value**	**Women with breast cancer only Unadjusted model Ratio (95% CI)**	***P* value**
Previous benign breast disease (BBD)	Yes	1		1	
	No	0.61 (0.42, 0.89)	0.01	0.45 (0.28, 0.73)	0.001
Previously diagnosed HTN or diabetes	Yes	1		1	
	No	1.12 (0.78, 1.60)	0.529	1.32 (0.84, 2.08)	0.220
Family history of BC	Yes	1			
	No	0.94 (0.54, 1.61)	0.809	0.86 (0.42, 1.75)	0.668
BMI	< 25 (normal weight)	1		1	
	25-29 (overweight)	0.22 (0.07, 0.72)	0.01	0.28 (0.04, 1.81)	0.180
	≥ 30 (obese)	0.20 (0.06, 0.62)	0.005	0.22 (0.03, 1.36)	0.100
	Unknown	0.21 (0.07, 0.65)	0.007	0.22 (0.03, 1.37)	0.101
	P for trend		0.990		0.987
WHR	< 0.80 (low)	1		1	
	0.8-0.85 (moderate)	1.87 (1.07,3.24)	0.027	1.72 (0.76, 3.89)	0.191
	> 0.85 (high)	1.53 (0.95, 2.45)	0.077	1.38 (0.67, 2.82)	0.380
	P for trend		0.122		0.103

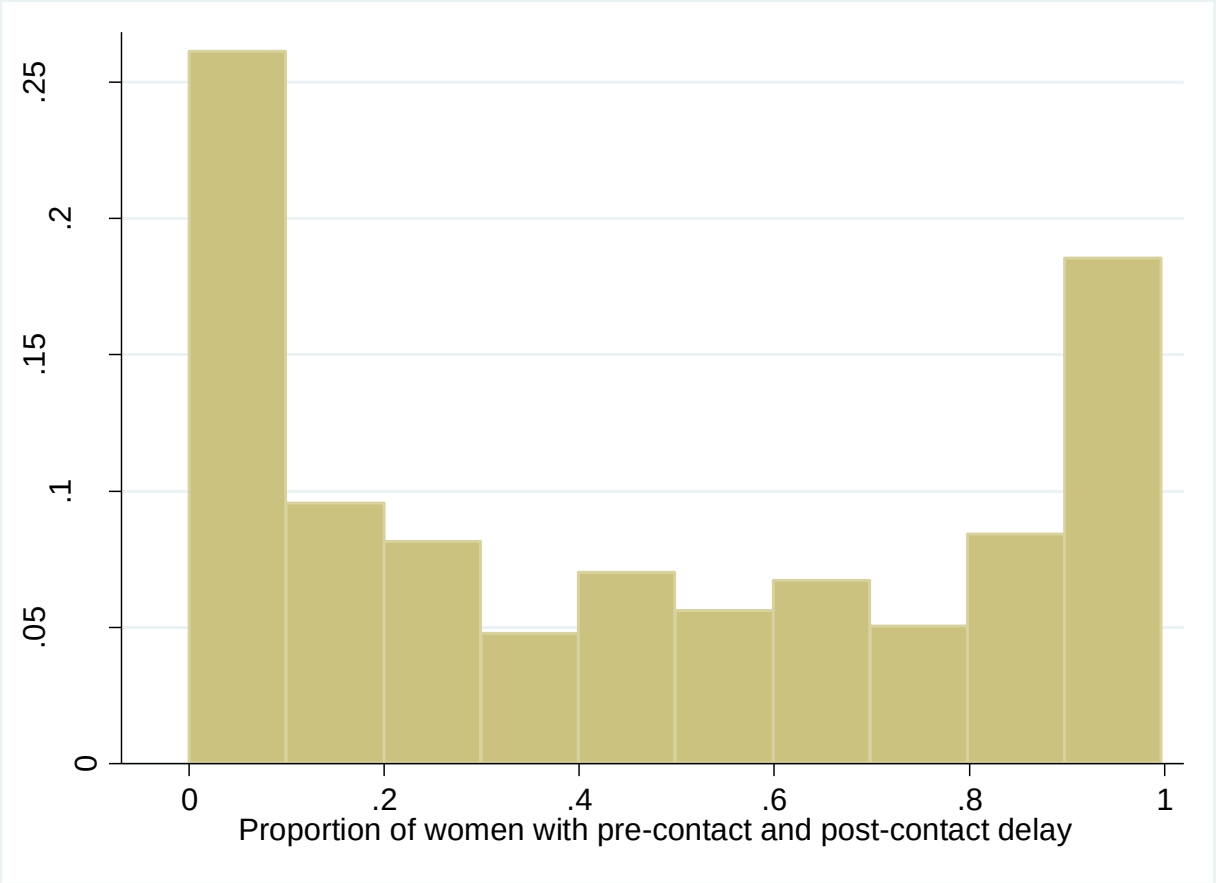
Table 4: Factors associated with post-contact delays - fully adjusted model

Patient Characteristics		All women with breast symptoms				Breast cancer			
		Unadjusted	*P* value	Fully adjusted*#	*P* value	Unadjusted	*P* value	Fully adjusted*#	*P* value
Age at diagnosis	< 40	1		1		1		1	
	40-49	1.12 (0.80, 1.58)	0.509	1.14 (0.79, 1.65)	0.470	1.03 (0.67, 1.62)	0.862	1.17 (0.74, 1.86)	0.495
	50-59	1.28 (0.85, 1.95)	0.240	1.03 (0.65, 1.64)	0.884	1.01 (0.58, 1.75)	0.982	0.91 (0.51, 1.65)	0.761
	> 60	1.71 (0.99, 3.06)	0.069	0.96 (0.49, 1.88)	0.902	1.77 (0.85, 3.68)	0.128	1.15 (0.50, 2.66)	0.731
	P for trend per 10 years		0.024		0.561		0.131		0.702
Educational level attained	Tertiary/Postgraduate	1		1		1		1	
	Primary/Secondary	0.97 (0.70, 1.34)	0.852	0.81 (0.57, 1.13)	0.216	1.05 (0.70, 1.59)	0.803	0.96 (0.63, 1.47)	0.164
	None	1.72 (1.09, 2.71)	0.019	1.16 (0.69, 1.95)	0.577	1.83 (1.03, 3.26)	0.039	1.34 (0.72, 2.50)	0.358
	P for trend		0.023		0.578		0.044		0.454
Personal income	Yes	1		1		1		1	
	No	1.38 (1.00, 1.90)	0.047	1.49 (1.04, 2.00)	0.030	1.47 (0.98, 2.22)	0.064	1.51 (0.98, 2.31)	0.060
Total number of children	None	1				1			
	1-2	0.90 (0.47, 1.72)	0.747	0.87 (0.46, 1.64)	0.681	1.09 (0.51, 2.38)	0.808	0.98 (0.47, 2.01)	0.963
	3-4	1.03 (0.54, 1.96)	0.932	1.04 (0.54, 1.94)	0.898	0.94 (0.45, 1.98)	0.876	0.89 (0.43, 1.82)	0.746
	5 or >	1.94 (1.02, 3.71)	0.042	1.88 (0.96, 3.67)	0.064	1.90 (0.89, 4.05)	0.094	1.73 (0.80, 3.74)	0.161
	P for trend		0.110		0.310		0.343		0.901
Region of residence	North Central (Abuja)	1		1		1		1	
	South East (Enugu)	1.39 (0.96, 2.01)	0.084	1.15 (0.79, 1.68)	0.466	1.54 (1.01, 2.36)	0.047	1.31 (0.83, 2.06)	0.241
Facility type	Tertiary	1		1		1		1	
	Secondary	0.69 (0.48, 0.99)	0.045	0.76 (0.52, 1.11)	0.153	0.69 (0.42, 1.13)	0.140	0.76 (0.46, 1.26)	0.285
Knowledge of BC symptoms	Good	1		1		1		1	
	Fair	1.25 (0.79, 1.98)	0.337	1.19 (0.75, 1.88)	0.459	1.23 (0.79, 1.93)	0.361	1.19 (0.75, 1.88)	0.459
	Poor	1.51 (0.98,2.33)	0.063	1.30 (0.82, 2.06)	0.270	1.38 (0.89, 2.11)	0.142	1.30 (0.82, 2.06)	0.270
	P for trend		0.060		0.166		0.176		0.391
Previous BBD	Yes	1		1		1		1	
	No	0.61 (0.42, 0.89)	0.01	0.61 (0.42, 0.89)	0.010	0.45 (0.28, 0.73)	0.001	0.43 (0.27, 0.70)	0.001
Previously diagnosed HTN or diabetes	Yes	1		1		1		1	
	No	1.12 (0.78, 1.60)	0.529	1.41 (0.97, 2.05)	0.070	1.32 (0.84, 2.08)	0.220	1.39 (0.87, 2.22)	0.164

*The variable selection for the fully adjusted model was performed by including all variables significant at the 0.1 level from Tables 3 (Unadjusted post-contact delay) and 5 (Unadjusted total delay) #Adjusted for all variables in the table

BC: breast cancer; BBD: benign breast disease; HTN: hypertension

Figure 3: Proportion of women with pre- and post-contact delays



The first five bars towards 0 represent women with the majority of their delay being post-contact and the last five bars towards 1 represent those with majority of their delay being pre-contact.

5.5.2 FACTORS ASSOCIATED WITH TOTAL DELAY

The unadjusted analyses showed total delay in all women with breast symptoms to be associated with the number of children a woman had, the type of facility visited, the increasing number of providers visited and having no previous history of benign breast disease (Table 5). In the fully adjusted analyses, the type of facility visited (OR 0.68; 95% CI; 0.51, 0.92; *p*=0.013), having no previous history of BBD (OR 0.64; 95% CI; 0.47, 0.88; *p*=0.006) remained significant with the trend for an association, with an increasing number of children being borderline significant (*p*t= 0.056) (Table 6).

In women with breast cancer, there was no association between any sociodemographic or breast cancer awareness factors and the total delay. However, the total delay in breast cancer was positively associated with factors measuring the access to health care, such as an increasing number of providers visited (*p*t=0.014), and clinical factors including having no previous history of hypertension or diabetes (OR 1.41; 95% CI 1.03, 1.94; *p*=0.032) and no previous history of BBD. (OR 0.56; 95% CI 0.39, 0.81; *p*=0.002) (Table 5). In the fully adjusted analyses in women with breast cancer, the total delay was only associated with having no previous history of BBD (Table 6).

Previous benign breast disease and delays to diagnosis

BBD was associated with both post-contact and total delays in women with all symptoms and in those with breast cancer, in both the unadjusted and the fully adjusted analyses (Tables 3-6). Among all women with breast symptoms, the median (IQR) post-contact delay (months) was 2.67, (0.7-8.2) in those with no previous history of BBD, and 5.19 (2.0-15.6) in those with a previous history of BBD. Similarly, the median (IQR) total delay (months) was 7.6 (3.2-17.0) months in women with no previous BBD and 13.5 (5.6-28.6) in those with a previous history of BBD.

Barriers to seeking and obtaining care

The most common reason given by women for the delay in seeking care was believing that it was not a serious problem (58.4% of all women with symptoms; 64.1% of women with breast cancer) (Table 7). Fear of a diagnosis was reported by 11.8% and 10.5% of all women with symptoms and of those with breast cancer, respectively. Financial constraints were mentioned by 10% of women with symptoms and 11% of those with breast cancer. Only 1.4% of women with breast symptoms and 2.2% of women with breast cancer attributed the delay to their belief in traditional medicine (Table 7).

Sensitivity Analyses

In sensitivity analyses conducted among women with breast cancer, six women with stage IV breast cancer and 17 women with stage III breast cancer who experienced total delay of < 3 months, likely to be implausible delay times, were excluded from the analyses. However, similar results to the previous findings were obtained. In the fully adjusted analysis, having 3 or more children remained the only factor significantly associated with pre-contact delay in women with breast cancer (OR 2.37; 95% CI1.02, 5.52 p=0.046). Post-contact delay remained associated with having no previous history of benign breast disease (OR 0.35; 95% CI 0.20, 0.59; p<0.001). Total delays in women with breast cancer also remained associated with having no previous history of benign breast disease (OR 0.52; 95% CI 0.36, 0.76 p=0.001).

Figure 4: Unadjusted odds ratio of late stage (III/IV) at diagnosis for total delay, post- contact delay, number of providers visited and time taken to first provider

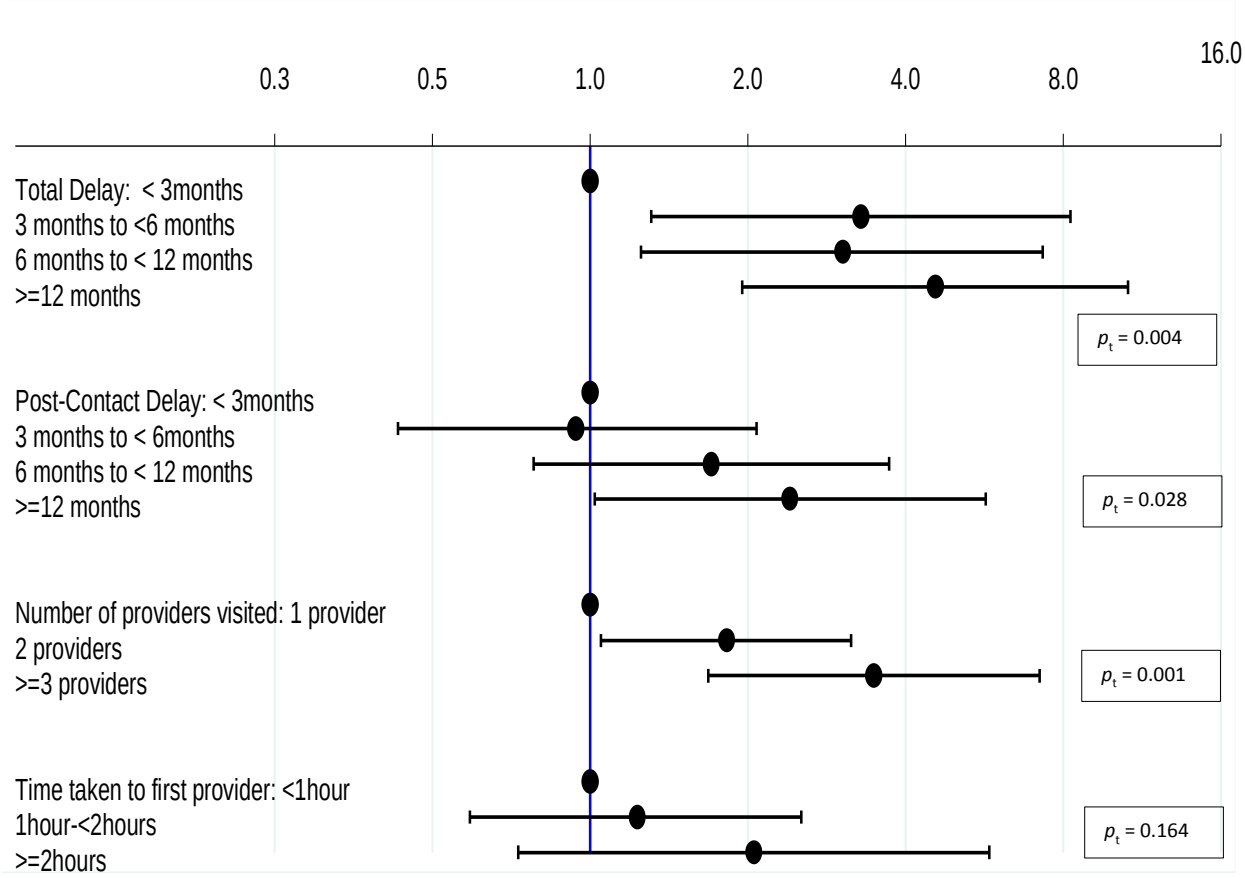


Table 5: Factors associated with total delay in Nigerian women – unadjusted model

Characteristics	**Categories**	**All women Unadjusted model Ratio (95% CI)**	***P* value**	**Breast cancer Unadjusted model Ratio (95% CI)**	***P* value**
Sociodemographic					
Age at diagnosis	< 40	1		1	
	40-49	1.11 (0.84, 1.48)	0.459	1.22 (0.88, 1.70)	0.227
	50-59	0.90 (0.65, 1.26)	0.545	0.78 (0.53, 1.15)	0.204
	> 60	1.11 (0.72, 1.71)	0.631	1.34 (0.81, 2.19)	0.252
	P for trend per 10 years		0.799		0.464
Marital status	Married	1		1	
	Single	1.07 (0.82, 1.40)	0.608	0.94 (0.68, 1.28)	0.681
Religion	Christian	1		1	
	Muslim	0.89 (0.62, 1.27)	0.515	0.75 (0.48, 1.16)	0.189
Socioeconomic class	High	1		1	
	Middle	0.99 (0.69, 1.42)	0.973	0.73 (0.48, 1.09)	0.121
	Low	0.91 (0.64, 1.29)	0.590	0.76 (0.52, 1.12)	0.163
	P for trend		0.491		0.271
Educational level attained	Tertiary/Postgraduate	1		1	
	Primary/Secondary	0.91 (0.70, 1.18)	0.475	1.07 (0.79, 1.45)	0.936
	None	1.26 (0.88, 1.81)	0.207	1.24 (0.82, 1.89)	0.513
	P for trend		0.209		0.293
Personal income	Yes	1		1	
	No	1.13 (0.87, 1.47)	0.359	1.22 (0.90, 1.66)	0.200
Total number of children	None	1		1	
	1-2	0.93 (0.55, 1.55)	0.775	1.02 (0.57, 1.82)	0.937
	3-4	1.17 (0.70, 1.96)	0.540	1.24 (0.71, 2.17)	0.453
	5 or >	1.35 (0.81, 2.26)	0.255	1.37 (0.77, 2.42)	0.279
	P for trend		0.015		0.362
Breast cancer awareness					
Ever heard of breast cancer	Yes	1		1	

Characteristics	Categories	All women Unadjusted model Ratio (95% CI)	*P* value	Breast cancer Unadjusted model Ratio (95% CI)	*P* value
	No	1.09 (0.80, 1.50)	0.586	1.01 (0.69, 1.46)	0.978
Practise SBE	Yes	1		1	
	No	1.09 (0.86, 1.40)	0.470	1.17 (0.88, 1.56)	0.290
	Never heard of SBE	1.41 (0.81, 2.46)	0.222	1.34 (0.71, 2.51)	0.367
Knowledge of BC symptoms	Good	1		1	
	Fair	1.00 (0.67, 1.45)	0.986	1.23 (0.79, 1.94)	0.817
	Poor	1.22 (0.86, 1.73)	0.274	1.38 (0.90, 2.11)	0.322
	P for trend		0.206		0.176
Belief in a cure for BC	Yes	1		1	
	No	1.04 (0.83, 1.31)	0.709	1.18 (0.89, 1.57)	0.243
First symptom	Breast lump	1		1	
	Other symptom	0.93 (0.64, 1.37)	0.728	1.05 (0.68, 1.63)	0.820
Health care access					
Region of residence	North Central (Abuja)	1		1	
	South East (Enugu)	1.20 (0.87, 1.59)	0.281	1.26 (0.96, 1.72)	0.157
Facility type	Tertiary	1		1	
	Secondary	0.66 (0.50, 0.87)	0.004	0.90 (0.63, 1.28)	0.544
Time taken to first provider	< 1 hour	1		1	
	≥ 1 hour - < 2 hours	0.84 (0.60, 1.18)	0.319	0.76 (0.50, 1.14)	0.176
	≥ 2 hours	0.98 (0.61, 1.57)	0.924	0.79 (0.45, 1.38)	0.408
	P for trend		0.651		0.562
No. of providers visited before diagnosis	1	1		1	
	2	1.42 (1.07, 1.88)	0.015	1.27 (0.91, 1.77)	0.165
	≥ 3	1.90 (1.36, 2.65)	<0.001	1.63 (1.10, 2.40)	0.014
	P for trend		<0.001		0.014
Clinical					
Previous benign breast disease (BBD)	Yes	1		1	

Characteristics	**Categories**	**All women Unadjusted model Ratio (95% CI)**	***P* value**	**Breast cancer Unadjusted model Ratio (95% CI)**	***P* value**
	No	0.61 (0.45, 0.83)	0.002	0.56 (0.39, 0.81)	0.002
Previously diagnosed HTN or diabetes	Yes	1		1	
	No	1.24 (0.94, 1.65)	0.131	1.41 (1.03, 1.94)	0.032
Family history of BC	Yes	1		1	
	No	0.89 (0.58, 1.38)	0.615	1.04 (0.62, 1.72)	0.891
BMI	< 25 (normal weight)	1		1	
	25-29 (overweight)	0.72 (0.31, 1.70)	0.452	0.54 (0.16, 1.81)	0.312
	≥ 30 (obese)	0.60 (0.25, 1.41)	0.237	0.46 (0.14, 1.53)	0.202
	Unknown	0.52 (0.22, 1.23)	0.138	0.40 (0.19, 1.34)	0.136
	P for trend		0.140		0.535
WHR	< 0.80 (low)	1		1	
	0.8-0.85 (moderate)	1.37 (0.88, 2.12)	0.159	1.33 (0.76, 2.32)	0.311
	> 0.85 (high)	1.23 (0.85, 1.79)	0.268	1.21 (0.75, 1.96)	0.431
	P for trend		0.852		0.237

BC: breast cancer; HTN: hypertension; BBD: benign breast diseases; BMI: body mass index; WHR: waist-hip ratio; CI: confidence interval

Table 6: Factors associated with the total delay - fully adjusted model

Patient Characteristics		All women with breast symptoms				Breast cancer			
		Unadjusted	*P* value	Fully adjusted*#	*P* value	Unadjusted	*P* value	Fully adjusted*#	*P* value
Age at diagnosis	< 40	1		1		1		1	
	40-49	1.11 (0.84, 1.48)	0.459	1.21 (0.89, 1.63)	0.226	1.22 (0.88, 1.70)	0.227	1.37 (0.96, 1.96)	0.079
	50-59	0.90 (0.65, 1.26)	0.545	0.89 (0.61, 1.28)	0.523	0.78 (0.53, 1.15)	0.204	0.84 (0.55, 1.28)	0.429
	> 60	1.11 (0.72, 1.71)	0.631	0.89 (0.54, 1.46)	0.647	1.34 (0.81, 2.19)	0.252	1.41 (0.81, 1.46)	0.223
	P for trend per 10 years		0.799		0.702		0.464		0.702
Educational level attained	Tertiary/Postgraduate	1		1		1		1	
	Primary/Secondary	0.91 (0.70, 1.18)	0.475	0.85 (0.64, 1.13)	0.268	1.07 (0.79, 1.45)	0.936	0.99 (0.63, 1.57)	0.756
	None	1.26 (0.88, 1.81)	0.207	1.13 (0.75, 1.71)	0.566	1.24 (0.82, 1.89)	0.513	1.13 (0.69, 1.31)	0.980
	P for trend		0.209		0.481		0.293		0.481
Personal income	Yes	1		1		1		1	
	No	1.13 (0.87, 1.47)	0.359	1.21 (0.92, 1.58)	0.170	1.22 (0.90, 1.66)	0.200	1.23 (0.89, 1.70)	0.170
Total number of children	None	1		1		1		1	
	1-2	0.93 (0.55, 1.55)	0.775	0.91 (0.55, 1.50)	0.701	1.02 (0.57, 1.82)	0.937	1.04 (0.59, 1.83)	0.889
	3-4	1.17 (0.70, 1.96)	0.540	1.13 (0.68, 1.88)	0.631	1.24 (0.71, 2.17)	0.453	1.22 (0.70, 2.12)	0.478

	5 or >	1.35 (0.81, 2.26)	0.255	1.32 (0.77, 2.27)	0.307	1.37 (0.77, 2.42)	0.279	1.36 (0.76, 2.46)	0.300
	P for trend		0.015		0.056		0.362		0.689
Region of residence	North Central (Abuja)	1		1		1		1	
	South East (Enugu)	1.18 (0.87, 1.59)	0.281	1.00 (0.73, 1.36)	0.977	1.26 (0.92, 1.72)	0.157	1.23 (0.88, 1.73)	0.220
Facility type	Tertiary	1		1		1		1	
	Secondary	0.66 (0.50, 0.87)	0.004	0.68 (0.51, 0.92)	0.013	0.90 (0.63, 1.28)	0.544	0.98 (0.67, 1.44)	0.927
Knowledge of BC symptoms	Good	1				1			
	Fair	1.00 (0.67, 1.45)	0.986	0.99 (0.68, 1.44)	0.944	1.00 (0.67, 1.45)	0.986	1.23 (0.78, 1.94)	0.370
	Poor	1.22 (0.86, 1.73)	0.274	1.16 (0.79, 1.69)	0.449	1.22 (0.86, 1.73)	0.274	1.32 (0.84, 2.06)	0.223
	P for trend		0.206		0.246		0.206		0.246
Previous BBD	Yes	1		1		1		1	
	No	0.61 (0.45, 0.83)	0.002	0.64 (0.47, 0.88)	0.006	0.56 (0.39, 0.81)	0.002	0.54 (0.37, 0.78)	0.001
Previously diagnosed HTN or diabetes	Yes	1		1		1		1	
	No	1.24 (0.94, 1.65)	0.131	1.32 (0.98, 1.78)	0.069	1.41 (1.03, 1.94)	0.032	1.32 (0.95, 1.86)	0.100

BC: breast cancer; BBD: benign breast diseases; HTN: hypertension; BMI: body mass index; WHR: waist-hip ratio; CI: confidence interval

*The variable selection for the fully adjusted model was performed by including all variables significant at the 0.1 level from Tables 3 (Unadjusted post-contact delay) and 5 (Unadjusted total delay) #Adjusted for all variables in the table

Table 7: Self-reported reasons for delays in seeking care given by the participants in the NIBBLE study

Reasons for delays		**Total number of responses in all women with breast symptoms N (%)**	**Total number of responses in all women with breast cancer N (%)**
Total number of responses received		279 (100)	181 (100)
Poor knowledge of BC	Ignorance of the nature of illness (did not think it was a serious problem)	163 (58.4)	116 (64.1)
Fear	Fear of diagnosis and treatment (possibility of a cancer diagnosis)	33 (11.8)	19 (10.5)
Financial constraints	Limited financial resources (lack of resources, no money for transportation to hospital)	28 (10.0)	20 (11.0)
No permission	Partner/Husband did not give their consent	2 (0.7)	1 (0.6)
Other commitments	No one to look after children, job, exams, too busy, family member sick	6 (2.1)	6 (3.3)
Health care system related	Doctors' strike	3 (1.0)	2 (1.1)
Belief in traditional medicine	Receiving traditional treatment	4 (1.4)	4 (2.2)
Others	Psychological issues, pregnancy, lack of knowledge on how to access care, thought it was a spiritual attack	41 (14.6)	13 (7.2)

*Categories are not mutually exclusive as some women gave more than one response

5.6 DISCUSSION

In this chapter, I identified the extent of the pre-, post-contact and total delays in Nigerian women and examined the sociodemographic, breast cancer awareness, health care access and clinical determinants of these delays in all women who presented with breast symptoms and a subset of those women with histologically confirmed breast cancer. The findings showed that on average, there was a total (median (IQR)) delay of 7.8 (3.3-18.7) months from when a symptom was initially noticed to when a definitive diagnosis was made. The study identified having no personal income and a previous history of BBD as factors positively associated with the post-contact delay in all women with breast symptoms and in the women with breast cancer. The total delay was inversely associated with contact with a secondary health facility rather than a tertiary facility and no previous history of BBD in all women with symptoms. The pre-contact delay was only associated with having 3-4 children compared with having none in women with breast cancer.

The median total delay found in this study was comparable to reports from various African countries including Nigeria (60), Uganda (79), Libya (232) and South Africa (77), but it was reported to be significantly longer than the total delays reported in HICs such as Canada (73), Germany (75) and the USA .(76) In contrast to the HICs where less than 20% of women report a total delay of over 3 months (75), only 18.1% of all women with symptoms and 12.4% of women with breast cancer in this study sought treatment within 3 months of noticing a symptom. This finding is similar to the reports from Malaysia (233) and Nigeria where ~70% of women were diagnosed after a delay of over 3 months (60).

An association between diagnostic delay and stage at diagnosis has been consistently confirmed in the literature.(79, 220). Delays have been reportedly found to be associated with later stage at diagnosis in studies conducted in various countries including Thailand

(72), Uganda (79) and Rwanda (78) and in a systematic review by Richards *et al*. (220). In my PhD research, as expected, both post-contact and total delays were significantly associated with higher odds of a late stage disease. Women who visited 2 or more providers before a diagnosis was confirmed, also had higher odds of late stage (III/IV) disease, similar to results by Pace *et al*. in Rwanda (78). There was no association between the age at diagnosis and the aforementioned delays in this study, as has been reported by other authors (79).

Women who did not have a personal income were more likely to delay seeking help than those who did. A similar finding has been reported in the case of patient delays by Facione *et al.* in the United States (234). In unadjusted analyses, although a significant trend for longer post-contact delay was found for women with no education compared to those with tertiary education in all women and in women with breast cancer, this finding did not persist in the fully adjusted model. Surprisingly, there was no association between educational level and the total delay in this study, in line with findings from Uganda (79). Interestingly, women with poor financial ability rather than no education or poor knowledge of breast cancer symptoms and causes were more likely to experience post-contact delays. This finding suggests that even among women with a higher educational level or with previous knowledge of breast cancer, the absence of the financial ability to seek care may still result in a significant proportion of these women reporting diagnostic delays.

Women who initially sought care at secondary facilities were less likely to delay than those who did so at tertiary facilities. Possibly, women first seek help at secondary facilities and are subsequently referred to a tertiary facility. In some cases there may be a significant delay following the initial contact with the health care system that may be an interplay of patient and system level factors, thereby prolonging the time following the referral, and prior to the presentation at the tertiary facility.

A distinct group of women with a previous history of BBD were identified, who were more likely to delay (post-contact and total delays) compared to the women with no previous history of BBD. This was an unexpected finding, as one would reason that women with a previous history of BBD have had previous contact with the health care system and would therefore be better at navigating the system when they notice another breast symptom and thus urgently seek care. This contrasted with what was found in this study. Some studies that have investigated this matter did not find an association between previous BBD and delays (79). However, two precedents were found in the literature, where women with previous BBD became complacent about breast symptoms and consequently reported longer delays than women with no previous breast symptoms (72, 77).

Pre-contact/patient delays and post-contact/provider delays were both important components of the total delay, as a bimodal trend was observed showing a large proportion of women who themselves delay a long time and strongly need education on breast awareness and seeking adequate help. Another similarly large group of women who are delayed in the system for a long time and need education on pushing for referrals was also identified. This group of women are those for whom the system is failing, and institutional bottlenecks as well as a lack of clear referral pathways may contribute to their delay. Deciphering the characteristics of these two groups of women will help target the different interventions needed to shorten delay times.

The most important reasons reported by women for their delays in seeking help for breast symptoms were the belief that the symptom was not a serious problem, fear of a diagnosis of breast cancer and financial constraints to pay for the diagnosis and treatment. These findings are similar to the reports collated from other studies in Nigeria (81, 222), Uganda (79) and South Africa (77).

This is the first multi-centre study to examine the determinants of diagnostic delays in Nigerian women. A PubMed search identified only 5 previous studies to date that had characterised delays in Nigerian women (60, 81, 82, 139, 222). This study is therefore an important contribution to the scarce literature in this area. Secondly, detailed information was collected in the questionnaire to enable the characterisation of a woman's journey from her first symptom to the first 6 care providers visited.

An important limitation of this study is the possibility that women may not be able to accurately recall past events related to their breast disease. It has been shown that women do not provide an accurate account of the beginning of their breast symptoms (216). Consequently, this may affect the measurement of patient or pre-contact delays. However, in this study, the research assistants employed means of using significant life events and calendar prompts to obtain information from women who did not initially recall when the first symptom was noticed, thereby minimising recall errors. The extent to which such errors were random (non-differential) or systematic (differential, e.g. by educational level) is not known. Secondly, owing to concerns of 'social desirability', women might have under-estimated delays or might have avoided mentioning previous visits to traditional or alternate care providers, due to concerns about how these would be interpreted by the interviewer (216). Although previous studies have reported significant proportions of Nigerian women visiting traditional or alternate care providers (60), we did not observe this in our study. Additionally, the enrolment interview was conducted at the time when a woman was clinically diagnosed and understandably, some women were not emotionally ready to provide a clear account of their symptoms or their diagnostic journey. Finally, this study included only the women who sought care at a health care facility for their symptoms, therefore the findings may not be generalisable to patients with breast symptoms who never reach a health care facility.

5.7 CONCLUSIONS

This study confirms previous reports that long delays to diagnosis exist in Nigerian women with breast cancer and that these delays were associated with higher odds of a late stage (III/IV) disease. Diagnostic delays, through their impact on tumour progression, can significantly affect breast cancer survival in SSA. Women should be educated on the need to seek help once a symptom is noticed and health care practitioners should be encouraged to make prompt referrals in order to reduce provider delays in this setting. By understanding the determinants of delay, it may be possible to develop targeted interventions to reduce delays and improve breast cancer survival in SSA.

CHAPTER 6

6.1 DISCUSSION AND CONCLUSIONS

The objectives of this PhD thesis were, as stated in Chapter 1, to: 1. Systematically review the published literature on the stage at diagnosis of breast cancer in sub-Saharan Africa and identify the reasons for variations in the stage at diagnosis across this region; 2. Design and implement a multi-centre study at 6 government hospitals in Nigeria; and 3. Identify the sociodemographic, breast cancer awareness, health care access and clinical determinants of (i) Stage at breast cancer diagnosis and (ii) Diagnostic delays in Nigerian women with breast cancer. This chapter provides a critical assessment of the major findings presented in this thesis, and reviews the implications for research and policy in SSA.

6.2 SUMMARY AND SYNTHESIS OF RESEARCH FINDINGS

This PhD thesis focused on breast cancer, the most common female cancer worldwide and one of the most common types in SSA, and a type of cancer of significant global health importance. A major contribution made to the literature has been to provide a clearer understanding of the magnitude and reasons for the variation in the percentage of the late stage diagnosis of breast cancer and its associated factors in the region. Additionally, the determinants of late stage at diagnosis and of diagnostic delays in Nigeria have been described to provide insights on how downward stage-migration of breast cancer can be achieved, including reductions in the delays in a woman's journey to diagnosis.

6.2.1 Stage at diagnosis of breast cancer in sub-Saharan Africa

The first objective sought to review the literature on the stage at diagnosis of breast cancer in SSA to examine the relevant trends over time and to identify the reasons for variations across the region. A systematic review and a meta-analysis were undertaken in order to achieve this objective, as previously reported in Chapter 2. Overall, 83 studies from 17 SSA countries were identified. This review highlighted the limited information available on the stage at diagnosis in the region, particularly from middle Africa where no published studies were identified, and the limited data available from Southern Africa in recent years, where only 2 studies have been published after year 2000. Furthermore, we did not identify any studies from population based cancer registries. Secondly, the results revealed that majority (77%) of women with breast cancer in SSA were diagnosed at advanced stages, although South African non-black women reported a significantly better stage at diagnosis than black women in South Africa and from other SSA regions. A key finding of this review was the significant inter-study variation in the percentage of late-stage disease at diagnosis across SSA. However, the reasons for this variation were somewhat unclear, as no clear differences were seen in the study design, age at breast

cancer diagnosis, the type of health facility visited or the staging methods used. The only exceptions were the associations with the degree of urbanisation and the calendar time. Studies conducted in mixed settings (urban and rural settings) were more likely to report a later stage at diagnosis as opposed to the studies conducted in urban settings only. Additionally, the stage at diagnosis improved in the region over time, comparing the time-period starting from year 2000 and later to the time-period including year 1980 or earlier. Nevertheless, and despite improvements having been made over time, the percentage of late stage at diagnosis in SSA in 2010 was still higher than it was for US white and black women 40 years ago, i.e. prior to the introduction of mammographic screening.

6.2.2 Determinants of the stage at diagnosis of breast cancer in Nigerian women

In order to investigate the third objective of my PhD thesis, I designed and implemented a multi-centre case control study of breast cancer in Nigeria, namely the Nigerian Integrative Epidemiology of Breast Cancer Study (NIBBLE). Within this larger study, I studied the factors affecting the stage at diagnosis of breast cancer cases (objective 3(i) of my PhD), i.e. women diagnosed with histologically confirmed invasive breast cancer and recruited within the initial 2.5-year period of the NIBBLE study. I examined four categories of factors - i.e. sociodemographic, breast cancer awareness, health care access and clinical factors - and how these affected the stage at diagnosis of breast cancer in Nigerian women (Chapter 4). Findings showed that women with a lower educational level, those who did not believe in a cure for breast cancer, were Christian and resided in rural areas, were more likely to be diagnosed at a later stage. There was no association between later stage and the age at diagnosis or clinical characteristics such as tumour grade and oestrogen receptor status. In line with the findings from other SSA studies, the study showed that Nigerian women with breast cancer are diagnosed, on average, at a younger age than women in western countries, reflecting the much younger age structure of the SSA populations.

A higher percentage of late stage at breast cancer diagnosis in SSA populations could occur as a result of breast cancer being particularly aggressive in these populations or because of diagnosis delays. The findings presented in Chapter 4 suggest that sociodemographic, breast cancer awareness and health care access factors, rather than the clinical factors associated with increased tumour growth rates, are the key determinants of later stage at diagnosis in Nigerian women.

6.2.3 Diagnostic delays and its associated factors in Nigerian women with breast cancer

The objective 3(ii) of my PhD, which sought to investigate a woman's journey from the first reported symptom to a confirmed diagnosis of breast cancer, was also examined using data from the NIBBLE study conducted on all women who presented with breast symptoms, irrespective of whether the final diagnosis was breast cancer or BBD. Detailed information on a woman's diagnostic trajectory was collected using a pre-tested and piloted structured questionnaire (Chapter 3). The findings from this analysis showed that there were significant delays from the first self-reported symptoms to the diagnosis of breast cancer or BBD. On average, all women with breast symptoms took approximately 3 months from their first reported symptom to presentation at any health care provider (including alternative providers, such as traditional and spiritual healers). From their first contact with a care provider, it took another 3 months for a confirmed diagnosis of breast cancer or BBD to be made. The total delay in all women with symptoms was 7.8 months. On average, women visited two care providers before a diagnosis was made, although the number of providers visited ranged from 1-6. There was also an increasing trend of increased delay with a higher number of providers visited. Women who were diagnosed in stages III/IV self-reported longer delays as opposed to women in stages I/II. The factors associated with delays to diagnosis were examined using the conceptual framework described in Chapter 1. Sociodemographic, breast cancer awareness, health care access

and clinical factors were investigated and their associations with the pre-, post-contact and total delays were subsequently examined. Findings showed that pre-contact delay in women with breast cancer was only associated with one factor, i.e. having 3 or more children. Post-contact delays were associated with a lack of a personal income and inversely associated with having no previous history of BBD while the total delay was inversely associated with visiting a secondary facility and no having previous history of a benign breast disease. The three most important self-reported reasons for delays to the first presentation at a care provider included ignorance/not believing it was a serious problem, fear of a cancer diagnosis and financial constraints.

6.3 CONTRIBUTION OF THESIS TO CURRENT KNOWLEDGE

One of the most significant contributions of this thesis to the current knowledge in the field is the publication of the first comprehensive systematic review and meta-analysis of the stage at diagnosis of breast cancer in sub-Saharan Africa (Chapter 2) (133). Prior to the publication of this review, there had been no detailed synthesis of the literature on stage at diagnosis, a crucial prognostic indicator of breast cancer outcomes in SSA. This review provides an original framework to assess the quality of the previous studies on stage at diagnosis in SSA. Although we found a wide range of estimates in the percentage of late stage at diagnosis across the region, and the reasons not being entirely clear, we did note that the stage at diagnosis was better in non-black African populations in SA than in black populations in SA and across East and Western Africa. Secondly, we found some improvements in the stage at diagnosis of breast cancer over time.

A second important contribution of this thesis is the finding on the determinants of stage at diagnosis of breast cancer in Nigerian women. This is the first study that has investigated the determinants of later stage at diagnosis of breast cancer in Nigerian women. These findings stating that breast cancer awareness and health care access

factors, which are amenable to intervention, rather than intrinsic tumour characteristics and clinical factors, are the major determinants of stage at diagnosis in Nigerian women delivers a clear message on what factors need to be addressed by the non-governmental and governmental organisations involved in breast cancer control in Nigeria and SSA. By providing a long-term perspective on possible policy and research interventions, this thesis demonstrates the importance of developing research interventions based on evidence derived from conducting epidemiological studies in specific populations.

Thirdly, while previous studies have investigated the factors associated with the delays to diagnosis in women with breast cancer in Nigeria, none qualified as a multi-centre study in two distinct regions of the country. These findings identify a distinct group of women, with a previous history of benign breast diseases as a target group when developing relevant interventions to reduce diagnostic delays in SSA women. While one would reason that these women have had previous contact with the health care system for a breast lump, and therefore should seek treatment early, this is not what these findings suggest. It does appear that women with a previous history of BBD develop a false sense of security and believe that because a previous breast lump was non-cancerous, any subsequent breast lumps do not require serious attention. This is similar to the findings of Poum *et al.* in Thailand (72).

6.4 STRENGTHS AND LIMITATIONS OF THE THESIS

The strengths and limitations of the specific methods used for each of the study objectives have been discussed in the previous relevant chapters. This section focuses on the strengths and limitations of the entire thesis project.

Study setting/location

The choice of Nigeria as a study location could be considered as a strength of this research project. Firstly, Nigeria is SSA's most populous country with a population of well over

180 million inhabitants which is more than half of the population of Western Africa. Therefore, any information on breast cancer from Nigeria is significant for policy not just for the country but for SSA. Secondly, Nigeria has one of the highest age-standardised incidence rates of breast cancer in SSA, contributing 15% to the estimated 681,000 new cases of breast cancer that occurred in Africa in 2008. Thirdly, my close affiliation with the research department of the Institute of Human Virology Nigeria afforded an increased level of access, and facilitated the recruitment of well-trained field staff and an experienced data manager that might have been difficult to achieve elsewhere (Chapter 3).

Design and implementation of the research study

This PhD thesis provided the opportunity to design and implement from the beginning, a multi-centre case-control study of breast cancer in Nigeria. An important strength of this study was the opportunity to collect primary data in the Nigerian population and develop a new dataset that can be used in future research studies on breast cancer in Nigeria where other research questions can be investigated. The case-control design is most commonly used with breast cancer given that breast cancer is a seemingly rare disease. While this PhD thesis was primarily focused on breast cancer cases and the data analysed pertained to women with breast symptoms or histologically confirmed breast cancer, further research could be conducted using both cases and controls.

Limitations

As with any research endeavour, particularly one conducted in SSA, there were challenges and several limitations to the research described in my thesis. An important limitation of this study was the inability to reach the sample size of the cases initially calculated for this study. This was due to several long intervals of strike actions over the course of the research project. Secondly, following the initial training of field staff at the

initiation of the study, field staff had to undergo consistent retraining owing to the high turn-over of staff members working on the project.

6.5 IMPLICATIONS FOR RESEARCH, POLICY AND PRACTICE

This section considers the research, policy and practice implications of this work, and the generalisability of my findings to other SSA settings.

6.5.1 Implications for research

The findings presented in this thesis highlight the next steps for future research on stage at diagnosis and downward stage-migration of breast cancer in SSA. Firstly, the systematic review and meta-analysis revealed the dearth of information on stage at diagnosis of breast cancer from Middle Africa, Southern Africa and from the population-based cancer registries (PBCRs). Following the publication of this review, only one study has been done to report on the stage at diagnosis of breast cancer using data from the PBCR, and this study was conducted in Middle Africa (235). This research highlights the need for more studies from these SSA regions. More population-based studies in collaboration with cancer registries are needed on the stage at diagnosis of breast cancer in SSA. Secondly, the paper on the determinants of the stage at diagnosis of breast cancer in Nigerian women is the first paper to examine these factors in the Nigerian setting. Given that Nigeria is a large country with differences in religion, education and culture across the country, it would be important to replicate this study in other regions of the country where the percentage of late stage diagnosis and its determinants may differ from the findings reported in North Central and South Eastern Nigeria. An important subsequent step would be to estimate cancer survival in Nigerian women with breast cancer. I had originally planned to include this component in my PhD study but the smaller than anticipated sample size and the delays in patient recruitment caused by reasons outside my control (e.g. due to strikes) precluded this. However, considering that

the women in this study and their relatives gave consent to be contacted at a future date, it would be useful to follow-up these women and describe survival in association with stage at diagnosis in Nigerian women.

Research is also required in order to assess the impact of the interventions that aim to achieve downward stage-migration in SSA.

6.5.2 Implications for policy and practice

Policy Implications

This research study has important implications for policy and practice. National efforts are required to increase awareness about the benefits of early detection and downward stage-migration even in the absence of screening. This thesis highlights the evidence in the literature that suggests that HICs, such as the USA, achieved stage-migration to a lower stage at diagnosis prior to the introduction of population-wide mammographic screening by means of an increase in breast cancer awareness and early detection of the symptomatic disease through BSE and CBE. However, a low educational level and poor knowledge of breast cancer symptoms and the signs, which were important findings in this study, may indicate a limited awareness of the benefits of BSE and CBE. There is therefore a need for synchronised awareness campaigns organised by the government, health care providers and organisations working in cancer prevention and control. Information on breast health and how to readily identify symptoms and who to contact in those circumstances should constitute the 'standard of care' and should be integrated into existing programmes or clinics such as HIV and reproductive health clinics. Health professionals at the primary and secondary health care level should be encouraged to incorporate CBE into their practice and to ensure quick referrals for any suspicious symptoms.

Practice Implications

Interventions that aim to achieve downward stage migration of breast cancer in SSA have been proven successful in many settings within and outside SSA, as previously discussed in Chapter 4. However, there has been no previous intervention of this type implemented in Nigeria.

The positive association found between a later stage at diagnosis with the increasing number of care providers visited and the delays to diagnosis indicates that the health care system and factors that influence a woman's journey from her first reported symptom to when she seeks care and is informed of her diagnosis need to be addressed. This study identified the important reasons why women delay in seeking help for their breast symptoms. Most women did not consider their breast problem to be serious and hoped it would heal on its own. We found that on average women visit 2-3 providers before a diagnosis is made. This is in contrast with the findings from Rwanda, where women visit 4-5 providers on average. This finding suggests that when a woman makes contact with the health care system and is referred to a centre for further management, there may be factors outside the health care system, such as financial capability and inability to find childcare while she is away from home that could result in the median total time delay of ~7 months found in this study. In our study, we identified a distinct group of women with a previous history of benign breast disease who were more likely to delay seeking help than women with no previous breast symptoms, similar to the findings in Thailand by Poum *et al*. (72). Interventions seeking to shorten delay times should target this group of women who may have a false sense of security and belief that they have a lower cancer risk owing to their previous history of benign breast disease.

6.6 CONCLUSIONS

Breast cancer remains a significant global health issue in sub-Saharan Africa. This thesis set out to review the literature on the stage at diagnosis of breast cancer across SSA and to investigate the reasons for variations across the region. Additionally, stage at diagnosis and the factors associated with stage and delays to diagnosis were investigated in SSA's most populous country, Nigeria. It was found that there is a vast variation in the percentage of late stage breast cancer across SSA with an improvement in stage at diagnosis over time. These findings also highlight the significant difference in late stage at diagnosis between women in SSA and US black and white women, with stage at diagnosis still being higher in SSA in 2010 than it was 40 years before in the US. The factors identified in this thesis as determinants of stage at diagnosis and diagnostic delays in Nigerian women are breast cancer awareness factors and health care access factors, which are amenable to intervention, rather than intrinsic clinical factors. This thesis has demonstrated the need for research into stage at diagnosis from certain regions of Africa where information is lacking, and offered recommendations for strategies aimed at improving stage at diagnosis with the goal of achieving better breast cancer outcomes and survival in the region.

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APPENDICES

APPENDIX 1: SYSTEMATIC REVIEW PROTOCOL

Title: Stage at Diagnosis of Breast Cancer in Sub-Saharan Africa: A Systematic Review and Meta-analysis

Reviewers: Elima Jedy-Agba, Valerie McCormack and Isabel dos-Santos-Silva

Background
Breast cancer is by far the most common cancer affecting women worldwide(230). In 2012, there were 1.67 million new cases of breast cancer constituting 25% of all cancers worldwide of which 883,000 new cases occurred in less developed regions(5). Breast incidence rates in sub-Saharan Africa (SSA) are increasing, and although they remain among the lowest in the world, mortality rates from this disease are as high as those in high-income countries due to poor survival.

Stage at diagnosis is a major determinant of survival from breast cancer, with early disease (stages I/II) being associated with a better prognosis than late stage disease (stages III/IV). In high-income countries mortality rates from breast cancer have declined sharply in recent decades due to earlier stage at diagnosis, better diagnosis and improved treatment. However, in SSA where systems and facilities for accurate and timely diagnosis are scarce, the majority of breast cancer patients present late and are diagnosed at an advanced stage(90-96), in part contributing to poor outcomes(87, 97, 98). Variations in stage of breast cancer at diagnosis across SSA, and over time in some of its settings(30), have been previously reported in individual settings(47, 87, 89, 90, 94) but, to our knowledge, have not been examined systematically across SSA.

In this study, we will systematically review the published literature on stage at presentation of breast cancer in SSA countries, examine trends over time, and investigate possible sources of between-study heterogeneity. The findings may help to identify locally-appropriate approaches for early detection and treatment of this disease.

Objectives
The main objective of this review is to ascertain the distribution of stage at diagnosis of breast cancer patients in SSA.
The specific aims of the systematic review are:

(i) To provide an overview of stage at diagnosis of breast cancer across SSA;
(ii) To identify and investigate the extent and sources of variations in stage at diagnosis of breast cancer across SSA and over time;
(iii) To compare the frequency of late stage breast cancer in SSA to the corresponding figures for Black and White women in the US over a similar time period.

Search Strategy
The search strategy will aim to identify all published studies conducted in SSA on stage at diagnosis of breast cancer.

Inclusion criteria

Studies will be included if they met the following inclusion criteria:

- Studies that reported on the distribution of stage at diagnosis of primary invasive breast cancer in women in any sub-Saharan African country (as defined by the United Nations(99));
- Studies conducted and published before 1st January 2014;
- Studies published in any language (no language restrictions will be imposed);

Exclusion criteria

Studies will be excluded if they were:

- Not conducted in humans;
- Not conducted in SSA (articles from North Africa – i.e. Algeria, Egypt, Libya, Morocco, Sudan, Tunisia, Western Sahara – and those among African-Americans will be excluded);
- Studies with no information on breast cancer;
- Studies which included only male patients *;
- Meeting abstracts, review papers, reports, and commentaries;

- Studies whose eligibility criteria restricted patient entry to those with a particular stage (e.g. metastatic breast cancer only)**.**

* Studies that include both male and female breast cancer cases recruited over a given period of time will not be excluded even if data are not presented separately by gender because the number of male cases is expected to be rather small.

Database searches

The databases to be searched will include:

- EMBASE
- Medline
- Web of Science
- Africa Wide Information (including African Journals Online)

Only these four databases will be searched as it is expected that saturation will be reached with the majority of studies appearing in all databases.

Search Terms

Keywords and Medical Subject Headings (MeSH) will be used to search the databases listed above. Broad search terms such as "breast cancer", "Sub-Saharan Africa or SSA" will be used. A complete list of search terms will be developed and used across all four databases [see Webappendix-Text3]. Hand-searching of references from retrieved articles, meeting abstracts, review papers, reports and commentaries will also be performed to identity any additional papers not captured by the electronic searches.

Title and abstract screening

The databases listed above will be searched and the citations retrieved will be downloaded into the Endnote software. Any duplicate articles identified by more than one data will be removed.

The titles and abstracts will be screened by one reviewer, with a random sample being also screened independently by a second reviewer. Any study excluded from the review will be documented and the reason(s) for exclusion noted in a systematic way.

Full text screening and data extraction

The full text of all the papers identified during the abstract screening step will be retrieved for full text screening to confirm eligibility and, if eligible, to extract relevant data. For each eligible paper data will be abstracted on the number of patients with breast cancer who presented in each one of the four stages (I, II , III and IV) or in early (i.e. stages I and II combined) and late (i.e. III and IV combined) stages if data were only presented in these aggregated categories. If a study provides numbers of patients in each specific American Joint Committee Cancer Tumour Node Metastases (TNM) category (e.g. T2, N0, M0) these will also be extracted. Information on the following variables will also be extracted: country, study design, study population and type of clinical setting (e.g. primary, secondary, tertiary, population-based cancer registry), years when breast cancer patients were diagnosed, age at time of diagnosis, methods and classification used to ascertain tumour stage. Whenever available data will also be extracted on reproductive history (e.g. age at menarche, age at first birth, parity and menopausal status at presentation); tumour's characteristics (e.g. histology, size, grade, node positivity, receptor status); and time from first symptoms to breast cancer diagnosis. In the course of the data abstraction, should there be any eligible papers resulting from the same study, only the one with the most complete information on stage will be included in the systematic review. The full-text of any potentially eligible studies identified through hand searches will also be reviewed using the methodology described above.

The full-text review and data extraction will be done independently by two reviewers using an adapted version of a pre-tested data entry form(103). Any discrepancies will be resolved by discussion among the reviewers.

Assessment of Methodological Quality of the Papers

The quality of the papers included in the review will be assessed independently by two reviewers using an adapted version of a standardised form(103), which was developed using an approach similar to that of the Cochrane collaboration. The quality assessment form will be designed to capture three broad categories of items which will aim to assess the potential for selection bias and information bias as well as the availability of data on other variables relevant to stage. Each item within these three categories will be allocated a score ranging from 0 (if it did not meet the criteria or if the information provided was unclear) to a maximum of 2 or 4, depending on the item. The overall quality of the study will be expressed as a sum of the item-specific scores. The higher the score the higher the quality of the paper.

Data Analysis

The extracted data will be analysed using the STATA Statistical Software version 13 (StataCorp, Texas). An initial descriptive analysis will be done to provide information about the study population, study design, the region of Sub-Saharan Africa, stage at presentation and other variables described above in the section on data abstraction. These results will be presented in both narrative and tabular form.

The percentage (p_{34}) of breast cancer patients diagnosed at late stages (III and IV) will be the primary outcome of interest in this review. This will be defined as the percentage $p_{34}=n_{34}/n$ where n_{34} is the number of women who presented at stages III or IV and n is the total number of women with known stage information. The suite of *metan* and *metaprop* commands will be used to graphically display population-specific late stage percentages and, if appropriate, to estimate pooled percentages using random effect models. Between-study heterogeneity will be examined using the I^2-statistics and the *P*-value for heterogeneity (Cochrane's *Q* statistic) test. Meta-regression analysis will be performed to identify independent sources of heterogeneity (e.g. calendar year, country/region, type of clinical setting). Small study bias will be assessed using funnel plots and the Egger test.

The findings on late stage breast cancer in SSA will be compared with those from African-American and Caucasian populations in the United States (US), for the same time period, using data from the US Surveillance Epidemiology and End Results (SEER) database. The SEER database includes data on all cancer incident cases from nine population-based cancer registries in the US.

APPENDIX 2: PRISMA 2009 CHECKLIST

Section/topic	*#*	*Checklist item*	*Reported on page #*
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5, 6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3, Webappendix-Text 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5, 6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, 6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Webappendix-Text 3

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5, 6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5, 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7, Webappendix Text 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6,7
Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 5, Webappendix Text 4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Webappendix Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Webappendix - Table1, References
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Text 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 1b, Figure 2,

			Webappendix Figures 2 and 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures 1b, Figure 2, Webappendix Figures 2 and 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Webappendix-Figure 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 2
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12, 13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11, 13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

APPENDIX 3: SYSTEMATIC REVIEW SEARCH STRATEGY

Database	Search Terms
Embase	1. (breast cancer* or breast neoplasm* or breast carcinoma* or breast sarcoma* or breast tumour* or breast tumour* or breast malignanc*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 2. (Stage or presentation or grade or clinical features or clinical findings).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 3. (Africa or sub-saharan Africa or Angola or Benin or Botswana or Burkina Faso or burundi or cameroun or cape Verde or Chad or central african republic of comoros or Congo or Cote d'Ivoire or democratic republic of congo or equatorial guinea or eritrea or ethiopia or Gabon or Gambia or Ghana or Guinea or Guinea-Bussau or kenya or Lesotho or Liberia or Madagascar or Malawi or Mali or Mozambique or Namibia or Niger or Nigeria or Rwanda or Soa Tome or Senegal or seychelles or sierra Leone or somalia or south Africa or Swaziland or Togo or Uganda or Tanzania or Zambia or Zimbabwe).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 4. 1 and 2 and 3 5. exp Breast Neoplasms/ 6. cancer staging.mp. or exp Neoplasm Staging/ 7. Africa, Western/ or South Africa/ or Africa, Eastern/ or Africa.mp. or "Africa South of the Sahara"/ or Africa, Central/ or Africa/ or Africa, Southern/ 8. 1 or 5 9. 2 or 6 10. 3 or 7 11. 8 and 9 and 10
Africa-wide Information	1.breast cancer* or breast neoplasm* or breast carcinoma* or breast sarcoma* or breast tumour* or breast tumour* or breast malignanc* 2.breast neoplasms 3. Stage or presentation or grade or clinical features or clinical findings 4.Neoplasm staging 5. Africa 6. Africa or sub-saharan Africa or Angola or Benin or Botswana or Burkina Faso or burundi or cameroun or cape Verde or Chad or central african republic of comoros or Congo or Cote d'Ivoire or democratic republic of congo or equatorial guinea or eritrea or ethiopia or Gabon or Gambia or Ghana or Guinea or Guinea-Bussau or kenya or Lesotho or Liberia or Madagascar or Malawi or Mali or Mozambique or Namibia or Niger or Nigeria or Rwanda or Soa Tome or Senegal or seychelles or sierra Leone or somalia or south Africa or Swaziland or Togo or Uganda or Tanzania or Zambia or Zimbabwe 7.1 or 2 8.3 or 4 9. 5 or 6

	10.7 and 8 and 9
Medline	1.(breast cancer* or breast neoplasm* or breast carcinoma* or breast sarcoma* or breast tumour* or breast tumour* or breast malignanc*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 2. (Stage or presentation or grade or clinical features or clinical findings).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 3.(Africa or sub-saharan Africa orAngola or Benin or Botswana or Burkina Faso or burundi or cameroun or cape Verde or Chad or central african republic of comoros or Congo or Cote d'Ivoire or democratic republic of congo or equatorial guinea or eritrea or ethiopia or Gabon or Gambia or Ghana or Guinea or Guinea-Bussau or kenya or Lesotho or Liberia or Madagascar or Malawi or Mali or Mozambique or Namibia or Niger or Nigeria or Rwanda or Soa Tome or Senegal or seychelles or sierra Leone or somalia or south Africa or Swaziland or Togo or Uganda or Tanzania or Zambia or Zimbabwe).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 4.exp breast cancer/ 5.1 or 4 6.exp cancer staging/ 7.2 or 6 8. "Africa south of the Sahara"/ or South Africa/ or Africa/ or Central Africa/ or Africa.mp. 9. 3 or 8 10. 5 and 7 and 9
Web of Science	1. Topic= (breast cancer* or breast neoplasm* or breast carcinoma* or breast sarcoma* or breast tumour* or breast tumour* or breast malignanc*) 2.Topic=(Stage or presentation or grade or clinical features or clinical findings) 3.Topic=(Africa or sub-saharan Africa or Angola or Benin or Botswana or Burkina Faso or burundi or cameroun or cape Verde or Chad or central african republic of comoros or Congo or Cote d'Ivoire or democratic republic of congo or equatorial guinea or eritrea or ethiopia or Gabon or Gambia or Ghana or Guinea or Guinea-Bussau or kenya or Lesotho or Liberia or Madagascar or Malawi or Mali or Mozambique or Namibia or Niger or Nigeria or Rwanda or Soa Tome or Senegal or seychelles or sierra Leone or somalia or south Africa or Swaziland or Togo or Uganda or Tanzania or Zambia or Zimbabwe) 4.1 and 2 and 3

APPENDIX 4: ASSESSMENT OF STUDY QUALITY

The methodological quality of the papers included in the review was evaluated by adapting a standardized quality assessment form previously used by Eng *et al*.(103). Each paper was scored separately on ten individual parameters within three broad categories aimed at evaluating the potential for biases in the way breast cancer patients were recruited or in the way stage at diagnosis was assessed and reported, as well as the availability of information on stage-related variables. A full list of all items considered is given below.

Minimizing selection bias

1. Timing of data collection
   Score 0 if unclear
   Score 2 if retrospective
   Score 4 if prospective

2. Study Design
   Score 0 if unclear
   Score 1.5 if opportunistic case series
   Score 2.5 if consecutive case series
   Score 4 if population-based study

3. Percentage of overall study sample size for which information on stage is provided
   Score 0 if unclear
   Score 2 if < 80% of total cases
   Score 4 if ≥ 80% of total cases

Minimizing information bias

4. What staging criteria was used?
   Score 0 if staging criteria was not reported
   Score 4 if TNM or Manchester criteria were used

5. Staging methods
   Score 0 if unclear
   Score 2 if clinical only
   Score 4 if clinical and imaging and other complementary exams

6. How were data on stage at presentation reported?
   Score 0 if unclear
   Score 2 if only data for aggregated categories of early (stages I and II combined) and late stage (stages III and IV combined) were given
   Score 4 if data provided separately for each one of the four stages (I, II, III and IV)

Assessment of other important variables related to stage at presentation

7. Age at presentation (e.g. mean, median or age-categories)
   Score 0 if not reported
   Score 1 if reported

8. Menopausal status at presentation
   Score 0 if not described
   Score 1 if described

9. Year of Diagnosis
   Score 0 if not reported
   Score 1 if reported

10. Tumour grade
    Score 0 if not reported
    Score 1 if reported

More weight was given to the items in the selection and information bias categories with each one being given a score between 0 and 4, as indicated above.

The category of other variables related to stage at diagnosis included items on the availability of information on age at diagnosis, year at diagnosis, menopausal status at diagnosis and tumour grade. Tumour size was not included in this category because this variable is a component of the TNM staging, and the latter was included as an item in the information bias category. Tumour receptor status was also considered but not included because receptor testing is not routinely carried out in most SSA settings. For each of the four items in this category, a score of 0 was assigned if no information on that variable was provided or a score of 1 if such information was given.

Individual item-specific scores were summed up across the three categories to arrive at a total score for each study. The total score for a study could range from 0 to 28. The lower the score the poorer the methodological quality of the study, i.e. the higher the likelihood it would have been affected by bias. We did not use an arbitrary cut off point to classify studies as being high vs. low quality; instead, we reported the individual scores for each study.

APPENDIX 5: ETHICAL APPROVALS

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636
www.lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

Elima Jedy-Agba
Research Degree Student
NCDE / EPH
LSHTM

8 October 2013

Dear Dr. Jedy-Agba,

Study Title: **Breast Cancer in Nigeria: Determinants of Presentation, Tumour Biology and Survival. This study will be nested within a larger study (The Nigerian Integrative Epidemiology of Breast Cancer Study).**
LSHTM ethics ref: **6515**

Thank you for your letter of 1 October 2013, responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

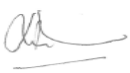
The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
LSHTM ethics application	n/a	
Parent (Main) Study Proposal	1	30/08/2013
Information Sheet	2	20/09/2013
Baseline Questionnaire - draft	1	30/08/2013
Clinical Information Form - draft	1	30/08/2013
Consent Form- Next of Kin	2	
NIBBLE Study: Participant's Consent Form	2	20/09/2013
Follow-up Questionnaire	1	30/08/2013
Main NIBBLE Questionnaire on Risk factors - draft	1	30/08/2013
Study Proposal	1	30/08/2013

After ethical review

Any subsequent changes to the application must be submitted to the Committee via an E2 amendment form. All studies are also required to notify the ethics committee of any serious adverse events which occur during the project via form E4. At the end of the study, please notify the committee via form E5.

Yours sincerely,



Professor John DH Porter
Chair
ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

National Health Research Ethics Committee of Nigeria (NHREC)

Promoting Highest Ethical and Scientific Standards for Health Research in Nigeria

Federal Ministry of Health

NHREC Protocol Number NHREC/01/01/2007-17/05/2013
NHREC Approval Number NHREC/01/01/2007-09/06/2013
Date: June 9, 2013

Re: Nigerian Integrative Epidemiology of Breast Cancer (NIBBLE) Study

Health Research Ethics Committee (HREC) assigned number: NHREC/01/01/2007

Name of Principal Investigator: Dr. Clement Adebamowo

Address of Principal Investigator: Institute of Human Virology Nigeria
Plot 252 Herbert Macaulay Way, Abuja
Phone: +2348033404950; E-mail: elymah99@yahoo.com

Date of receipt of valid application: 17-05-2013
Date when final determination of research was made: 09-06-2013

Notice of Full Committee Review and Approval

This is to inform you that following the review of the protocol, consent forms, questionnaires, and other supporting documents in relation to the above titled study the National Health Research Ethics Committee (NHREC) has granted full committee approval for this study.

This approval dates from 09/06/2013 to 08/06/2014. If there is delay in starting the research, please inform the HREC so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of these dates. All informed consent forms used in this study must carry the HREC assigned number and duration of HREC approval of the study. In multiyear research, endeavor to submit your annual report to the HREC early in order to obtain renewal of your approval and avoid disruption of your research.

The National Code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the Code including ensuring that all adverse events are reported promptly to the HREC. No changes are permitted in the research without prior approval by the HREC except in circumstances outlined in the Code. The HREC reserves the right to conduct compliance visit to your research site without prior notice.

Signed

Clement Adebamowo BMChB Hons (Jos), FWACS, FACS, DSc (Harvard)
Honorary Consultant Surgeon, Director, West African Center for Bioethics and
Chairman, National Health Research Ethics Committee of Nigeria (NHREC)

FEDERAL CAPITAL TERRITORY

HEALTH RESEARCH ETHICS COMMITTEE

Research Unit, Room 10, Block A Annex, HHSS

FCT Secretarial No. 1 Kapital Street Area 11, Garki, Abuja - Nigeria

Name of Principal Investigator:	Prof. Clement Adebamowo
Address of Principal Investigator:	Institute of Human Virology Abuja, Plot 252, Herbert Macaulay Way CBD, Abuja.
Date of receipt of valid application:	12/06/2013

NOTICE OF APPROVAL AFTER COMMITTEE REVIEW

Protocol Approval Number: FHREC/2013/01/26/22-07-13

TITLE: The Nigerian Integrative Epidemiology of Breast Cancer (NIBBLE STUDY)

The research described in the submitted protocol has been reviewed.

Documents Reviewed:
(i)Application form
(ii)Curriculum Vitae of the Investigator
(iii)Research Protocol;
*Questionnaire
* Participant Information Sheet
* Informed Consent Form

On the basis of the review, this research has been approved by the Committee (FHREC). Subsequent changes are not permitted in this research without prior approval by the FHREC.

This approval dates from **23/07/2013 to 22/07/2014**. Note that no participant accrual or activity related to this research may be conducted outside of these dates. All informed consent forms used in this study must carry FHREC assigned protocol approval number and duration of FHREC approval of the study.

The National Code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the code including ensuring that all adverse events are reported promptly. The FHREC reserves the right to conduct compliance visit to your research site without previous notification.

In multiyear research, endeavor to submit your annual report to the FHREC early in order to obtain renewal of your approval and avoid disruption of your research. At the end of the research, a copy of the final report of the research should be forwarded to FHREC for record purposes.

Dr. Olayinka Douglas Tarkidzy Abuja
Secretary, FHREC
July 23, 2013

23 JUL 2013
APPROVED

NATIONAL HOSPITAL

(Established by Act No 36 of 1999).

ABUJA

NHA/ADMIN/236/V.VII/ **19th Junc, 2013**

Re: Nigerian Integrative epidemiology of breast cancer (NIBBLE) Study

Health Research Ethics Committee (HREC) Assigned number: **NHA/EC/221/2013**

Name of Principal Investigator: **Prof. Clement Adebamowo**

Address of Principal Investigator: Institute of Human Virology, Nigeria
Plot 252 Herbert Macaulay Way,
Abuja

Date of Receipt of Valid Application: 20th May, 2013

Notice of Approval

This is to inform you that the research described in the submitted protocol, the consent forms, advertisements and other participant information materials have been reviewed and *given full approval by the Health Research Ethics Committee, National Hospital Abuja.*

This approval dates from **19th June, 2013** to **18th June, 2015.** If there is delay in starting the research, please inform the HREC National Hospital Abuja so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of these dates. *All informed consent forms used in this study must carry the HREC assigned number and duration of HREC approval of the study.*

The National Code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the Code including ensuring that all adverse events are reported promptly to the HREC. No changes are permitted in the research without prior approval by the HREC except in circumstances outlined in the Code. The HREC reserves the right to conduct compliance visit to your research site without previous notification.

Dr. JAF Momoh
Chairman, HREC, National Hospital Abuja

UNIVERSITY OF NIGERIA TEACHING HOSPITAL

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Chairman UNTH Management Board

Barr. (Mrs.) J. C. OKAFOR
LLB.(HONS),BL., LL.M, FIHAN, MCIA
Ag. Director of Administration/Secretary
UNTH Management Board

Dr. C. C. AMAH, MBBS, FWACS, FICS,FIAM,FNIM,FCE
Chief Medical Director

Dr. (Mrs.) ANNE C. NDU, MBBS,FWACP, MPH
Chairman Medical Advisory Committee

Our Ref. UNTH/CSA/329 /VOL. 5

Date 28th July, 2013.

NHREC/05/01/2008B-FWA00002458-1RB00002323

ETHICAL CLEARANCE CERTIFICATE

TOPIC: NIGERIAN INTEGRATIVE EPIDEMIOLOGY OF BREAST CANCER (NIBBLE) STUDY

BY: **DR. ELIMA JEDY-AGBA, PROF. EZEOME, E.R**
(UNTH Collaborator)

FOR: RESEARCH PURPOSE

This research project on the above topic was reviewed and approved by the University of Nigeria Teaching Hospital Health Research Ethics Committee. This certificate is valid for **one** year from date of issue.

Prof. R.E. Umeh Date: 21/08/13
Chairman, Health Research Ethics Committee

APPENDIX 6: DATA COLLECTION INSTRUMENTS

Baseline Questionnaire on Determinants of Stage at Presentation

The Interview:

Study Site: ☐☐☐☐☐

Interviewer name: _____

Interviewer code*:* ☐☐☐☐☐

Date of Interview: _ _ /_ _ / _ _ _ _
Day Mo Year

Type of interview:

- Face-to-face at hospital clinic ☐
- Face-to-face at home ☐
- Telephone ☐
- Other. Please specify_____ ☐

Language used:

- English ☐
- Other, but no translation assistance required ☐
- Other, with translation assistance ☐

If other language please specify which one:

- Hausa ☐
- Yoruba ☐
- Igbo ☐
- Other ☐ Please specify_____ ☐☐

The Participant:

Full name of the participant:_____

Date of birth: _ _ /_ _ / _ _ _ _
Day Mo Year

Study ID: ☐☐☐☐☐☐☐☐☐☐

Hosp ID: ☐☐☐☐☐☐☐☐☐☐

Notes for Interviewer:

To the participant: *"Thank you for agreeing to take part in this research study. I am going to start by asking you a few questions about your beliefs and attitudes towards breast illnesses."*

Section 1. Patient's Knowledge, Attitudes and Practices

1.1. Have you heard of self-breast examination (SBE)?

a. Yes ☐
b. No ☐
c. I have heard of SBE, but don't know what it means ☐

1.2. If you have heard of SBE, who showed you how to do it? *Tick only one option.*

Notes for Interviewer:

Do **NOT** read out the choices below to the participant. Only tick what she says.
If the participant answered "*No*" or "*I have heard of SBE, but don't know what it means*" to question 6 above, tick box g) below

a. Breast cancer awareness campaign ☐
b. Nurse, doctor or other health professional ☐
c. Relative or friend ☐
d. Other. Please specify_____ ☐☐
f. Have heard of SBE, but have never been shown how to do it ☐
g. Have never heard of SBE / have heard but don't know what it means ☐

1.3. Have you ever practiced SBE?

a. Yes ☐
b. No ☐

c. Have never heard of SBE / have heard but do not know what it means ☐

1.4. If you have ever practiced SBE how frequently, on average, did you practice this before the start of your current breast problem? ☐☐ times/per year

Never practiced SBE ☐

1.5. In the past, prior to the start of your current breast problem, had you ever had a clinical breast examination (CBE) done by a health care professional?

a. Yes ☐
b. No ☐
c. Can't remember/Not sure ☐

1.6. Have you ever had mammography (i.e. an x-ray of the breast)?

a. Yes ☐
b. No ☐
c. Can't remember/Not sure ☐
d. I don't know what mammography means ☐

1.7. If you have ever had mammography, what was the reason for undergoing it?

a. There was a problem with my breasts ☐

b. There was nothing wrong with my breasts but my doctor thought I should have mammography to detect early signs of cancer (i.e. screening) ☐

c. Can't remember/Not sure ☐

d. Never had mammography ☐

1.8. Before the start of your current breast problem, had you ever heard of breast cancer?

a. Yes ☐

b. No ☐

c. Can't remember ☐

1.9. If you had heard about breast cancer previously what was your main source of information? *Tick all appropriate options.*

Notes for Interviewer:

Do **NOT** read out the choices below to the participant. Only tick what she says.
If the participant answered "*No*" or "*Can't remember*" to question 1, tick box i) below

a. Friend/Relative ☐

b. Another family member with breast cancer ☐

c. Radio/TV/Magazine ☐

d. Breast cancer awareness campaigns/NGOs ☐

e. Church/Religious organization ☐

f. Nurse/doctor ☐

g. Traditional healer ☐

h. Other. Please specify_____ ☐☐

i. Never heard about breast cancer before ☐

1.10. Which of the following do you believe may cause breast cancer?

a. A woman's lifestyle (e.g. her diet and alcohol intake)	Yes ☐	No ☐	Not sure ☐
b. Having breastfed for long periods	Yes ☐	No ☐	Not sure ☐
c. Getting older	Yes ☐	No ☐	Not sure ☐
d. Having other family member affected with breast cancer	Yes ☐	No ☐	Not sure ☐
e. A curse	Yes ☐	No ☐	Not sure ☐
f. An injury to the breast	Yes ☐	No ☐	Not sure ☐
g. A bite from an insect	Yes ☐	No ☐	Not sure ☐
h. Caught from others suffering from the disease	Yes ☐	No ☐	Not sure ☐
i. Other. Please specify_____ ☐☐	Yes ☐	No ☐	Not sure ☐

1.11.Which of the following do you think are signs of breast cancer?

a. A lump or thickening in an area of the breast Yes ☐ No ☐ Don't know ☐

b. A painful breast Yes ☐ No ☐ Don't know ☐

c. A change in the size or shape of the breast Yes ☐ No ☐ Don't know ☐

d. Dimpling of the skin or a wound on breast Yes ☐ No ☐ Don't know ☐

e. Fluid coming from the nipple in a woman who is not breastfeeding Yes ☐ No ☐ Don't know ☐

f. A swelling or lump in the armpit Yes ☐ No ☐ Don't know ☐

g. A change in the shape of the nipple Yes ☐ No ☐ Don't know ☐

h. Other. Please specify_____ ☐☐ Yes ☐ No ☐ Don't know ☐

1.12. How common do you think breast cancer is among Nigerian women?

a. The most common cancer ☐

b. Frequent, but not the most common cancer ☐

c. A rare cancer ☐

d. Don't know ☐

1.13. Do you think breast cancer can be cured if caught early?

a. Yes, it can be cured if caught early ☐

b. No, there is no treatment ☐

c. I don't know if breast cancer can be cured ☐

1.14. Before noticing your current breast problem, had you ever heard of the following treatment options for patients with breast cancer?

a. Surgery Yes ☐ No ☐ Not sure ☐

b. Hormone therapy Yes ☐ No ☐ Not sure ☐

c. Chemotherapy Yes ☐ No ☐ Not sure ☐

d. Radiotherapy Yes ☐ No ☐ Not sure ☐

Section 2. Patient's Breast Symptoms

Notes for the interviewer:

To the participant: "*Thank you. I am going to ask you now a few questions about your current breast problem*."

2.1. What was the first change you noticed on your breast? *Tick all appropriate boxes.*

Notes for Interviewer:

Do **NOT** read the choices below to the participant. Only tick what she says.

a. A lump or thickening in an area of the breast ☐

b. Pain in the breast ☐

c. Dimpling of the skin or a wound ☐

d. Fluid coming from the nipple ☐

e. A swelling or lump in the armpit ☐

f. A change in the shape of the nipple ☐

g. I did not notice any change myself ☐

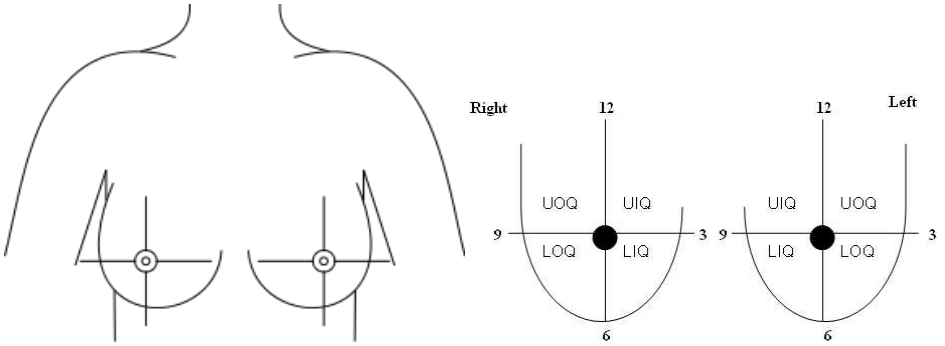
h. Other. Please specify_____ ☐☐

2.2. Using the picture (i) below, mark <u>which</u> breast (R or L), and which <u>part of that breast</u>**,** the change was <u>first noticed</u> and tick the corresponding option below.

<u>Notes for Interviewer:</u>

Ask the participant on which breast (right or left) the change was noticed. Show her the picture below and then ask her to show you where the change was located and mark the spot on diagram (i). Diagram (ii) is only to help you to identify the breast quadrants.

(i) (ii)



a. Right upper inner quadrant (UIQ) ☐

b. Left upper inner quadrant (UIQ) ☐

c. Right upper outer quadrant (UOQ) ☐

d. Left upper outer quadrant (UOQ) ☐

e. Right lower inner quadrant (LIQ) ☐

f. Left lower inner quadrant (LIQ) ☐

g. Right lower outer quadrant (LOQ) ☐

h. Left lower outer quadrant (LOQ) ☐

i. Under the armpit ☐

j. Can't remember ☐

2.3. When was this breast change <u>first noticed</u>?

<u>Notes for Interviewer:</u>

- Try to obtain the exact date from the participant. You can try to jog her memory by referring to special events (e.g. festivals, religious and family celebrations, school holidays). If the woman cannot remember the day enter month and year only. If she cannot remember the date ask how many days/weeks/months/years (as appropriate) ago. Tick the "*Can't remember*" box ONLY if she is unable to provide an approximate date.

- **Enter this date in the timeline of key events provided on the last page of the questionnaire.**

Date: _ _ /_ _ / _ _ _ _ , or ____weeks, or ____months, or ___years ago

Day Mth Year Can't remember ☐

2.4. Who first noticed this change? *Tick only one box*

a. Myself ☐
b. Husband/partner ☐
c. Doctor or nurse ☐
d. Traditional healer ☐
e. Other. Please specify_____ ☐☐

2.5. When the change in your breasts was first noticed, what did you think it was? *Tick only one box.*

Notes for Interviewer:

Do **NOT** read out the choices below to the participant. Only tick the boxes that correspond to what she says.

a. A spiritual attack ☐
b. An infection/boil ☐
c. An insect bite ☐
d. Breast lump or cancer ☐
e. Blocked milk duct/complication of recent breastfeeding ☐
f. Worried but didn't know what it was ☐
g. Nothing serious to worry about ☐
h. Other. Please specify_____ ☐☐

2.6. Whom did you first tell when you first noticed a change in your breasts? *Tick only one box*

Notes for Interviewer:

Do **NOT** read out the choices below to the participant. Only tick what she says.

a. Family member or member of household ☐
b. Neighbour/Friend ☐
c. Church pastor/elder ☐
d. Doctor/Nurse at clinic or hospital ☐
e. Chemist/pharmacist ☐
f. Traditional healer ☐
g. Other. Please specify _____ ☐☐

2.7. How long did it take from when the change(s) in your breast were first noticed to when you first told {*Interviewer: enter option selected in 2.6 above*} _____?

____days, or ____weeks, or _____months, or _____years Can't remember ☐

2.8. Did you delay telling {*Interviewer: enter option selected in 2.6 above*}_____ about your breast problem(s) because of:

Notes for Interviewer:

Do **NOT** read out the choices below to the participant. Only tick what she says.

a. Did not think the problem was serious ☐
b. Hoped the problem would go away ☐
c. Embarrassed to talk about problems in my breasts ☐
d. Fear of being told that it could be serious ☐
e. Fear of treatment ☐
f. Fear of being rejected ☐
g. Other. Please specify_____ ☐☐
g. No delay as I told them as soon as I noticed the change in my breast ☐

Section 3. Patient Navigation Pathway

Notes for Interviewer:

To the participant: "*Thank you for all your help so far. I am now going to ask you a few questions about all the facilities you visited to seek help after noticing a change in your breast. I will ask you to start from the earliest to the latest facility you visited to seek any type of help (medical, traditional or spiritual care) after your initial symptoms until you arrived at this hospital.*"

- Complete a contact form (1, 2, 3, etc) for each contact/provider the participant had **until the participant arrived at your hospital.** Use additional forms if she mentions more than 6 providers and staple them to this questionnaire.

- For each contact, the date of first visit and the type of provider should be entered below and on the timeline of key events shown on the last page before moving to the next questions.

- The **date of first visit** is that of the first appointment/test with that care provider. Try to jog the participant's memory by referring to festivals, family events, public and school holidays, etc. If she cannot remember the exact date of visit, record month and year only. If, for instance, she mentions '3 months ago' record that below. The "*Can't remember*" option should be used ONLY if she cannot give any approximate date.

- **Home** is the place where the woman usually lives. Temporary residence elsewhere (e.g. due to her illness or for other reason) should not be considered.

Contact 1

3.1. What is the name of the provider (e.g. hospital, clinic, traditional healer) you visited? _____ ☐☐

3.2. What type of care provider did you visit?

Notes for Interviewer:

Do **NOT** read the choices provided for each question to the participant. Only tick what she says.

Care Provider	*Tick only 1 option*
a. Private doctor (General Practitioner)	
b. Community clinic sister/doctor	
c. Private hospital sister/nurse/doctor	
d. Public hospital sister/nurse/doctor	
e. Social worker or counsellor	
g. Chemist/pharmacist	
g. Home/community based care worker	
h. Traditional healer/herbalist	
i. Church Pastor/Elder	
j. Other. Please specify _____	☐☐

3.3. Date of first visit: _ _ /_ _ / _ _ _ _, or ___days, or ___weeks, or ___months, or ___years ago

Can't remember ☐

3.4. How far away is this provider from your home? _____km, or _____miles Don't Know ☐

3.5. How long did it take you to get there from your home? ____hrs and/or ____ mins

Can't remember ☐

3.6. Which means of transport did you use?

a. Own car ☐

b. Lift from relative/friend ☐

c. Rented car (e.g. taxi) ☐

d. Bus ☐

e. Other. Please specify_____ ☐☐

3.7. What was your reason for visiting this provider at the time you did? *Tick all appropriate boxes*

a. Symptoms did not go away ☐

b. Symptoms worsened ☐

c. Advice from people/family/friends ☐

d. Other. Please specify_____ ☐☐

3.8. How long did it take from first noticing the change(s) in your breast to your first visit to this care provider?

a. Less than 2 weeks ☐

b. 2-4 weeks ☐

c. 1-3 months ☐

d. 4-6 months ☐

e. More than 6 months ☐

Notes for Interviewer:

If the delay was greater than 1 month, ask the question below. If the "Other" option is selected enter details in the box provided.

3.9. What was the cause of the delay? *Tick all appropriate boxes.*

□ Delay caused by woman I delayed because:	Fear of: □ diagnosis □ treatment	□ Did not think it was a serious problem	□ No transport money □ Other financial constraints	Partner /Husband □ Did not give permission □ Fear of rejection	□ No one to look after children	□ Other reason
If Other (explain): ☐☐						
□ Delay caused by clinic	□ They gave me medicine and told me to come back after ___ weeks	□ There was a delay for test results	□ It took a _____weeks or____Months before I got an appointment to see a doctor	□ The doctor told me it was not serious/ there was nothing to worry about	□ Other reason	
If Other (explain): ☐☐						

3.10. What was the outcome of the contact with this provider? *Tick all appropriate boxes.*

Notes for Interviewer:

Do **NOT** read out the choices provided for each question to the participant. Tick what she says.

a. Reassurred and told not to worry ☐
b. Tests done but I was never told the results ☐
c. Told I had breast cancer but no treatment offered ☐
d. Told I had breast cancer and treatment offered ☐
e. Told I had something else but no treatment offered ☐
f. Please specify (i) type of diagnosis_____ ☐☐
g. Told I had something else and treatment offered ☐
h. Please specify: (i) type of diagnosis_____ ☐☐
(ii) type of treatment_____ ☐☐
i. Referred to another provider/facility ☐
j. Not applicable (this provider is one of the study hospitals) ☐

3.11. Did you visit any other provider?

a. Yes ☐ *(To the interviewer: go to the next page)*
b. No ☐ *(To the interviewer: skip to page 20)*

Contact 2

3.12. What is the name of the provider (e.g. hospital, clinic, traditional healer) you visited?
_____ ☐☐

3.13. What type of care provider did you visit?

Notes for Interviewer:

Do **NOT** read out the choices provided for each question to the participant. Only tick what she says.

Care Provider	*Tick only 1 option*
a. Private doctor (General Practitioner)	
b. Community clinic sister/doctor	
c. Private hospital sister/nurse/doctor	

d. Public hospital sister/nurse/doctor	
e. Social worker or counsellor	
f. Chemist/pharmacist	
g. Home/community based care worker	
h. Traditional healer/herbalist	
i. Church Pastor/Elder	
j. Other. Please specify _____	☐☐

3.14. Date of first visit: _ _ /_ _ / _ _ _ _, or ___days, or ___weeks, or ___months, or ___years ago

Can't remember ☐

3.15. How far away is this provider from you're your home? ____km, or ___miles Don't know ☐

3.16. How long did it take you to get there from your home? _____hrs and/or ____ mins

Can't remember ☐

3.17. Which means of transport did you use?

a. Own car ☐
b. Lift from relative/friend ☐
c. Rented car (e.g. taxi, mini-cab) ☐
d. Bus ☐
e. Other. Please specify_____ ☐☐

3.18. What was your reason for visiting this care provider at the time you did? *Tick all appropriate boxes*

a. Symptoms did not go away ☐
b. Symptoms worsened ☐
c. Previous provider was not helpful ☐
d. Treatment(s) given by previous provider didn't work ☐
e. Too long to get test results from previous provider ☐
f. Advice from people/family/friends ☐
g. Referred from previous provider ☐
h. Other. Please specify_____ ☐☐

3.19. How much time went by between the date of first visit to provider 1 to date of first visit to provider 2?

a. Less than 2 weeks ☐
b. 2-4 weeks ☐
c. 1-3 months ☐
d. 4-6 months ☐
e. More than 6 months ☐

Notes to Interviewer:

If the delay was greater than 1 month, ask the question below. If "Other" is selected enter details in the box below.

3.20. What was the cause of the delay? *Tick all appropriate boxes*

☐ Delay caused by woman I delayed	Fear of: ☐ diagnosis ☐ treatment	☐ Did not think it was	☐ No transport money	Partner /Husband ☐ Did not give permission	☐ No one to look after children	☐ Other reason

because:		a serious problem	□ Other financial constraints	□ Fear of rejection		
If Other (explain): ☐☐						
□ Delay caused by clinic	□ They gave me medicine and told me to come back after ___ weeks	□ There was a delay for test results	□ It took a _____weeks or____Months before I got an appointment to see a doctor	□ The doctor told me it was not serious/ there was nothing to worry about	□ Other reason	
If Other (explain): ☐☐						

3.21. What was the outcome of the contact with this provider? *Tick all appropriate boxes.*

a. Reassurred and told not to worry ☐
b. Tests done but I was never told the results ☐
c. Told I had breast cancer but no treatment offered ☐
d. Told I had breast cancer and treatment offered ☐
    i. Please specify type of treatment_____ ☐☐
e. Told I had something else but no treatment offered ☐
    i. Please specify (i) type of diagnosis_____ ☐☐
f. Told I had something else and treatment offered ☐
    i. Please specify: (i) type of diagnosis_____ ☐☐
        a. (ii) type of treatment_____ ☐☐
g. Referred to another provider/facility ☐
h. Not applicable (this provider is one of the study hospitals) ☐

3.22. Did you visit any other provider?

a. Yes ☐ *(To the interviewer: go to the next page)*
b. No ☐ *(To the interviewer: skip to page 20)*

Contact 3

3.23. What is the name of the provider (e.g. hospital, clinic, traditional healer) you visited? _____ ☐☐

3.24. What type of care provider did you visit?

Notes for Interviewer:

Do **NOT** read out the choices provided for each question to the participant. Only tick what she says.

Care Provider	*Tick only 1 option*
a. Private doctor (General Practitioner)	
b. Community clinic sister/doctor	
c. Private hospital sister/nurse/doctor	
d. Public hospital sister/nurse/doctor	
e. Social worker or counsellor	
f. Chemist/pharmacist	
g. Home/community based care worker	
h. Traditional healer/herbalist	
i. Church Pastor/Elder	

j. Other. Please specify _____	☐☐

3.25. Date of first visit: _ _ /_ _ / _ _ _ _, or ___days, or ___weeks, or ___months, or ___years ago

Can't remember ☐

3.26. How far away is this provider from your home? ____km, or ____miles Don't know ☐

3.27. How long did it take you to get there from your home? _____hrs and/or ____ mins

Can't remember ☐

3.28. Which means of transport did you use?

a. Own car ☐
b. Lift from relative/friend ☐
c. Rented car (e.g. taxi, mini-cab) ☐
d. Bus ☐
e. Other. Please specify_____ ☐☐

3.29. What was your reason for visiting this care provider at the time you did? *Tick all appropriate boxes*

a. Symptoms did not go away ☐
b. Symptoms worsened ☐
c. Previous provider was not helpful ☐
d. Treatment(s) given by previous provider didn't work ☐
e. Too long to get test results from previous provider ☐
f. Advice from people/family/friends ☐
g. Referred from previous provider ☐
h. Other. Please specify_____ ☐☐

3.30. How much time went by between the date of first visit to provider 2 to date of first visit to provider 3?

a. Less than 2 weeks ☐
b. 2-4 weeks ☐
c. 1-3 months ☐
d. 4-6 months ☐
e. More than 6 months ☐

Notes to Interviewer:

If the delay was greater than 1 month, ask the question below. If "Other" is selected enter details in the box below.

3.31. What was the cause of the delay? *Tick all appropriate boxes*

☐ Delay caused by woman I delayed because:	Fear of: ☐ diagnosis ☐ treatment	☐ Did not think it was a serious problem	☐ No transport money	Partner /Husband ☐ Did not give permission ☐ Fear of rejection	☐ No one to look after children	☐ Other reason

			□ Other financial constraints			
If Other (explain): ☐☐						
□ Delay caused by clinic	□ They gave me medicine and told me to come back after ___ weeks	□ There was a delay for test results	□ It took a _____weeks or____Months before I got an appointment to see a doctor	□ The doctor told me it was not serious/ there was nothing to worry about	□ Other reason	
If Other (explain): ☐☐						

3.32. What was the outcome of the contact with this provider? *Tick all appropriate boxes.*

a. Reassured and told not to worry ☐
b. Tests done but I was never told the results ☐
c. Told I had breast cancer but no treatment offered ☐
d. Told I had breast cancer and treatment offered ☐
    i. Please specify type of treatment_____ ☐☐
e. Told I had something else but no treatment offered ☐
    i. Please specify (i) type of diagnosis_____ ☐☐
f. Told I had something else and treatment offered ☐
    i. Please specify: (i) type of diagnosis_____ ☐☐
        a. (ii) type of treatment_____ ☐☐
g. Referred to another provider/facility ☐
h. Not applicable (this provider is one of the study hospitals) ☐

3.33. Did you visit any other provider?

a. Yes ☐ *(To the interviewer: go to the next page)*
b. No ☐ *(To the interviewer: skip to page 20)*

Contact 4

3.34. What is the name of the provider (e.g. hospital, clinic, traditional healer) you visited? _____ ☐☐

3.35. What type of care provider did you visit?

Notes for Interviewer:

Do **NOT** read out the choices provided for each question to the participant. Only tick what she says.

Care Provider	*Tick only 1 option*
a. Private doctor (General Practitioner)	
b. Community clinic sister/doctor	
c. Private hospital sister/nurse/doctor	
d. Public hospital sister/nurse/doctor	
e. Social worker or counsellor	
f. Chemist/pharmacist	
g. Home/community based care worker	
h. Traditional healer/herbalist	
i. Church Pastor/Elder	

j. Other. Please specify _____	☐☐

3.36. Date of first visit: _ _ /_ _ / _ _ _ _, or ___days, or ___weeks, or ___months, or ___years ago

Can't remember ☐

3.37. How far away is this provider from your home? ____km, or ___miles Don't know ☐

3.38. How long did it take you to get there from your home? _____hrs and/or ____ mins

Can't remember ☐

3.39. Which means of transport did you use?

a. Own car ☐
b. Lift from relative/friend ☐
c. Rented car (e.g. taxi, mini-cab) ☐
d. Bus ☐
e. Other. Please specify_____ ☐☐

3.40. What was your reason for visiting this care provider at the time you did? *Tick all appropriate boxes*

a. Symptoms did not go away ☐
b. Symptoms worsened ☐
c. Previous provider was not helpful ☐
d. Treatment(s) given by previous provider didn't work ☐
e. Too long to get test results from previous provider ☐
f. Advice from people/family/friends ☐
g. Referred from previous provider ☐
h. Other. Please specify_____ ☐☐

3.41. How much time went by between the date of first visit to provider 3 to date of first visit to provider 4?

a. Less than 2 weeks ☐
b. 2-4 weeks ☐
c. 1-3 months ☐
d. 4-6 months ☐
e. More than 6 months ☐

Notes to Interviewer:

If the delay was greater than 1 month, ask the question below. If "Other" is selected enter details in the box below.

3.42. What was the cause of the delay? *Tick all appropriate boxes*

☐ Delay caused by woman I delayed because:	Fear of: ☐ diagnosis ☐ treatment	☐ Did not think it was a serious problem	☐ No transport money ☐ Other financial constraints	Partner /Husband ☐ Did not give permission ☐ Fear of rejection	☐ No one to look after children	☐ Other reason
If Other (explain): ☐☐						

□ Delay caused by clinic	□ They gave me medicine and told me to come back after ___ weeks	□ There was a delay for test results	□ It took a _____weeks or____Months before I got an appointment to see a doctor	□ The doctor told me it was not serious/ there was nothing to worry about	□ Other reason
If Other (explain): ☐☐					

3.43. What was the outcome of the contact with this provider? *Tick all appropriate boxes.*

a. Reassurred and told not to worry ☐
b. Tests done but I was never told the results ☐
c. Told I had breast cancer but no treatment offered ☐
d. Told I had breast cancer and treatment offered ☐
    i. Please specify type of treatment_____ ☐☐
e. Told I had something else but no treatment offered ☐
    i. Please specify (i) type of diagnosis_____ ☐☐
f. Told I had something else and treatment offered ☐
    i. Please specify: (i) type of diagnosis_____ ☐☐
        a. (ii) type of treatment_____ ☐☐
g. Referred to another provider/facility ☐
h. Not applicable (this provider is one of the study hospitals) ☐

3.44. Did you visit any other provider?

a. Yes ☐ *(To the interviewer: go to the next page)*
b. No ☐ *(To the interviewer: skip to page 20)*

Contact 5

3.45. What is the name of the provider (e.g. hospital, clinic, traditional healer) you visited? _____ ☐☐

3.46. What type of care provider did you visit?

Notes for Interviewer:

Do **NOT** read out the choices provided for each question to the participant. Only tick what she says.

Care Provider	*Tick only 1 option*
a. Private doctor (General Practitioner)	
b. Community clinic sister/doctor	
c. Private hospital sister/nurse/doctor	
d. Public hospital sister/nurse/doctor	
e. Social worker or counsellor	
f. Chemist/pharmacist	
g. Home/community based care worker	
h. Traditional healer/herbalist	
i. Church Pastor/Elder	
j. Other. Please specify _____	☐☐

3.47. Date of first visit: _ _ /_ _ / _ _ _ _, or ___days, or ___weeks, or ___months, or ___years ago

Can't remember ☐

3.48. How far away is this provider from your home? ____km, or ___miles Don't know ☐

3.49. How long did it take you to get there from your home? _____hrs and/or ____ mins

Can't remember ☐

3.50. Which means of transport did you use?

a. Own car ☐
b. Lift from relative/friend ☐
c. Rented car (e.g. taxi, mini-cab) ☐
d. Bus ☐
e. Other. Please specify_____ ☐☐

3.51. What was your reason for visiting this care provider at the time you did? *Tick all appropriate boxes*

a. Symptoms did not go away ☐
b. Symptoms worsened ☐
c. Previous provider was not helpful ☐
d. Treatment(s) given by previous provider didn't work ☐
e. Too long to get test results from previous provider ☐
f. Advice from people/family/friends ☐
g. Referred from previous provider ☐
h. Other. Please specify_____ ☐☐

3.52. How much time went by between the date of first visit to provider 4 to date of first visit to provider 5?

a. Less than 2 weeks ☐
b. 2-4 weeks ☐
c. 1-3 months ☐
d. 4-6 months ☐
e. More than 6 months ☐

Notes to Interviewer:

If the delay was greater than 1 month, ask the question below. If "Other" is selected enter details in the box below.

3.53. What was the cause of the delay? *Tick all appropriate boxes*

☐ Delay caused by woman I delayed because:	Fear of: ☐ diagnosis ☐ treatment	☐ Did not think it was a serious problem	☐ No transport money ☐ Other financial constraints	Partner /Husband ☐ Did not give permission ☐ Fear of rejection	☐ No one to look after children	☐ Other reason
If Other (explain): ☐☐						
☐ Delay caused by clinic	☐ They gave me medicine and told me to come back after ___ weeks	☐ There was a delay for test results	☐ It took a _____weeks or____Months before I got an	☐ The doctor told me it was not serious/ there was	☐ Other reason	

			appointment to see a doctor	nothing to worry about	
If Other (explain): ☐☐					

3.54. What was the outcome of the contact with this provider? *Tick all appropriate boxes.*

a. Reassurred and told not to worry ☐
b. Tests done but I was never told the results ☐
c. Told I had breast cancer but no treatment offered ☐
d. Told I had breast cancer and treatment offered ☐
    i. Please specify type of treatment_____ ☐☐
e. Told I had something else but no treatment offered ☐
    i. Please specify (i) type of diagnosis_____ ☐☐
f. Told I had something else and treatment offered ☐
    i. Please specify: (i) type of diagnosis_____ ☐☐
        a. (ii) type of treatment_____ ☐☐
g. Referred to another provider/facility ☐
h. Not applicable (this provider is one of the study hospitals) ☐

3.55. Did you visit any other provider?

a. Yes ☐ *(To the interviewer: go to the next page)*
b. No ☐ *(To the interviewer: skip to page 20)*

Contact 6

3.56. What is the name of the provider (e.g. hospital, clinic, traditional healer) you visited? _____ ☐☐

3.57. What type of care provider did you visit?

Notes for Interviewer:

Do **NOT** read out the choices provided for each question to the participant. Only tick what she says.

Care Provider	*Tick only 1 option*
a. Private doctor (General Practitioner)	
b. Community clinic sister/doctor	
c. Private hospital sister/nurse/doctor	
d. Public hospital sister/nurse/doctor	
e. Social worker or counsellor	
f. Chemist/pharmacist	
g. Home/community based care worker	
h. Traditional healer/herbalist	
i. Church Pastor/Elder	
j. Other. Please specify _____	☐☐

3.58. Date of first visit: _ _ /_ _ / _ _ _ _, or ___days, or ___weeks, or ___months, or ___years ago

Can't remember ☐

3.59. How far away is this provider from your home? ____km, or ___miles Don't know ☐

3.60. How long did it take you to get there from your home? _____hrs and/or ____ mins

Can't remember ☐

3.61. Which means of transport did you use?

a. Own car ☐
b. Lift from relative/friend ☐
c. Rented car (e.g. taxi, mini-cab) ☐
d. Bus ☐
e. Other. Please specify_____ ☐☐

3.62. What was your reason for visiting this care provider at the time you did? *Tick all appropriate boxes.*

a. Symptoms did not go away ☐
b. Symptoms worsened ☐
c. Previous provider was not helpful ☐
d. Treatment(s) given by previous provider didn't work ☐
e. Too long to get test results from previous provider ☐
f. Advice from people/family/friends ☐
g. Referred from previous provider ☐
h. Other. Please specify_____ ☐☐

3.63. How much time went by between <u>the date of first visit to provider 5 to date of first visit to provider 6</u>?

a. Less than 2 weeks ☐
b. 2-4 weeks ☐
c. 1-3 months ☐
d. 4-6 months ☐
e. More than 6 months ☐

<u>Notes to Interviewer:</u>

If the delay was greater than 1 month, ask the question below. If "Other" is selected enter details in the box below.

3.64. What was the cause of the delay? *Tick all appropriate boxes*

☐ Delay caused by woman I delayed because:	Fear of: ☐ diagnosis ☐ treatment	☐ Did not think it was a serious problem	☐ No transport money ☐ Other financial constraints	Partner /Husband ☐ Did not give permission ☐ Fear of rejection	☐ No one to look after children	☐ Other reason
If Other (explain): ☐☐						
☐ Delay caused by clinic	☐ They gave me medicine and told me to come back after ___ weeks	☐ There was a delay for test results	☐ It took a _____weeks or____Months before I got an appointment to see a doctor	☐ The doctor told me it was not serious/ there was nothing to worry about	☐ Other reason	
If Other (explain): ☐☐						

3.65. What was the outcome of the contact with this provider? *Tick all appropriate boxes.*

a. Reassurred and told not to worry ☐
b. Tests done but I was never told the results ☐
c. Told I had breast cancer but no treatment offered ☐
d. Told I had breast cancer and treatment offered ☐
    i. Please specify type of treatment_____ ☐☐
e. Told I had something else but no treatment offered ☐
    i. Please specify (i) type of diagnosis_____ ☐☐
f. Told I had something else and treatment offered ☐
    i. Please specify: (i) type of diagnosis_____ ☐☐
        a. (ii) type of treatment_____ ☐☐
g. Referred to another provider/facility ☐
h. Not applicable (this provider is one of the study hospitals) ☐

3.66. Did you visit any other provider?

a. Yes ☐ *(To the interviewer: use additional contact forms)*
b. No ☐ *(To the interviewer: go to the next page)*

Section 4. Local Health Care Services

Notes for Interviewer:

To the participant: "*Many thanks. I am now going to ask you a few question about the health care services available where you live at the time when you first noticed your breast changes*".

- The questions below refer to the place where the woman lived when her current breast problems were first noticed.

4.1. Do you still live in the same area where you lived when you your current breast problem was first noticed?

a. Yes ☐
b. No, I moved to another area because of my illness
(e.g to be close to relatives/friends, medical facilities) ☐
c. No, I moved somewhere else for other reasons ☐

4.2.Is there any health care service or hospital located within easy access or reach of where you lived when your current breast problem was first noticed?

a. Yes ☐
b. No ☐

4.3.If there is a health centre near where you lived when your current breast problem was first noticed please indicate type of health facility:

a. Primary Health Centre ☐
b. General Hospital ☐

c. Teaching Hospital ☐
d. Private Hospital ☐
e. Other. Please specify_____ ☐
f. There is no health care service/hospital where I live(d) ☐

4.4. Did you visit this health center within easy access of your home for your current breast problem?

Note to Interviewer:

If the participant replies "Yes", find out which provider number does it refer to and add the number in the space provided below.

a. Yes ☐ Contact no.___ *{To Interviewer: Enter contact no. from section 3 here}*
b. No ☐
c. There is no health care service/hospital where I live(d) ☐

4.5. If you did NOT visit the health center near your home, what was the main reason for that? *Tick all appropriate options.*

Note to Interviewer:

Do **NOT** read out the choices below to the participant. Only ticks what she says.

a. I did not want my neighbours to see me going to the health center ☐
b. The clinic was too expensive ☐
c. The health center had little experience in dealing with breast conditions ☐
d. It took too long to get an appointment there ☐
e. Its doctors/nurses asked you to go elsewhere ☐
f. It took too long to get test results ☐
g. I had a private doctor in another hospital who I wanted to see first ☐
h. I wanted to go to a center close to where my children live ☐
i. Other. Please specify_____ ☐☐

Section 5. Patient's Perception of Family/Community Support

Note for Interviewer:

To the participant: "*Many thanks for your help so far. I am now going to ask you a few questions about the support you are getting from your family and community.*"

5.1. After your breast problem was noticed who decided what to do next?

a. You ☐
b. Your husband/partner ☐
c. You jointly with your husband partner ☐
d. Other family member ☐
e. Other. Please specify_____ ☐☐

5.2. Did you try to hide your breast problem from:

a. Your husband ☐
b. Your children ☐
c. Other relatives ☐
d. Some friends ☐
e. Some of your neighbours ☐
f. Others. Please specify_____ ☐☐
g. I did not try to hide the problem from anyone ☐

5.3. Who usually accompanies you during your visits to the clinic/hospital?

a. Your husband/partner ☐
b. Your children ☐
c. Others. Please specify_____ ☐
d. A friend ☐
e. No one ☐

5.4. Would you prefer to be accompanied by someone else? If so, by whom:

a. Yes, by husband/partner ☐
b. Yes, by your children ☐
c. Yes, by a friend ☐
e. Yes, by someone else. Please specify_____ ☐☐
f. No, I am happy as it is ☐

5.5. Since the start of your health problems, have you felt that you are being supported by your:

a. Family?	Yes ☐	No ☐	Not sure ☐
b. Friends?	Yes ☐	No ☐	Not sure ☐
c. Community?	Yes ☐	No ☐	Not sure ☐
d. Employer(s)?	Yes ☐	No ☐	Not sure ☐

5.6. Who is covering/will cover your health related expenses?

a. Self ☐
b. Family/Friends ☐
c. National Health Insurance Scheme (NHIS) ☐

d. Employer ☐
e. Church/Pastor/Elder ☐
f. Other. Please specify_____ ☐☐
g. Don't know ☐

5.7. If you held a job outside your home prior to your current breast problem do you still hold the same job?

Note to Interviewer:

Tick option e) if the woman did not have a job outside her home before the start of her current breast problem.

a. Yes, I still hold the same job ☐
b. No, I had to move to a different job because of my breast health problem ☐
c. No, I am no longer able to hold a job because of my breast problem ☐
d. No, I move to a different job for reasons unrelated to my health problem ☐
e. I did not have a job prior to the start of my current health problems ☐

5.8. Are you getting additional help to carry out your home chores because of your breast problem?

a. Yes, from my husband/partner or children ☐
b. Yes, from other relatives ☐
c. Yes, from friends ☐
d. Yes, from others. Please specify_____ ☐☐
e. No, I feel the need but there is no one available/willing to help ☐
f. No, I haven't felt the need to get any additional help ☐

Section 6. Hurdles to Seeking Help for Breast Condition

Notes for Interviewer:

To the participant: "*Many thanks. To finish off this interview I would like to ask you a few questions on factors that may have affected the way in which you sought medical help for your breast condition*".

6.1. After your breast problem was first noticed how long (in total) did it take for you to reach this hospital?

Notes for Interviewer:

Check consistency of her answer with the timeline of key events you completed throughout the interview.

_____weeks, or _____months, or _____years and _____months

Can't remember ☐

6.2. If more than 3 months, which of the following factors do you think contributed to the delay in reaching this hospital?

Note for Interviewer:

- To be completed **ONLY if there was a delay of more than 3 months**.

- Below is a list of potential barriers a woman might face that prevent her from seeking early help after her breast problem was noticed. Read out this list.

Ask her to answer "*Yes*", "*No*" or "*Not sure*" for each of the factors as it applies to her particular circumstances. Tick only one answer per factor. If the woman mentions a factor not listed enter the details in the "Other" box.

Personal barriers			
	Yes	No	Not sure
1. Did not think it was a serious problem			
2. Embarrassed or worried about what the doctor might find			
3. Did not believe breast problem could be taken care of in the hospital			
4. Fear of treatment caused delay			
5. Fear of dying caused delay			
6. Believe in traditional medicine (TM) and wanted to try it first			
*7. Other. Please specify*_____ ☐☐			
Family/Community barriers			
8. Husband did not give permission			
9. Fear of rejection by husband/family members			
10. No one at home to look after the children			
11. Family/community members believe in traditional medicine (TM) / recommended TM over western medicine			
12. Was confused with the advice I was getting from others (e.g. relatives, friends, others) on where to go for help			
13. Fear of rejection by community members			
*14. Other. Please specify*_____ ☐☐			
Economic barriers			
15. Employed and could not get time off work to go to the hospital so delayed			
16. Could not afford transportation to the hospital			
17. Could not afford treatment so delayed			
18. Was worried of loosing my job so delayed			
19. Too many other financial commitments			
*20. Other. Please specify*_____ ☐☐			
Health Service Barriers {To Interviewer: Do NOT include access to traditional or alternative medicines}			
21. Clinic/hospital(s) located too far away from home			
22. Difficulty in getting earlier appointment(s) to see the doctor			
23. Was told by doctors in other clinic/hospital that my problem was not serious			
24. Had to wait a long time to be told of test results			
25. Was given treatment but it did not work			
26. The clinic/hospital(s) I went first did not have the necessary resources			
27. It took a long time before I was finally sent to this hospital			
*28. Other. Please specify*_____ ☐☐			
Other barriers			
*29. Please specify*_____ ☐☐			

Notes for Interviewer:

To the participant*: "Many thanks for your time and help with this study. Very much appreciated"*

TIMELINE OF KEY EVENTS: SUMMARY

Notes for Interviewer:

This section should be competed by you as the interview progresses.

It will help you to keep track of key dates of a woman's journey. Please check that the dates follow a logical sequence (e.g. the date of first visit to provider 2 should not come before date of first visit to provider 1).

Contacts	**Date symptoms were first noticed**	**Contact 1**	**Contact 2**	**Contact 3**	**Contact 4**	**Contact 5**	**Contact 6**
Care Provider							
Date of first visit							

Contacts	**Contact 7**	**Contact 8**	**Contact 9**	**Contact 10**	**Contact 11**	**Contact 12**
Care Provider						
Date of first visit						

The Nigerian Integrative Epidemiology of Breast Cancer (NIBBLE) Study

Main Risk Factor Questionnaire

Study Site: ☐☐☐☐☐

Study ID: ☐☐☐☐☐☐☐☐☐☐ Hosp ID: ☐☐☐☐☐☐☐☐☐☐

Interviewer code:☐☐☐☐

Date Of Interview: __ __ / __ __ / __ __ __ __

Day Mo Year

First name: _____ Last name: _____

Phone no: ☐☐☐☐ ☐☐☐ ☐☐☐☐ Phone no 2: ☐☐☐☐ ☐☐☐ ☐☐☐☐

Contact Address: _____

_____

Name of next of kin 1: _____

Relationship of next of kin:_____

Phone no of next of kin : ☐☐☐☐ ☐☐☐ ☐☐☐☐

Contact Address: _____

of next of kin_____

Name of next of kin 2: _____

Relationship of next of kin 2:_____

Phone no of next of kin 2: ☐☐☐☐ ☐☐☐ ☐☐☐☐

Contact Address: _____

of next of kin_____

Date of First Diagnosis: __ __ / __ __ / __ __ __ _

DAY MO YEAR

Section A: Background Information

1. What is your date of birth? _ __ / __ __ / __ __ __ __ Age: ☐☐☐ years

DAY MO YEAR

2. Where do you work: _____
   Office number Street name

   _____

   City State

3. Do you have a personal income? a. Yes ☐ b. No ☐

4. If yes, what was the type of job you held most recently:

   a. Housework ☐ b. Petty Trader/Odd jobs ☐

   c. Unskilled occupations (e.g. Security guard, porter, farmer) ☐

   d. Non-Manual skilled occupations (office workers) ☐

   e. Manual skilled occupations (bricklayers, coalminers, trader) ☐

   f. Managerial and lower professionals (managers, teachers) ☐

   g. Professional (doctor, lawyer, nurse, pharmacist, accountant) ☐

5. For how long have you been doing this work: ☐☐years ☐☐ Months

6. What is the range of annual income for yourself, your husband or others in your household?

   a. Less than N150,000/year b. N150,000-N500,000/year c More than N500,000/year

7. What religion do you practice:

   a. Christianity ☐ b. Islam ☐ c. Traditional ☐ d. None ☐

   e. Others ☐ please specify: _____

8. Please tell us about your tribe, that of your parents and grandparents. If the tribe is not listed, please write it in the "others" row under the person's name:

No	Tribes	Family members

		You	Father	Mother	Father's father	Father's mother	Mother's father	Mother's mother
a.	Fulani							
b.	Hausa							
c.	Igbo							
d.	Ijaw							
e.	Kanuri							
f.	Nupe							
g.	Yoruba							
h.	Others							

9. What is your marital status:

   a. Married ☐ b. Single ☐ c. Separated ☐

   d. Divorced ☐ e. Widowed ☐ f. Cohabiting ☐

   g. Others, ☐ please specify: _____

10. What type of marital arrangement do you have:

   a. Monogamous (Living together) ☐ b. Polygamous (All living together) ☐

   c. Monogamous (Living separately) ☐ d. Polygamous (Living separately) ☐

   e. Not married and living alone ☐ f. Not married and living with family ☐

   g. Not married and living with Boyfriend ☐ h. Not married but living with friends ☐

11. What is the highest level of education that you attained:

   a. No formal schooling ☐ b. Koranic school only ☐ c. Vocational only ☐

   d. Less than 5 years of formal schooling (Did not complete primary school) ☐

   e. Completed primary school only (6 years) ☐

   f. Some high school (7 – 11 years) ☐

   g. Completed high school (12 years) ☐

h. Had post high school education but not university ☐

i. Completed university education ☐

j. Postgraduate degree ☐

Section B: Determination of household wealth (Modified Filmer-Prichett Index)

12. House ownership

a. Owned ☐ b. Rented ☐ c. Other ☐

Specify_____

13. Type of house

a. Stand-alone family unit ☐ b. Duplex ☐

c. 2-3 bedroom apartments ☐ d. Self-contained (studio) apartment ☐

e. Single room f. Others ☐, please specify: _____

14. How many people live in your home ☐☐

15. Source of water

a. Go to fetch ☐ b. Surface well in residence ☐

c. Deep well in residence ☐ d. Borehole in residence ☐

e. Municipal water supply ☐ f. Bottled water ☐

g. Public water tap ☐ h. Surface water (river, pond) ☐

i. Tanker ☐ j. Others ☐, please specify: _____

16. Do you do anything to make your water safer to drink

a. Yes ☐ b. No ☐

17. What do you do to make your drinking water safer to drink (Mark all that apply)

b. Filtering ☐ b. Boiling ☐

c. Adding chemicals ☐ d. Others ☐, please specify: _____

18. What is your main source of cooking fuel

a. Gas ☐ b. Electricity ☐

c. Kerosene stove ☐ d. Firewood/charcoal ☐

e. Others, ☐ please specify: _____

19. Do you have a separate room for cooking where you live (like a kitchen)

a. Yes ☐ b. No ☐

20. What type of toilet facility do you use

a. Water cistern ☐ b. Aqua privy ☐

c. Pit toilet ☐ d. None ☐

21. Which of these goods do you or your partner own

a. Car ☐ b. Motorcycle ☐

c. Refrigerator ☐ d. TV ☐

e. Bicycle ☐ f. Electric fan ☐

22. What would you consider your social class

Participants view		Interviewer's view	
a.	Lower class ☐	a.	Lower class ☐
b.	Lower middle class ☐	b.	Lower middle class ☐
c.	Upper middle class ☐	c.	Upper middle class ☐
d.	Upper class ☐	d.	Upper class ☐

Section C: Reproductive History

22. At what age did you start having regular menstrual periods? ☐☐ years ☐don't know

23. How long ago was your last menstrual period? ☐☐ years ☐☐ months ☐☐days

24. Have your menstrual periods stopped for 1 year or more? Please do not include times when your periods stopped because of pregnancy, breast-feeding, or serious illness.

Yes ☐ No ☐

25. How old were you when you had that period before your periods stopped for 1 year or more?

☐☐ years

26. Did your menstrual periods stop because of:

a. The periods stopped by themselves
b. Past surgery
c. Past medical treatment
d. Current treatment for any cancer

27. Have you ever taken any medications (oestrogen, progestin, or other female hormones) for menopause? If No Skip to 30

Yes ☐ No ☐

28. How old were you when you <u>first</u> took these medications for menopause?

☐☐ years

29. How many years in total did you take these medications for menopause?

☐☐ years

30. Have you ever used hormonal contraceptives, in the form of birth control pills, implants, or injections? If no skip to 33

Yes ☐ No ☐

31. How old were you when you first started taking hormonal contraceptives?

☐☐ years

32. In total, how many years did you use hormonal contraceptives for?

☐☐ years

33. Have you ever been pregnant? If No skip to question 35

Yes ☐ No ☐

IF YES:

a. How many pregnancies have you had? ☐☐

. b. How many live births have you had? ☐☐

c. How old were you when you had your first live birth? ☐☐

d. How old were you when you had your last live birth? ☐☐

e. Did you ever breast-feed a child for one month or longer?

Yes ☐ No ☐

34. Pregnancy history

	1st PREGNANCY	2nd PREGNANCY	3rd PREGNANCY
What was the outcome of your pregnancy?			
Use the following code for outcome of pregnancies – *Currently pregnant* 1 *Single live birth* 2 *Multiple birth* 3 *Stillbirth* 4 *Miscarriage* 5 *Tubal or ectopic pregnancy* 6 *Induced abortion* 7 *Don't know* 9			
During what month and year (was your baby born / did this pregnancy end)?	__ __ /__ __ __ _ MO YEAR	__ __ /__ __ __ _ MO YEAR	__ __ /__ __ __ MO YEAR
How long was this pregnancy in months?	____	____	____
IF <u>SINGLE</u> LIVE BIRTH OR STILLBIRTH: Did you have a boy or a girl?	____ # of BOYS	____ # of BOYS	____ # of BOYS
IF <u>MULTIPLE</u> LIVE BIRTHS OR STILLBIRTHS:	____ # of GIRLS	____ # of GIRLS	____ # of GIRLS

IF SINGLE OR MULTIPLE <u>LIVE</u> BIRTH(S): Did you breast-feed (this child / these children)? **<u>IF YES:</u>** For how many **months** did you breast-feed (this child / these children)?	YES NO	YES NO	YES NO
	4th PREGNANCY	**5th PREGNANCY**	**6th PREGNANCY**
What was the outcome of your pregnancy?	_____	_____	_____

Use the following code for outcome of pregnancies –

Currently pregnant	*1*	*Single live birth*	*2*
Multiple birth	*3*	*Stillbirth*	*4*
Miscarriage	*5*	*Tubal or ectopic pregnancy*	*6*
Induced abortion	*7*	*Don't know*	*9*

During what month and year (was your baby born / did this pregnancy end)?	__ __ /__ __ __ _ MO YEAR	__ __ /__ __ __ _ MO YEAR	__ __ /__ __ __ MO YEAR
How long was this pregnancy in months?	____	____	____
IF <u>SINGLE</u> LIVE BIRTH OR STILLBIRTH: Did you have a boy or a girl? **IF <u>MULTIPLE</u> LIVE BIRTHS OR STILLBIRTHS:**	____ # of BOYS ____ # of GIRLS	____ # of BOYS ____ # of GIRLS	____ # of BOYS ____ # of GIRLS
IF SINGLE OR MULTIPLE <u>LIVE</u> BIRTH(S): Did you breast-feed (this child / these children)? **<u>IF YES:</u>** For how many **months** did you breast-feed (this child / these children)?	YES NO	YES NO	YES NO

	7th PREGNANCY	8th PREGNANCY	9th PREGNANCY
What was the outcome of your pregnancy?	_____	_____	_____
Use the following code for outcome of pregnancies – *Currently pregnant* 1 *Single live birth* 2 *Multiple birth* 3 *Stillbirth* 4 *Miscarriage* 5 *Tubal or ectopic pregnancy* 6 *Induced abortion* 7 *Don't know* 9			
During what month and year (was your baby born / did this pregnancy end)?	__ __ /__ __ __ __ MO YEAR	__ __ /__ __ __ __ MO YEAR	__ __ /__ __ __ MO YEAR
How long was this pregnancy in months?	____	____	____
IF <u>SINGLE</u> LIVE BIRTH OR STILLBIRTH: Did you have a boy or a girl? **IF <u>MULTIPLE</u> LIVE BIRTHS OR STILLBIRTHS:**	____ # of BOYS ____ # of GIRLS	____ # of BOYS ____ # of GIRLS	____ # of BOYS ____ # of GIRLS

IF SINGLE OR MULTIPLE <u>LIVE</u> BIRTH(S): Did you breast-feed (this child / these children)? **<u>IF YES:</u>** For how many **months** did you breast-feed (this child / these children)?	YES NO	YES NO	YES NO

35. Have you ever taken a drug for infertility to try to become pregnant, or because your periods stopped unexpectedly?

Yes ☐ No ☐

<u>IF YES:</u>

a. What type of medication?

i. Pill ☐ ii. D&C ☐ iii. Others ☐, please specify: _____

3

b. How old were you when you <u>first</u> started to take this medication?

☐☐ years

c. How many months in total did you use this treatment?

☐☐ years

d. Which, if any, of the following drugs did you take?

	YES	NO	Don't know	
Clomid	☐	☐	☐	
Pergonal	☐	☐	☐	
Serophene	☐	☐	☐	
hCG	☐	☐	☐	
Other	☐	☐	☐	Please specify: _____

Section D: Medical History

36. Has a doctor ever told you that you had cancer, leukaemia, or a malignant tumour?

Yes ☐ No ☐

IF YES:

	CANCER #1	CANCER #2	CANCER #3
What type of cancer did you have?			
How old were you when this cancer was first diagnosed in years?			
In what year were you diagnosed with this cancer?			
How was the cancer treated?			

37. Has a doctor ever told you that you had benign breast disease, such as non-cancerous cyst or a breast lump?

Yes ☐ No ☐

IF YES:

a. How old were you when this was first diagnosed? ☐☐

b. How was the benign breast disease, such as non-cancerous cyst or a breast lump

Traditional ☐ Surgery ☐ Medical treatment ☐ No treatment ☐

Section E: Lifestyle factors

Smoking

38. Do you smoke cigarettes or any other tobacco containing products? If No skip to No 44.

a. Yes ☐ b. No ☐

39. Have you ever smoked up to 100 cigarettes (5 packets) in total in your entire life? If No skip to No 44

b. Yes ☐ b. No ☐

IF YES:

40. How old were you when you started smoking regularly? ☐☐ years

41. When you smoke, how often do you smoke?

<1/month ☐ 1/month but < 1/week At lea☐week but < 1/day Daily ☐ ☐

42. When you smoke, how many sticks of cigarettes do you smoke daily?

1☐ 2-10 11☐ More thar☐ ☐

43. Are you currently exposed to second hand smoke (passive smoking) in your working place or at home?

Drinking

44. Do you drink alcohol? If No skip to No 49

    a. Yes ☐ b. No ☐

45. Have you ever drank at least a measure of alcohol - *bottle of beer, a glass of alcoholic wine, a shot of "hot" drink or more or regularly taken any alcohol containing medicines* - in the past 5 years? If No skip to No 49

    b. Yes ☐ b. No ☐

46. How old were you when you first started drinking regularly? ☐☐ years

47. How often did you drink alcohol in the last 1 year?

<1/month ☐ 1/month but < 1/week At lea☐ week but < 1/day Daily ☐ ☐

48. How many measures of alcohol do you usually drink at a time on the days when you drink?

1 ☐ 2-5 5 -☐ More thar☐ ☐

Physical activity

49. What is your usual walking pace

    Slow/Casual ☐ Normal ☐ Brisk ☐ Very brisk/striding ☐

Unable to walk ☐

50. How many flights of stairs/staircase (not individual steps) do you climb daily?

None ☐ 1 – 2 ☐ 4 – 5 ☐ 5 – 9 ☐ 0 – 14 1 ☐ more ☐

51. During the past year, what was the *average amount of time you spent per week* on each of the activities listed below

Activity	0	1–4 mins	5–19 mins	20–59 mins	One hour	1–1.5 hrs	2–3 hrs	4–6 hrs	7–10 hrs	11+ hrs
Walking to and from work										
Jogging										
Running										
Bicycling (including stationary bikes)										
Dancing – church, social occasions etc										
Table tennis/Lawn Tennis										
Soccer										
Squash										
Golf										

Hiking/Walking										
Swimming										
Aerobics										
Weight lifting or resistance exercises										
Other vigorous activities, please specify: _____										

52. During the past year, how *many hours per week* did you spend on the activities listed below

Activity	0 hours	One hour	2-5 hrs	6-10 hrs	11-20 hrs	21-40 hrs	41-60 hrs	61-90 hrs	Over 90 hrs
Standing or walking around at work or away from home (hrs/week)									
Standing or walking around at home (hrs./week)									
Sitting while working or while away from home									

include time you were driving or sitting in a vehicle (hrs/week)									
Sitting at home watching TV (hrs/week)									
Sitting at home doing other things – resting, working on computer, reading, eating (hrs/week)									

53. In an average week, how many days do you usually exercise (include brisk walking or more strenuous activity)?

None ☐ day ☐ days 3 d☐s 4 d☐s ☐

5 days ☐ 6 days ☐ 7 days ☐

54. Do you have doctor confirmed –

a. Hypertension ☐ b. Diabetes ☐

c. Any other chronic illness, ☐lease specify: _____

d. None at all ☐

Section F: First Degree – (Parents, Brothers and Sisters and Children) - Family History of Cancer

55.

No	Which of your relatives was diagnosed with cancer?	What type of cancer does/did he/she have?	How old was he/she when the cancer was first diagnosed?	How was the cancer treated – orthodox or unorthodox or both?

Section G. Measurements

56. Anthropometric measurements

a. Standing Height (cm) ☐☐☐

b. Sitting Height (cm) ☐☐☐

c. Weight (kg) ☐☐☐

d. Waist (cm) ☐☐☐

e. Hip (cm) ☐☐☐

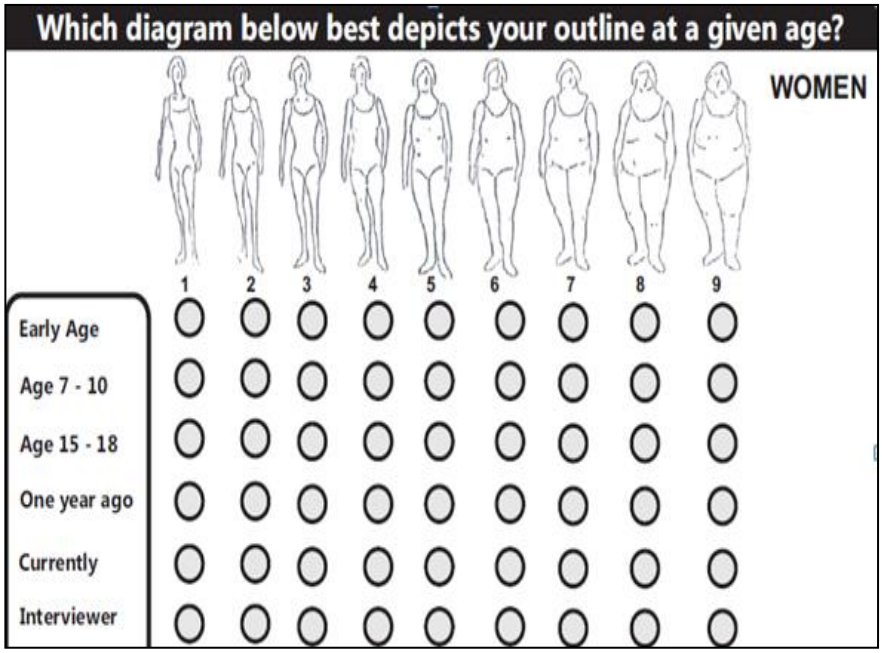
f. Blood pressure Sys ☐☐☐
Dias☐☐☐

57. What was your weight at age 18 ☐☐☐ (kg)

58. What was your weight at age 30? ☐☐☐ (kg)

59. What was your weight at age 40? ☐☐☐ (kg)

60. Somatotype images



END: Thank you very much for taking the time to complete this interview.

Clinicopathological Information Form

Section 1 – Clinical and Pathological Information

Note to Clinician: This form is to be completed by the attending clinician during the patient's first visit.
Sections on **Morphology, Histology and Grade** for which information is not available until after a biopsy is done and results received can be completed afterwards.
Please tick the appropriate options.

Clinical Information

Diagnosis
Date **(Day / Month / Year)**
__ __ / __ __ / __ __ __ __

□1 **New primary**

□2 **Recurrence (not to be included)**

Histology

□1 **Invasive malignant neoplasms**

□2 **In-situ malignant neoplasm**

□3 **Benign breast disease**

Grade (differentiation)

□1 **Well**

□2 **Moderately**

□3 **Poorly**

□4 **Not specified**

Presenting Signs

□1 **Lump**

□2 **Skin changes**

□3 **Nipple discharge**

□4 **Ulceration**

□5 **Axillary nodes**

□6 **Metastases**

Laterality

□1 **Left**

□2 **Right**

□3 **Bilateral**

Morphology

□1 **Ductal**

□2 **Lobular**

□3 **Medullary**

□4 **Mucinous/colloid**

□5 **Papillary**

□6 **Tubular**

□7 **Paget's Disease**

□8 **Ductular**

□9 **Inflammatory**

□10 **Other _____**

Receptor staining scores

ER (0,1+,2+,3+): ___

PR (0,1+,2+,3+): _____

HER2 (0,1+,2+,3+): _____

TNM Clinical Staging

Tumour	**N**ode (No. lymph nodes affected)	Distant **M**etastases
□TX (NK)	□NX (NK)	□MX (NK)
□T0 (no primary)	□N0 (0)	□MO (none)
□Tis (in situ)	□N1 (1-3)	□M1 (present)
□T1 (<2cm)	□N2 (4-9)	
□T2 (>2 to 5 cm)	□N3 (10+)	
□T3 (>5cm)		
□T4 (chest wall/ skin/inflammatory)		

STAGE **(0, I, IIA, IIB, IIIA, IIIB, IIIC, IV): ____**

Metastases present/suspected at diagnosis

□1 **None** □4 **Lung**

□2 **Bone** □5 **Brain**

□3 **Liver** □6 **Metastases but site NK**

Basis of diagnosis

□1 **Clinical only** □4 **Cytology**

□2 **Imaging** □5 **Histology of primary**

□3 **Surgery** □6 **Histology of metastases**

Dates	**Day/Mo/Year**
First attended this hospital	
First Clinical Examination	
First Clinical Diagnosis	
Patient first informed of diagnosis	
First Histology	
Result of Histology	
Interval between first presentation to hospital and commencement of definitive treatment (In months)	

Section 2 -Treatment

Treatment	Intended	Actual			Radiotherapy and Chemotherapy only	
		Date received	**Response to Treatment**	**Side-effects**	**No of cycles recommended**	No of cycles attended
Surgery (Lumpectomy)						
Surgery (Mastectomy)						
Radiotherapy						
Axillary lymphectomy						
Tamoxifen						
Chemotherapy						
Herceptin						

APPENDIX 7: LABORATORY STANDARD OPERATING PROCEDURES

Breast Biopsies

This procedure will be done by the collaborating surgeon/site investigator at the hospital. The biopsy sample can be obtained through either TruCut biopsy needles, excisional or incisional biopsies. The research associate is expected to liaise with the site collaborator and get information on the dates when the participants have been booked to come in for their biopsies. She should be present on the days when biopsies are done.

The fixation process outlined below is intended to ensure that tissue samples collected from study participants are collected, fixed and preserved in a safe and efficient manner while contamination and loss of molecular and structural integrity are minimal. It is important that the procedure is done similarly across all sites to ensure that reliable and comparable results are obtained.

1. Fixation should be performed as soon as possible after the specimen is collected. Optimally tissue should be fixed within 4 hours of biopsy.
2. Have materials and equipment ready. Have the container containing 10% neutral pH buffered formalin labeled and ready.
3. Record time from when biopsy is done to when tissue is fixed. Record this time as 'time from resection to fixation'.
4. Perform fixation at room temperature (25º C).
5. The volume of the fixative should be at least 10-15 times greater than the volume of the tissue (i.e., 10-15 ml for every gram of tissue).
6. If needed particularly in cases of large tissue, dissect the tissue before fixation to ensure adequate penetration of the fixative. This can be done either by surgeon or research associate using a surgical blade to slice or make incisions on the tissue.
7. It is recommended that specimen should be thin slices of tissue in order to be adequately fixed. If this is not possible, do not use specimens that are over 4-5 mm in thickness.
8. For sites in Abuja, duration of fixation should be overnight to 24 hours but no more than 48 hours before the sample reaches the IHVN laboratory in Abuja.
9. For sites outside Abuja, duration of fixation should be overnight to 48 hours and fixed tissue should be transported to the pathology laboratory at the site for embedding in paraffin blocks. Blocks should be stored by the site collaborator or research associate until transported to Abuja in monthly or 2 monthly batches depending on the number collected.
10. Record time from fixation to when sample is received at the IHVN laboratory in Abuja. Record this time as 'time from fixation to laboratory'.

Embedding of breast tissue prior to transportation

1. For samples collected outside Abuja, tissue should be processed, embedded and made into paraffin blocks at the pathology laboratory at the site before transporting it to Abuja.
2. All blocks should be properly labeled.
3. Paraffin blocks should be stored at or below room temperature. Excessive exposure to sun or extreme temperatures should be prevented.
4. Blocks should be stored in moisture resistant cardboard boxes or plastic storage boxes.
5. Record storage location

Transport of biopsy specimens

For sites within Abuja, sample collection should be done on Mondays-Thursdays and no biopsy specimens should be collected on Fridays. This is to avoid logistic issues in transporting samples on the last working day of the week or over the weekend to the IHVN laboratory.

For centers outside Abuja, biopsy specimens should be fixed in formalin and sent to the hospital's pathology laboratory where these tissue will be embedded in paraffin and then tissue blocks stored and sent to the IHVN laboratory in Abuja on a monthly or 2 monthly basis depending on the number of specimens retrieved every month at each specific site.

Tissue Fixation

- 10% Neutral Buffered Formalin (10% NBF) is used for the fixation of tissue.

Note: Fixation time is dependent on tissue size. Small tissue pieces (10x10x3 mm), specimens less than 3 mm thickness (e.g. CNB) may be placed in fixative directly. Specimens greater than 3 mm thicken (e.g. mastectomy) must be dissected immediately, and the final tissue samples (ideally less than 2 mm thick) should be placed in fixative as soon as possible. Loss of antigenicity due to delayed fixation cannot be recovered. If large specimens cannot be dissected immediately, they should be incised ("bread loafed") to a thickness of 3 mm or less, and the entire specimen should be placed in fixative immediately. The fixative should freely circulate around all surfaces of the specimen. Temporary storage of specimens at 4 C to delay fixation is not acceptable. This is true regardless of biopsy method (e.g. CNB or trimmed or incised excisional specimens). The fixation time starts when tissue is placed in formalin, and ends when the fixation portion of the automated tissue processor ends. Given that most automated tissue processors provide only two to three hours of fixation, several hours of fixation prior to automated processing is usually required. Therefore, it is advisable to allow all specimens to fix overnight prior to automated tissue processing. The optimal length of fixation is 24 hours (12 hours minimum, 36 hours maximum). Longer fixation times may be acceptable if using robust antigen recovery, but this should be verified empirically.

Slide baking and deparaffination

It is advised that paraffin slides be baked at 60 degrees C for between 1-14 hrs. This temperature must not be exceeded as a higher temperature may result in antigen destruction. Insufficient baking may also lead to uneven immunoreactivity. For the simpler techniques, sections will adhere well to clean slides with no coating, particularly if they have been well dried; but to ensure that sections and cells will not detach from slides during the longer procedures of immunohistochemical staining, an adhesive is usually applied to the slide before the section is picked up or the cells are allowed to settle. This is an essential precaution if heat induced antigen retrieval method have to be used. Among the many slide coating that have been suggested and universally accepted are poly-L lysine and Histogrip from Invitrogen. Positively charged slides are now sold commercially.

Antigen Recovery

During routine tissue fixation, tissue specimens are typically fixed in 10% buffered formalin for long period of time, prior to embedding in paraffin. The formalin preserves the tissue by forming cross-linking aldehyde bonds. While excellent for the preservation of cellular morphology, the formalin cross-linking often denatures and disrupts the epitopes of investigational interest. Antigen retrieval is the process by which the cross-linked molecules are unmasked so that proper antibody-antigen reaction can take place. Tissue section pretreatments are therefore essential for obtaining the best possible results when attempting to detect epitopes in formalin-fixed, paraffin embedded tissue sections. These pretreatments are also excellent for increasing antigenicity (e.g. staining signal) in archival material. There are two main types of antigen retrieval namely:

Heat induced epitope retrieval (HIER)

This is the technique of heating a slide in buffer prior to staining. Heating provides the energy not to only rupture the hydroxyl bonds formed by the fixative with the protein antigen, freeing some antigens, but also to release tissue –bound calcium ions which contribute to tighter bonds with the fixative. HIER is a major step forward in IHC and has been found to be effective in not only formalin fixed tissue. HIER is carried out after the section has been cut, baked, deparaffinized and hydrated. There is a myriad of available heating sources for HIER such as autoclaves, microwave and pressure cooker but the source selected should be one that allows for sustained high temperature and uniform heating. When using microwave, the same no of coupling jars filled with buffer should be kept in the oven at all time to maintain consistency of heating. At least 2-3 heat/cool cycles are needed (5-10 minutes each) with replenishment of evaporated buffer in between each cycle. These slides should be cooled in their original containers at room temperature and not allowed to air-dry. The duration of heating is inversely proportional to the maximum temperature reached. The actual amount of time to heat the slides in the buffer should be determined in each laboratory according to the overall fixation time. After a certain amount of time, heating will not produce anymore benefit and will result in deterioration in morphology.

Assay development

Studying gene expression at the protein level on histological slides is best done with IHC. Almost any protein can be measured provided that a sufficiently sensitive and specific primary antibody is available. No two antibodies are identical in their abilities to immunostain fixed tissue and the assay for each new antibody must be individually "tweaked" for optimum performance.

The first step, referred to as Level I, determines the need and optimum type of antigen retrieval (AR), as well as confirms the specificity of the antibody. AR is the generic term for methods used to expose antigens that have been masked by tissue fixation (usually in 10% formalin). Without AR, many antibodies are unable to generate an IHC signal in routine archival tissue. With AR, most antibodies can successfully generate a staining signal, although the chemistry is poorly understood and the best strategy has to be determined empirically. Sometimes the resulting IHC signals are unexpected, (e.g. a cytoplasmic signal is observed using an antibody against a putative nuclear protein, etc.), revealing unwanted cross-reactivity of the primary antibody or, occasionally, novel biology. There are several AR strategies, most employing either pre-incubation with various proteolytic enzymes or heating slides in buffers of varying chemical composition (salts, chelators, and denaturing agents) and pH. Level I involves heating slides at 120°C for 10 minutes in a pressure cooker in a panel of 5 AR buffers (none; Tris-HCL at pH 9; sodium-citrate at pH 6; sodium-citrate at pH 3; Tris-EDTA at pH 8; and 10% urea in saline) representing the most useful and popular in the IHC literature. Tris-HCL at pH 9 (T9) works best for the majority of antibodies in our experience, but there are exceptions. Level I testing is usually performed on control slides of tissue arrays composed of many types of normal and cancerous tissues (3mm cores arrays 5X6 = 30 total tissues), so there is a high likelihood that one or more cell/tissue type will be positive for a given antibody/protein. We can start with a moderately high concentration (5 μg/ml) of primary antibody or the manufacturer's recommended dilution to eliminate inadequate reagent as a cause of failure, although in many cases this is too high and causes background staining and occasional spurious signals.

The second step, referred to as Level II, then optimizes the assay's sensitivity to detect the maximum range of expression possible for a given protein (e.g. from entirely negative to highly positive) by tittering the primary antibody concentration, and sometimes the detection system, under one AR condition.

Immunohistochemistry procedure

1. Bake 3-4 um thick section for 1hr at 58°C.
2. Deparaffinze and hydrate the baked slides as below ;
    a. Xylene 5 min
    b. Xylene 5 min
    c. Xylene 5 min
    d. 100% EtOH 20 dips
    e. 100% EtOH 20 dips
    f. 100% EtOH 20 dips
    g. 95% EtOH 20 dips
    h. Water 1 min
    i. Transfer the slides to PT Module for antigen recovery
3. Rinse slides with distilled water (3times) and place in TBS-20 or PBS
4. Rinse the slides 3 times with water and place in TBS-20 for at least 5 min.
5. Clean around tissue section with tissue paper and circle the section with a PAP Pen
6. Block endogenous peroxidase with hydrogen peroxide -------5 mins
7. Rinse with buffer (PBS or TBS)----------2 mins
8. Apply ultra V block enough to cover sections----------5 mins
9. Rinse with buffer ----------2 mins

13. Optional Step: Apply Protein block for additional blocking, if needed.
Incubate for 1hr. at RT.
14. Add primary antibody (check incubation time for antibody) --------60 mins
15. Rinse with buffer ----------2 mins
16. Add primary antibody enhancer ----------20 mins
17Apply HRP polymer conjugate----------30 mins
18. Rinse with buffer ----------2 mins
19. Prepare DAB solution (1 drop chromogen to 1 mls DAB substrate and mix) and use immediately
20. Add the DAB solution prepared above to cover sections ----------5 mins
21. Rinse with buffer ----------2 mins
22. Counterstain with haematoxylin ----------2 mins
23. Rinse with Distilled water----------2 mins
24. Blue with PBS
25. Wash in distilled water
26. Dehydrate, clear and mount in DPX as below:
    a. 95% EtOH 20 dips
    b. 100% EtOH 20 dips
    c. 100% EtOH 20 dips
    d. 100% EtOH 20 dips
    e. Xylene 1 min
    f. Xylene 30 sec
    g. Xylene 30 sec

**** PAP Pen should wash off after going through all of the above steps, if not then take a cotton swab with Xylene on it and rub the PAP Pen off the slide before coverslipping.

NOTE: Section should not be allowed to dry at any point during the staining procedure.

Apply 200ul of solution/reagent to each section or enough to cover section on slide

** 1 drop = 50 ul

Results:
Positive staining: Brown
Negative staining and other tissue elements: Blue

NB: Negative and Positive control should be included in each batch of staining.

APPENDIX 8: CONSENT FORM/INFORMATION SHEET

Consent Form

Consent for participation as someone who has breast cancer or someone who does not, in a research protocol

Title of Study: Nigerian Integrative Epidemiology of Breast Cancer Study (NIBBLE)
Health Research Ethics Committee's approval number: **HREC/01/01/2007-09/06/2013**

Name(s) and affiliation(s) of researcher(s) of applicant(s): This study is being conducted by Dr. Clement Adebamowo of the Institute of Human Virology, Nigeria (Principal Investigator)
Sponsor(s) of research: The research is partly supported by a training grant from the National Institutes of Health (NIH), the Training Programme in Nigeria for Non-Communicable Research (TRAPING) Grant.

Why have I been invited to participate in this research: You have been invited to participate in this research either because your doctors have diagnosed that you have breast cancer in which situation, you are referred to as a case for the purposes of this research or we have verified that you have no cancer or hormonal diseases in which case you are designated as a control for this research.
Purpose(s) of research: The purpose of this research is to examine the various reasons that contribute to development of breast cancer such as diet, traits inherited from ancestors, education, marital status, number of children and other factors in a woman's everyday life by comparing their occurrence between cases and controls. We will also examine how these factors differ among individuals who have breast cancer according to the different types of breast cancer that they have based on some of the tests that we will conduct on the cancer. We will also ask questions about your journey from when you first noticed your breast symptom to a diagnosis of breast cancer.

Procedure of the research - what shall be required of each participant: We will ask questions about your health, daily living and family life. We will measure your height, weight and hips size. A trained nurse will take 3 tablespoons of blood and a stool sample from you. The blood will be used to examine the risk that you have inherited any factor (called genes) that may increase your chances of getting breast cancer. In the stool, we will examine the pattern of germs in the stool and how they may affect digestion of certain food items.

If you have been diagnosed with breast cancer, as part of your care, your doctor will do a biopsy to confirm the diagnosis and determine the type of breast cancer you have. Leftovers from this biopsy will be provided to the research team for tests on the genes and type of breast cancer that you have. The result of some of these tests will be provided to your doctor to aid in your treatment.

Approximate total number of participants that would be involved in the research: We expect to invite 1,000 women with breast and 2,000 women without to participate in this research.

Expected duration of research and of participant(s)' involvement: Participation in this study should take not more than 2 hours of your time. If you have cancer, we will contact you on phone every 3 months for 2 years to ask about your health and how well you are responding to treatment.

Risk(s): Some of the questions that we will ask may make you feel uncomfortable. In addition, the risks of drawing blood may include temporary discomfort from the needle stick, bruising, bleeding, and, rarely, infection. The possibility of a sharps injury is also a potential safety risk to participants and staff therefore will ensure safe and prompt disposal of sharps used in the procedure. However, the research staff who will work with you are competent and have been trained on how to ask questions and take blood samples as gently and as carefully as possible. These should reduce the discomfort associated with the questions. Though unlikely, should any of the aforementioned adverse effects occur, the study nurse will immediately take you to the general outpatient clinic for prompt review and management.

Costs to the participants, if any, of joining the research: Your participation in this research will not cost you anything.

Compensation: You will be given N1000 ($7.5) to contribute to the cost of your transportation to hospital. This will be given to you by the study nurse at the end of the session.

Confidentiality: All information provided in this study will be confidential. All forms will be coded and information will be entered into password protected computers. We will do all that is in power to ensure that your identity and the information that you have provided is kept confidential. However we will like you to know that modern research methods can identify individuals from their blood samples. We do not intend to do such research with your samples. Researchers from the London School of Hygiene, UK and the Harvard School of Public Health, USA and ethics committees providing oversight may have access to your records.

Voluntariness: You participation in this research is entirely of your own free will and you are free to withdraw at anytime during the course of the study without offering any reasons why. Withdrawal from this study will not affect your care in this hospital in anyway.

Are there any benefits to taking part in the study?

If you are one of those who have breast cancer, participating in this research will enable us to provide your doctor with information about your breast cancer type and this may be used to guide your treatment.

The research may lead to identification of genes that may be of benefit to future cancer patients or their family members. In most instances, we do not intend to return the results of genetic tests because they require further study at this time except we find genetic information that is currently well understood and of clinical relevance to you or your family, you will be notified with appropriate counseling.

Contact of next of kin: As part of this study, we request that you also give us permission to contact a specific next of kin and the person's phone number in the event that we are unable to reach you for your 3 monthly telephone follow up. You should ensure that this person agrees to receive our phone calls to inquire only about matters related to this research.

Future unspecified use research: A portion of the biopsy and blood samples obtained in the course of this study will be stored for future unspecified use research into how cancer develops in the human body and is passed from generations to generations. However we do not know the detailed nature of this research at this time.

What happens to research participants and communities when the research is over: Participants will be informed of the outcome of the research through a news bulletin. For women

with breast cancer, the result of the laboratory tests identify types of breast cancer will be shared with your doctors and this will be used by your doctor in planning your treatment and advising you on the outcome of treatment.

Statement of person obtaining informed consent:

I have fully explained this research to _____ and have given sufficient information, including about risks and benefits, to make an informed decision.

DATE: _____ SIGNATURE: _____

NAME: _____

Statement of person giving consent:

I have read the description of the research or have had it explained in a language I understand. I have also talked it over with the doctor to my satisfaction. I understand that my participation is voluntary. I understand that I may freely stop being part of this study at any time. I have received a copy of this consent form and additional information sheet to keep for myself.

I understand that my next of kin/ relative may also be contacted in the event that I cannot be reached on phone after several repeated phone calls and I have obtained permission of this person to be contacted.

I hereby consent to take part in the study components marked "yes" and refuse to consent to participate in the components marked "no".

YES NO Study Component

____ ____ _____

[ ] [ ] Interview at start

[ ] [ ] Phone call every 3 months

[ ] [ ] Tumour tissue collection, storage and testing

[ ] [ ] Access to hospital records

[ ] [ ] Contact next of kin/relative

Future unspecified use research

[ ] I do not wish to participate in future unspecified use research
[ ] I do not wish to be re-contacted for permission before use
[ ] I wish to be re-contacted for permission before use

DATE: _____ SIGNATURE/THUMBPRINT: _____

NAME: _____

WITNESS' SIGNATURE (if thumbprint): _____

WITNESS' NAME (if thumprint): _____

Ethics approval: This research has been reviewed and approved by the National Health Research Ethics Committee and any inquiries can be directed at the Desk Officer, NHREC, Federal Ministry of Health, Abuja Nigeria Phone no: 08065479926.

If you have any queries or complaints you can contact the Head of IHVN at 252 Herbert Macaulay Way, Abuja, Phone no: 08033047250

Detailed contact information including contact address, telephone, fax, e-mail and any other contact information of researcher(s),

Dr. Clement Adebamowo
Institute of Human Virology Nigeria
Plot 252 Herbert Macaulay Way, Abuja
+2348033520571

PLEASE KEEP A COPY OF THE SIGNED INFORMED CONSENT.

APPENDIX 9: BOX PLOTS AND HISTOGRAMS FOR CONTINUOUS VARIABLES USED IN DELAY ANALYSES

Figure 1: (a) Pre-contact (b) Post-contact in months by early vs late stage diagnosis in women with breast cancer

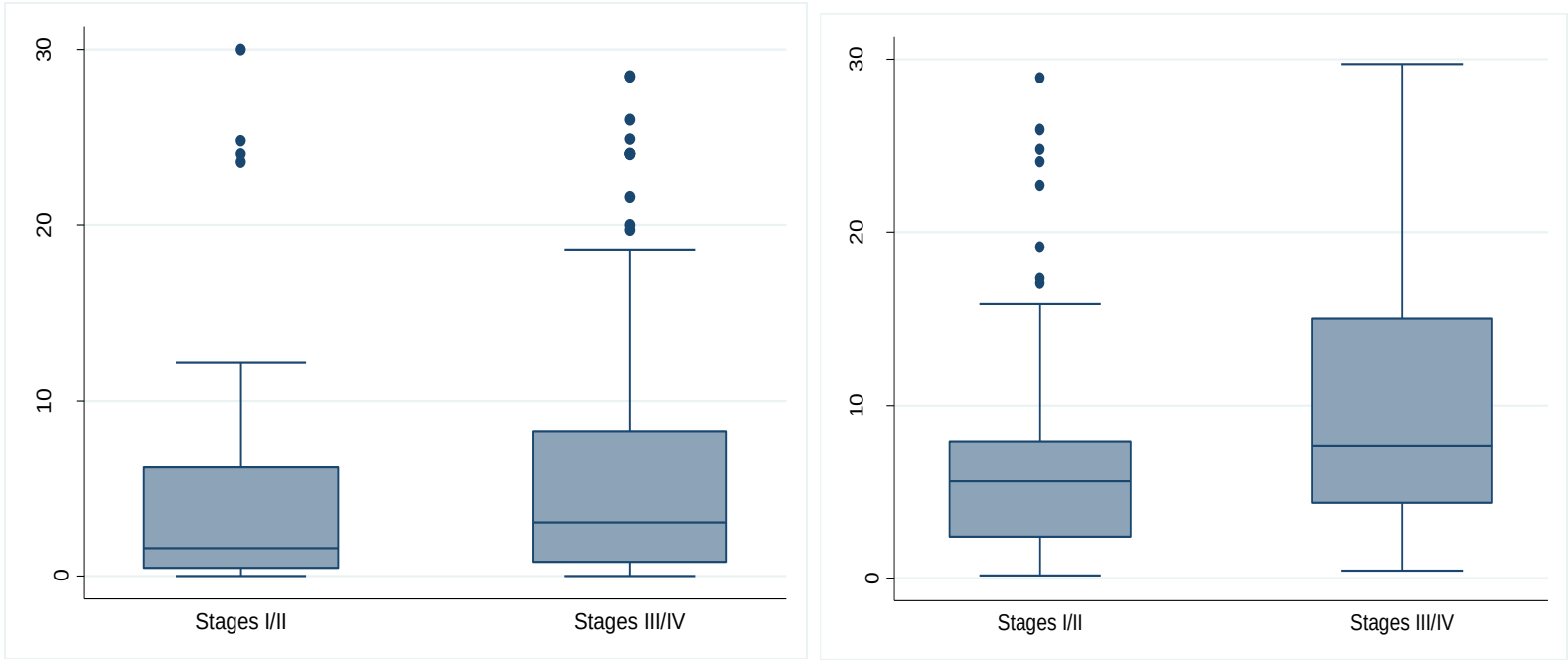


Figure 1c: Total delay in months by early vs late stage diagnosis in women with breast cancer

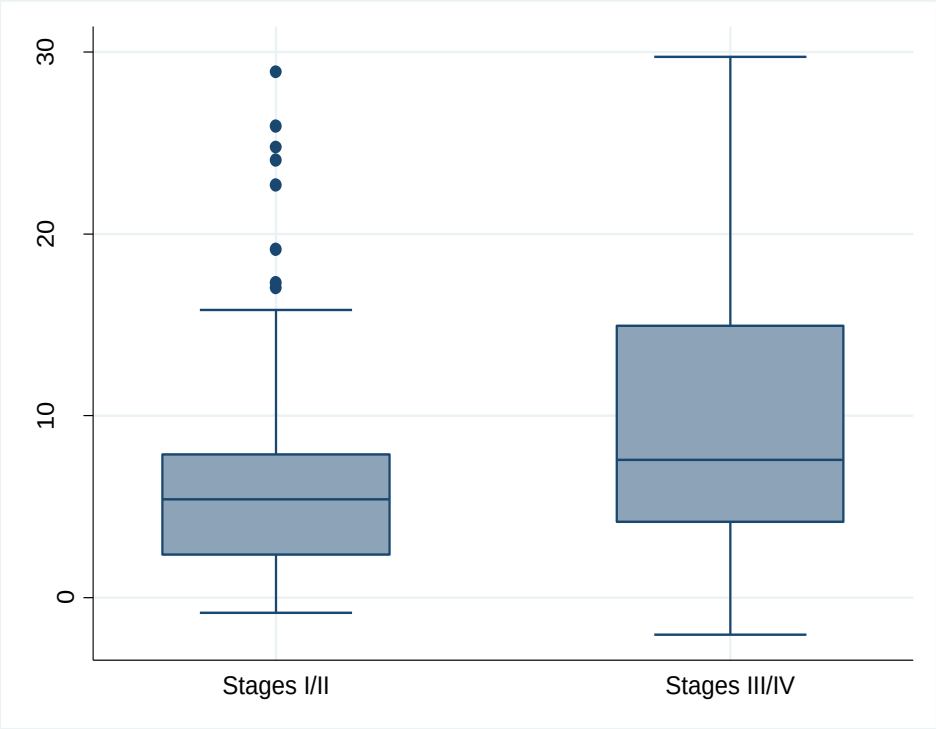


Figure 2: (a) Normal (time1) (b) Log-transformed (time1rlog) pre-contact delay time in months

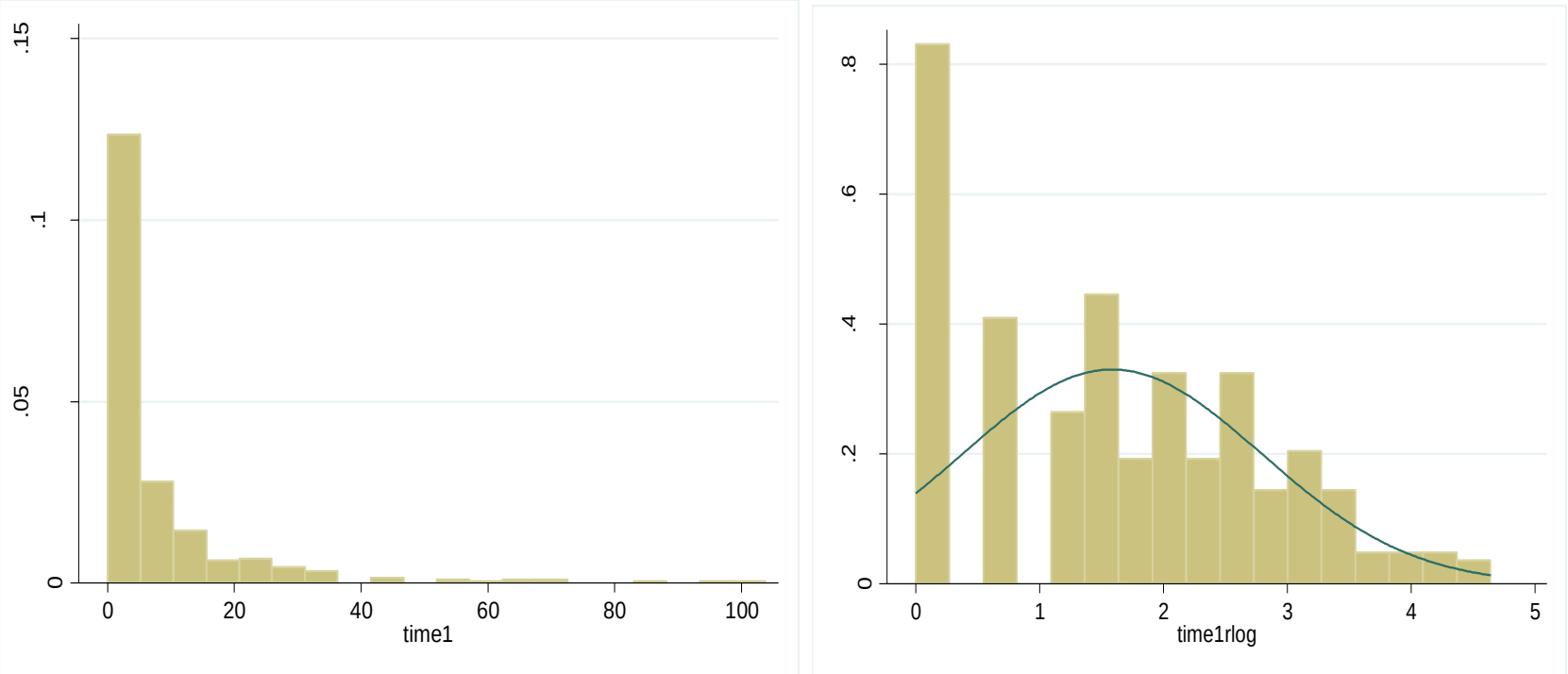
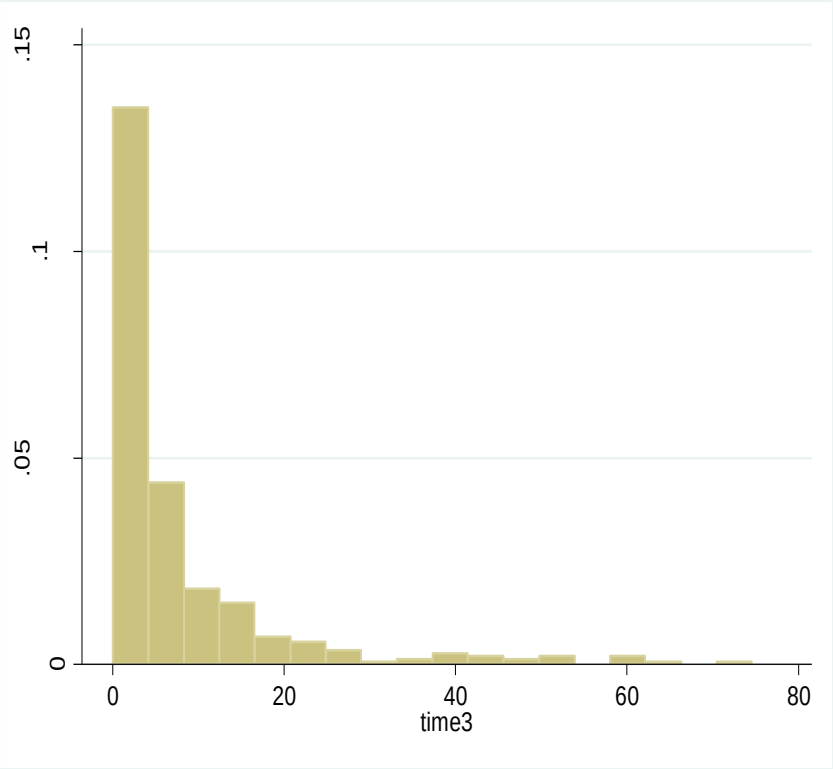


Figure 3: (a) Normal (time3) (b) Log-transformed (time3rlog) post-contact delay time in months



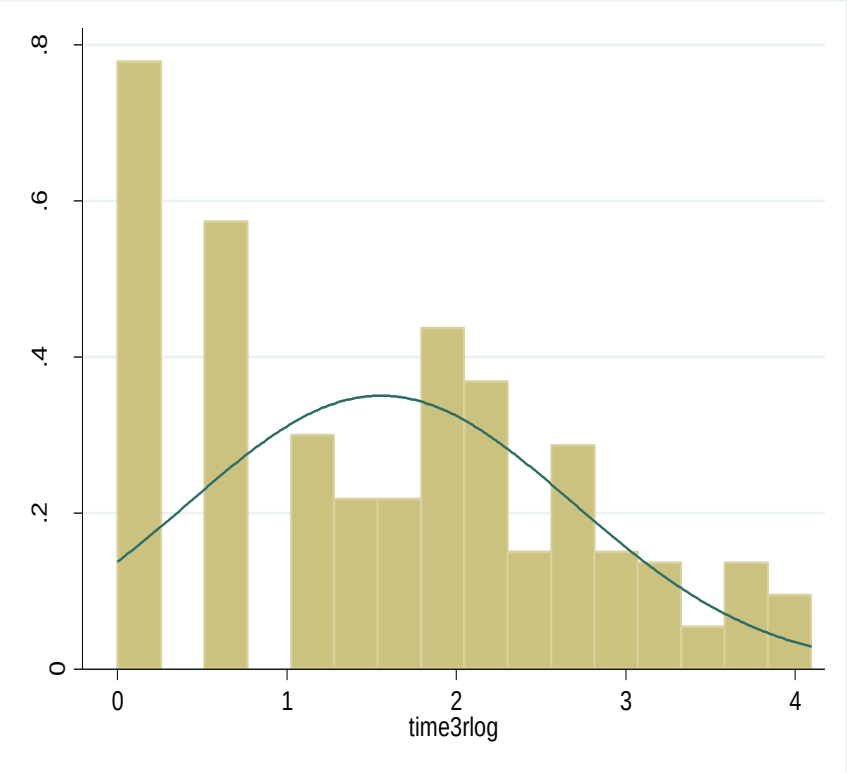
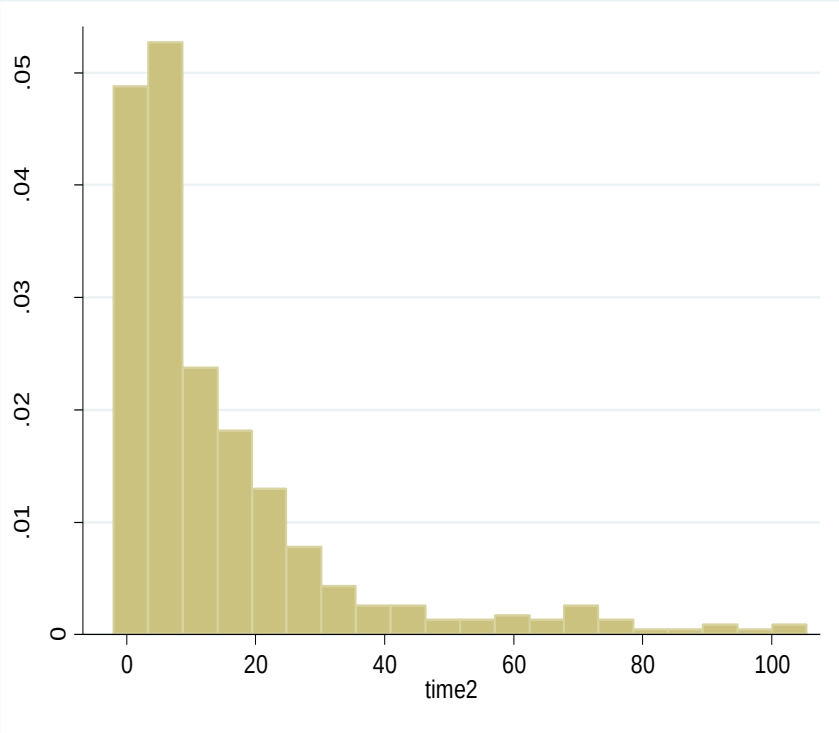
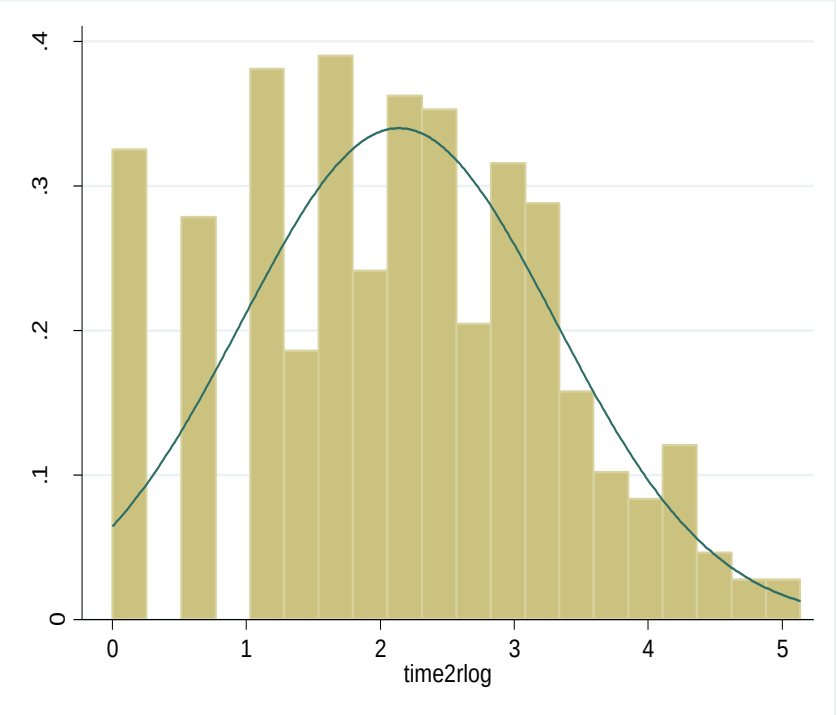


Figure 4: (a) Normal (time2) (b) Log-transformed (time2rlog) total delay time in months





APPENDIX 10: ARTICLE PUBLISHED FROM THE PHD STUDY

Stage at diagnosis of breast cancer in sub-Saharan Africa: a systematic review and meta-analysis

Elima Jedy-Agba, Valerie McCormack, Clement Adebamowo, Isabel dos-Santos-Silva

Summary

Background The incidence of breast cancer in sub-Saharan Africa is relatively low, but as survival from the disease in the region is poor, mortality rates are as high as in high-income countries. Stage at diagnosis is a major contributing factor to poor survival from breast cancer. We aimed to do a systematic review and meta-analysis on stage at diagnosis of breast cancer in sub-Saharan Africa to examine trends over time, and investigate sources of variations across the region.

Methods We searched MEDLINE, Embase, Web of Knowledge, and Africa-Wide Information to identify studies on breast cancer stage at diagnosis in sub-Saharan African women published before Jan 1, 2014, and in any language. Random-effects meta-analyses were done to investigate between-study heterogeneity in percentage of late-stage breast cancer (stage III/IV), and meta-regression analyses to identify potential sources of variation. Percentages of women with late-stage breast cancer at diagnosis in sub-Saharan Africa were compared with similar estimates for black and white women in the USA from the Surveillance, Epidemiology, and End Results database.

Findings 83 studies were included, which consisted of 26 788 women from 17 sub-Saharan African countries. There was wide between-study heterogeneity in the percentage of late-stage disease at diagnosis (median 74·7%, range 30·3–100%, I^2=93·3%, p<0·0001). The percentage of patients with late-stage disease at diagnosis did not vary by region in black women, but was lower in non-black women from southern Africa than in black women in any region (absolute difference [AD] from black women in western Africa [reference group] –18·1%, 95% CI –28·2 to –8·0), and higher for populations from mixed (urban and rural) settings rather than urban settings (13·2%, 5·7 to 20·7, in analyses restricted to black women). The percentage of patients with late-stage disease at diagnosis in black Africans decreased over time (–10·5%, –19·3 to –1·6; for 2000 or later *vs* 1980 or before), but it was still higher around 2010 than it was in white and black women in the USA 40 years previously.

Interpretation Strategies for early diagnosis of breast cancer should be regarded as a major priority by cancer control programmes in sub-Saharan Africa.

Funding None.

Lancet Glob Health 2016; 4: e923–35

See **Comment** page e875

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Introduction

The incidence of breast cancer is highest in high-income countries (HICs), but has been rising in low-income and middle-income countries (LMICs).[1,2] Survival rates for breast cancer are poorer in LMICs than in HICs and most deaths from breast cancer now occur in less developed parts of the world. In 2012, about 53% of all newly diagnosed cases of breast cancer, and about 58% of deaths, occurred in LMICs.[3] Breast cancer incidence in LMICs is likely to increase further in forthcoming decades as a result of population ageing and increased adoption of the lifestyles of HICs.[1,2]

Breast cancer incidence in sub-Saharan Africa is among the lowest in the world. Estimated age-standardised rates in 2012 ranged from 27 cases per 100 000 women in middle Africa to 39 cases per 100 000 women in southern African regions. However, mortality due to cancer is as high as in high-incidence countries; estimated age-standardised rates in 2012 ranged from 15 deaths per 100 000 women in middle Africa to 20 deaths per 100 000 women in western Africa.[3] These rates are higher than that of North America for the same year (age-standardised rate 14·8 cases per 100 000 women), which has a higher breast cancer incidence (age-standardised rate 91·6 cases per 100 000 women).[3]

Stage at diagnosis is a major determinant of survival from breast cancer; early-stage disease is associated with a better prognosis than late-stage disease,[4] a pattern present in sub-Saharan Africa.[5–8] Earlier stage at diagnosis, combined with therapeutic advances, was a major contributor to the sharp reductions in breast cancer mortality rates in the past two decades in most HICs.[4] By contrast, most patients with breast cancer in sub-Saharan Africa present with late-stage disease, thought to be due to poor awareness, an absence of organised early detection programmes, and poor facilities for accurate and timely diagnosis and treatment.[5,9–17] Variations in stage of breast cancer at diagnosis across sub-Saharan Africa and over time in some countries in sub-Saharan Africa have been previously reported in individual settings,[5,7,9,13,18,19] but have not, to our knowledge, been examined systematically across sub-Saharan Africa.

Research in context

Evidence before this study

We preliminarily searched MEDLINE with the terms "Breast Cancer" OR "Breast Carcinoma" AND "Stage" AND "Diagnosis" or "presentation" AND "Africa" OR "Sub-Saharan Africa". No language restrictions were used. Previous studies have reported a wide variation in stage at diagnosis of breast cancer across sub-Saharan Africa, but none has examined trends in stage at diagnosis over time or investigated potential sources of variations across the region.

Added value of this study

We provide the most comprehensive synthesis to date of the available evidence on stage at diagnosis of breast cancer in sub-Saharan Africa. This review showed that most patients in sub-Saharan Africa were diagnosed at a late stage (stages III/IV). There was, however, a wide range of estimates across the region; the reasons for which were unclear. The percentage of women with late-stage disease at diagnosis was, as expected, higher in black women than non-black women; however, no clear differences exist in black women by region or type of health facility, except that the percentage was lower in urban settings than in rural or urban areas. This review also highlights the paucity of published data on breast cancer stage from certain parts of the region (eg, from middle Africa).

Implications of all the available evidence

Although some improvements in stage at diagnosis of breast cancer in sub-Saharan Africa have occurred over the past few decades, very advanced disease is still prevalent at diagnosis in many settings. Nevertheless, within the region, public-sector settings exist with a much improved stage profile, indicating that stage migration is achievable in such settings—ie, in the absence of organised screening. To prevent avoidable deaths from this potentially good-prognosis cancer, breast cancer control measures require a strong emphasis on early diagnosis and treatment. Earlier diagnosis is dependent on the time window in which the patient has symptomatic disease; thus efforts to promote early presentation and faster referrals, diagnosis, and treatment need strengthening.

In this study, we aimed to systematically review the published literature on stage at diagnosis of breast cancer in sub-Saharan Africa, examine trends over time, and investigate possible sources of between-study heterogeneity, which might help to identify appropriate approaches for stage-migration of this disease in the region.

Methods

Search strategy and selection criteria

See Online for appendix

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For this systematic review and meta-analysis, we developed a study protocol (appendix p 1) based on the PRISMA guidelines (appendix p 4). We searched four databases (MEDLINE, Embase, Web of Knowledge, and Africa-Wide Information) to identify all studies published before Jan 1, 2014, which reported on stage at diagnosis of primary invasive breast cancer in women in sub-Saharan Africa. The UN classification[20] was used to define sub-Saharan African countries and to group them according to region (ie, southern, eastern, western, and middle Africa). We did an initial keyword search and subsequent searches based on Medical Subject Headings (MeSH) with various combinations of search terms "breast cancer*", "breast neoplasm*", "breast carcinoma*", "breast sarcoma*", "breast tumor*", "breast tumour*", or "breast malignanc*", AND "stage", "presentation", "grade", "clinical features", or "clinical findings", AND "Africa" (appendix p 7). No restrictions were imposed on the ethnicity or race of women, whether diagnoses were done in public or private settings, age at diagnosis, or language of the publication.

We identified and reviewed articles in a two-step process. The first step consisted of a title and abstract review to identify records that were deemed potentially eligible for inclusion. This review was done by one of three authors (EJ-A, Id-S-S, or VM) to exclude publications that were duplicates; that were from north Africa (ie, Algeria, Egypt, Libya, Morocco, Sudan, Tunisia, and Western Sahara[20]); that did not focus on breast cancer (eg, studies of "all cancers"); that did not include women with breast cancer (eg, surveys on awareness); that did not provide information on stage (eg, pathology series, papers about screening); or that focused exclusively on breast cancer in men. Articles that restricted inclusion to a particular stage (eg, metastatic breast cancer) were also excluded. Reviews and conference proceedings were not included, but their references were cross-checked for completeness. Studies that included both female and male patients with breast cancer were included, even if they did not provide enough information to allow the exclusion of male patients, because men typically represented less than 2% of all study participants. A random sample of 50% of the total abstracts was independently reviewed by one of the other two authors, which showed no disagreements on which papers to select for full-text review.

Quality assessment and data extraction

In the second step, all full-text articles retrieved were reviewed to confirm eligibility and, if eligible, data were extracted. EJ-A assessed all articles for eligibility and extracted the data, using an adapted version of a pre-tested data entry electronic form.[21] All articles were independently reviewed by one of the other two reviewers (Id-S-S or VM). Data were extracted from each eligible paper on the numbers of patients who presented in stages I, II, III, and IV at diagnosis, or at early (I/II) and late (III/IV) stages if

only this combined information was provided; country; study design; study population and type of clinical setting (eg, primary, secondary, or tertiary clinical facility; population-based cancer registry; public, private, or mixed patients); year of diagnosis; race; average age at time of diagnosis (mean or median; if only age categories were reported the mean age was estimated from the mid-point and the reported numbers in each category); and methods and classification used to ascertain stage. Time at diagnosis in the original papers was either the time at clinical or pathological diagnosis.

If a study provided numbers for each specific American Joint Committee Cancer Tumour Node Metastases (TNM) category (eg, T2, N0, M0; appendix p 14), we used these to derive numbers in each one of the four stages. Whenever available, we extracted data on menopausal status, tumour characteristics (eg, histology, size, grade, receptor status), and time from first symptoms to diagnosis. Disagreements between extractors were discussed and a consensus reached. Most papers with missing information were from studies done several decades ago, hence no attempt was made to contact their authors because it was unlikely that the required information could still be retrieved. If there were several papers for the same study period, setting, and author, the paper with the most information on tumour stage was selected for inclusion.

The quality of the papers included in the review was assessed independently by two reviewers. An adapted version of the standardised quality assessment criteria developed by Eng and colleagues[21] was used to assess the potential for selection and information bias as well as the availability of data on key variables (eg, age at diagnosis and year of diagnosis, tumour grade; details in the appendix; p 9). A quality score ranging from 0–28 (low to high quality) was given to each paper.

Data analysis

The primary outcome was percentage (p_{34}) of breast cancer diagnosed at late stages (stages III/IV), defined as $p_{34}=n_{34}/n$, where n_{34} is the number of women who presented at stages III or IV and n is the number of women with known stage information. The suite of metan and metaprop commands from Stata (version 13) were used to graphically display population-specific late-stage percentages and to estimate pooled percentages using random effect models. The metaprop command was specifically designed to model binary data, thereby allowing for proportions near boundaries (ie, in this instance near 100% late-stage cancer). Between-population heterogeneity was assessed using I^2 statistic and the p value for heterogeneity (Cochrane's Q statistic). To examine potential sources of heterogeneity, population-specific estimates were stratified by relevant clinicoepidemiological variables, and meta-regression analyses were done to identify independent correlates of percentage of late-stage disease. Study-level determinants of late-stage disease are expressed as absolute differences (AD) in the percentage of patients with late-stage disease (p_{34}). Analyses were first done in all study populations (black and non-black African) and then in black African populations only. The latter analyses excluded non-black African populations, which were from South Africa, because of their known privileged access to health care. The potential for small study bias was assessed using funnel plots and the Egger test.[22]

To compare late-stage breast cancer in sub-Saharan Africa with corresponding figures for white women and black women in the USA, relevant data were extracted from the Surveillance, Epidemiology, and End Results (SEER) database, which includes information on all cases of invasive primary breast cancer in women from nine US population-based cancer registries[23] for two time periods: 1973–2002 and 1998–2011. The SEER database provided numbers of in-situ, localised, regional, and distant (metastatic) breast cancer cases as well as numbers with unknown or missing stage. There were no age restrictions. The SEER summary staging classification was used to estimate the percentage of patients with regional or distant disease (proxy for stages III/IV) out of all patients with breast cancers of known stage.

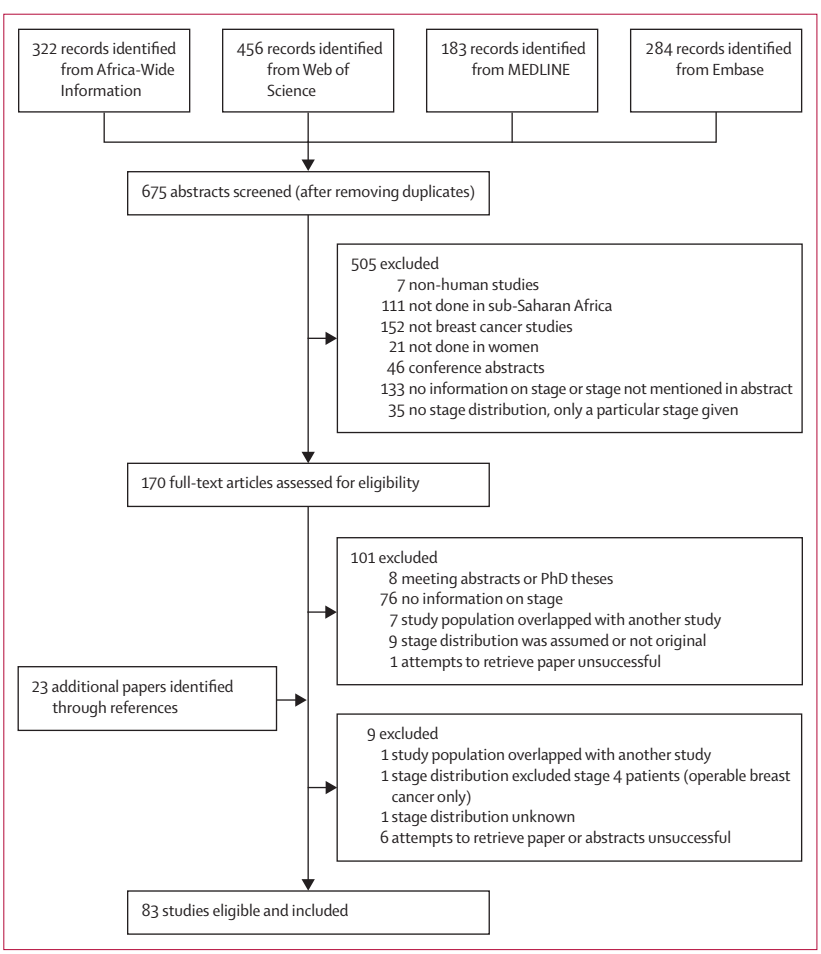

Figure 1: **Study selection**

	Studies	Study populations	Patients with breast cancer	Patients with known breast cancer, n (%)
Total	83	91	26 788	24 213 (90·4%)
Race				
Black†	75	76	18 805	16 669 (88·6%)
Non-black‡	8	15	7983	7544 (94·5%)
Region or country				
Western Africa	48	49		
Nigeria	36	37	8623	8407 (97·5%)
Benin	2	2	204	204 (100%)
Ghana	5	5	1969	1191 (60·5%)
Mali	2	2	324	324 (100%)
Other§	3	3	797	719 (90·2%)
Eastern or middle Africa	19	19		
Tanzania	5	5	1310	1151 (87·7%)
Kenya	2	2	287	157 (54·7%)
Ethiopia	3	3	1267	841 (66·4%)
Madagascar	2	2	289	233 (80·6%)
Uganda	3	3	562	502 (89·3%)
Other¶	4	4	445	302 (67·9%)
Southern Africa	16	23		
South Africa	16	23	10 711	10 182 (95·1%)
Study design				
Convenience case series	48	55	10 780	9788 (90·8%)
Consecutive case series	35	36	16 008	14 425 (90·1%)
Study population				
Urban	27	34	15 571	14 208 (91·2%)
Mixed (rural and urban)	56	57	11 217	10 005 (89·2%)
Type of health facility				
Tertiary, secondary, or primary‖	9	12	1639	1503 (91·7%)
Tertiary	72	77	24 742	22 399 (90·5%)
Not reported in original study	2	2	407	311 (76·4%)
Age at diagnosis (years)**				
<45 years	28	29	5475	4840 (88·4%)
≥45 to <50 years	36	37	7882	7218 (91·6%)
≥50 years	16	22	11 056	9841 (89·0%)
Not reported in original study	3	3	2375	2314 (97·4%)

(Table 1 continues on next page)

Role of the funding source

There was no funding source for this study. EJ-A, VM, and Id-S-S had full access to all the data in the study and EJ-A and Id-S-S had final responsibility for the decision to submit for publication.

Results

Our search retrieved 675 articles, of which 170 were considered as potentially relevant (figure 1). The full text was retrieved for all of these articles except for six, which could not be traced through institutional libraries or direct contact with the authors (attempts to contact authors proved futile). The sample sizes of two of the untraceable studies[24,25] were 47 and 120 according to Edmund and colleagues.[26]

The full-text review identified 83 eligible papers from 17 sub-Saharan African countries consisting of late-stage disease estimates for 91 distinct study populations; five studies provided separate estimates for different subsets of participants (ie, for pregnant or lactating and non-pregnant or non-lactating women[27] or different racial groups[12,28–30]). For three studies,[31–33] we obtained estimates that differed from those published because T3N1M0 tumours in the original articles were classified as stage II, but they should be stage III according to the 7th edition of the American Joint Committee on Cancer Breast Cancer Staging Manual.[34] Four studies[35–38] provided information on the tumour (T1–4) only and, for these, T3/T4 was regarded as a proxy for stages III/IV. The characteristics of the included studies are summarised in table 1; study-specific details and references are given in the appendix (p 14). They comprised 26 788 patients with breast cancer, with sample sizes ranging from 12 to 2346 (median 141; appendix p 14). Stage information was available for 24 213 (90·4%) patients. 36 studies (43%) were from Nigeria (8407 patients with cancer staging) and 16 studies (19%) were from South Africa (10 182 patients with cancer staging). 35 studies (42%) were consecutive case series and the remaining were convenience case series (ie, patients seen in pathology or radiotherapy departments only or studies in which not all eligible patients who reported at the surgery or oncology clinics were included; table 1). The average age at diagnosis was less than 45 years in 34% of studies, between 45–49 years in 43% of studies, and 50 years or older in 19% of studies. Age was not reported in only three studies (4%; table 1). The mean year of diagnosis ranged from 1960 to 2011, and was 2000 or later for 40% of the studies.

There was wide variation in the distribution of stage at diagnosis in sub-Saharan Africa. For example, in studies that provided stage IV-specific estimates, the percentage of women diagnosed with stage IV breast cancer ranged from 4%[56] to 70%[27] (figure 2). Consequently, between-population heterogeneity was wide (I^2=93·3%; p<0·0001) in the percentage of late-stage cancers (III/IV) (median 74·7%; range 30·3–100), with 59 (65%) of study populations yielding an estimate of greater than 70% (figure 3).

Nine studies from western and eastern Africa were done exclusively in black women.[5,37,38,42–47] The remaining 58 studies did not report on race, but their populations were assumed to have the racial composition of their countries' population and, hence, to consist predominantly (≥80%) of black women. Studies from South Africa included exclusively[39–41] or predominantly (≥80%) black women;[18] or predominantly (≥80%) non-black women (ie, white, Indian, or coloured women[14,36,50–53]); or provided separate estimates for black women and non-black women[12,28–30] (appendix p 14).

Black women from South Africa presented much later than their non-black counterparts, but with marked

between-population heterogeneity within each racial group (I^2>97% for both groups; figure 4). Four South African studies examined racial differences (appendix p 11), which consistently showed a higher percentage of late-stage cancer in black Africans (range 74–91%) than white Africans (30–44%); the percentages of late-stage cancer in Indian and coloured women were intermediate, even when all the participants were diagnosed at the same health facility. However, these results were not adjusted for socioeconomic status because of a scarcity of information from the original publications.

Fully-adjusted meta-regression analysis (adjusting for region or race, study design, setting, facility type, age, and year of diagnosis) confirmed the difference between racial groups; the percentage of late-stage cancers was 18·1% lower (95% CI –28·2 to –8·0) for non-black women from South Africa than for black women in western Africa. By contrast, analysis restricted to black Africans revealed no difference in late-stage cancer diagnosis between the three sub-Saharan African regions (table 2).

After adjustment for region or race, no differences in late-stage disease were observed between consecutive or convenience case series, or by type of health facility (table 2). Studies done in mixed urban or rural populations had a higher percentage of women with late-stage disease than those done in urban populations, and this finding remained significant in the fully adjusted model (AD 12·9%, 95% CI 5·5 to 20·3) and in the analysis restricted to black Africans (AD 13·2%, 5·7 to 20·7; table 2).

A smaller percentage of women aged 50 years or older had late-stage disease than those younger than 45 years (AD –13·2%, 95% CI –21·2 to –5·3), but most studies of older women consisted predominantly of non-black South Africans. Consequently, the age difference attenuated markedly on adjustment for region and race, and disappeared in analyses restricted to black Africans (table 2). A slight improvement in stage at diagnosis was observed over time (appendix p 12). In the fully-adjusted meta-regression model, the percentage of women with late-stage disease was lower in black Africans diagnosed since 2000 compared with women diagnosed before 1980 (AD –10·5%, 95% CI –19·3 to –1·6; table 2). In analyses restricted to black Africans, the percentage of women with late-stage cancer was lower in studies that did not report year of diagnosis than studies published before 1980, but this finding was not statistically significant (table 2). Because the years of publication of these studies ranged from 2002 to 2011, it is likely that patients recruited into these studies would have been diagnosed in recent years.

The TNM or the Manchester staging classification (appendix p 14) were used in most studies, but this information was missing in 21 studies (table 1). No clear differences in the percentage of late-stage disease were observed between studies that reported the staging classification used and studies that did not, or between studies done in facilities where there was access to imaging methods (eg, radiographs)—either routinely or in clinically suspicious cases—and studies done in settings without imaging facilities (table 2).

Few studies reported on tumour characteristics or duration of symptoms (appendix p 21). In studies of black African populations that reported on these characteristics, late-stage disease at diagnosis was positively associated with mean tumour size (Pearson correlation coefficient r=0·63, p=0·004, based on data

	Studies	Study populations	Patients with breast cancer	Patients with known breast cancer stage, n (%)
(Continued from previous page)				
Year of diagnosis††				
Before 1980	11	16	3971	3782 (95·2%)
1980–1999	32	34	11125	10737 (96·5%)
2000 or after	33	33	8648	6733 (77·8%)
Not reported in original study	7	8	3044	2961 (97·3%)
Staging methods				
Clinical and imaging	25	26	10416	9516 (91·4%)
Clinical only	10	10	975	967 (99·2%)
Not reported in original study	48	55	15397	13730 (89·2%)
Staging classification				
TNM	50	57	20388	18048 (88·5%)
Manchester	11	11	1436	1426 (99·3%)
Not reported in original study	22	23	4964	4739 (95·5%)
Study quality scores‡‡				
≥23 (highest quality)	12	12	4067	3569 (87·8%)
22–20	26	27	6181	5721 (92·6%)
19–17	31	38	14541	13327 (91·7%)
<17 (lowest quality)	14	14	1999	1596 (79·8%)

Data are n or n (%). TNM=Tumour, Lymph Node, and Metastasis staging system. *Five studies provided separate estimates for different subsets of participants (ie, for pregnant or lactating and non-pregnant or non-lactating women[27] or different ethnic groups[12,28–30]). †Includes seven southern African studies[12,28–30,39–41] that reported estimates for black women only; one southern African study[18] that presented only an overall (all ethnic groups combined) estimate, but reported that >80% of their study population was black; nine studies[5,37,38,42–47] from western and eastern Africa that were done exclusively in black women, as well as the remaining 58 studies from these two regions that did not report on race, but were assumed to have been done in predominantly black women (ie, >80% black; see appendix p 14), which corresponded to 76 study population groups because one Nigerian study[27] presented separate estimates for pregnant or lactating and non-pregnant or non-lactating women (appendix p 14). ‡Includes 15 southern African study population groups: four studies[14,48–50] that did not report on race but were assumed to be predominantly non-black, four studies[36,51–53] that present only overall estimates but reported an ethnically mixed population with ≤80% being black, and four multi-ethnic studies[12,28–30] that together reported separate estimates for seven non-black population groups (appendix p 14). §Includes one study from Guinea (178 cases, 124 cases with known stage), one from Niger (146 cases, 146 cases with known stage), and one from Senegal (473 cases, 449 cases with known stage). ¶Includes one study from Rwanda (145 cases, seven cases with known stage), one from Zimbabwe (84 cases, 79 cases with known stage), one from Eritrea (82 cases, 82 cases with known stage), and one from Democratic Republic of the Congo (formerly known as Zaire; 134 cases, 134 cases with known stage). ||All studies that recruited participants from secondary and primary health centres also included a tertiary centre. **Mean or median age at breast cancer diagnosis. If only age categories were reported, mean or median age was estimated from the mid-point and the reported number in each age category. The three studies in which age was not reported in the original category did not provide sufficient information to allow their allocation into one of the three age categories: Ajekigbe[54] reported that 50·8% of the participants were aged <50 years; Amir and colleagues[55] reported that 90% of the participants were aged <50 years; and Pegoraro and colleagues[36] reported that 50% were between aged 45–64 years (appendix p 14). ††Middle year of the time interval during which patients were recruited. ‡‡Categories represent quartiles of the overall score distribution (appendix p 9).

***Table 1*: Study characteristics**

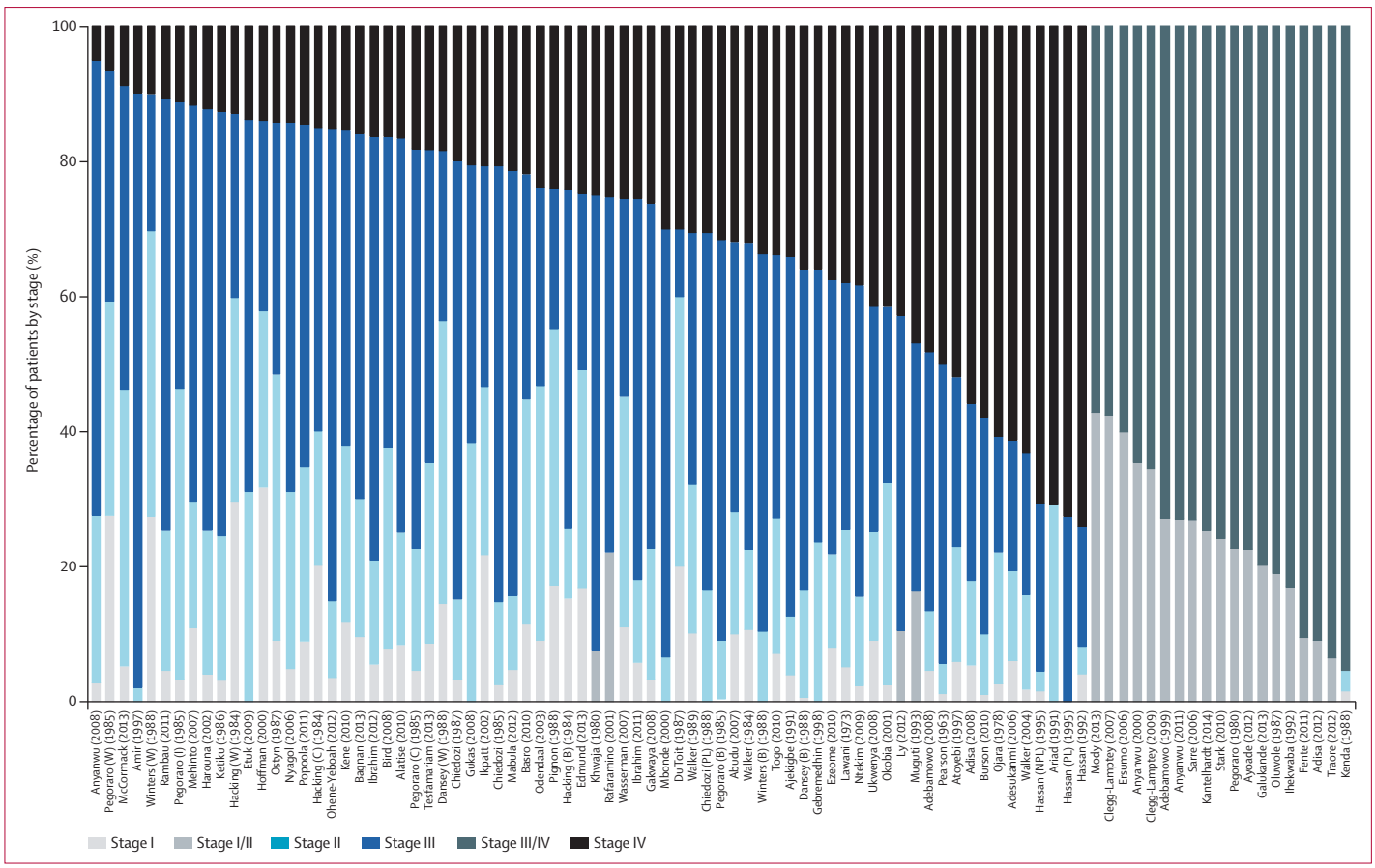

Figure 2: **Study-specific breast cancer stage at diagnosis**

Study-specific distribution of stages I, II, III, and IV cancers. Percentage of T3/T4 cancers was used as a proxy for percentage of stage III/IV cancers in four studies.[35-38] Percentage with metastases (M1) was given in three studies[24,35,37] and was used as percentage of stage IV. Race as defined in table 1 and in the appendix (p 14). Study-specific references given in the appendix (p 14). B=black. C=coloured. I=Indian. NPL=non-pregnant or non-lactating women. PL=pregnant or lactating women. W=white.

from 19 studies), but not with self-reported mean duration of symptoms (r=–0·14, p=0·42, 35 studies) or with percentages of tumours classified as invasive ductal carcinomas (r=0·09, p=0·50, 53 studies), oestrogen-receptor positive (r=–0·03, p=0·91, 15 studies), or grade 3 (r=0·21, p=0·26, 32 studies; appendix p 21).

The median study quality score was 19·5 (IQR 17·5–21·5), with no evidence of regional or racial differences. No variation in the percentage of women diagnosed with late-stage breast cancer was observed by study quality (table 2). The funnel plot (appendix p 13) and the value of the Egger's test for small study bias (p=0·01) were difficult to interpret because of the marked between-population heterogeneity.

The proportion of women with late-stage breast cancer at diagnosis declined markedly in the USA between 1973 and 2011: from 50% to 27% in white women, and from 60% to 32% in black women[23] (figure 5). By contrast, most study-specific estimates of late-stage disease in black sub-Saharan African women remained well above 60% from the 1970s to 2011, albeit with some indication of a slight downward trend in some settings (figure 5). Notably, the proportion of late-stage disease in black women in sub-Saharan Africa in the most recent study years (around 2010) was still higher than in black women from the USA 40 years previously. The proportion of women with late-stage disease in southern Africa remained unchanged for non-black Africans, but seemed to decline somewhat in black Africans. Remarkably, only two studies were done after 2000 in the southern African region. Both studies were done in South Africa: one in non-black Africans[14] and one in black Africans.[18] By contrast, the number of studies from eastern and western Africa published after 2000 was higher than in previous decades, although most had relatively small sample sizes.

Discussion

To our knowledge, this is the first systematic review of stage at diagnosis of breast cancer in sub-Saharan Africa. We compiled data from 83 studies consisting of 24 213 patients with staged cancers. The findings highlight two main issues. First, our findings show the paucity of data on one of the most important clinical

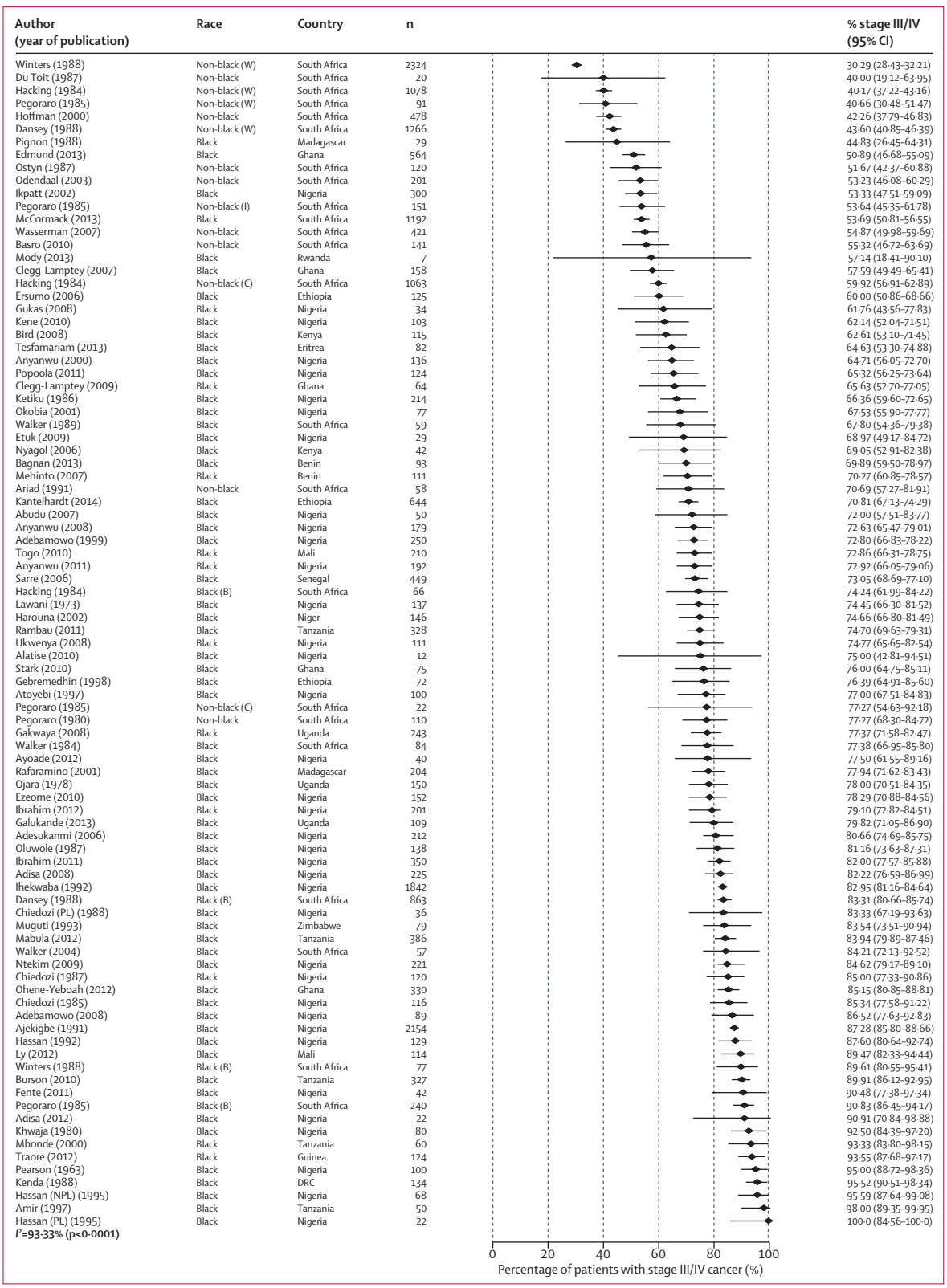

Figure 3: **Study-specific breast cancer stage at diagnosis**
Study-specific percentage of late-stage disease (III/IV) ranked by increasing magnitude. Percentage of T3/T4 cancers was used as a proxy for percentage of stage III/IV cancers in four studies.[35–38] Race as defined in table 1 and in the appendix (p 14). Study-specific references given in the appendix (p 14). B=black. C=coloured. DRC=Democratic Republic of the Congo. I=Indian. NPL=non-pregnant or non-lactating women. PL=pregnant or lactating women. W=white.

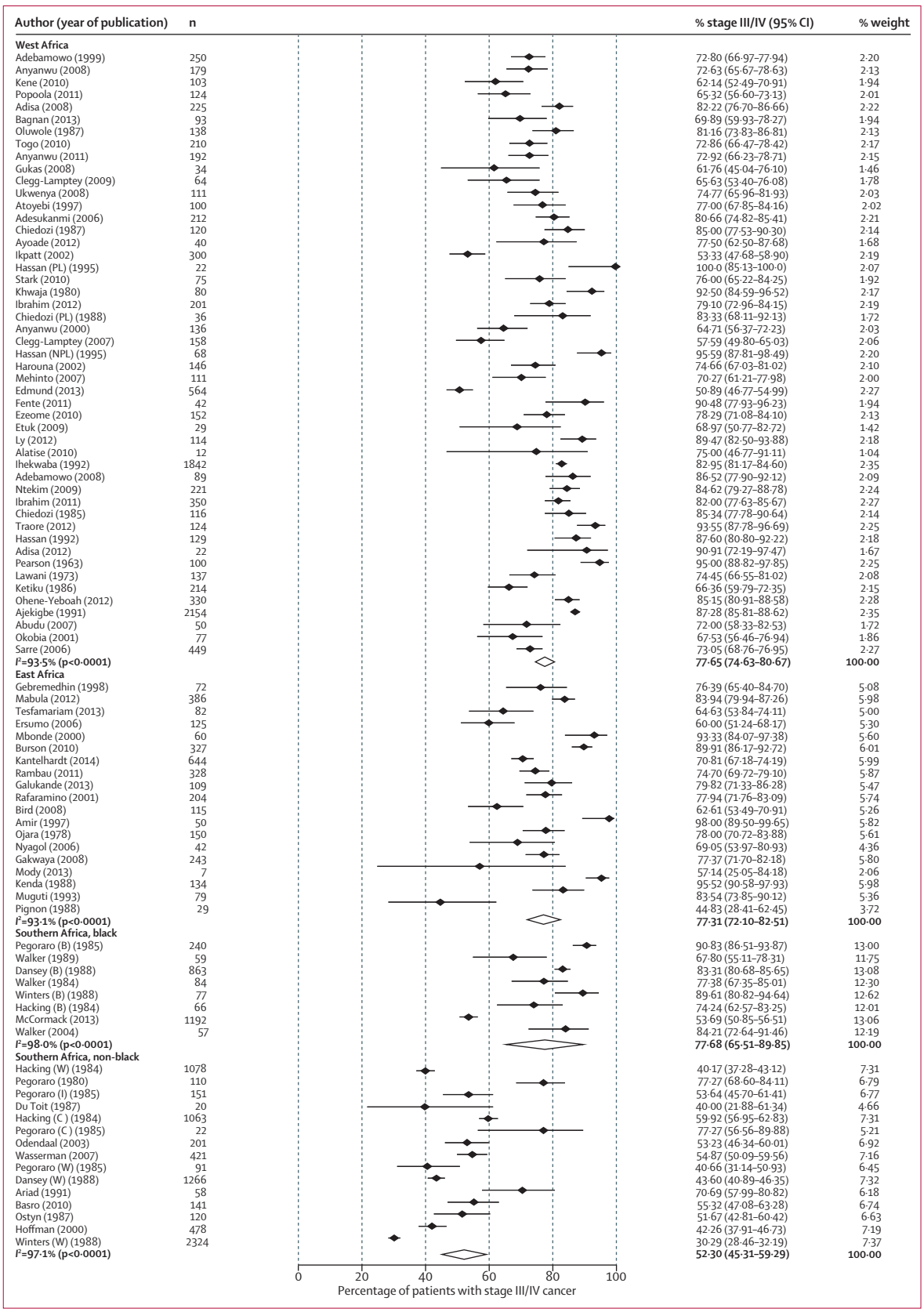

Figure 4: **Study-specific percentage of late-stage breast cancer at diagnosis, by region of sub-Saharan Africa**
B=black African. C=coloured. I=Indian. NPL=non-pregnant or non-lactating women. PL=pregnant or lactating women. W=white. Study-specific references given in the appendix (p 14). *Weights are from random effects analyses.

	Patients with breast cancer, n	All study populations						Black populations only			
		Unadjusted analysis		Region and race adjusted analysis		Fully-adjusted analysis*		Unadjusted analysis		Fully-adjusted analysis†	
		AD (%)	95% CI	AD (%)	95% CI	AD (%)	95% CI	AD (%)	95% CI	AD (%)	95% CI
Region, race‡											
West Africa, black	10 845	0 (ref)	..	..	..	0 (ref)	..	0 (ref)	..	0 (ref)	..
East Africa, black	3186	−0·2	−6·8 to 6·4	..	..	−3·0	−9·2 to 3·2	−0·2	−6·6 to 6·3	−3·3	−9·5 to 2·9
Southern Africa, black	2638	0·1	−9·0 to 9·3	..	..	8·6	−2·0 to 19·1	0·1	−8·9 to 9·1	5·8	−5·9 to 17·5
Southern Africa, non-black	7544	−25·5	−32·6 to −18·3	..	..	−18·1	−28·2 to −8·0	..	..	..	
Study design											
Convenience case series	14 425	0 (ref)	..	0 (ref)	..	0 (ref)	..	0 (ref)	..	0 (ref)	..
Consecutive case series	9788	−6·5	−12·9 to −0·4	−0·6	−6·1 to 4·9	−2·0	−7·1 to 3·1	−2·2	−7·9 to 3·6	−2·6	−8·0 to 2·8
Study population											
Urban	14 208	0 (ref)	..	0 (ref)	..	0 (ref)	..	0 (ref)	..	0 (ref)	..
Mixed (rural and urban)	10 005	16·3	10·6 to 22·0	10·7	3·4 to 17·9	12·9	5·5 to 20·3	7·7	1·7 to 13·7	13·2	5·7 to 20·7
Facility type											
Tertiary	22 399	0 (ref)	..	0 (ref)	..	0 (ref)	..	0 (ref)	..	0 (ref)	..
Tertiary, secondary, or primary	1503	−3·7	−13·2 to 5·8	−1·2	−8·8 to 6·4	−1·9	−9·1 to 5·4	−3·2	−11·5 to 5·1	−1·4	−9·5 to 6·6
Not reported in original study	311	−8·8	−30·5 to 12·9	14·8	−3·4 to 32·9	10·1	−0·8 to 28·3	..	..	..	..
Age at diagnosis (years)§											
<45 years	4840	0 (ref)	..	0 (ref)	..	0 (ref)	..	0 (ref)	..	0 (ref)	..
≥45 to <50 years	7218	0·8	−6·0 to 7·8	0·3	−5·5 to 6·0	3·9	−2·0 to 9·9	−0·3	−6·2 to 5·6	3·9	−2·3 to 10·1)
≥50 years	9841	−13·2	−21·2 to −5·3	−6·2	−14·4 to 2·0	−1·7	−9·9 to 6·4	−3·9	−12·0 to 4·1	1·8	−8·9 to 12·4
Not reported in original study	2314	12·0	−4·4 to 28·5	17·4	3·8 to 31·1	20·6	6·4 to 34·8	14·6	−1·3 to 30·6	20·4	4·8 to 36·1
Year of diagnosis¶											
Before 1980	3782	0 (ref)	..	0 (ref)	..	0 (ref)	..	0 (ref)	..	0 (ref)	..
1980–1999	10 737	4·8	−4·3 to 13·9	−3·0	−10·6 to 4·6	−5·2	−12·6 to 2·2	−4·7	−13·1 to 3·7	−6·8	−15·5 to 1·9
2000 or after	6733	4·3	−5·0 to 13·5	−6·2	−14·2 to 1·8	−8·5	−16·1 to −1·0	−8·4	−16·8 to −0·1	−10·5	−19·3 to −1·6
Not reported in original study	2961	−6·5	−19·9 to 6·9	−7·3	−18·2 to 3·6	−8·5	−19·0 to 2·1	−16·5	−29·7 to −3·3	−12·5	−26·9 to 1·8
Staging methods											
Clinical and imaging	9516	0 (ref)	..	0 (ref)	..	0 (ref)	..	0 (ref)	..	0 (ref)	..
Clinical only	967	5·0	−6·4 to 16·4	2·3	−7·0 to 11·6	−1·4	−10·4 to 7·6	3·0	−5·9 to 11·9	−1·3	−10·3 to 7·8
Not reported in original study	13 730	0·2	−7·1 to 7·4	3·0	2·7 to 8·8	3·2	−2·3 to 8·7	4·0	−1·9 to 10·0	4·1	−1·7 to 9·8
Staging classification											
TNM	18 048	0 (ref)	..	0 (ref)	..	..	..	..	..	..	..
Manchester	1426	2·4	−7·6 to 12·5	−3·7	−12·1 to 4·6	..	..	..	..	..	..
Not reported in original study	4739	3·1	−4·5 to 10·7	−0·8	−7·0 to 5·5	..	..	..	..	..	
Study quality scores||											
≥23 (highest quality)	3569	0 (ref)	..	0 (ref)	..	..	..	..	..	..	..
22–20	5721	−2·1	−12·7 to 8·5	−0·1	−8·5 to 8·3	..	..	..	..	..	..
19–17	13 327	−1·1	−11·2 to 9·0	2·1	−5·9 to 10·1	..	..	..	..	..	..
<17 (lowest quality)	1596	0·7	−11·5 to 12·9	2·9	−6·9 to 12·6	..	..	..	..	..	..

Data are n, absolute difference (%), or 95% CI. Ref=reference category. AD=absolute difference. TNM=Tumour, Lymph Node, and Metastasis staging system. *Adjusted for all other variables, except for staging classification and study quality because of concerns of overadjustment. †Adjusted for all other variables, except region or race, staging classification, and study quality. ‡The study population was classified as black if 80% of participants or more were black (appendix p 14, figure 3). §Mean or median age at breast cancer diagnosis. If only age categories were reported mean or median age was estimated from the mid-point and the reported number in each age category. ¶Taken as the middle year of the period during which patient recruitment took place. ||Categories defined using quartiles of the overall score distribution. Analyses were not further adjusted for the other variables in the table because most of them were integrated into the study quality scores (appendix p 9).

***Table 2*: Sources of between-population heterogeneity in the percentage of late-stage breast cancer (stages III/IV) from meta-regression analyses**

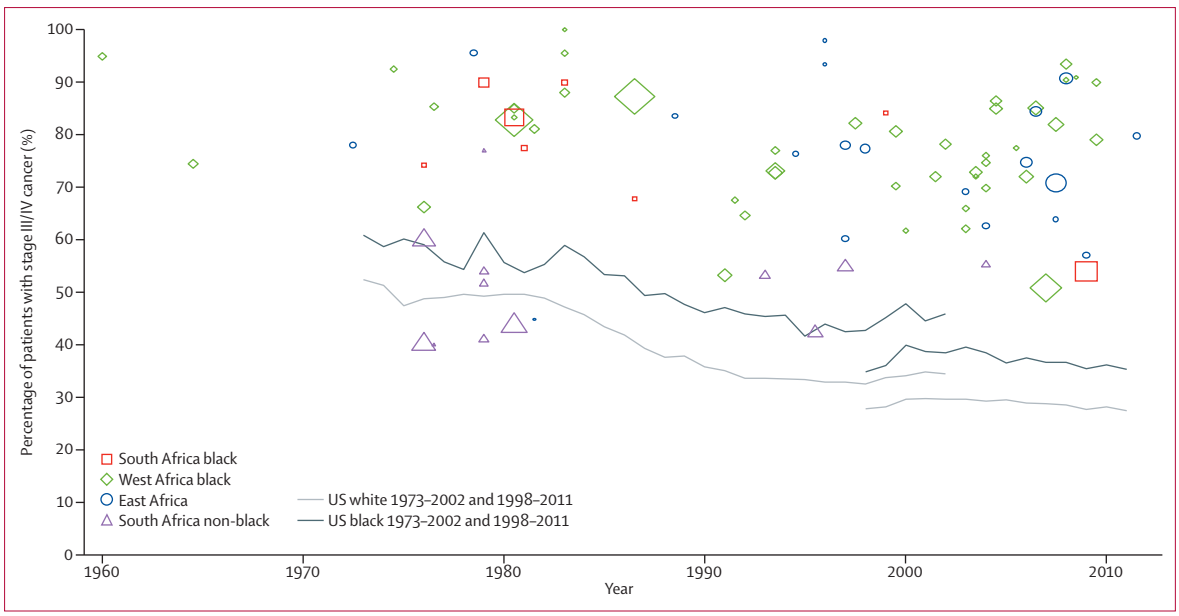

Figure 5: **Trends in stage of breast cancer at diagnosis in sub-Saharan Africa in 1960–2011, and in the USA in 1973–2002 and 1988–2011**
The US estimates represent percentage of patients with breast cancer with regional or distant disease (as a proxy for stages III/IV) out of all patients with known stage in the Surveillance Epidemiology End Results (SEER) database (see Methods); the SEER summary staging classification was used for both time periods: 1973–2002 (based on 365 695 white women and 31 781 black women with breast cancer in the USA) and 1998–2011 (based on 780 137 white women and 96 526 black women with breast cancer in the USA). The discontinuity between the two time series was due to a change in staging classification. The sub-Saharan Africa estimates correspond to percentage of patients with stage III/IV breast cancer at diagnosis; the size of the point estimate symbols are proportional to the size of the study.

For more on the **change in staging classification** see http://seer.cancer.gov/seerstat/variables/seer/yr1973_2009/lrd_stage/index.html

prognostic markers of breast cancer in this region. Specifically, no published data from middle Africa were identified, and data from southern Africa were restricted to one country (South Africa), with only two studies done after 2000 (one in black Africans and another in non-black Africans). Furthermore, no study presented data from population-based cancer registries. Second, the findings show that most patients in sub-Saharan Africa (77% across all black study populations) were diagnosed at stages III/IV. Although this overall situation might seem grave, the presence of public-sector sub-Saharan Africa settings with improved stage profile needs to be highlighted because those settings reveal that progress in stage migration of breast cancer can be made within the public sector setting in which mammography is often unavailable. However, the reasons for the marked heterogeneity between populations, which is present even in analyses restricted to black Africans, are not entirely clear—no distinct patterns define the better settings. Late-stage breast cancer was, as expected, more frequent in black Africans than in non-black Africans; however, no clear differences in the percentage of late-stage cancers at diagnosis by region or type of health facility were observed in black African women, except that the percentage of late-stage cancers at diagnosis was lower in urban settings. There was evidence of stage migration of breast cancer over time in black Africans diagnosed after 2000, consistent with the downward trend within studies in late-stage disease at diagnosis described by one of the studies in this review. McCormack and colleagues[18] reported a decrease in the frequency of stage III/IV cancers in South Africa from 66% in 2006–07 to 46% in 2010–12.

We did not find a strong association between age at diagnosis and late-stage cancer at diagnosis in black African women. Most patients were aged 35–49 years at diagnosis (approximately 10–15 years younger than patients in developed countries).[57] This finding likely reflects the younger age structure of the sub-Saharan African population, consequent to higher fertility and shorter life expectancy, and the lower prevalence of risk factors in older generations than in young generations, rather than any inherent biological differences in disease aggressiveness between black and white patients. Consistent with this interpretation is the fact that, at a study level, late-stage cancer at diagnosis was not correlated with tumour grade, which could indicate that late-stage cancer at diagnosis is not entirely a consequence of black African women having more biologically aggressive forms of disease—indeed a 2014 review[21] suggests that oestrogen-receptor-positive disease constitutes two-thirds of tumours in black women from sub-Saharan Africa. Late-stage disease was, however, positively correlated with mean tumour size (as expected given that tumour size is used to derive stage), consistent with delays in access to health care.

Increased breast cancer awareness and improvements in health care over time have been paralleled by decreases in tumour size and downstaging of breast cancer in other

LMICs.[58,59] However, studies have reported low levels of breast cancer awareness in the general population and health-care professionals in sub-Saharan Africa.[60,61] The poor awareness contributes to the high frequency of late-stage cancer at diagnosis seen in sub-Saharan Africa.[62,63] Other barriers to access, such as distance to health-care facility, also play a role in this region.[64]

Most studies used the TNM or the Manchester staging classifications, but only a quarter reported on the staging methods used. Of these, most studies relied on both clinical and imaging methods, but a few studies used clinical methods only. Although the clinical methods only approach leads to under-staging,[65] most women in settings where imaging procedures are unavailable or unaffordable are likely to have presented at advanced stages when clinical methods might suffice.[66] This is consistent with our finding of no differences in late-stage disease depending on whether staging methods were reported and, if reported, by the type used.

There was no correlation, at a study level, between percentage of late-stage disease and average self-reported duration of symptoms (ie, time between onset of symptoms and diagnosis). The extent to which this ecological-level association reflects a similar absence of an association at an individual level is unclear. Women might not recognise symptoms because of poor breast cancer awareness,[67,68] or they might not accurately remember the dates on which they first noticed symptoms. Nevertheless, the average duration of symptoms was between 8 months and 12 months in most studies (appendix p 21), indicating that for the most part advanced stage at diagnosis might be a result of delayed diagnosis. Hence, a large window exists in which delays to diagnosis can be shortened.

The frequency of late-stage disease at diagnosis in black women in sub-Saharan Africa was higher than in white and black women from the USA in 1970–2010, including during the pre-mammography screening era (screening in the USA began in 1976[69]). This shows that, through more rapid diagnosis of palpable clinical disease, considerable improvements can be made before expensive systems for the detection of preclinical disease are warranted. In sub-Saharan Africa, where mammography is often unavailable or unaffordable, stage migration through breast cancer awareness and improved access to diagnostic facilities, not mammographic screening, is urgently required.

Major strengths of this review include the detailed and inclusive search strategy, which included non-English publications; the large sample size of more than 24 000 women with breast cancer in the region; and the use of standard methods for study identification, and data extraction and synthesis. There were also limitations. The representativeness of the review might have been compromised by several factors. First, we included studies from only 17 of 49 sub-Saharan Africa countries, albeit together they represent 71% of the total population in the region, with most studies based on convenience samples of patients. Second, by definition, the large numbers of patients with breast cancer in the region who never reach a health-care facility could not be included. Dickens and colleagues[64] showed that distance to a tertiary care facility was a major determinant of access to diagnosis even within a relatively small geographical area (ie, Soweto in Johannesburg, South Africa). Because the patients included in this review are, by definition, patients who were able to reach a health-care facility, predominantly tertiary centres, they might not be a representative sample of all patients with breast cancer in sub-Saharan Africa. Third, some participants might have been included in more than one study; to minimise this, whenever papers from the same institution and recruitment period were identified, we only included the paper that had the more comprehensive information on stage at diagnosis. Fourth, six potentially eligible papers could not be retrieved; the sample sizes for two of these papers are known to be small, and therefore their exclusion is not likely to have substantially affected our findings. Finally, the absence of information on staging methods and procedures in many studies and the absence of standardisation in staging procedures between studies, and possibly even within studies, might have obscured some of the findings. Staging is affected by neoadjuvant chemotherapy, but this treatment is not available in most sub-Saharan Africa settings.[9] Neoadjuvant chemotherapy was mentioned in only two papers included in this review,[14,70] and whether staging was ascertained before or after chemotherapy was not clear.

This review showed that the percentage of late-stage breast cancer at diagnosis in black populations from sub-Saharan Africa around 2010 was higher than in black and white populations in the USA 40 years previously. Cancer control strategies in the region should target early detection and diagnosis of symptomatic disease as one essential component of the strategy to improve survival from breast cancer. In most settings, symptom duration of 8–12 months shows that there is a considerable delay between symptom onset and diagnosis and thus a considerable time window exists in which to realistically achieve early detection and diagnosis. Population-level interventions for the stage migration of breast cancer have been shown to be successful in Tanzania[71] and other LMICs, such as Malaysia.[72] Several sub-Saharan Africa studies have shown improved survival rates in women diagnosed at earlier stages,[6,19] which shows that early diagnosis coupled with timely and appropriate treatment can prevent deaths from this disease in this region.

Contributors

EJ-A extracted data, analysed data, drafted the manuscript, and made subsequent revisions to the manuscript. VM had the idea for the study, extracted data, analysed data, and provided critical revisions to the report. CA provided critical revisions to the manuscript. Id-S-S had the idea for the study, extracted data, supervised data extraction and analysis, and revised the manuscript.

Declaration of interests
We declare no competing interests.

Acknowledgments
We thank the Training Program in Nigeria for Non-Communicable Diseases Research (TRAPING-NCD; Fogarty International Center of the National Institutes of Health D43TW009106-CA) for providing funding support for EJ-A's PhD research work at the London School of Hygiene & Tropical Medicine. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Fogarty International Center of the National Institutes of Health.

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