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Carolina Espina, PhD, Fiona McKenzie, PhD, Isabel dos-Santos-Silva, PhD

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Delayed presentation and diagnosis of breast cancer in African women: a systematic review

Running title: Delays in breast cancer diagnosis in Africa

Carolina Espina, PhD[a], Fiona McKenzie, PhD[a], Isabel dos-Santos-Silva, PhD[b]

[a] International Agency for Research on Cancer (IARC), 150 Cours Albert Thomas, 69372 Lyon, France

[b] Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom

Correspondence to: Carolina Espina, Section of Environment and Radiation, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France. Tel.: +33 472738154; E-mail: espinac@iarc.fr

ABSTRACT

Purpose: Africa has low breast cancer incidence rates, but high mortality rates from this disease due to poor survival. Delays in presentation and diagnosis are major determinants of breast cancer survival but these have not been comprehensively investigated in Africa.

Methods: MEDLINE, Embase and Global Health were searched to identify studies reporting on delays in presentation and/or diagnosis of breast cancer published between 01/01/2000 and 31/05/2016. Data were synthesised in narrative, tabular and graphical forms. Meta-analyses were not possible due to between-study differences in the way delays were reported.

Results: 21 studies were included in the review. Study-specific average times between symptom recognition and presentation to a health care provider ranged from <1 to 4 months in North Africa and from <3 to >6 months in Sub-Saharan Africa (SSA). Study-specific average times from presentation to diagnosis were <1 month in North Africa, but ranged from <3 to >6 months in SSA. Reported reasons for these delays included patient-mediated (e.g. socio-economic factors) and health system-mediated factors (e.g. referral pathways).

Conclusions: This systematic review revealed marked delays in presentation and diagnosis of breast cancer in Africa. Identification of their drivers is crucial to the development of appropriate control strategies in the continent.

Keywords

Breast cancer, Africa, delayed presentation, delayed diagnosis, late-stage breast cancer

Conflict of interest

The authors declare no conflict of interest.

ABBREVIATIONS

BC: breast cancer

BSE: breast self-examination

CBE: clinical breast examination

CI: confidence interval

HCP: health care provider

HICs: high-income countries

HIV: human immunodeficiency virus

IDC: invasive ductal carcinoma

IQR: inter-quartile range

LABC: Locally advanced breast cancer

LMICs: low- and middle-income countries

Md: median

Me: mean

mths: months

n/a: not applicable as not reported in the original publication

OR: odds ratio

Ra: range

SD: standard deviation

SSA: Sub-Saharan Africa

wks: weeks

wMe: weighted mean

yrs: years

INTRODUCTION

Women in Africa currently have one of the lowest incidence rates of breast cancer worldwide (1). However, the burden from this cancer is expected to increase markedly in the next decades. A growing aging population alone, i.e. assuming incidence rates will remain constant, will lead to an estimated 119,918 new cases in 2030, a near doubling in the number of incident cases over 20 years (2). The increase will be even more marked as incidence rates are likely to rise due to the adoption by African women of more westernized lifestyle profiles, particularly reproductive patterns characterised by late age at first full-term pregnancy, lower parity, reduced lifetime breastfeeding duration as well as increases in postmenopausal weight (3).

Despite breast cancer incidence rates being still relatively low in Africa, mortality rates from this disease are as high, or higher, than in high incidence countries due to poor survival (1). Furthermore, the proportion of breast cancer cases and deaths at premenopausal ages is higher in Africa than in high-income countries (HICs), where disease incidence is highest, reflecting the younger age structure of the continent's population and possibly also distinctive risk factors and/or tumour characteristics. Consequently, breast cancer in Africa disproportionately affects women in the prime of their lives and hence it has particularly marked familial, societal and economic consequences.

A recent systematic review (4) shows that a high proportion of breast cancer patients in sub-Saharan Africa (SSA) are diagnosed with late-stage disease leading to poor survival (5). Studies from HICs have shown that delays between onset of symptoms and start of treatment are main determinants of late-stage presentation and poor survival (6). Previous studies have attempted to examine delays in breast cancer presentation, diagnosis and treatment in Africa (5,7) but, to our knowledge, these have not been comprehensively investigated across the continent. Knowledge of the length of time intervals between symptom recognition, presentation, diagnosis and start of treatment – and of the factors that may influence them – is key to the development of strategies to shorten them. Therefore, we conducted a systematic review to investigate delays in presentation and diagnosis of breast cancer in Africa, and their determinants.

MATERIAL AND METHODS

Conceptual framework

Figure 1 depicts a patient's trajectory from the moment she first notices symptom(s) to the time when treatment starts as well as the factors that may affect her journey. In HICs with free universal access to health care the delay from a woman first noticing potential symptoms of breast cancer to her presentation to a health care provider is labelled as "patient delay" as it is essentially driven by patient-mediated factors. In contrast, the time from first medical consultation to the beginning of definitive treatment is labelled as "provider delay" as it is driven predominantly by

health system-mediated factors. However, in many African settings the picture is likely to be far more complex as delays in both presentation and diagnosis are likely to result from a complex interplay between patient-mediated and health system-mediated factors. For instance, a woman may delay presentation not only because of her lack of breast cancer awareness but also because of the unavailability of health care providers in her area of residence. Similarly, a woman who first presents with a suspicious cancer may delay diagnosis due to fear of its consequences (e.g. mastectomy, death). In this review, we will consider *presentation delays* as the time interval from symptom recognition to presentation to the first health care provider, *diagnostic delays* as the time interval between presentation and breast cancer diagnosis, and *treatment delays* as the time interval between diagnosis and start of cancer treatment. These terms do not carry any judgement on whether these delays are primarily induced by patient-mediated or provider-mediated factors.

Search methodology

The PRISMA statement guidelines (8) were followed to select relevant publications on delays in breast cancer presentation and diagnosis in Africa. Papers were eligible for inclusion in the systematic review if they reported findings from primary research studies conducted in Africa; reported on delays in presentation and/or diagnosis of female breast cancer patients; and were published between the 1st January 2000 and the 31st May 2016. No language restrictions were imposed. Relevant publications were searched in the electronic databases MEDLINE, Embase, and Global Health. A search strategy using synonyms (including truncations) and subject headings of the search concepts "breast cancer", "late diagnosis", "Africa" and "determinants", and the Boolean operators "AND" and "OR" was used (Appendix A). All titles and abstracts were screened to identify potentially eligible papers and the full-text for these retrieved and critically reviewed to assess eligibility and, if eligible, to extract relevant data.

Data extraction

The data extraction from each eligible paper was carried out independently by two reviewers (CE and IdSS) using a specifically developed standardised data extraction form. The following information was extracted: the type of catchment population (e.g. country; urban, rural or mixed); the study design (quantitative, qualitative, mixed); the type of recruitment source (primary, secondary or tertiary hospital/clinic) and approach (eligibility criteria; recruitment period; type of sample: consecutive or convenience, i.e. opportunistic; sample size); patient (e.g. age) and tumour characteristics (e.g. stage, size, histology, symptoms); source (e.g. patient, medical records) and timing of collection (e.g. prior or after diagnosis) of data on delays and their reasons; reported times between symptom recognition,

presentation, diagnosis and start of treatment; and patient-mediated and health system-mediated factors that might have influenced them. Disagreements between the two reviewers were discussed and a consensus reached.

Quality assessment of the eligible papers

The quality of the articles included in the review was assessed independently by the same two reviewers. A standardized quality assessment form was developed which included parameters to assess the potential for selection and information bias as well as the appropriateness of the analytical methods used, including those for dealing with potential confounders (Appendix B). The overall quality score of a paper was expressed as the sum of its parameter-specific scores, which could range from 0 (lowest) to 30 (highest). The higher the score, the higher the methodological quality of the paper; the lower the score, the more likely its findings might have been affected by biases.

Data synthesis

Data were synthesised in narrative, tabular and graphical forms. Study-specific mean (SD), or median (range), presentation, diagnosis and treatment delays are presented; if only categorical data were reported in the original publication we used them to estimate the median, or a weighted mean, whenever possible. Studies differ greatly in the way they obtained information on potential reasons for delays and in the way such data were presented (Appendix C). Most studies simply presented data in a descriptive way (e.g. percentages), but a few used logistic regression methods to estimate crude and/or adjusted odds ratios (OR) for delayed presentation, diagnosis or treatment for each variable examined, with studies using different cut-off points to define such delays (e.g. from ≥2.2 to >6 months for delay in presentation and from >2 weeks to ≥6 months for delays in diagnosis; Appendix C). One study in North Africa (9) reported on delays but only examined factors associated with late (III/IV) versus early stage at diagnosis; late stage was taken here as a proxy for delays between symptom recognition and diagnosis. Findings are shown separately for studies conducted in North Africa (i.e. in Algeria, Egypt, Libya, Morocco, Sudan, Tunisia, and Western Sahara) and sub-Saharan Africa (SSA, i.e. countries in East, Middle, South and West Africa) as defined by the United Nations (10).

RESULTS

A total of 315 papers (after removal of duplicates) were identified through electronic searches and their titles and abstracts screened for potential eligibility (Figure 2). In all, 35 articles were retrieved for full-text review. Of these, only 21 were eligible for inclusion in the review: 16 quantitative studies, three qualitative studies and two mixed (quantitative and qualitative).

Study characteristics

Table 1 summarizes the main characteristics of each participating study. Of the 18 quantitative and mixed design studies, eight (44%) were conducted in North Africa and ten (56%) in SSA, with their sample sizes ranging from 44 to 350. In contrast, all three qualitative studies were conducted in SSA, with sample sizes ranging from 9 to 31. All studies were hospital-based cross-sectional surveys that relied on consecutive samples of patients, except for two small qualitative studies (11,12) which relied on convenience samples. Eligibility was restricted to women with advanced breast cancer in one study in North Africa (13) and in four (three quantitative (14-16) and one qualitative (11)) in SSA. The large majority recruited breast cancer patients diagnosed predominantly in the years 2000-2010, but two studies in North Africa (17,18) and two in SSA (19,20) included patients diagnosed after 2010 whereas one study in SSA recruited patients diagnosed prior to 2000 (21) (Table 1). The average (mean/median) age at breast cancer diagnosis was in the 40s in the large majority of studies. Most studies involved collection of data through structured or semi-structured questionnaires, usually administered by the researchers or medical staff around the time of diagnosis, but four were conducted retrospectively using medical records (14,15,17,22). Information on ethnicity was provided in only one study, which stated that its subjects were all Black (12). Information on tumour stage at diagnosis was available for seven (88%) studies in North Africa and nine (69%) in SSA. Among studies with stage information, and whose subject eligibility was not dependent on it, the proportion of patients with late stage (III/IV) was very high (range: 46%-61% in North Africa; 76%-91% in SSA; Table 1).

Quality scores were low for most quantitative studies (Table 1) albeit slightly higher for those from North Africa (median=18.5; range: 14-25) than for those from SSA (median=17.5; range: 7-25). Similarly, the quality of the qualitative and mixed design studies varied substantially, with three studies presenting more in-depth qualitative results (12,20,23).

Delays in presentation and diagnosis

The time interval between symptom recognition by the woman to presentation, i.e. to first visit to a health care provider, varied substantially across studies but, overall, it was shorter in North Africa than in SSA (Table 2; Figure 3a). Of the five North African studies that reported on presentation delays, most yielded median estimates of <2.5 months; the only exception was a study in Libya (24) with a median presentation time of 4 months. Of the five studies in SSA that provided estimates of time from symptom recognition to presentation only one (25) reported a median time

of <2.5 months, with the remaining reporting average times ranging from 3.4 months in Mali (21) to >6 months in South Africa (15).

Fewer studies in North Africa (18,24,26) and in SSA (19,25,27) gave estimates of the time between presentation and diagnosis, or between diagnosis and start of treatment. Nevertheless, the length of these intervals tended to be shorter than the length of the corresponding intervals between symptom recognition and presentation in North Africa (all <1 month), but not in SSA (Figure 3b).

Five North African studies provided median estimates of the total delay from symptom recognition to date of breast cancer diagnosis or start of treatment (Figure 3c). Two of these studies recruited only advanced breast cancer cases with average total delays of 8 (13) and 12 months (14). Median estimates of the total delay from symptom recognition to diagnosis for the remaining three studies ranged from 4 (18) to 8.5 months (17). Five SSA studies provided average times from presentation to diagnosis or start of treatment (Figure 3c), with their estimates ranging from 7.9 months in Ghana (28) to 15 months in Rwanda (19); median delays were known to be >6 months for two studies (25,27) but their exact values could not be estimated. In addition, a small qualitative study (n=11) in Botswana reported a median time from first symptom(s) to presentation at the hospital where the diagnosis was finally made of 3 years (12).

The number of health care providers visited prior to the one where the diagnosis was made were reported by only one study in North Africa (26) and four in SSA (19,21,23,27), with estimates ranging from a median of 1.5 in Egypt (26) to >5 in Rwanda (19); however, these estimates are not entirely comparable because traditional and religious healers were included in two of these studies (23,27).

A few studies examined whether delays were associated with late stage (III/IV) at diagnosis. The study by Benbakhta *et al*. (18) in Morocco reported a 6.81-fold (95% CI: 3.65, 12.7) increase in the odds of late stage among patients who delayed presentation by >64 days relative to those who presented ≤64 days of symptom recognition. Similarly, the odds of late stage among patients who experienced a diagnostic delay of ≥50 days was 1.84 (95% CI: 1.05, 3.23) times higher than among those diagnosed <49 days of their first presentation to a health care provider (18). The study by Mousa *et al.* (26) in Egypt also reported an association between late stage and delays in presentation >3 months (crude OR: 1.99; 95% CI: 1.01, 1.99), but not with delays in diagnosis >2 weeks. In Rwanda, late stage was positively associated with both presentation (median (range) in months: 2 (1-12) for stages I/II, 5 (1-13) for stage III and 9 (3-18) for stage IV; p=0.09) and diagnostic delays (4 (2-13) months for stage I/II, 4 (2-10) for stage III and 11 (5-28) for stage IV; p=0.005) (19).

Factors associated with delays

Appendix C summarises the reasons most commonly reported by the quantitative studies in the review for late presentation to the first health care provider. They fell into the following categories: (i) socio-economic factors such as low educational level; (ii) lack of breast cancer awareness and poor knowledge of early-detection methods (e.g. breast self-examination); (iii) type of initial symptoms: painless, not taken seriously or hoping they would resolve soon; (iv) fear of the disease, its treatment (e.g. mastectomy) or death, or of being a burden to the family; (v) belief in traditional medicine or spiritual cures; (vi) financial constraints; and (vii) poor access to health care (e.g. living too far away from a health care provider; lack of transportation). Benbakhta *et al*. (18) found in mutually-adjusted analysis that a delay in presentation of ≥2.2 months in Morocco was positively associated with low socio-economic conditions (e.g. living in a rural area, being illiterate, being a housewife (vs. being employed) and having low socio-economic level) and lack of breast cancer awareness (e.g. negative family history of cancer, no knowledge of breast self-examination) (Appendix C). In contrast, Mousa *et al.* (26) found no association between delay in presentation >3 months in Egypt and a woman's socio-economic characteristics or type of symptoms before or after adjustment for potential confounders. In South Africa, Marcus *et al*. (15) found in mutually-adjusted analysis positive associations with late presentation (>6 vs. 3-6 months) with increasing age and a previous cancer diagnosis, but not with educational level, marital status or being employed/unemployed. A mutually-adjusted analysis of data from a study in Rwanda (19) revealed a four to five-fold increase in the odds of late presentation (≥6 months) for patients with low or no education, and for those who visited a traditional healer first, but no independent associations with other socio-economic, breast cancer awareness, symptom or health services-related variables (Appendix C). Overall, the findings from the qualitative studies supported the evidence from the quantitative studies (11,12,20,23) (Appendix C).

The reasons given by the patients for delays between presentation and diagnosis, or start of treatment, included patient-mediated factors (e.g. socio-economic factors, type of symptoms, having tried traditional treatments first, financial problems, fear of the disease and/or its treatment, and denial) as well as health care provider-mediated factors (e.g. travel time to health care provider, the number and type of health care providers contacted prior to diagnosis, delayed referrals or non-referrals, misdiagnosis, wrong advice or false reassurances, delays in obtaining diagnostic confirmation and in starting treatment) (Appendix C). The study in Morocco by Benbakhta *et al.* (18) found in mutually-adjusted analyses that a delay >1.7 months between presentation and start of treatment was associated with older age, illiteracy, low socio-economic level, distance to health care provider ≥100 kms and ≥3 consultations prior to the diagnostic one. Mousa *et al*. (26) in Egypt showed that after adjustment for potential confounders the odds of a delay >2 weeks from the first medical consultation to arrival at the diagnostic centre was not associated with the

patient's age, socio-economic conditions or type of symptoms but was strongly associated with the type of the first health care provider visited and the navigation pathway followed by the patient (Appendix C). In Rwanda, Pace *et al.* (19) found in mutually-adjusted analyses a 2.69 (95% CI 1.24, 5.84) higher odds of a delay ≥6 months for patients who visited five or more health care facilities prior to diagnosis, but no associations with the patient's socioeconomic conditions, reproductive history or type of symptoms. In the qualitative studies (Appendix C), some women reported poor clinical practices (e.g. inadequate diagnosis by general doctors (11)), hospital strikes (20), or having sought alternative care after receiving the diagnosis).

DISCUSSION

To our knowledge, this is the first systematic review of studies that reported on delays in a woman's breast cancer journey in Africa. Its findings highlighted three main issues. Firstly, there is a paucity of published data on delays in the presentation and diagnosis of the most common female cancer in Africa (2). The systematic review identified only 21 published studies over the 16-year period (January 2000-May 2016), comprising only 2,788 breast cancer patients from across the continent (1,382 from North Africa; 1,406 from SSA). Secondly, the findings revealed marked delays in presentation and diagnosis of breast cancer patients in both North Africa and SSA. Thirdly, the reported reasons for such delays were complex and included both patient-mediated and health system-mediated factors; however, the relative importance of these two types of factors varied from setting to setting.

There is strong evidence that a delay from symptom recognition to diagnosis of more than three months is associated with later stage at presentation and poorer survival (6). This review revealed substantially longer delays in both North Africa and SSA, with reported average times from symptoms recognition to diagnosis between 4 and 15 months. These estimates are in line with those observed in other low and middle income countries (LMICs) (e.g. 7.6 months in Brazil (29); 5.5 months in Malaysia (30)) but much higher than those observed in HICs (e.g. 34 days in France (31); 48 days in the USA (32)). The very long time intervals from symptom recognition to diagnosis in Africa resulted from delays in both presentation and diagnosis. All studies in this review, with the exception of two (9,33), reported average presentation intervals between 2.2 months and >6 months, much longer that those observed in HICs (e.g. 9 days in the United Kingdom (34); 16 days in Germany (35)). Similarly, reported diagnostic intervals in Africa were much longer than those found in HICs (e.g. from 10 to 42 days in France (31), Germany (36) and the USA (32)), but similar to what has been described for other LMICs (e.g. median of 5 months in Brazil (29), Colombia (37) and Mexico (38)).

As we had hypothesized in our conceptual model, delays in presentation in Africa were found to be associated not only with patient-mediated factors (e.g. low educational level, poor breast cancer awareness, use of alternative care medicine) but also with health services-mediated factors (e.g. distance to the nearest health care centre). These results are similar to those from previous studies – e.g. being unaware of the warning signs or tests for breast cancer (5), patients only seeking conventional care when traditional treatment has failed (39), or inability to afford the costs of treatment (40). Similarly, delays in diagnosis in Africa were influenced by both patient-mediated factors (e.g. low educational level, financial problems) and health system-mediated factors (e.g. type of first health care provider visited, number of providers visited prior to diagnosis, type of navigation pathway followed before reaching the diagnostic centre). A high number of referrals makes the patient's journey through the health system longer resulting in a more advanced tumour stage at diagnosis; however, it is also conceivable that a low number of referrals might reflect a more aggressive tumour, or a longer time interval before presentation to the first health care provider, and thus a more advanced tumour that was easily identified by the physician. Of note, however, is the fact none of the papers directly examined health system factors, e.g. through interviews with health care providers, relying instead on patients' reports.

Strengths and limitations of the review

Major strengths of this review include the systematic search strategy used to identify eligible English and non-English publications, and the use of standardised methods for data extraction and synthesis. The review also has weaknesses. Its representativeness may have been compromised by several factors. First, publication bias cannot be excluded as grey literature was not included in this review. Second, the review included studies from only 4 of the 7 North African countries and 11 of 51 SSA countries, albeit the latter comprised studies from all four SSA regions (i.e. from Eastern, Western, Southern and Middle Africa). Third, none of the studies in the review were population-based; they were all hospital-based, predominantly from tertiary hospitals as these are the only ones in most African countries to have appropriate cancer diagnostic and treatment facilities. However, such studies excluded, by design, the large number of patients who never reach tertiary hospitals, some of whom are never diagnosed. Hence, the included patients who reached tertiary facilities are unlikely to be a representative sample of all breast cancer patients in Africa.

The methodological quality of most papers was low. In particular, measurement errors may have affected the validity of the review's findings as although most of the studies recruited women prospectively, patients were asked to remember the time from first symptom(s) to presentation, and this might have introduced recall errors, and even biases. Little detail was provided in the original papers on the specific instruments used to collect information and the methods

used to estimate times to presentation, diagnosis and treatment, including on the way questions to patients on time intervals were formulated and on how relevant time-related events (e.g. dates of contact with a first health care provider, breast cancer diagnosis and start of treatment) were defined. Between-study differences in these methodological issues may have affected their comparability. When questioned about the reasons for delays patients might have been reluctant to admit less orthodox behaviours such as the use of traditional medicine. Reassuringly, however, the studies that examined associations between self-reported delays and late stage at diagnosis showed, as expected, strong positive associations. Many studies had relatively small sample sizes and thus their ability to precisely quantify delays, and their power to detect associations, were limited. There were large variations across studies in the way data were analysed (e.g. only a few quantitative studies attempted to control for confounders; none of the qualitative studies conducted theoretical analyses), and summary findings presented, hampering between-study comparisons and precluding the conduct of meta-analyses.

CONCLUSIONS

Several studies in Africa have shown that early stage breast cancer is associated with better survival than late stage disease (41,42), consistent with early diagnosis and treatment being associated with reductions in mortality from this disease in the region. The long presentation and diagnostic delays identified by this review indicates that there is considerable potential to introduce interventions aimed at shrinking the time intervals between symptom recognition and diagnosis. Mammography screening is often advocated as the best intervention to improving early diagnosis of breast cancer but the findings from this review strongly argue against adopting such an approach in African settings. Screening can only reduce breast cancer mortality if women with suspicious screen-detected lesions have access to appropriate diagnosis and treatment. Despite the limitations of the existing data, and the high heterogeneity across African settings, the long diagnostic delays highlighted by the review indicate that the addition of women with asymptomatic screen-detected tumours would place significant additional burden on most, already over-stretched, healthcare systems in the region. Instead, downward stage migration of symptomatic breast cancer should be the priority in most settings as recommended by the Breast Health Global Initiative and the Breast Cancer Initiative 2.5 (43). To achieve this would require increased breast cancer awareness of the population, enhanced ability of primary and secondary health care professionals to diagnose breast cancer as well as clear patient navigation pathways to facilitate timely referral and admission of patients to tertiary care services for early care. The introduction of such an approach in other LMICs has demonstrated that downward stage migration of breast cancer is achievable in the absence of screening (44).

LIST OF FIGURES AND TABLES

Footnote to Figure 1:
BC: breast cancer; HCP: health care provider

Footnote to Figure 3:
BC: breast cancer; HCP: health care provider; IQR: inter-quartile range; Md: median; Me: mean; mths: months; SSA: Sub-Saharan Africa; wMe: weighted mean.
[a] Study eligibility restricted to advanced BC
See Table 2 for more detailed information on study-specific estimates of delay. A dashed line indicates that the delay estimate shown in the Figure is an under-estimation of the median value (the latter could not be calculated from the data provided in the original paper).
No delay estimates for Otieno *et al.* (16) are shown because average time from symptoms to diagnosis could not be estimated (>3 mths for 73% of patients – all with advanced BC – with no further information provided; see Tables 1 and 2).

APPENDICES

Table 1: Main characteristics of the 21 studies included in the review

Author, year [ref n°]	Country (sample size)	Hospital/clinic, location	Hospital/clinic-based catchment population[a]	Recruitment				Eligibility criteria	Age (yrs)	Tumour characteristics					Total quality score (max. score=30)
				Type of hospital/clinic[b]	Type of sample[c]	Timing of[d]	Time period			First symptom(s)	Late stage[e]	Size (cm)	Grade	ER status/ Histology	
QUANTITATIVE STUDIES (n=16)															
North Africa (n=8)															
Ahmed, 2014 (14)	Sudan (n=141)	National Cancer institute, Wad Medani city	M (U: 55.6 %; R: 44.4 %)	T	C	Re	April 2009 - May 2010	Locally advanced breast cancer (LABC) who attended the breast clinic	Md: 46 Ra: 25-71 Me: 47	n/a	LABC (IIIA: 13.2%; IIIB: 78.5%; IIIC: 8.3%)	n/a	I: 2.1% II: 20.1% III: 77.8%	ER+: 70.1% IDC: 77.1%	14
Aloulou, 2015 (17)	Morocco (n=130)	Department of radiotherapy, CHU Mohammed VI, Marrakech (public teaching hospital)	n/a	T	C	Re	Jan 2012 – Jan 2013	Histologically confirmed breast cancer (BC)	Me: 46 Ra: 20-78	Lump: 58.5%; Ulceration: 16.2%; Metastasis: 13.8%; Inflammation: 11.5%	T2-T4: 75%	Mean: 3.5	II: 56% III: 28%	IDC: 90%	14
Benbakhta, 2015 (18)	Morocco (n=200)	Department of radiotherapy, Institute National of Oncology, Rabat	U: 74%	T	C	P	Dec 2012-May 2013	Inclusion: All female patients with a BC diagnosis treated at this institution; Moroccan nationality; provided written consent. Exclusion: those who had started neo-adjuvant chemotherapy.	Me ± SD: 49.1 ± 10.7 Ra: 25-82	Breast lump: 46%	III: 43%; IV: 3%	Mean: 4.1	n/a	n/a	23

El-Shinawi, 2013 (33)	Egypt (n=45)	Ain Shams University (ASU) Hospital Breast Clinic	M (Greater Cairo: 63%)	T	C	P	Feb 2010 – Dec 2010	Inclusion: Recently diagnosed BC patients (< 6 mths). Exclusion: patients unaware of their disease, recurrence disease, poor general health (289 excluded)	Md ± SD: 47 ± 10.2 Me ± SD: 48.2 ± 10.2	Painless breast mass: 57.8%; painful breast mass: 15.6%	n/a	n/a	n/a	n/a	15
Ermiah, 2012 (24)	Libya (n=200)	African Oncology Institute (NOI), Sabratha	n/a	T	C	P	1 Jan 2008 – 31 Dec 2009	Female patients with BC diagnosed at NOI	Me: 45.4 Ra: 22-75	Lump: 68%; skin changes: 15.5%; nipple discharge: 13.5%; systemic: 3.0%	III: 54%; IV: 11.5%	T1 & T2 (≤5 cm): 40%; T3 & T4: 60%	n/a	n/a	19
Landolsi, 2010 (13)	Tunisia (n=160)	Dept Medical Oncology, Centre Hospitalier Universitaire Farhat Hached, Sousse	M (U: 37%; R: 63%)	T	C	P	1 Sept 2005 - 31 March 2006	Patients presenting with a locally advanced (T3 or T4) or a metastatic breast cancer	Me: 48 Ra: 27-85	n/a	T3: 25%; T4: 71%; M1: 24%	Mean: 6.3 cm (range: 3-15 cm)	n/a	n/a	18
Mousa, 2011 (26)	Egypt (n=163)	Tanta Cancer Center (TCC), Gharbiah province (the largest cancer centre in the Nile delta region)	M (U: 36.8%; R: 63%)	T	C	P	Dec 2009 - Nov 2010	Newly diagnosed BC cases	Md: 53 Me ± SD: 51.6±11.5	Mass: 77.4%; pain: 7.6%; nipple discharge: 3.1%; increased breast size: 2.5%; axillary mass: 2.5%; other: 6.9%	III & IV: 60.9%	n/a	n/a	n/a	25
Stapleton, 2011 [(9)]	Egypt (n=343)	National Cancer Institute (NCI), Cairo (n=200) & Tanta Cancer Center (TCC), Gharbiah (n=143)	M	T	C	P	July 2007-Aug 2008	Inclusion criteria: females with a newly diagnosed or treated BC between July 2007 and August 2008 recruited from chemotherapy outpatient clinics. Exclusion criteria: patients aged <18 yrs, pregnant or lactating, previous cancer diagnosis	Me ± SD: 49.2 ± 10.9 (early-stage) Me ± SD: 49.9 ± 11.0 (late-stage)	n/a	Late-stage: 46.1%	n/a	n/a	n/a	23
SUB-SAHARAN AFRICA (n=8)														

Clegg-Lamptey, 2009 (28)	Ghana (n=66)	Korle Bu Teaching Hospital	n/a	T	O	P	Sept 2007-July 2008	Newly diagnosed breast cancer	Md: 43 Ra: 20-84 Me: 44.8	n/a	n/a	n/a	n/a	n/a	16
Ezeome, 2010 (25)	Nigeria (n=162)	University of Nigeria Teaching Hospital Enugu (UNTH-E)	n/a	T	C	P	June 1999 - June 2001 & April 2003 - May 2005	Breast cancer patients managed at the Surgical Oncology unit at the UNTH-E who provided consent	Md: 45 Ra: 21-77 Me: 45.7	n/a	III: 40.8%; IV: 37.5%	n/a	n/a	n/a	23
Ibrahim, 2012 (45)	Nigeria (n=201)	Lagos State University Teaching Hospital (LSUTH)	U	T	C	P	Jan 2009 - Dec 2010	All female BC patients referred to one of the general surgery out-patient clinics of LSUTH	Mean: 49.82 (SD: 13.59) Ra: 23-104	n/a	III: 62.7%; IV: 16.4%	n/a	n/a	n/a	23
Marcus, 2013 (15)	South Africa (n=103)	Sebokeng Hospital, Gauteng	U	Level 2 public regional hospital	C	Re	Jan 2007 - Dec 2010	All patients presenting at the breast clinic with advanced BC (IIB or higher)	Me: 59 Ra: 34-83	Breast lump: 84.5%; axillary node abnormal: 19.4%; abscess/ulcers: 7.8%; nipple discharge: 6.8%; pain: 4.9% (not mutually exclusive)	III-IV: 95.1%	n/a	n/a	n/a	13
Otieno, 2010 (16)	Kenya (n=166; 98.8% females)	Kenyatta National Hospital (KNH)	M	T	C	P	1 Oct 2003 – 31 March 2006	Inclusion: all (male and female) patients who attended the breast clinic or were admitted to the three surgical wards with advanced BC (stages III/IV). Exclusions: patients with treated or recurrent BC	Me: 47 Ra: 17-88	Breast lump: 87.3%	III/IV: 100%	n/a	n/a	n/a	15

Pace, 2015 (19)	Rwanda (n=144)	Butaro and Rwinkwavu rural hospitals	R	S or T (n/a)	C	P	Nov 2012 - Feb 2014	Inclusion: Women aged ≥21 yrs with pathologically confirmed BC. Exclusions: women diagnosed elsewhere >6 mths without initial staging	Md: 49	Breast pain: 59%	III: 52%; IV: 24%	n/a	n/a	n/a	25
Price, 2012 (27)	Cameroon (n=50 BC cases; includes other cancers)	Yaounde General Hospital (YGH) – the only one in the country to offer chemotherapy	M	T	C	P	13 July - 12 Aug 2010	Patients aged ≥18 yrs with primary invasive BC (98% with histological confirmation) and who received chemotherapy; 96% female	Me: 46 Ra: 29-75	n/a	n/a	n/a	n/a	n/a	20
Toure, 2013 (22)	Cote d'Ivoire (n=350)	University Hospital of Treichville, Abidjan	M	T	C	Re	Jan 2008 - Dec 2011	Patients with a histologically-confirmed adenocarcinoma of the breast	Me: 42 Ra: 18-81	Breast lump: 6%; Inflammation: 54%; Ulcer: 18% Nipple blood discharge: 8% Metastases: 14%	III: 76.3%; IV: 14.3%	n/a	n/a	Adeno-carcinoma: 100%	19
QUANTITATIVE AND QUALITATIVE STUDIES (n=2)															
Dye, 2010 (23)	Ethiopia (n=69; 98.1% females)	Tikur Anbessa Hospital (TAH)	M	T	C	P	2008 (1 mth only)	Randomly selected female and male BC patients seen at TAH over the span of 1 mth (similar characteristics to the total population). Patients or their families were interviewed.	Me: 44.5	n/a	n/a	n/a	n/a	n/a	10
Ly, 2002 (21)	Mali (n=44; 43 females)	Hôpital du Point-G, Bamako	M	T	C	P	15 Sept 1998 - 15 Aug 2000	Newly-diagnosed and histologically-confirmed BC patients (male and female) seen at the haematology / oncology service	Me (SD): 46 ±19.5 Ra: 25-80	Breast lump: 39%; Breast pain: 39%; Pruritus (itching): 12% Nipple blood discharge: 6.8% Ulcer: 4.5%	III: 40.9%; IV: 45.5%	n/a	n/a	n/a	7
QUALITATIVE STUDIES (n=3)															
Ekortarl, 2007 (11)	Cameroon (n=9 BC cases; 11 subjects with other types of cancer)	Yaounde General Hospital	M	T	O	P	n/a	Cancer patients who presented with advanced disease or who re-appeared at an advanced stage after having abandoned treatment at the Oncology Division	Ra: 34-63	n/a	Advanced BC: 100%	n/a	n/a	n/a	n/a

Mbuka-Ongona, 2012 (12)	Botswana (n=11)	Princess Marina Hospital (PMH), Gaborone (the only hospital in the country with oncology services)	M	T	O	P	2007	Inclusion: All female adult BC patients seen and managed at PMH. Exclusions: aged <18 yrs; too ill or mentally incapacitated	Me: 54 Ra: 37-76	Most common: painless lump; second most common: bloody nipple discharge	Majority stage III	n/a	n/a	n/a	n/a
Pruitt,2015 (20)	Nigeria (n=31)	University College Hospital Ibadan	M	T	C	P	July 2011	All female BC patients seen in the radiotherapy and surgery clinics, aged ≥18 yrs, regardless of ethnicity, language or stage.	Md: 51 Ra: 28-80	n/a	n/a	n/a	n/a	n/a	n/a

[a] Population-based: urban (U), rural (R), mixed (M) area, or not reported (n/a)
[b] Primary (P), secondary (S) or tertiary (T) hospital/clinic
[c] Opportunistic (O) or consecutive (C) sample of patients
[d] Patients recruited prospectively (P) or retrospectively (Re)
[e] Stages III-IV (note: T2 can be staged as IIIA)

BC: breast cancer; BSE: breast self-examination; CBE: clinical breast examination; IDC: invasive ductal carcinoma; IQR: inter-quartile range; LABC: Locally advanced breast cancer; Md: median; Me: mean; mths: months; n/a: not reported in the original publication; Ra: range; SD: standard deviation; wks: weeks; yrs: years

Table 2. Time from recognition of potential symptoms of breast cancer to presentation to the first health care provider, diagnosis and start of treatment, and number of health care providers visited

Author, year [ref n°]	Country (sample size)	Time from:			No. health care providers (HPC) visited prior to visit to the one where diagnosis was made
		Symptom recognition to presentation	Presentation to diagnosis	Diagnosis to start of treatment	
North Africa					
Ahmed, 2014 (14)[a]	Sudan (n=141)	Md: 12 mths; Ra: 2-108 mths		n/a	n/a
Aloulou, 2015 (17)	Morocco (n=130)	Me: 8.47 mths; > 6 mths: 63.1%		n/a	n/a
Benbakhta, 2015 (18)	Morocco (n=200)	Md: 65 days (=2.17 mths); IQR: 31-121 days; Ra: 3-579 days	Md: 20 days (=0.67 mths); IQR: 10-40 days; Ra: 1-433 days	Md: 25 days (=0.83 mths); IQR: 9-42 days; Ra: 0-368 days	n/a
			Md: 50 days (=1.67 mths); IQR: 29, 77 days; Ra: 5-535 days		
		Md: 120 days (4.0 mths); IQR: 81-202 days; Ra: 14-860 days			
El-Shinawi, 2013 (33)	Morocco (n=45)	<1 mth: 46.7% 1- <6 mths: 37.8% 6 - <12 mths: 0% >12 mths: 15.6%	n/a	n/a	n/a
Ermiah, 2012 (24)	Libya (n=200)	Md: 4 mths (max. 24) <3 mths: 46% 3-6 mths: 14% >6 mths: 40%	Md: < 1 mth <1 mth: 84.5% 1-6 mths: 4.5% >6 mths: 11.0%	n/a	n/a
		Md: 7.5 mths (max. 25 mths) <3 mths: 30% 3-6 mths: 14% >6 mths: 56%			
Landolsi, 2010 (13)[a]	Tunisia (n=160)	Mean: 11.6 mths; Md: 8 mths		n/a	n/a
Mousa, 2011 (26)	Egypt (n=163)	Me: 6.2 mths; Md: 2.3 mths	*Presentation to arrival at TCC:* Me: 6.8 wks; Md: 2.5 wks	n/a	Me: 1.5 Range: 0-4 (does not mention traditional or spiritual healers)
Stapleton, 2011 (9)	Egypt (n=343)	Md: <1 mth	n/a	n/a	n/a
Sub-Saharan Africa					
Clegg-Lamptey, 2009 (28)	Ghana (n=66)	Me: 46 wks (=10.7 mths) Md: 34 wks (=7.9 mths) Ra: 1 wk, 5 yrs		n/a	Previous medical consultation: 39.4%

Ezeome, 2010 (25)	Nigeria (n=162)	<1 mth: 26.4% 1 - 3 mths: 28.3% >3 - 6 mths: 17.6% >6 mths: 27.7%	<1 mth: 17% 1 - 3 mths: 10.6% >3 - 6 mths:16% >6 mths: 56.4%		n/a
		<1 mth: 5.6% 1 - 3 mths: 4.3% >3 – 6 mths: 17.3% >6 mths: 72.8%			
Ibrahim, 2012 (45)	Nigeria (n=201)	Me (SD): 12.12 (5.18) mths Ra: 1 wk – 96 mths <1 mth: 4.5% 1-3 mths: 13.9% >3 – 6 mths: 32.8% >6-12 mths: 30.8% >12 mths: 17.9%	n/a	n/a	n/a
Marcus, 2013 (15)[a]	South Africa (n=103)	< 3 mths: 17.5% 3-6 mths: 30.1% >6 mths: 52.4%	n/a	n/a	n/a
Otieno, 2010 (16)[a]	Kenya (n=166; 98.8% females)	*From first symptoms to presentation at Kenyatta National Hospital (late stage only)* < 30 days: 6.62% 31 – 90 days: 20.4% > 90 days: 73.08%		n/a	n/a
Pace, 2015 (19)	Rwanda (n=144)	Md: 5 mths (IQR: 1-13)	Md: 5 mths (IQR: 2-14)	n/a	< 5 HCP visits : 44% ≥ 5 HCP visits: 56% (does not mention traditional or spiritual healers)
		Md: 15 mths (IQR: 8 – 32)			
Price, 2012 (27)	Cameroon (n=50)	n/a	>3 mths: 42% >6 mths: 32%	n/a	Consulted ≥4 HCP: 46% (including traditional and spiritual healers)
		>6 mths: 60%			
Toure, 2013 (22)	Cote d'Ivoire (n=350)	< 6 mths: 9.1% 6-10 mths: 12% 10-14 mths: 78.9% *Weighted mean: 10.7 mths*		n/a	n/a
QUANTITATIVE and QUALITATIVE STUDIES					
Dye, 2010 (23)	Ethiopia (n=69; 98.1% females)	n/a	n/a	n/a	>2 HCP visits: 73.2% (including traditional or spiritual healers)

Ly, 2002 (21)	Mali (n=44; 43 females)	1 - 12 wks (=2.8 mths): 63.6% 13 (=3.0 mths) – 48 wks (=11.2 mths): 36.4% Weighted mean: 3.4 mths	n/a	n/a	>3 HCP: 50% (only conventional HCP included)
		From symptoms to first appointment at the study (diagnostic) hospital: Ra: 8 wks (=1.87 mths) – 72 wks (=16.8 mths)			
QUALITATIVE STUDIES					
Ekortarl, 2007 (11)	Cameroon (n=9 BC cases; 11 subjects with other types of cancer)	n/a	n/a	n/a	n/a
Mbuka-Ongona, 2012 (12)	Botswana (n=11)	*Time from first symptom to presentation at study hospital (PMH):* Me: 3 yrs; Ra: 1 - 10 yrs		n/a	n/a
Pruitt, 2015 (20)	Nigeria (n=31)	n/a		n/a	n/a

[a] Study recruited only patients with advanced breast cancer (see Table 1)

BC: breast cancer; CI: confidence interval; HCP: health care provider; IQR: inter-quartile range; Md: median; Me: mean; mths: months; n/a: not reported in the original publication; Ra: range; TCC: Tanca Cancer Center; wks: weeks; yrs: years

References

1. Forouzanfar MH, Foreman KJ, Delossantos AM *et al.*(2011) Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. *Lancet* **378**: 1461-84.

2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM(2010) Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* **127**: 2893-917.

3. Akarolo-Anthony SN, Ogundiran T.O., Adebamowo CA(2010) Emerging breast cancer epidemic: evidence from Africa. *Breast Cancer Res* **12(Suppl 4): S8**.

4. Jedy-Agba E, McCormack V, Adebamowo C, Dos-Santos-Silva I(2016) Stage at diagnosis of breast cancer in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Glob Health* **4**: e923-e935.

5. Brinton L.A., Figueroa JD, Awuah B *et al.*(2014) Breast cancer in Sub-Saharan Africa: opportunities for prevention. *Breast Cancer Res Treat* **144(3)**: 467-78.

6. Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ(1999) Influence of delay on survival in patients with breast cancer: a systematic review. *The Lancet* **353**: 1119-25.

7. Adebamowo CA, Ajayi OO(2000) Breast cancer in Nigeria. *West Afr J Med* **19**: 179-91.

8. Moher D, Liberati A, Tetzlaff J, Altman DG(2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* **6**: e1000097.

9. Stapleton JM, Mullan PB, Dey S *et al.*(2011) Patient-mediated factors predicting early- and late-stage presentation of breast cancer in Egypt. *Psycho-Oncology* **20**: 532-7.

10. United Nations Statistics Division (2016) United Nations methods and classification: composition of macro geographical (continental) regions, geographical sub-regions, and selected economic and other groupings.

11. Ekortarl A, Ndom P, Sacks A(2007) A study of patients who appear with far advanced cancer at Yaounde General Hospital, Cameroon, Africa. *Psycho-Oncology* **16**: 255-7.

12. Mbuka-Ongona D, Tumbo JM(2013) Knowledge about breast cancer and reasons for late presentation by cancer patients seen at Princess Marina Hospital, Gaborone, Botswana. *African Journal of Primary Health Care and Family Medicine; 2013* **5**: Art.

13. Landolsi A, Gahbiche S, Chaafii R *et al.*(2010) [Reasons of diagnostic delay of breast cancer in Tunisian women (160 patients in the central region of Tunisia)]. *Tunis Med* **88**: 894-7.

14. Ahmed AA(2014) Clinicopathological profile of female Sudanese patients with locally advanced breast cancer. *Breast Disease* **34**: 131-4.

15. Marcus TS, Lunda S, Fernandez L(2013) Delayed breast cancer presentation: hospital data should inform proactive primary care. *African Journal of Primary Health Care and Family Medicine; 2013* **5**: Art.

16. Otieno ES, Micheni JN, Kimende SK, Mutai KK(2010) Delayed presentation of breast cancer patients. *East African Medical Journal* **87**: 147-50.

17. Aloulou S, El MA, El OA, Khouchani M(2015) [Factors related to late diagnosis of breast cancer: experience of CHU Mohammed VI Marrakech]. *Pan Afr Med J* **21**: 162.

18. Benbakhta B, Tazi M, Benjaafar N, Khattabi A, Maaroufi A(2015) [Determinants of patient and health system delays for women with breast cancer in Morocco, 2013]. *Rev Epidemiol Sante Publique* **63**: 191-201.

19. Pace LE, Mpunga T, Hategekimana V *et al.*(2015) Delays in Breast Cancer Presentation and Diagnosis at Two Rural Cancer Referral Centers in Rwanda. *Oncologist* **20**: 780-8.

20. Pruitt L, Mumuni T, Raikhel E *et al.*(2015) Social barriers to diagnosis and treatment of breast cancer in patients presenting at a teaching hospital in Ibadan, Nigeria. *Global Public Health* **10**: 16.

21. Ly M, Diop S, Sacko M, Baby M, Diop CT, Diallo DA(2002) [Breast cancer: factors influencing the therapeutic itinerary of patients in a medical oncology unit in Bamako (Mali)]. *Bull Cancer* **89**: 323-6.

22. Toure M, Nguessan E, Bambara AT, Kouassi YK, Dia JM, Adoubi I(2013) [Factors linked to late diagnosis in breast cancer in Sub-Saharan Africa: case of Cote d'Ivoire]. *Gynecol Obstet Fertil* **41**: 696-700.

23. Dye TD, Bogale S, Hobden C *et al.*(2010) Complex care systems in developing countries: breast cancer patient navigation in Ethiopia. *Cancer* **116**: 577-85.

24. Ermiah E, Abdalla F, Buhmeida A, Larbesh E, Pyrhonen S, Collan Y(2012) Diagnosis delay in Libyan female breast cancer. *BMC Research Notes* **5**: 452.

25. Ezeome ER(2010) Delays in presentation and treatment of breast cancer in Enugu, Nigeria. *Nigerian Journal of Clinical Practice* **13**: 311-6.

26. Mousa SM, Seifeldin IA, Hablas A, Elbana ES, Soliman AS(2011) Patterns of seeking medical care among Egyptian breast cancer patients: relationship to late-stage presentation. *Breast* **20**: 555-61.

27. Price AJ, Ndom P, Atenguena E, Mambou Nouemssi JP, Ryder RW(2012) Cancer care challenges in developing countries. *Cancer* **118**: 3627-35.

28. Clegg-Lamptey J, Dakubo J, Attobra YN(2009) Why do breast cancer patients report late or abscond during treatment in Ghana? A pilot study. *Ghana Medical Journal; 2009* **43**: 127-31.

29. Barros AF, Uemura G, de Macedo JL(2013) [Interval for access to treatment for breast cancer in the Federal District, Brazil]. *Rev Bras Ginecol Obstet* **35**: 458-63.

30. Norsa'adah B, Rampal KG, Rahmah MA, Naing NN, Biswal BM(2011) Diagnosis delay of breast cancer and its associated factors in Malaysian women. *BMC Cancer* **11**: 141.

31. Molinie F, Leux C, Delafosse P *et al.*(2013) Waiting time disparities in breast cancer diagnosis and treatment: a population-based study in France. *Breast* **22**: 810-6.

32. Richardson LC, Royalty J, Howe W, Helsel W, Kammerer W, Benard VB(2010) Timeliness of breast cancer diagnosis and initiation of treatment in the National Breast and Cervical Cancer Early Detection Program, 1996-2005. *Am J Public Health* **100**: 1769-76.

33. El-Shinawi M, Youssef A, Alsara M *et al.*(2013) Assessing the level of breast cancer awareness among recently diagnosed patients in Ain Shams University Hospital. *Breast* **22**: 1210-4.

34. Allgar VL, Neal RD(2005) Delays in the diagnosis of six cancers: analysis of data from the National Survey of NHS Patients: Cancer. *Br J Cancer* **92**: 1959-70.

35. Arndt V, Sturmer T, Stegmaier C, Ziegler H, Dhom G, Brenner H(2002) Patient delay and stage of diagnosis among breast cancer patients in Germany -- a population based study. *Br J Cancer* **86**: 1034-40.

36. Arndt V, Sturmer T, Stegmaier C, Ziegler H, Becker A, Brenner H(2003) Provider delay among patients with breast cancer in Germany: a population-based study. *J Clin Oncol* **21**: 1440-6.

37. Pineros M, Sanchez R, Perry F, Garcia OA, Ocampo R, Cendales R(2011) [Delay for diagnosis and treatment of breast cancer in Bogota, Colombia]. *Salud Publica Mex* **53**: 478-85.

38. Unger-Saldana K, Miranda A, Zarco-Espinosa G, Mainero-Ratchelous F, Bargallo-Rocha E, Miguel Lazaro-Leon J(2015) Health system delay and its effect on clinical stage of breast cancer: Multicenter study. *Cancer* **121**: 2198-206.

39. Opoku SY, Benwell M, Yarney J(2012) Knowledge, attitudes, beliefs, behaviour and breast cancer screening practices in Ghana, West Africa. *The Pan African medical journal* **11**: 28.

40. Adisa AO, Gukas ID, Lawal OO, Adesunkanmi AR(2010) Breast cancer in Nigeria: is non-adherence to chemotherapy schedules a major factor in the reported poor treatment outcome? *Breast J* **16**: 206-7.

41. Galukande M, Wabinga H, Mirembe F(2015) Breast cancer survival experiences at a tertiary hospital in sub-Saharan Africa: a cohort study. *World J Surg Oncol* **13**: 220.

42. Kantelhardt EJ, Zerche P, Mathewos A *et al.*(2014) Breast cancer survival in Ethiopia: a cohort study of 1,070 women. *Int J Cancer* **135**: 702-9.

43. Yip CH, Smith RA, Anderson BO *et al.*(2008) Guideline implementation for breast healthcare in low- and middle-income countries: early detection resource allocation. *Cancer* **113**: 2244-56.

44. Harirchi I, Kolahdoozan S, Karbakhsh M *et al.*(2011) Twenty years of breast cancer in Iran: downstaging without a formal screening program. *Ann Oncol* **22**: 93-7.

45. Ibrahim NA, Oludara MA(2012) Socio-demographic factors and reasons associated with delay in breast cancer presentation: a study in Nigerian women. *Breast* **21**: 416-8.

Figure 1

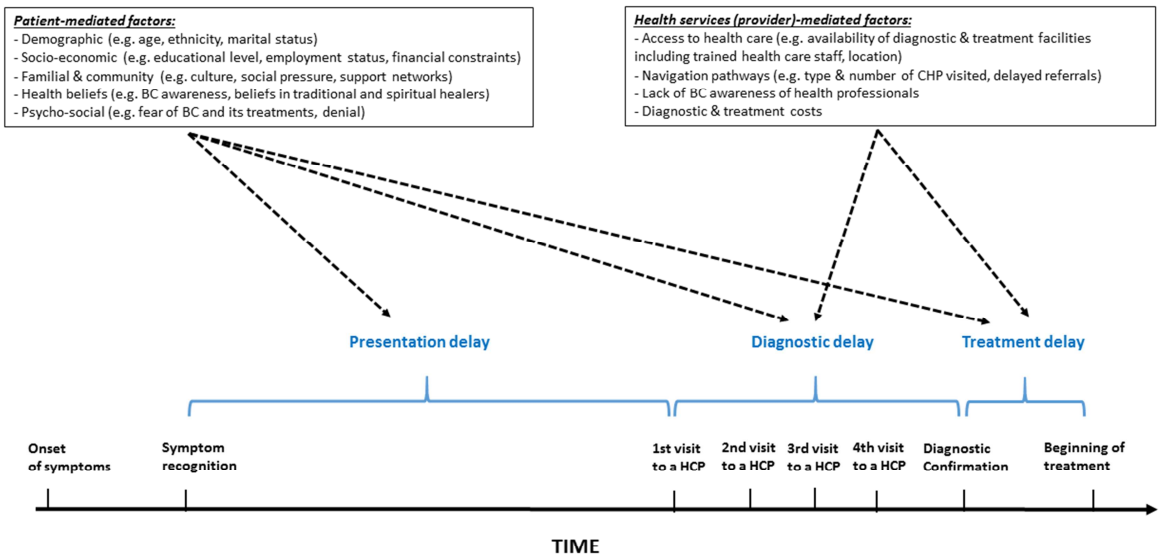
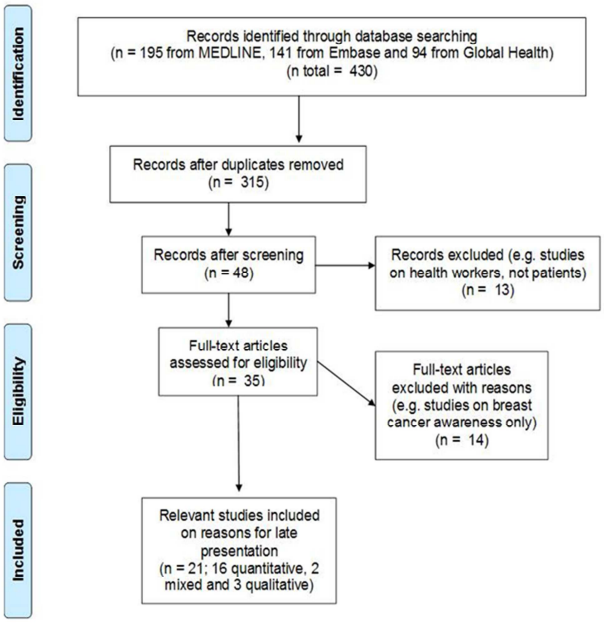
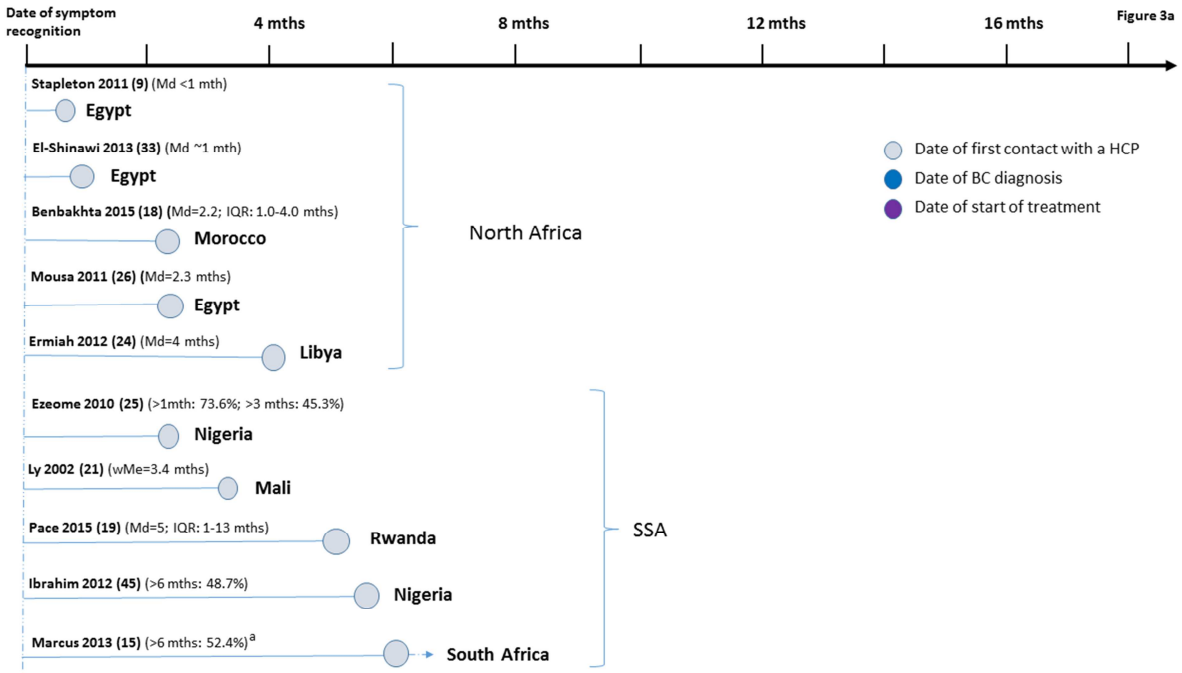
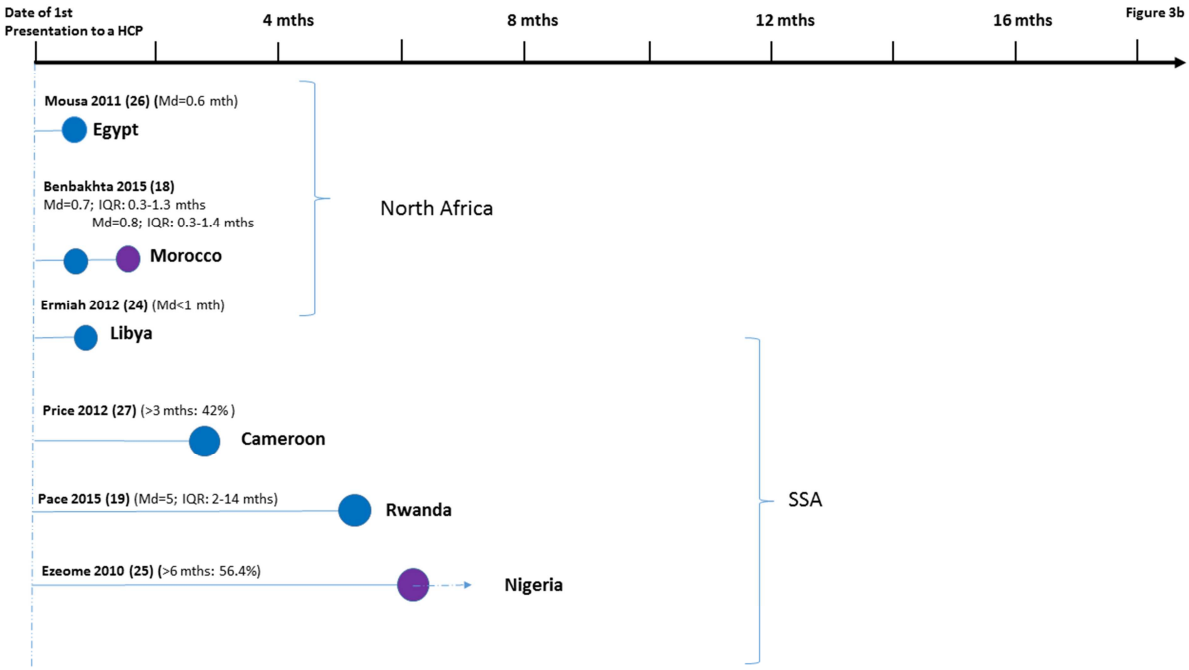
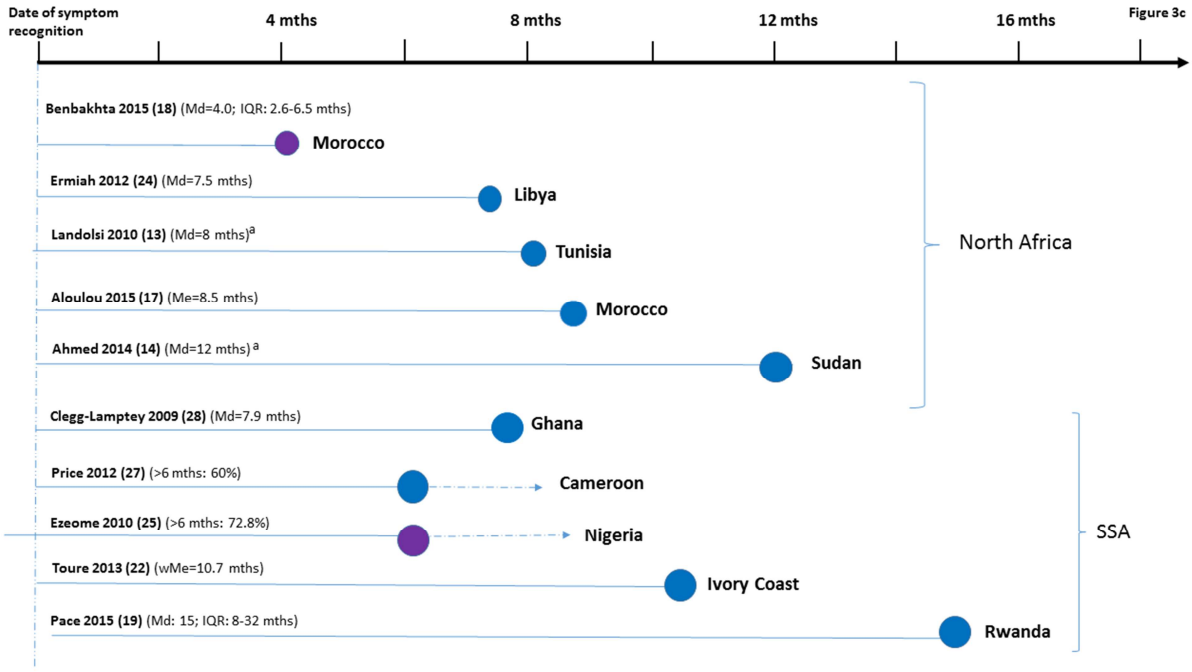


Figure 2









Article title: Delayed presentation and diagnosis of breast cancer in African women: a systematic review

Journal name: Annals of Epidemiology

Carolina Espina, PhD[a], Fiona McKenzie, PhD[a], Isabel dos-Santos-Silva, PhD[b]

[a] International Agency for Research on Cancer (IARC), 150 Cours Albert Thomas, 69372 Lyon, France

[b] Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom

Correspondence to: Carolina Espina, Section of Environment and Radiation, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, Tel.: +33 472738154;E-mail: espinac@iarc.fr

Appendix A: Example of the search string used in MEDLINE

1 (breast OR mammary) ADJ3 (neoplasm* OR cancer* OR tumo?r* OR carcinoma)
2 exp Breast Neoplasms

3 1 OR 2

4 (delay* OR late OR poor) ADJ1 (presentation OR attendance OR diagnosis OR stage OR detection OR prognosis)
5 exp Delayed Diagnosis
6 exp Prognosis
7 exp Early Diagnosis

8 4 OR 5 OR 6 OR 7

9 (determinant* OR **factor*** OR **reason*** OR **barrier*** OR attitude* OR belie* OR awareness OR knowledge OR fear* OR cultur* OR perception*)

10 (uptake OR utilization OR access OR accept* OR intent* OR distance OR transport* visit* OR presentation*) ADJ3 (health care centre OR hospital OR clinic OR health service OR doctor OR physician OR mammogram* OR screening OR exam*)

11 exp "**Behavior and Behavior Mechanisms"**
12 exp **Attitude to Health**
13 exp **Socioeconomic Factors**
14 exp **Health Status Disparities**
15 exp **Communication Barriers**

16 OR/9-15

17 Africa OR Algeria OR Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroon OR Cape Verde OR Central African Republic OR Chad OR Democratic Republic of the Congo OR Djibouti OR Egypt OR Equatorial Guinea OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea-Bissau OR Guinea OR Ivory Coast OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Republic of Congo OR Rwanda OR Senegal OR Sierra Leone OR Somalia OR South Africa OR South Sudan OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR Zambia OR Zimbabwe

18 exp Africa
19 17 OR 18
20 3 AND 8 AND 16 AND 19

Appendix B: Quality assessment of the eligible papers

The quality of the articles included in the review was assessed by developing a standardized quality assessment form which included parameters on three main domains: (1) *Selection bias*: study design (score 0 if unclear, 1 if retrospective case series, 2 if prospective study); study population (score 0 if unclear, 1 if opportunistic hospital-based study, 2 if consecutive hospital-based study, 3 if population-based study); restricted to late stage/advanced disease (score 0 if unclear, 1 if yes, 3 if no); participation rate (score 0 if unclear, 1 if <70%, 2 if ≥70%). (2) *Information bias*: source of the information (i) for patient-mediated factors (score 0 if unclear or n/a (not applicable), 1 if medical records, 2 if proxy (relative), 3 if patient); (ii) for health service-mediated factors (score 0 if unclear or n/a, 1 if proxy (relative), 2 if patient, 3 if medical records); timing of information collection (score 0 if unclear or n/a, 1 if after patient was aware of her breast cancer diagnosis, 2 if around the time of her diagnosis, 3 if before her diagnosis); potential of observer/interviewer bias (score 0 if unclear, 1 if likely, 2 if unlikely as information was validated against medical records or a previously-validated questionnaire was used). (3) *Analytical methods including dealing with potential confounders*: definition of delays in presentation, diagnosis and/or treatment (score 0 if not given, 1 if given but unclear or stage used as a proxy, 2 if clear); distinction between patients' and health system's related factors (score 0 if not given, 1 if focus only on one of these, 2 if given but unclear, 3 if clear); statistical methods (score 0 if not properly described, 1 if only descriptive, 2 if analytical or in-depth); adjustment for potential confounders (score 0 if n/a, 1 if only crude estimates given, 2 if adjusted). The overall quality score of a paper was expressed as the sum of its parameter-specific scores, which could range from 0 (lowest) to 30 (highest). The higher the score, the higher the methodological quality of the paper and, hence, the lower the score, the more likely its findings might have been affected by biases.

Appendix C: Factors associated with delayed presentation and delayed diagnosis or start of treatment of breast cancer in Africa: summary of the findings reported by the studies included in the review.

Author, Year [ref n°] (country)	Factors associated with delay between symptoms recognition and first visit to a health care provider (HCP)		Factors associated with delay between first visit to a health care provider (HCP) and breast cancer (BC) diagnosis or start of treatment	
	Crude	Adjusted	Crude	Adjusted
North Africa				
Ahmed, 2014 (14)[a] (Sudan)	**Factors associated with late presentation in patients with LABC (%)** Lack of education: 39.5% Financial aspects: 28.6% Use of traditional medicine: 13.8% Limited access to medical care: 9% Ignorance: 6.9% Fear of being a burden to relatives: 2.7%		n/a	
Aloulou, 2015 (17) (Morocco)	**Reasons for delays from symptoms recognition to diagnosis:** *Fear* of cancer and/or treatment: 4%; *Financial problems*: 40%; Tried t*raditional treatments*: 20% *Health services:* Distance from health centre: 23%; Wrong diagnosis: 6%; Inadequate medical care: 7%			
Benbakhta, 2015 (18) (Morocco)	**Delay from symptoms recognition to presentation ≥2.2 mths: OR (95% CI)** <u>*Socio-economic:*</u> Aged >65 vs. <45 yrs: 1.68 (0.64, 4.38) Rural vs. urban area of residence: **4.62 (2.24, 9.52)** Illiteracy vs. secondary/university: **4.56**	**Delay from symptoms recognition to presentation ≥2.2 mths: OR* (95% CI)** <u>*Socio-economic:*</u> Rural vs. urban area of residence: **3.00 (1.24, 7.23)** Illiteracy vs. secondary/university: **4.90**	**Delay between presentation and start of treatment ≥1.7 mths: OR (95% CI)** <u>*Socio-economic:*</u> Aged >65 vs. <45 yrs: **1.94 (1.36, 2.40)** Rural vs. urban area of residence: **2.10 (1.18, 4.40)** Illiteracy vs. secondary/university: **2.70**	**Delay between presentation and start of treatment ≥1.7 mths: OR* (95% CI)** <u>*Socio-economic:*</u> Aged >65 vs. <45 yrs: **2.51 (1.50, 11.42)**

	(2.26, 9.18) Employed vs. housewife: **0.23 (0.13, 0.57)** Low vs. mid socioeconomic level: **8.55 (3.16, 23.17)** >5 people in household: **2.05 (1.14, 3.69)** *BC awareness:* No knowledge vs. knowledge of BSE: **17.88 (8.74, 36.56)** Positive vs. negative family history: **2.51 (1.23, 5.13)** *Type of symptoms:* Presence of typical vs. atypical symptoms: 0.75 (0.33, 1.67) *Health services related:* Distance from HCP of presentation ≥100vs <100 kms kms: **8.62 (1.01, 67.14)**	**(2.50, 6.30)** Employed vs. housewife: **0.1 (0.03, 0.47)** Low vs. mid socioeconomic level: **7.60 (2.24, 25.77)** *BC awareness:* No knowledge vs. knowledge of BSE: **11.51 (5.18, 25.57)** Negative vs. positive family history: **2.11 (1.10, 4.16)** *Mutually-adjusted	**(1.38, 5.27)** Low vs. mid socioeconomic level: **2.61 (1.20, 23.17)** *Health services:* Distance to HCP of diagnosis ≥100 vs. <100 kms: **2.46 (1.26, 5.20)** ≥3 vs <3 consultations before diagnostic one: **11.44 (4.83, 27.08)**	Illiteracy vs. secondary/university: **1.40 (1.12, 6.50)** Low vs. mid socioeconomic level: **2.59 (1.04, 6.50)** *Health services:* Distance to HCP of diagnosis ≥100 vs. 100 kms: **2.58 (1.12, 3.56)** ≥3 vs <3 consultations before diagnostic one: **11.27 (4.12, 28.34)** *Mutually-adjusted
El-Shinawi, 2013 (33) (Egypt)	**Delay from symptoms recognition to presentation to a HCP** *BC awareness:* Higher awareness of BSE associated with less delay in seeking medical advice (2.9±2.3 months) relative to low awareness (15.5±22.6 months) (P=0.04)	n/a	n/a	n/a
Ermiah, 2012 (24) (Lybia)	**Delay from symptom recognition to diagnosis ≥3 mths** *Socio-economic:* Aged ≥50 vs <50 yrs: **64% vs 51% (P=0.033)** Single vs married: 52% vs 56% (P=0.6) Housewife vs employed: 61% vs 48% (P=0.09) Illiteracy vs literacy: **69% vs 38% (P=0.009)**			

	Reproductive: Post- vs. pre-menopausal: 64% vs 50% (P=0.05) No vs. breastfeeding: 38% vs 58.6% (P=0.09) OC use >5 yrs vs. <5yrs or no use: **86% vs 53% (P=0.04)** *BC awareness:* Positive vs negative family history: 45% vs 57% (P=0.3) Positive vs. negative history of benign breast disease: **73% vs. 52% (P=0.03)** Knowledge of BSE vs no knowledge: **0% vs 58% (P<0.0001)** *Type of symptoms:* Initial symptom being a lump vs being other symptoms: **41% vs 86% (P<0.0001)**			
Landolsi, 2010 (13)[a] (Tunisia)	**Delay from symptoms recognition to presentation at study setting, i.e. to diagnosis** *93% delay related to personal reasons:* Not aware of disease: 35% Not having practiced BSE: 23.5% Fear of cancer and/or treatment: 14% Financial problems: 14% Others: 13.5% *24% delay related to health services:* Wrong reassurance: 47.5% Misdiagnosis: 18%			
Mousa, 2011 (26) (Egypt)	**Delay from symptoms recognition to first medical consultation >3 mths: OR (95% CI)** *Socio-economic:* Aged ≥50 vs <50 yrs: 1.1; 95%CI: 0.6, 2.1 Urban vs rural residence: 1.3; 95%CI: 0.7, 2.6 ≥Bachelor vs <bachelor education:	**Delay from symptoms recognition to first medical consultation >3 mths: OR* (95% CI)** *Socio-economic:* Aged ≥50 vs <50 yrs: 0.9 (0.4, 1.9) Urban vs. rural residence: 1.4 (0.7, 2.9) ≥Bachelor vs. <bachelor education: 0.6 (0.3, 1.2)	**Delay from first medical consultation to arrival at TTC >2 wks: OR (95% CI)** *Socio-economic:* Aged ≥50 vs <50 yrs: 0.6 (0.3, 1.2) Urban vs. rural residence: 0.8 (0.4, 1.5) ≥Bachelor vs. <bachelor education: 1.2 (0.7, 2.3)	**Delay from first medical consultation to arrival at TTC >2 wks: OR* (95% CI)** *Socio-economic:* Aged ≥50 vs <50 yrs: 0.6 (0.3, 1.4) Urban vs. rural residence: 1.1 (0.5, 2.3) ≥Bachelor vs. <bachelor education: 1.3 (0.5, 2.9)

	0.6 (0.3, 1.2) *Type of symptoms:* Breast mass vs. other first symptom: 2.1 (0.9, 4.8)	 *Type of symptoms:* Breast mass vs. other first symptom: 2.1 (0.9, 4.8) *Adjusted for age, residential status and education	*Type of symptoms:* Breast mass vs. other first symptom: 0.8 (0.4, 1.8) *Health services-related:* First health care provider vs TCC: Primary care: **11.0 (2.9, 41.7)** Gynaecologist: **9.0 (1.6, 52.3)** Medical oncologist: **5.6 (1.0, 30.9)** General surgeon: **5.5 (1.7, 18.0)** Surgical oncologist: 3.0 (0.7, 13.4) Other: **12.0 (2.2, 66.5)** Navigation pathway vs directly to TCC: General surgeon → Surgical oncologist→ TCC: **29.3 (4.6, 184.4)** General surgeon → Medical oncologist→ TCC: 6.0 (0.9, 38.1) Primary care→ Others→ TCC: **19.5 (3.7, 102.4)**	*Type of symptoms:* Breast mass vs. other first symptom: 1.3 (0.6, 3.1) *Health services-related:* First health care provider vs TCC: Primary care: **12.2 (2.9, 51.0)** Gynaecologist: **8.6 (1.4, 53.4)** Medical oncologist: **8.3 (1.3, 55.0)** General surgeon**: 7.6 (2.1, 27.6)** Surgical oncologist: 3.4 (0.7, 16.0) Other: **11.0 (1.9, 63.3)** Navigation pathway vs directly to TCC: General surgeon → Surgical oncologist→ TCC: **35.4 (5.3, 237.5)** General surgeon → Medical oncologist→ TCC: **8.1 (1.0, 62.2)** Primary care→ Others → TCC: **23.2 (4.0, 134.5)** *Adjusted for age, residential status, education level, tumour stage, and first symptom
Stapleton, 2011 (9) (Egypt)	**Late vs early stage at diagnosis: Mutually-adjusted OR (95%CI)** >33 wks vs. ≤33 delay in seeking treatment: 1.57 (0.76, 3.23) *Financial and other constraints* Social, financial and time constrains vs. no delay: 1.72 (0.86, 3.46) *Type of symptoms:* No pain vs. no delay: **2.68 (1.18, 6.08)**			

	BC awareness: Knowledge of BSE vs. no knowledge: **0.24 (0.06, 0.94)** Previous CBE vs. no previous CBE: 1.00 (0.28, 3.62) Previous mammogram vs. no previous mammogram: 2.17 (0.48, 9.72) *Health services related:* Site of treatment NCI-Cairo vs. TCC: **5.05 (1.30, 19.70)** Visited vs. not visited a second provider: 0.72 (0.30, 1.74) First diagnosed vs. not first diagnosed as BC: 0.99 (0.52, 1.89) Referral vs. no referral: 1.10 (0.57, 2.12) Treated in a hospital vs present facility: 0.80 (0.43, 1.48) Travel time to facility >1 hr vs. ≤1 hr: **1.64 (0.96, 2.79)**			
Sub-Saharan Africa				
Clegg-Lamptey, 2009 (28) (Ghana)	**Reasons for delay from symptoms recognition to presentation at the study hospital where diagnosis was made (%)** Lack of BC awareness: 28.8%; Fear of diagnosis or mastectomy: 34.8%; Tried traditional/alternative treatments: 19.7%; Tried spiritual cures: 19.7%; Financial problems: 18.2%; Lack of knowledge of BSE: 57.6% Other: 4.5% *Health services related:* Previous medical consultation: 39.4%; Previous hospital consultations at a different hospital: 72.7%, with diagnosis made in only 52% of these.			
Ezeome, 2010 (25) (Nigeria)	**Reasons for delay between symptoms recognition and visit to first HCP** Symptom(s) not serious/hoping they will resolve: 27.8%; Lack of BC awareness: 23.3%; Tried traditional/ spiritual treatments:	n/a	**Reasons for delay between symptoms recognition and start of BC treatment** *Patient-related* Lack of BC awareness: 25.3% Finance: 16.9% Thought it was harmless/will disappear:	n/a

	12.6%; Financial problems: 13.9%; Painless: 12%; Fear/refusal of mastectomy: 5.6%; Family/social problems: 5.6%; Though it was pregnancy/lactation effect: 3.2% Discouraged by friends/relatives: 3.2% Others: 15.7%		15.4% Fear/refused surgery/mastectomy: 9.2% Painless/not disturbing her: 6.9% Delayed by family/social problems: 6.9% Traditional/spiritual treatments: 5.4% Discouraged by friends/relatives: 5.4% *Health Care Provider-related:* Delayed referrals or non-referrals: 17.8%; Wrong advice and false reassurance by health professionals: 11.5%; Delayed histology report: 6.2%; No histology after biopsy: 5.4%; Industrial actions: 4.6%	
Ibrahim, 2012 (45) (Nigeria)	**Delay from symptoms recognition to first medical consultation >3 mths** *Reasons given:* Lack of BC awareness: 34.1%; Belief in spiritual healing: 32.3%; Fear of mastectomy: 29.3%; Belief in herbal treatment: 22%; Belief in alternative therapy: 7.3%; Lack of funds: 3%; Reassurance by non-medical health worker: 3% *Crude analysis:* Being single: OR=2.05, 95%CI: 0.25, 16.8; Primary level of education: OR=3.06, 95%CI: 0.96, 9.73; Negative history of benign breast disease: OR=1.65, 95%CI: 0.76, 3.59	**Delay from symptoms recognition to first medical consultation >3 mths** "In the multivariate analysis, being pre-menopausal (OR=1.86; 95% CI: 0.38, 9.4) was the additional factor associated with increased risk of late presentation" (sic)	n/a	n/a

Marcus, 2013 (15)[a] (South Africa)	**Delay from first symptoms to presentation >6 mths vs 3-6 mths: OR (95% CI)** *Socio-economic:* Age (vs 34-45 (sic)): 45-54: 0.15 55-64: 0.18 65-83: 0.77 Education (vs. none): Primary: 0.41 Secondary or higher: 0.18 Employed vs unemployed: 0.26 Married vs single/divorced/widowed: 0.31 *BC awareness:* Previous cancer diagnosis: 0	**Delay from first symptoms to presentation >6 mths vs 3-6 mths: Adjusted* OR (95% CI)** *Socio-economic*: Age (vs 34-45 (sic)): 45-54: 2.05 55-64: **2.55 (P<0.05)**; 65-83: 2.28 Education (vs. none): Primary: 0.27 Secondary or higher: 1.56 Employed vs unemployed: 0.63 Married vs single/divorced/widowed: 0.84 *BC awareness:* Previous cancer diagnosis: **22.13 (P<0.01)** *for all variables in the model	n/a	n/a
Otieno, 2010 (16)[a] (Kenya)	**Reasons for delays from first symptoms to presentation at diagnostic hospital, i.e. to diagnosis** Lack of BC awareness: 7.8%; Painless symptom(s): 23.5%; Fear of cancer: 19.9%; Symptoms considered benign by health professionals: 24.1% Tried traditional treatments: 9.6% Others: 15.1%			
Pace, 2015 (19) (Rwanda)	**Reasons for delay between first symptoms to first visit to a HCP (%)**	**Reasons for delay between first symptoms to first visit to a HCP: OR* (95% CI) for delay ≥6 vs <6 mths**	**Reasons for delay between first visit to a HCP and date of pathology report confirming BC (%)**	**Reasons for delay between first visit to a HCP and date of pathology report confirming BC OR* (95% CI) for delay ≥6vs. 6 mths**

	Did not think it was a problem at first: 76%; Thought it would go away: 63%; Visited traditional healer first: 21%; Thought treatment was too expensive: 14% Too busy at home or job: 7%; Fear of cancer: 6% Afraid of treatment & mastectomy: 5%	*Socio-economic:* Age (yrs) vs. <40 yrs: 40-49: 2.26 (0.69, 7.43); 50-59: 1.22 (0.36, 4.11); >60: 2.30 (0.60, 8.74) Married vs. unmarried: 1.11 (0.51, 2.48) No education/primary school vs secondary/university: **4.88 (1.72, 13.88)** *Reproductive:* Breastfeeding (yes vs. no): 2.09 (0.44, 9.87) *BC awareness:* BC family history (yes vs no): 0.53 (0.14, 2.04) Ever done BSE (yes vs no): 0.73 (0.31, 1.74) Ever heard of BC (yes vs no): 1.86 (0.69, 5.00) *Type of symptoms & co-morbidities:* Breast pain as initial symptom (yes vs no): 0.57 (0.25, 1.30) HIV or other comorbidities (yes vs no/unknown): 1.15 (0.43, 3.07) *Alternative treatments:* Saw traditional healer first: **4.26 (1.56, 11.60)**	Non-referral from another health care centre: 69% Did not know this cancer existed: 30% Did transfer form from another health facility: 27% Too expensive to travel from home to hospital: 21% Told by a health care provider there was no cure: 3% Hospital to far to travel to: 2%	*Socio-economic:* Age (yrs) vs. <40 yrs: 40-49: 0.57 (0.20, 1.68); 50-59: 0.85 (0.28, 2.62); >60: 0.64 (0.18, 2.24) Married vs. unmarried: 1.11 (0.51, 2.41) No education/primary school vs secondary/university: 1.19 (0.48, 2.97) *Reproductive:* Breastfeeding (yes vs. no): 0.81 (0.15, 4.30) *BC awareness:* BC family history (yes vs no): 0.60 (0.15, 2.34) Ever done BSE (yes vs no): 1.15 (0.50, 2.65) Ever heard of BC (yes vs no): 1.19 (0.45, 3.10) *Type of symptoms & co-morbidities:* Breast pain as initial symptom (yes vs no): 1.15 (0.52, 2.55) HIV or other comorbidities (yes vs no/unknown): 0.84 (0.32, 2.17) *Health services related:* Travel time to HCP (>2 vs ≤2 hrs): 1.26 (0.46, 3.42) Regular CHW visits (yes vs no): 1.14 (0.50, 2.58)

		Health services related: Travel time to HCP (>2 vs ≤2 hrs): 0.96 (0.36, 2.57) Regular CHW visits (yes vs no): 1.51 (0.66, 3.46) * Mutually-adjusted for all variables in the model		No. visits to other healthcare facilities prior to diagnosis (<5 vs ≥5): **2.69 (1.24, 5.84)** Referred by (vs health centre): District hospital: 0.51 (0.09, 2.78) Private hospital: 0.36 (0.06, 2.09) Unknown: 0.49 (0.07, 3.45) * Mutually-adjusted for all variables in the model
Price, 2012 (27) (Cameroon)	Financial problems: 16% Spent >$10 on 1-way transportation: 42% Travelled >4h to hospital: 46%		n/a	
Toure, 2013 (22) (Côte d'Ivoire)	**Reasons for delay between symptoms recognition and date of histological confirmation**			
	Crude OR (95% CI) for delay >6 mths Initial symptom (vs. nodule) Inflammation: **23.6 (7.5, 74.0)** Ulcer: **18.1 (4.3, 76.9)** Nipple discharge: 1.9 (0.6, 6.2) Metastases: **13.9 (3.3, 59.3)** Self-reported reason for delay (vs. having financial problems) Traditional medicine: 0.5, (0.2, 1.2) Fear of cancer: 0.4, (0.1, 2.3) Misdiagnosis: 1.8 (0.2, 15.3) Inadequate medical care: 1.1 (0.2, 5.4) Monthly income in euros (vs. none): <91.46: 1.4 (0.5, 3.6) 91.46 – 182.8: 0.8 (0.3, 2.1)		**Mutually-adjusted OR (95% CI) for delay >6 mths** (having financial problems taken as the reference category) Self-reported reason for delay (vs. having financial problems) Traditional medicine: 0.7, (0.7, 3.2) Fear of cancer: 1.2, (0.0, 12.3) Misdiagnosis: 3.0 (0.3, 5.7) Inadequate medical care: 0.6 (0.1, 17.4) Monthly income in euros (vs. none): <91.46: 0.3 (0.0, 1.7) 91.46 – 182.8: 4.4 (0.2, 91.2) 182.9 – 274.4: 12.7 (0.4, 376.6) >274.4: 47.8 (0.7, 3.103 (sic))	

	182.9 – 274.4: 0.8 (0.3, 2.3) > 274.4: 3.2 (0.4, 25.9)	
QUANTITATIVE & QUALITATIVE STUDIES		
Dye, 2010 (23) (Ethiopia)	**Reasons for delays between symptom recognition and presentation at diagnostic centre (TA)** Lack of BC awareness <u>*Health services:*</u> High travel distance Too expensive >3 HCP visits: 73.2% *First HCP: % of patients (Me ±SE number of care nodes visited including study setting (TAH)):* Primary care: 53.7% (3.3 ± 1.8) Traditional healer: 16.4% (3.8 ± 0.26) Local/regional hospital: 16.4% (2.3 ± 0.19) Private hospital: 9% (2.8 ± 0.48) TAH: 4.5%	
Ly, 2002 (21) (Mali)	**Reasons for delays between symptom recognition and presentation at first HCP** Symptom(s) not serious: 82%; Caused by witchcraft: 14%	n/a
QUALITATIVE STUDIES		
Ekortarl, 2007 (11) (Cameroon)	**Reasons for delays between symptom recognition and presentation at first HCP** Ignorance and beliefs Fears Financial problems Inadequate diagnosis by general doctors	
Mbuka-Ongona, 2012 (12) (Botswana)	**Reasons for delays between symptom recognition and visit to diagnostic centre** Lack of BC awareness Misinterpretation of signs Infrequently BSE	

	Fear diagnosis and death Influence of traditional healers <u>*Health services:*</u> Poor clinical practices of health workers Overemphasis on HIV infection Long travel distance to hospital	
Pruitt, 2015 (20) (Nigeria)	**Reasons for delays between symptom recognition and first visit to a HCP** Lack of BC awareness Symptom(s) not serious Tried traditional & spiritual treatments	**Reasons for delays between presentation and diagnosis & treatment** Inappropriate medical care given Delays in getting diagnostic confirmation or treatment Return to traditional care Denial Fear of surgery Strikes by hospital staff Treatment costs

[a] Study recruited only patients with advanced breast cancer (see Table 1)

BC: breast cancer; BSE: breast self-examination; CBE: clinical breast examination; CHW: community health worker; CI: confidence interval; HCP: health care provider; HIV: Human immunodeficiency virus; IQR: inter-quartile range; km: kilometres; LABC: Locally advanced breast cancer; Md: mean; Me: mean; mths: months; n/a: not reported in the original publication; OC: oral contraceptives; OR: odds ratio; Ra: range; SE: standard error; TAH: Tikur Anbessa Hospital; TCC: Tanca Cancer Center; wks: weeks; yrs: years