UNIVERSITY of RWANDA

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Prevalence of molecular breast cancer subtypes and associated clinico-pathological characteristic in Africa: systematic review and met-analysis (2014-2018).

A dissertation submitted in partial fulfillment of the requirements for the degree of

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By

Clarisse MUSANABAGANWA (21729612)

SUPERVISOR:

JOSEPH NTAGANIRA MD, MSC, PHD

PROFESSOR OF EPIDEMIOLOGY

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DEDICATION

I dedicate my work to my father Jehovah for his mercy and unconditional love to me. I owe special thanks to my lovely husband Eng.Kamugunga.M.Jules for his continued and unfailing love, support and understanding during my pursuit of this Masters that made the completion of thesis possible. You were always around at times I thought that it is impossible to continue, you helped me to keep things in perspective. I greatly value his contribution and deeply appreciate his belief in me. I appreciate my son Kamugunga E. Prince for abiding with my busy schedule and the patience he showed during the journey of two years on this Master's program. Special thanks to my beloved Mother Odette Kayirere for her support and words of encouragement and push for tenacity ring in my ears I acknowledge the moral support from my mother in Law Maître Kamugunga. K. Epiphany. Words would never say how grateful I am to both of you. I am proud to have such a lovely and caring family.

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ABBREVIATIONS & ACRONYMS

ER: Estrogen Receptor

PR: Progesterone Receptor

HER2: Human Epidermal Growth Receptor

TBNC: Triple Negative Breast Cancer

JBI: Joanna Briggs Institute

O.R: Odds Ratio

SA: Sub-Saharan Africa

NA: Northern Africa

WHO : World Health Organization

HR : Hormone Receptor

BC : Breast Cancer

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ABSTRACT

Background:

Breast cancer survival rate in developed countries is above 80 % and vary according to the diagnostic stage. This is contrary in less developed countries where the survival rates are generally low where it is estimated at 60% in middle income countries and 40% low income countries. This has been attributed to lack of early detection programs and diagnostic and treatment facilities. Differences among breast cancer subtypes and their association with clinico-pathological features have been proven to be important for prognosis, prediction and treatment selection. The review question was to determine the prevalence of breast cancer sub types and KI67 proliferation markers in African context in the past five years. The current review aimed to synthesize evidence on distribution status of breast cancer molecular subtypes (Luminal A, Luminal B, HER2 Overexpression, TNBC or Basal Like and Ki67 proliferation marker) as well as determining their clinical pathological characteristics with in past 5 years (16/April /2014-2018).

Methodology: Studies published after April 2014 were systematically identified, appraised and synthesized. The total sample size of the studies included in the review was 13114 women with breast cancer.

Results: The systematic search yielded 1260 studies. After removing duplicates, 1170 were left for screening (Figure 1). 1118 articles were removed by screening titles and abstracts. After reading full text articles, 52 papers were left for appraisal. 25 papers were excluded with reasons (appendix).27 were included in the review. The most molecular subtypes reported with high proportion was luminal A estimated at at 29 % CI:]22,36[. Triple Negative Breast cancer (TNBC) or basal like was reported at the pooled prevalence estimated 28% CI:]21,35[(Figure). The luminal B and HER Overexpression were reported at the lowest proportion 23% CI:]16,32[and 11% CI]9,13[. pooled prevalence of ER+ or PR+ was reported at 60% CI:]55, 64[with heterogeneity reduced at (I^2=11.939). The pooled prevalence of KI67 expressed at <20% was estimated at 6% CI:]4,8[, whereas KI67 overexpression (>20%) was estimated at 80% in sub-Sahara Africa among women of age beyond 45 years old (I^2=61.431). The most commonly diagnosed grade status was grade II (45%) (pooled estimate) CI:] 35,53[. The commonly diagnosed BC clinical stage was early stage (stage I & II) corresponding to 33% CI:]21 ,47[followed by stage III estimated at 31% CI]24,39[.The most commonly diagnosed BC histological types was Ductal carcinoma which ranged from 49% to 96% among specific studies where the pooled prevalence was estimated to 84% CI (78,89) with (I^2 :98).

Conclusion: We observed change in trends of BC clinical stage where early stage(I&II) (33%) was more prevalent than other stage .which is different to many previous literature where Late stage BC was mainly reported among African women .Our findings may lead to the conclusion that within past 5 years breast cancer awareness and early screening interventions may have produced a positive impact .However, we suggest integration of routine testing for molecular receptors and proliferation markers before initiating hormonal Therapy in order to improve breast cancer survival rate as well as alleviating cancer morbidity in African population. In addition, availability of Trasuzumub targeted therapy in Health facilities may benefit patient who overexpress HER2. Ki67 proliferation marker may be used in the follow up of patient outcome particularly in sub-Sahara Africa where It is over proliferated at older age.

Keywords: Breast cancer, women of 18 and above, clinical pathology, molecular subtypes, Africa,

CHAPTER I
INTRODUCTION

1.0 Introduction

Cancer is considered among the important diseases globally and the statistics shows that 14,9 million new cases were recorded in 2012.[1] Each year, 8.2 million people die from cancer which is 13 percent of total deaths worldwide, and above 70 percent increase is projected in the next 2 decades.[2] Breast cancer is commonly diagnosed in women globally and breast cancer incidence raised globally at 3.1% during a period from 1980 to 2010.[3] Evidences rank breast cancer as the 5th cause of cancer death for women from low and middle income countries (324,000 deaths, 14.3% of total), and ranked as the second cause of cancer death high in developed countries (198,000 deaths, 15.4%).[4] According to the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, the number of women living with breast cancer in the US in 2013 was estimated at 3,053,450 with a projection of 246,660 new cases and 40,450 deaths in 2016.[5] The lifetime risk for developing breast cancer among women in the US is 12.4%.[5] Furthermore, breast cancer survival rate in developed countries is above 80 % and vary according to the diagnostic stage .This is contrary in less developed countries where the survival rates is generally low for example in middle income countries (60%) and low income (40%) countries and this has been attributed to lack of early detection programs and diagnostic and treatment facilities.[6] Eastern Africa has the lowest incidence rates (19.3 per 100,000 women).[6] However, generally, incidence rates in Africa is rising. In Ethiopia, 35% of breast cancer express estrogen (ER)-negative.[7] A study conducted in 2015 by E. M. Der et all reported 58.3% triple negative breast cancer among Ghanaian women.[8] In Rwanda, breast cancer is placed as the second leading cause of cancer mortality and contributing 8.9% of all deaths due to cancer. The incidence of breast cancer in Rwanda is estimated to be 576 new cases every year.[9] In Tanzania ,75% of the tumors expressed high proliferation Ki-67.[10]

Among 50 Sudanese patients suffering from breast cancer 58% were reported to express positive for ki67[11] .

Breast cancer are grouped depending on whether the cancerous cells express ER or not. ER-positive breast cancer cells express oestrogen (ER) and PR positive breast cancer cells express progesterone (PR) receptors and nearly 80% of all breast cancers are ER-positive. HER2-positive cells express Human Epidermal Growth Receptor 2 (HER-2 receptors) and nearly 20% of all breast cancer cells over-express the HER2 protien.[12] Triple positive breast cancer cells express ER, PR, and HER-2 receptors while triple negative cells do not express any of the 3 receptors.[12] KI67 proliferation marker is currently used in breast cancer diagnosis and management and it is predominantly present in cycling cells.[13] Current evidences recommend that KI67 can be used in combination with other breast cancer molecular subtypes such as ER, PR and HER2 to orienting prognostic and treatment of breast cancer.[16,17], for example Chang et al. have used KI67 in addition to ER, PR and HER2 to classify breast tumors. Previous review evidence published on 16 April 2014 provided evidence on the distribution of receptor subtypes of breast cancer with limited data representing sub-Sahara Africa [14] .The current review aimed to synthesize evidence on distribution of breast cancer molecular subtypes as well as determining their association with clinico-pathological characteristics in the African context by systematically synthesizing Studies published from 16th / April 2014 to 2018 . This systematic review will add more value on the existing literature by providing information on prevalence of Ki67 proliferation marker, clinic-pathological characteristics of breast cancer as well as adding more information on the prevalence breast cancer subtypes by synthesizing evidence based on the earlier published studies and hence orient in the prognosis and treatment standards of breast cancer in Africa.

1.1 Problem Statement

Breast cancer survival rate in less developed countries including African countries is genrally low where it is estimated at 60% in middle income countries and 40% low income countries. This has been attributed to lack of early detection programs and diagnostic and treatment facilities. Differences among breast cancer subtypes and their association with clinic-pathological features have been proven to be important for prognosis, prediction and treatment selection. However, based on number of primary studies conducted on African continent, there is lack of synthesized evidence on distribution of breast cancer molecular subtypes as well as determining their association with clinico-pathological characteristics in the African context

1.2 Objectives

1.2.1 General Objective

The main aim of this review was to determine the prevalence of breast cancer sub types (Luminal A,Luminal B, TNBC , HER2) as well as hormone receptors (ER, PR, HER2) and KI67 proliferation marker in African context and determining their clinical pathological

1.2.2 Specific Objectives:

- To determine the prevalence of breast cancer sub types (Luminal A,Luminal B, TNBC , HER2)
- To determine the prevalence of breast cancer hormone receptors (ER, PR, HER2, KI67)in Africa.
- To determine the association of breast cancer subtypes with clinical pathological characteristics in African context.

CHAPITER II

LITERATURE REVIEW

Five-year survival rates vary from around 80% in developed countries to 60% in middle-income countries and 40% in low-income countries.[15]Thefore, Globally Breast cancer is considered as a serious public health problem as it also represents the first cancer found in women 's different cancer sites and statistics shows that one million cases of breast cancer have been diagnosed annually (23% of all cancer cases newly diagnosed in 2008.[16]Breast cancer is liable for one in four diagnosed cancers and one in five cancer deaths in sub-Saharan African women [16] .According to WHO, the histological types of breast cancer are classified into 17 categories as invasive ductal carcinoma, invasive lobular carcinoma, tubular carcinoma, invasive cribriform carcinoma, medullary carcinoma, mucinous carcinoma, neuroendocrine carcinoma, invasive papillary carcinoma, invasive micropapillary carcinoma, apocrine carcinoma, metaplastic carcinoma, lipid-rich carcinoma, secretory carcinoma, oncocytic carcinoma, adenoid cystic carcinoma, acinic-cell carcinoma, glycogen-rich clear cell carcinoma, and seba- ceous carcinoma[17,18] The majority of the studies on African population reported a poorly differentiated Grade 3 tumors 40 – 83%[19,20]

The data in 2011 by Elima and colleagues revealed high percentage of late stage diagnosis of breast cancer in black compared to white women 32% and 27% respectively.[21]On the other hand though, the proportion of women with late-stage disease in southern Africa remained stable among non-black Africans, the decline in black Africans was fairly observed.[21] Other studies showed that breast cancer tended to occur at early age and the majority were at stage (III and IV) with hormone negative expression in African population [22,23.]

Molecular differences among breast cancer subtypes and their association with clinico-pathological features have been proven to be important for prognosis, prediction and treatment

selection for breast cancer[24].On this note, classification of breast cancer per gene expression profiling recognized four main intrinsic molecular subtypes of breast cancer known as luminal A, luminal B, HER2-enriched and triple-negative breast cancer (TNBC).[25],[26] Luminal A cancers are known to express high levels of estrogen receptors (ER)and progesterone receptor (PR), and low levels of HER2 whereas, luminal B cancers are estrogen receptor positive (ER+) with high level HER2 expression 22.In addition , HER2-enriched breast cancer constitutes 15–25% of invasive breast cancers, and have poor prognosis. whereas triple negative breast cancer (TNBC) are characterized by the absence of ER, PR and HER2 overexpression.22,23

Generally, ER positive tumors account for 70% of breast cancer. ER positive tumours constitute 65% and 80%, respectively, of patients under and above 50 years.[18] ER positive tumours are mainly well-differentiated, and they result in better outcome than ER-negative. ER-negative tumours are hormone-independent and considered to show aggressive behaviour. In addition, ER negative tumours show less chance to respond to endocrine therapy.[27] PR is induced by estrogen and is a favorable prognostic marker. PR positive tumours contain 65% to 75% breast cancers. ER -PR+ patients benefit from endocrine therapy which would be excluded from such treatment if the decision was based on ER status alone. Nearly 40% ER positive tumours are PR negative[20.] ER+PR- tumors are less responsive to endocrine treatment than ER+PR+ tumors.[21] PR is conventionally used together with ER in breast tumor subtyping classified as follow: ER+PR+, ER+PR-, ER-PR+, ER-PR-.[28]Human Epidermal Growth Receptor 2 (HER2) is the most well-known prognostic member of the epidermal growth factor receptor family. Studies revealed that HER2 gene amplification or protein over-expression is associated with poor prediction and good clinical outcome when using systemic chemotherapy treatment[26,27.] Triple negative phenotypic tumors (TNP) frequently demonstrate clinically poor prognosis and difficult to treat. The protein over-expression and gene amplification of HER2 happen in 13% to 20% of invasive ductal breast cancer which mostly appear to account

approximately 55% as ER-PR-.[29,30,31] .The prognostic value of HER2 positivity is higher in node-positive than node-negative patients. HER2 is considered as an essential target of a diversity of novel cancer therapies. It is reported that triple positive (ER+|PR+HER2+) tumors have a promising prognosis regardless of the achievement of a pathological complete response. On the other hand patients with ER-PR-HER2+ and ER-PR-HER2- tumors demonstrate the worst prognosis[32]. Ki-67 proliferation marker has been recommended to predict the neoadjuvant response or outcome from adjuvant chemotherapy for breast cancer. In addition, KI67 has also been used in combination with other markers in breast cancer to provide prognostic and predictive values [33,34]. Chang et al.[9] have used KI67 in addition to ER, PR and HER2 to classify breast tumors, where ER+|PR+ tumours are divided into three prognostic ally distinct subclasses based on the expression of KI67 and HER2. In their study, they classified ER+PR+HER2- tumors into [ER+|PR+]HER2-KI67- and [ER+|PR+]HER2-KI67+ tumors, correspondingly, with [ER+|PR+]HER2-KI67+ being associated with poorer outcome regardless of systemic therapy [33]. Evidence demonstrated that ER+PR+ includes 55% to 65% of breast tumors [24,35] among which 75% to 85% are responsive to endocrine treatment. Comparing with the other subgroups, patients having the mentioned tumors are linked with older age, lower grade (I), smaller tumor size and lower mortality rate. On the other hand, ER-PR-comprises 18% to 25% of the tumors, among which around 85% are of higher grade like 3.[27] The later ones are associated with a higher recurrence rate, lower overall survival and do not respond to endocrine therapy.[35,36] . The double positive (ER+PR+) is the most favorable compared to ER-PR- which is the most hostile cancers vis-à-vis tumor size, grade, stage, patient outcome and response to hormonal therapies.[37,35,30] To predict tumors response, the analysis of the over-expression of both ER and PR is measured as follow ER > 50% and PR > 50% . Tumours expressing low levels of either or both receptors are measured as follow 10% < ER < 50% or PR < 50%. The double negative tumours are quantified as follow ER < 10% and PR <

10%[28].Furthermore, it has been demonstrated that ER-PR-HER2+ and ER-PR-HER2- tumours are poorly differentiated, show aggressive behaviour and poor outcome, and fail to respond to hormone therapy.[34] In addition , the findings from recent study assessed the association of preoperative Ki67 and other biomarkers in south Arabia and Egypt and some of the recommendation was consider ki67 in prognosis of breast cancer (63.2%).[38]

Recent evidences reported a noticeably higher proportion of TNBC in African populations which is responsible for generally poor survival rate reported for African breast cancer patients.[39,40]

Conventional known strategies to treat breast cancer include surgery, radiation and chemotherapy. However, the selection of breast cancer treatment is generally based on molecular subtype of the patient.Though a number of targeted treatment options are available for estrogen receptor (ER) and Human Epidermal Receptor (HER2) breast cancers ,there is still lack of targetted therapy for TNBCs and therefore only surgery, radiation therapy, and chemotherapy the current options TNBC treatment .[41,42] Endocrine therapy is mostly used for the treatment of ER+ breast cancer and HER2 overexpression .Some of the examples of endocrine therapy for ER+ Breseast cancer treament include tamoxifen, and fulvestrant, and aromatase inhibitors (AIs) such as anastrozole (FDA and letrozole.[42,43,44] HER2 overexpression has been generally reported to be associated with poor diagnosis .the targeted therapy used in the treatment of HER2 overspression include trastuzumab (sold under the brand name Herceptin) , lapatinib, pertuzumab, and trastuzumab-emtansine (T-DM1) and all of them have been proven to have benefial effects on the treatment of HER2 overexpression breast cancer.[45,46,47,48] Early-stage HER2 breast cancers with a combination of trastuzumab and sequential chemotherapy, followed by breast surgery, radiotherapy (if recommended) is recognized as the standard approach that has signififcantly improved survival rates in the HER2 subgroup to nearly 40–75% in the period of 10 years.[49,50]

Through there has been improvement in the treatment and management of breast cancer ,the accessibility to some targeted therapies with promising cure is still a challenge particulary on African continent[51] .

Updated synthesized models of Breast cancer molecular subtypes and its associated clinic pathological characteristics are currently inefficient on African population. Such models are of critical importance to direct proper clinical decision and inform public health approaches to manage breast cancer disease on the continent of Africa and hence improve the survival rate. To address this gap, here we synthesize and evaluate existing evidence regarding breast cancer subtypes and its associated pathological characteristics in African population and the current model will complement the existing evidence on the status of breast cancer subtypes in black women and indigenous African population published in the past five years.

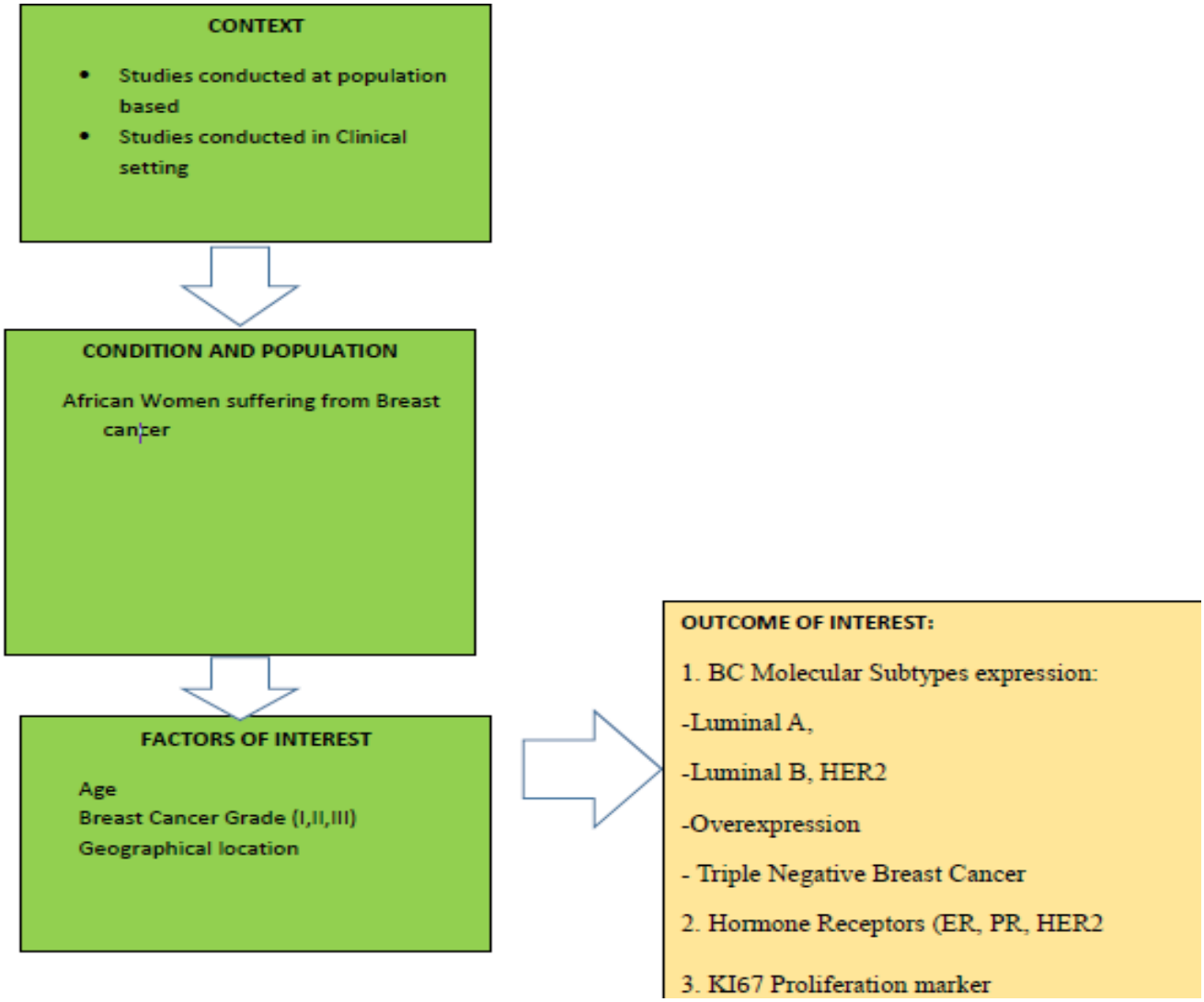

Figure 1. Conceptual Framework

CHAPITER III

RESEARCH METHODOLOGY

This systematic review was conducted in accordance with the Joanna Briggs Institute methodology for systematic reviews of prevalence and incidence [52] and the JBI guidance for systematic reviews of prevalence studies and risk factor studies (Guidance be cited)

3.1Inclusion Criteria

3.1.1 Participants:

This review considered studies that included females aged 15 years and above with breast cancer.

3.1.2 Condition

This review considered studies conducted assessing the expression of Breast Cancer subtypes and clinical pathological characteristics.

3.1.3 Context

This review considered studies on prevalence of Breast Cancer Subtypes Estrogen (ER), Progesterone (PR), HER2, Triple Negative and KI67 new proliferation marker and clinico-pathological characteristics in African countries conducted both in the community and in the health care setting such as hospitals and clinics.

3.1.4 Exposure:

- Tumor grade status
- Age
- Geographical location

3.1.5 Outcomes:

Breast cancer home receptors (ER, PR, HER2, and KI67) and Molecular subtypes (Luminal A, Luminal B, HER2 overexpression and TNBC or Basal like)

3.1.5 .1 Molecular subtypes

a) Luminal A: Hormone-receptor positive (estrogen-receptor and/or progesterone-recptor positive. HER2 negative, and has low levels of the protein Ki-67, which helps control how fast cancer cells grow. Luminal A cancers are low-grade, tend to grow slowly and have the best prognosis.

b) Luminal B**:** Hormone-receptor positive (Estrogen-receptor and/or progesterone-receptor positive), and either HER2 positive or HER2 negative with high levels of Ki-67. Luminal B cancers generally grow slightly faster than luminal A cancers and their prognosis is slightly worse.

c) HER2 Overexpression**:** Hormone-receptor negative (estrogen-receptor and progesterone-receptor negative) and HER2 positive. HER2-enriched cancers tend to grow faster than luminal cancers and can have a worse prognosis

d) TBNC : Hormone-Receptor negative (estrogen-receptor and progesterone-receptor negative) and HER2 negative. This type of cancer is more common in women with *BRCA1* gene mutations. This type of cancer is more common among younger and African-American women.

3.1.5 .2 Hormone Receptors

a) ER positive tumours are mainly well-differentiated, and they result in better outcome than ER-negative.

b) PR is induced by oestrogen and is a favourable prognostic marker. PR positive tumours contain 65% to 75% breast cancers. PR is conventionally used together with ER in breast tumour subtyping classified as follow: ER+PR+, ER+PR-, ER-PR+, ER-PR- .[28]

c) Human Epidermal Growth Receptor 2 (HER2) is the most well-known prognostic member of the epidermal growth factor receptor family. Studies revealed that HER2 gene amplification or protein over-expression is associated with poor prediction and good clinical outcome when using systemic chemotherapy treatment[26,27.]

d) HER Enriched :The protein over-expression and gene amplification of HER2 happen in 13% to 20% of invasive ductal breast cancer which mostly appear to account approximately 55% as ER-PR- .[29,30,31] The prognostic value of HER2 positivity is higher in node-positive than node-negative patients. HER2 is considered as an essential target of a diversity of novel cancer therapies.

3.1.5 .3 Ki-67 Proliferation Marker

a). Ki-67 is one of the proliferation marker which is currently used in breast cancer prognosis, and it is mainly present in cycling cells. KI67 has been recommended to predict the neoadjuvant response or outcome from adjuvant chemotherapy for breast cancer. In addition, KI67 has also been used in combination with other markers in breast cancer to provide prognostic and predictive values [33,34]. Chang et al.[9] have used KI67 in addition to ER, PR and HER2 to classify breast tumours, where ER+|PR+ tumours are divided into three prognostic distinct subclasses based on the expression of KI67 and HER2[33].

3.1.6 Study Design

This review considered analytical observational studies including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies considered for

inclusion. This review also considered descriptive observational study designs including case series, individual case reports and descriptive cross-sectional studies for inclusion. Only studies published in English or French language were included. Studies published after April 16th, 2014 were included. The reason for limiting the time is because the previous systematic review evidence which reported Receptor-defined subtypes of Breast Cancer on indigenous African population included the majority of studies published prior April 2014.19

3.1.7 Search Strategy

The search strategy included both published and unpublished studies on molecular subtypes of breast cancers and clinico-pathological characteristics of Breast cancer reported/published in Medline/PUBMED, Google Scholar, Trip database and Science database. The search period was from April 16th 2014 to 2018 and the reason of choosing this time period is because the previous systematic review evidence available included studies published prior April 15th 2014[14]. Analysis of the text words contained in the title and abstract, and of the index terms were used to describe an article by using all identified keywords and index terms. Finally, the reference lists of all identified reports and articles were searched for additional studies. Studies published in English met the inclusion criteria. Those published in other languages other than English were excluded.

3.1.8 Study Selection

Following the search, all identified citations were ordered and uploaded into Mendeley and duplicates were removed. Titles and abstracts were then screened by two independent reviewers for assessment against the inclusion criteria for the review. Studies that met the inclusion criteria were recovered in full and their details imported into JBI SUMARI. The full text of the selected studies was retrieved and assessed in detail against the inclusion criteria.

Full text studies that do not meet the inclusion criteria were excluded and reasons for exclusion were provided in an appendix in the final systematic review report. The results of the search were reported in full in the final report and presented in a PRISMA flow diagram. Any disagreements that aroused between the reviewers were resolved through discussion, or with a third reviewer. The decision to exclude was based on the following decision rules: exposure, context, population and outcomes.

3.1.9 Exclusion Criteria:

- studies published prior April 15th 2014 were excluded
- Studies published which did not report on the outcome of interest were also excluded

3.2 Statistical Methods

For statistics calculations, the proportion of hormone receptor-positive (ER+, PR+, HER2+) breast cancers (event rate or prop), proliferation marker KI67 (Event rate or prop) and molecular subtypes breast cancer (Event rate or prop) were the statistic of interest. The proportion or event rate was calculated as (number of hormone receptor positive tumors) or (molecular subtypes) or (KI67 highly expressed tumors) / (n= number of tumors with known receptor status). Effect sizes were expressed as a proportion with 95% confidence intervals around the summary estimate. Meta analyses were conducted CMA software to estimate pooled proportions using random effects or effect models where needed. Study heterogeneity was assessed using CMA Software and the p-value for heterogeneity (Cochrane's Q statistic) was 25%. The ISQ statistic represents the percentage of between-study variation due to heterogeneity rather than chance. To examine potential sources of heterogeneity, methodologically variables and clinical factors were taken into consideration (i.e storage of sample, age at diagnosis, geographical location, tumor stage, and grade) and therefore a

subgroup analysis and sensitivity analysis were conducted where necessary. Funnel plots were performed to assess publication bias.

Another statistics of interest was the association between clinical pathological characteristics

(Tumors grade status) with molecular subtypes expressions. This association was assessed by using Cochrane Review manager software.

3.3. Data Synthesis

Where possible, paper was pooled in statistical meta-analysis using R, CMA software and ReviewManager Software, JBI SUMARI software. Effect sizes were expressed as a proportion with 95% confidence intervals around the summary estimate. Heterogeneity were assessed statistically using the standard chi-squared, Tau2 and I2 tests. A fixed effects model was applied when studies were less hat 5 and random effect model was applied when studies were more than 5. Subgroup analyses were conducted where there is sufficient data to investigate heterogeneity. Sensitivity analyses were conducted to test decisions made regarding inclusion and excision of papers. Where statistical pooling is not possible the findings were presented in narrative form including tables and figures to aid in data presentation where appropriate.

3.3.1 Assessment of Study Quality

The studies selected were critically appraised by two independent reviewers at the study level for methodological quality in the review using standardized critical appraisal instruments from the Joanna Briggs Institute for: case series, case reports, case control Studies, quasi-experimental studies (non-randomized experimental studies), Randomized Controlled Trials, and analytical Cross Sectional Studies. Any disagreements that arise were resolved through

discussion, or with a third reviewer. Following critical appraisal, studies that do not meet a certain quality threshold were excluded. A critical appraisal was conducted on 62 Full-text articles based on JBI Appraisal criteria and standard tool. Disagreements that arise between the reviewers were resolved through discussion, or with a third reviewer. Authors of papers were contacted to request missing or additional data where required.[1]

3.3.2. Assessment of Methodological Quality

The appraisal scores of the included studies ranged from 4 to 9. All the included studies have described the study subjects, settings, condition and outcomes of the studies (status of hormone receptors and molecular subtypes classification) (Table 4). All studies conducted analysis with sufficient coverage of the identified sample and measured the condition of breast cancer in standard, reliable way for all participants (have met the appraisal criteria Q4, Q5, Q6, Q7). The following items were considered for study eligibility for review : Was the sample frame appropriate to address the target population , Were study participants sampled in an appropriate way, Was the sample size adequate, Were the study subjects and the setting described in details , Were data analysis conducted with sufficient coverage of the identified sample , Were valid methods used in the identification of the condition , Was the condition measured in valid and reliable way , Was statistical analysis appropriate, was the response rate adequate if not was the low response rate managed appropriately .Areas of weakness include not being able to report response rate and, inadequate description of how low response rate was managed [53,53,54,55,56,57, 11]. In addition, the participants sampling frame was not appropriately described. The sample size applied were not adequate as the authors of some of the studies failed to show their calculation of sample size and the sample size reported was far less than the expected optimal sample size in some studies (Table 3).

CHAPITER IV

RESULTS

4.1 Characteristics for the included studies:

The systematic search yielded 1260 studies. After removing 90 duplicates, 1170 were left for screening (Figure 1). 1118 articles were removed by screening titles and abstracts. After reading full text articles, 52 papers were left for appraisal. 25 papers were excluded with reasons (appendix).27 were included in the review. The total sample size of the studies included in the review was 13114 women with breast cancer. When classified per regional distribution, 13 studies from North Africa with the sample size equal to 10123 corresponding to 77% of the

total women with breast cancer reported clinical and pathological characteristics, hormone receptor status as well as molecular subtypes. The remaining 14 studies from sub-Saharan Africa with sample size equal to 2991 (23%) of women with breast cancer reported clinical pathological characterizes, molecular subtypes and hormone status. The majority of the studies (23) were conducted in clinical setting whereas most of them were from sub-Saharan Africa with the largest sample size equal to (N =2406) and (N=1213) respectively[58],[59]. Only 4 studies were conducted on population based context where two among them hard the largest sample size equal to (N=3014) and (N=877) [60616263] (Table 4) .In Most of the studies, classification of molecular subtypes: Luminal A, Luminal B, HER 2 Over expression and Triple negative or Basal like were done Using the classification outlined in the 13th St. Gallen International Breast Cancer Conference and Immunohistochemistry (IHC) and TMA was applied to test the hormone receptor expression (ER, PR,KI67). HER2 was ascertained by FISH, CISH, or SISH techniques and KI67 was assessed by using Dako Antibodies and Dako Autotimer (Dako, CA). The clinical stage of the disease was determined by using TNM (AJCC cancer staging manual) a staging system which measures the anatomical extent of disease based on the extent of a primary tumor (T), Grade status was measured based on the Nottingham modification of Scarf-Bloom, Histological type was measured based on Richardson classification.

15 studies reported the expression of molecular subtypes. Luminal A was reported in 1911 cases out of 6641 Luminal B was reported among 1477 patients out of 6183 breast cancer women and 14 studies reported expression of HER 2 with 579 cases out of 6028 women diagnosed with breast cancer (Table4). In addition, 15 studies reported the expression of Triple Negative Breast cancer (TNBC) or Basal like where 1596 cases out of 7293 breast cancer women were reported. 13 studies reported ER and PR positive among women with BC. 6 studies have reported the over expression of KI67 Proliferation marker in 850 among 1396 women with Breast cancer (Table 1). 20 studies have reported on Breast cancer tumor grade

status. The most commonly diagnosed grade status was grade II where 3406 women with Grade II breast cancer out of 7312 total sample size was observed. 14 studies reported on breast cancer clinical stage where the commonly diagnosed BC clinical stage was early stage (l& II) with 2019 out of 5503 total sample size.

Breast cancer histological types reported were categorized into three types. Ductal Carcinoma, Lobular carcinoma and others. The most commonly diagnosed BC histological types were Ductal carcinoma where 20 studies by which 6515 cases out of 9256 total sample size was reported. 17 studies reported on Lobular carcinoma with 576 cases out of 9047. 16 studies reported on other BC histological types where 707 cases out of 8393were reported (Table 2)

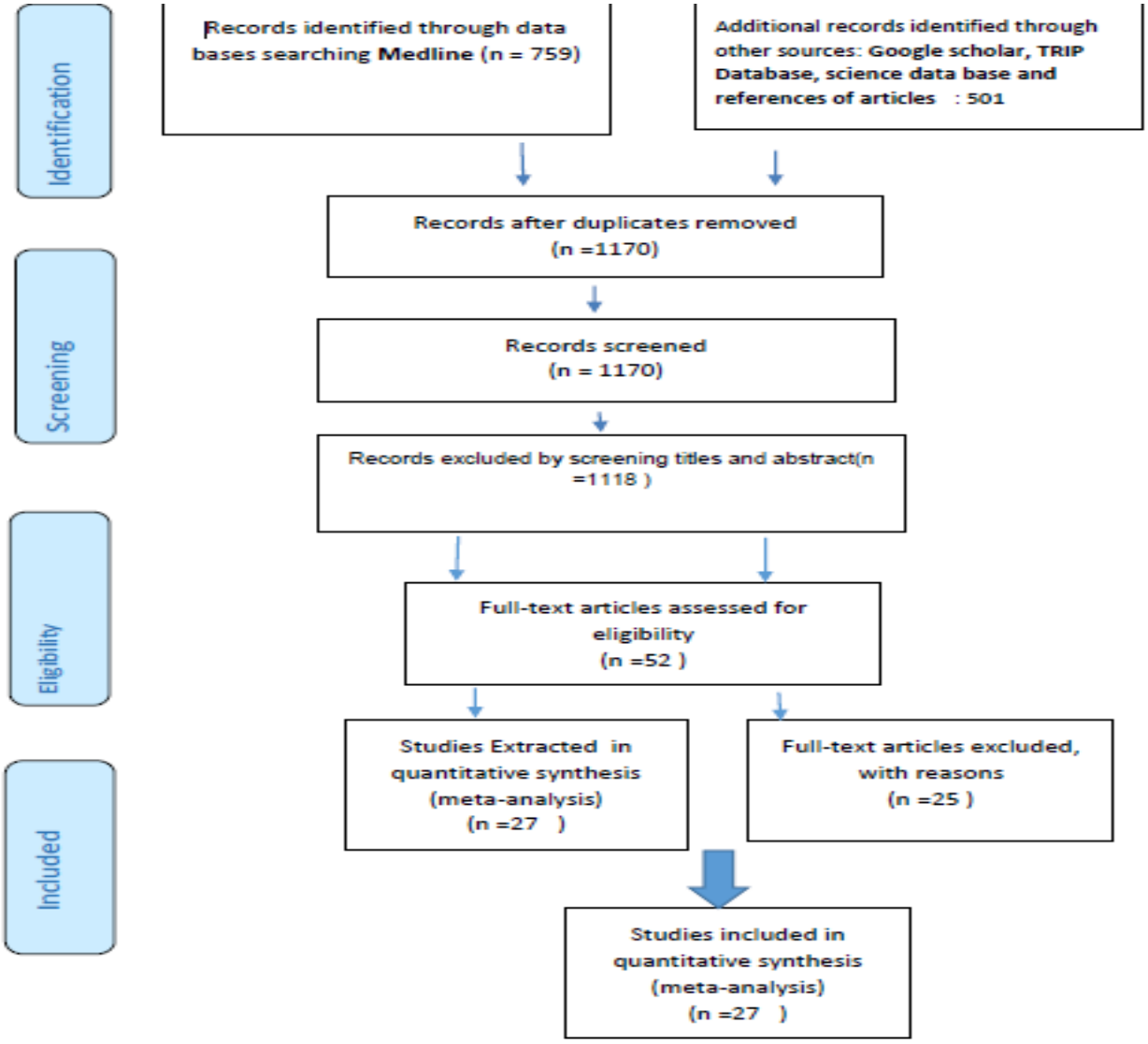

Figure 2: PRISMA Flow Diagram (JBI)

4.2. METANALYSIS:

4.2.1 PREVALENCE OF MOLECULAR SUBTYPES:

4.2.1.1 Luminal A

luminal A was reported to be more prevalent among molecular subtypes estimated at 29% CI]22,36[with $I^2$96. Luminal A by Age category >- 45 was 31% in northern Africa with I^2 57 whereas in Sub-Saharan Africa in population aged >45 the proportion was estimated at 27%

with I^2 95. The pooled prevalence in Northern Africa among group aged <- 45 was reported at 25% and I^2=97.

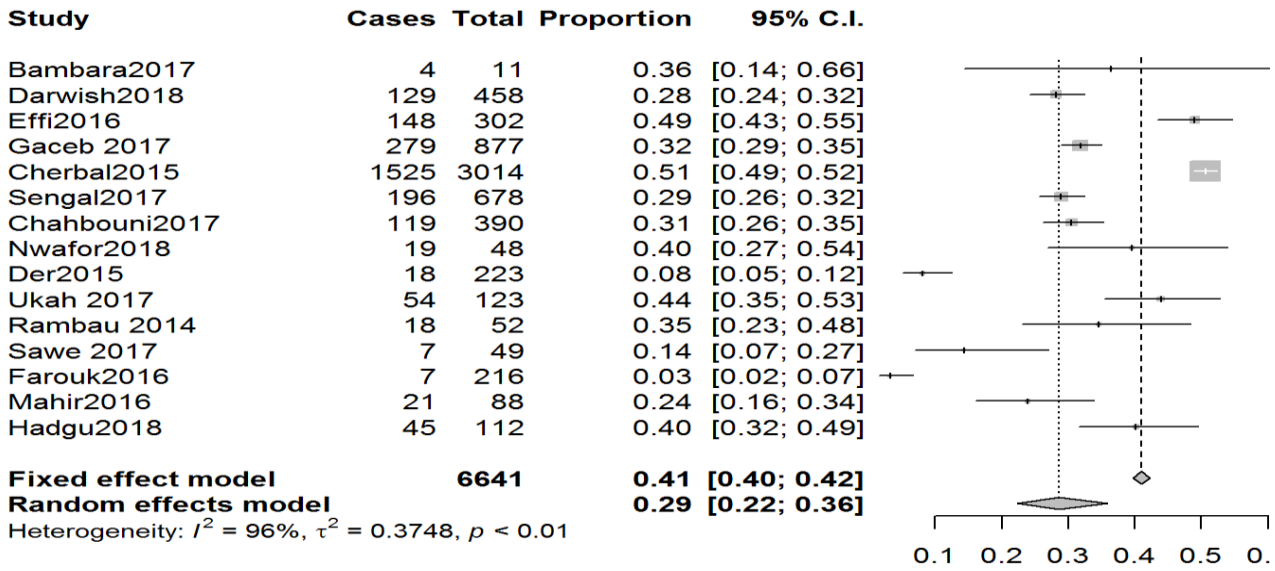

Figure 3: Prevalence of Luminal A in Africa –Studies published April /2014-2018

4.2.1.2 Triple Negative Breast Cancer

Triple Negative Breast cancer (TNBC) or basal like ranged from 5% and 73 % across specific studies at the pooled prevalence estimated at 28%, CI]21,35[(I^2 96) . The pooled prevalence of TNBC in sub-Saharan Africa among women aged > 45 was estimated at 39% CI:]29,49[with I^2=91.249. [71,72,73,74,75,76,77] We failed to calculate the pooled prevalence among women aged <= 45 in sub-Saharan Africa because no studies reported on TNBC status at that age **(Figure 4).** The prevalence of TNBC in age group (<=45), from northern Africa was estimated at 16% CI:]12,19[I^2=98.064 [68,69].The prevalence of TNBC, at age (>45), from north was estimated at 19% CI:]14,24[I^2=93.428[70,67,57,61,66,53] .

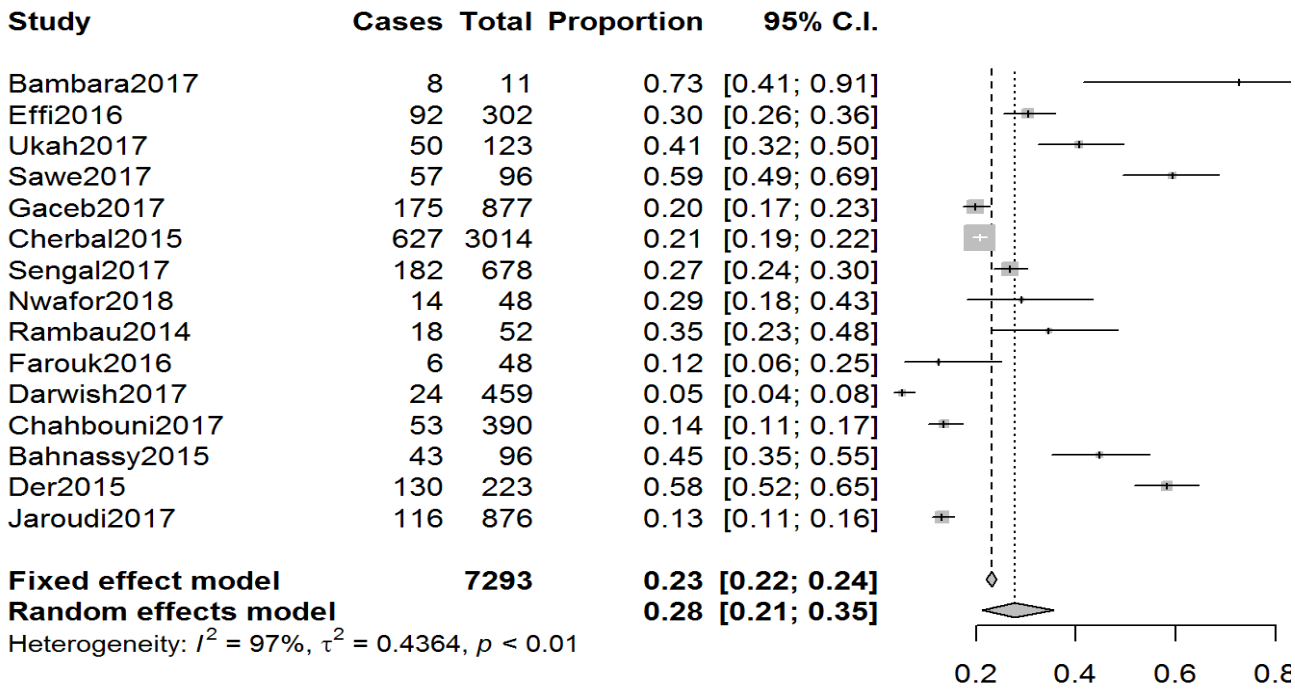

Figure 4: *Prevalence of TNBC or Basal Like in Africa*

4.2.1.3 Luminal B

Luminal B among specific studies range from 18% to 50% and the pooled proportion was estimated at 23% CI]16,32[(0,000) (ISQ 97**).** The prevalence of Luminal B in age (>45), from northern Africa was estimated at 26% CI:25,28[with I^2=98.581[67,57,61,66] whereas in Sub-Saharan Africa in the same age the prevalence was reported at 13% CI:]9.20[with I^2=84.461.[71,72,54,73,74,75,76,77]We failed to calculate the proportion of Luminal B among women in North Africa aged <= 45 because only one study reported on luminal B events at the age <=45 available .[68] **(Figure 5**)

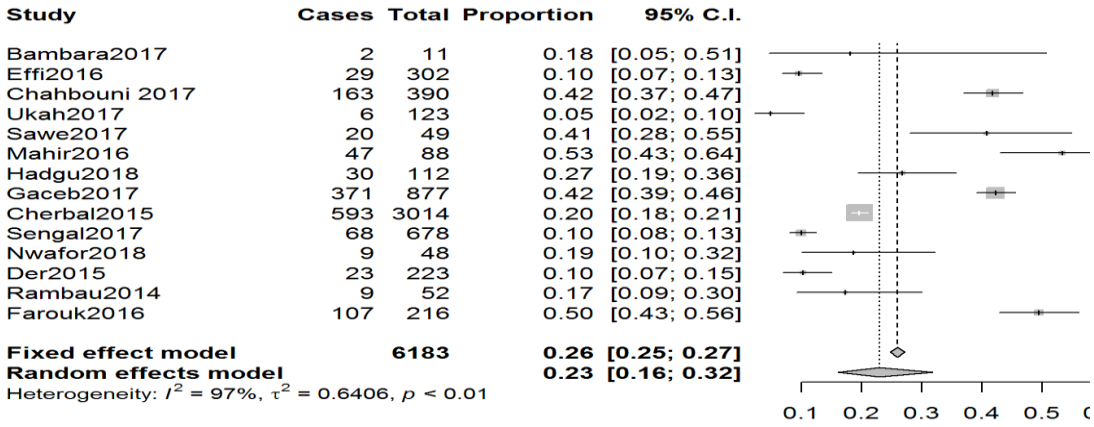

Figure 5: Prevalence of Luminal B in Africa –Studies published April /2014-2018

4.2.1.4 HER2 Over expression

HER2 over expression Breast cancer corresponded to the low prevalence compared to other molecular subtypes ranging from 6% to 21% where pooled estimate was 11% (CI:]9 ,13[) and I^2 81. **(Figure 6)** The heterogeneity was reduced to 42 ISQ by subgroup analysis by region and age group (Sub-Saharan Africa in age group >45 years) where the proportion ranged from 6% to 21% with the pooled proportion was estimated to 10%.In addition ,the proportion among specific studies ranged from 9% to 21 % with pooled prevalence 14% in sub-Sahara among women aged <=45.In North African the proportion of HER Overexpression among women aged >45 years across specific studies ranged from 5% to 15% with pooled proportion of 8% (85ISQ) . The proportion among women <=45 years in North Africa ranged from 12% to 21 % among specific studies with the pooled prevalence equal to 15% (88 ISQ).

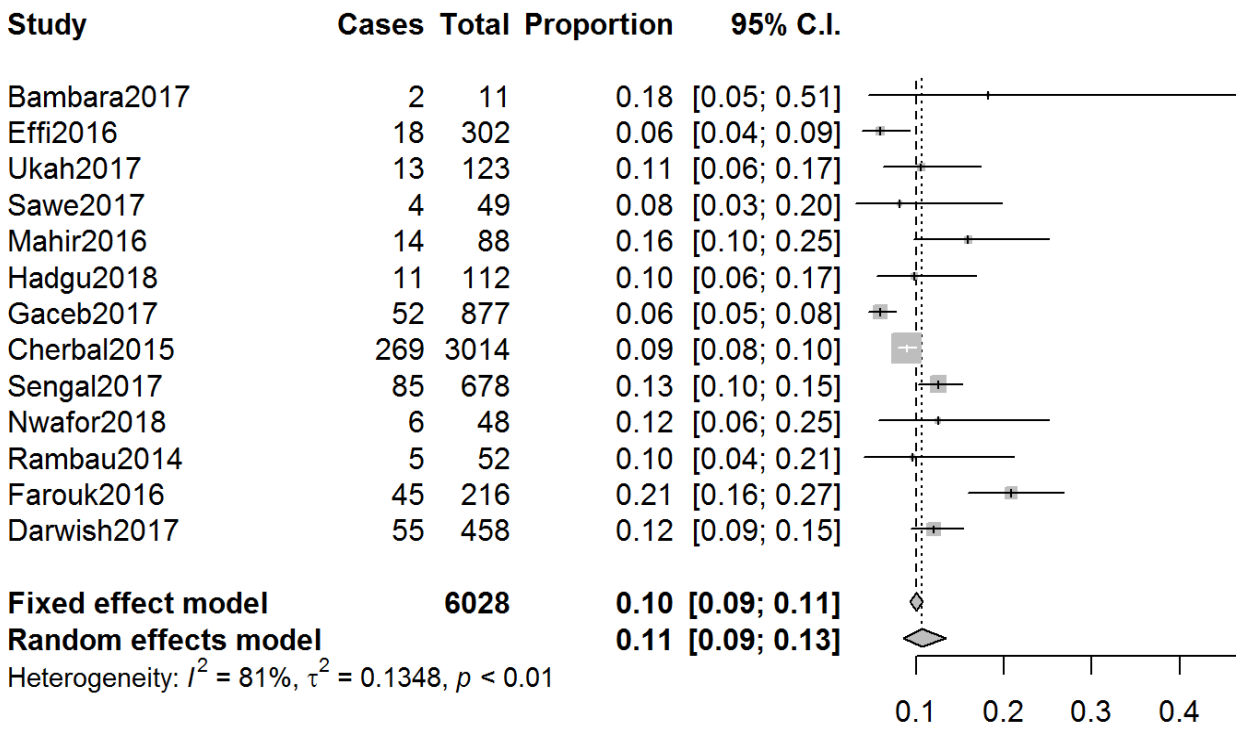

Figure 6: ***Prevalence of HER2 Enriched in Africa –Studies published April /2014-2018***

4.2.2 Prevalence of Hormone Receptor status (ER, PR)

4.2.2.1 ER+

13 studies reported ER and PR positive among women with BC. The proportion BC ER+ among specific studies ranged from 42% to 64% (table 1). The poled estimate was 50%] 39, 61[(IS 97). The heterogeneity was reduced among studies which reported prevalence of ER+ to **(I^2=11.939)** by Age categorization (<= 45) where the pooled prevalence increased at **60% CI:]55, 64[** which was statistically significant**. (Figure 7)** [68,79] ER+ Proportion by age (<=45) in studies conducted in sub-Saharan Africa, was estimated at 26% CI]23,28[with I^2=98.117[80,59,11] whereas prevalence of ER+ Proportion by age(>45), from sub-Saharan Africa,

estimated at 39% CI]25,53[which was not statistically significant with I^2=95.589.[71,72,73,74,10,76]. The heterogeneity was reduced from I^2 97 to I^2= 42.465 by age categorization (<=45) in studies which used data collected after 2009.The pooled proportion increased at 61% with CI :]54,68[in sub-Saharan Africa (Figure :8) [81,11] .

The prevalence of ER+ Proportion by age (>45), in northern Africa was estimated at 69% CI:]66.71[which was statistically significant with I^2=96.676 [56,55].The ER+ Proportion by age (<=45), from northern Africa was estimated at 58% CI:]62,64[which was statistically significant with I^2=95.064[68,69] .

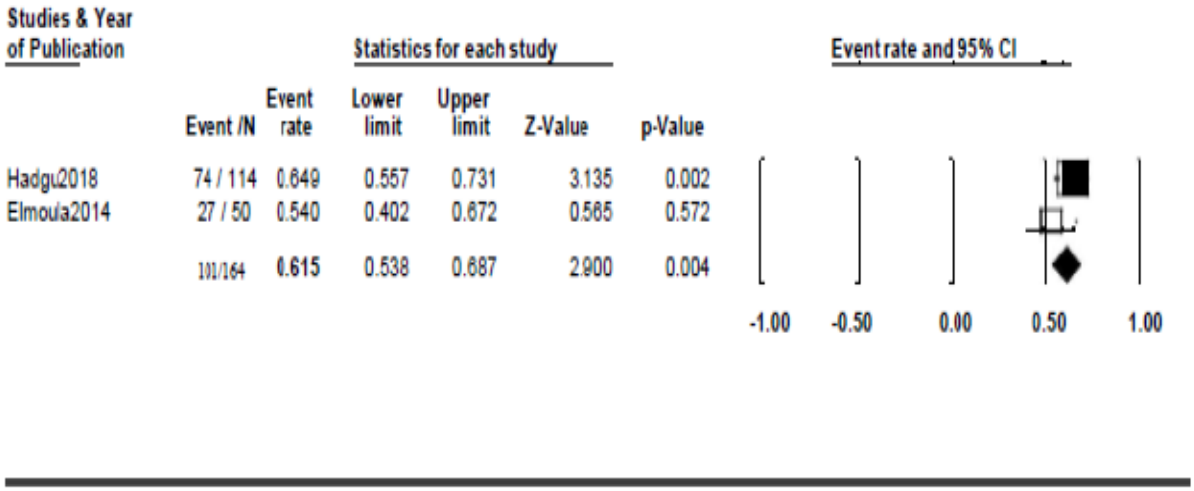

Figure 7: ER+ Proportion by Age (<=45), By data collected after 2009 I2: 42.465

4.2.2.2 PR+

The proportion of PR+ among women with BC ranged from 26% to 51% with the pooled estimate of 49% which was not statistically significant with (CI] 47% to 51% [and 95 I^2.

4.2.2.3 ER+ OR PR+

6 studies reported the expression of ER+ or PR+ and the pooled prevalence was estimated at 50% CI:]35, 65[with I^2 96% ISQ. The proportion of PR+ in northern Africa was estimated at 55% with ISQ of 79%. The heterogeneity was reduced to ISQ=58.914 PR, by subgroup analysis by region (sub-Saharan) in studies which used data collected before 2009, ISQ=58.247 and the pooled prevalence was adjusted to 40% with CI:]36,46[which was statistically significant. Women aged <=45 years had high prevalence of ER+ or PR+ estimated at 60% with a very low heterogeneity **(ISQ:11.939) (Figure 8)** compared to the combined pooled prevalence of ER+ or PR+ (50%) CI:]35, 65[with I^2 96% ISQ.

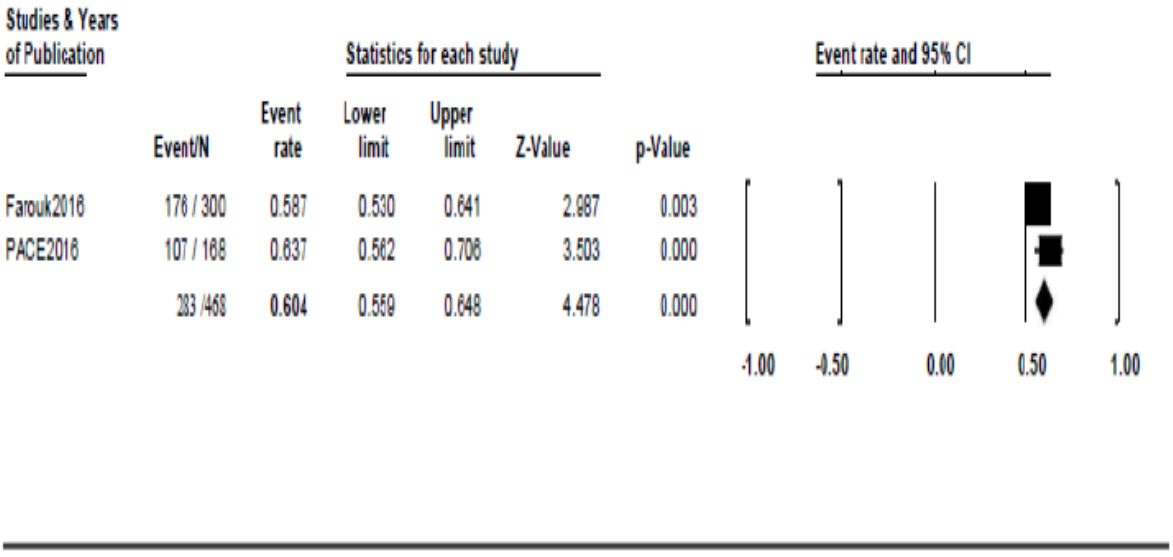

Figure 8: ER+ or PR+ By Age <=45 (ISQ:11.939)

4.2.2.4 KI67 Proliferation marker

6 studies reported the overexpression of KI67 Proliferation marker in 850 among 1396 women with Breast cancer. The proportion of KI67 Proliferation marker ranged from 63% to 87 %.

The pooled prevalence was 60%] 57,63[(I^2 86%). The heterogeneity was reduced to 61 I^2 by region (sub-Sahara), aged beyond 45 years old, I^2=61.431 [64,65] and the proportion ranged from 75% to 87% among specific studies with the pooled prevalence equal to 80% . Ki67 Proliferation marker was less expressed among women with BC at the proportion ranging from 25% to 28% and the pooled estimate was 20%] 11,34[with I^2 96%. In north Africa the KI67 overexpression occurred at the proportion ranging from 36% to 63% among specific studies with the pooled estimated of 59% ($I^2$90) in the women aged > 45 years old[38,82,66]The heterogeneity was reduced to zero in the studies which reported less expression of Ki67 by categorization of age (<=45) in studies conducted in northern African with $I^2$0% [68,69] where the proportion ranged from 5% to 7% among specific studies with pooled prevalence equal to 6% (I^2 0). In addition, the heterogeneity was reduced by time of data collection (before 2009), I^2=0 (Figure 6).[68,69]The proportion of KI67 among age group >45 years old ranged from 28% to 39% among specific studies with the pooled prevalence equal to 38% with $I^2$55 [38,82,66]. In sub-Saharan Africa KI67 was less expressed at the proportion ranging from 12% to 25% with pooled estimate of 19% (I^2 61) among women aged >45 years old.[64,10].

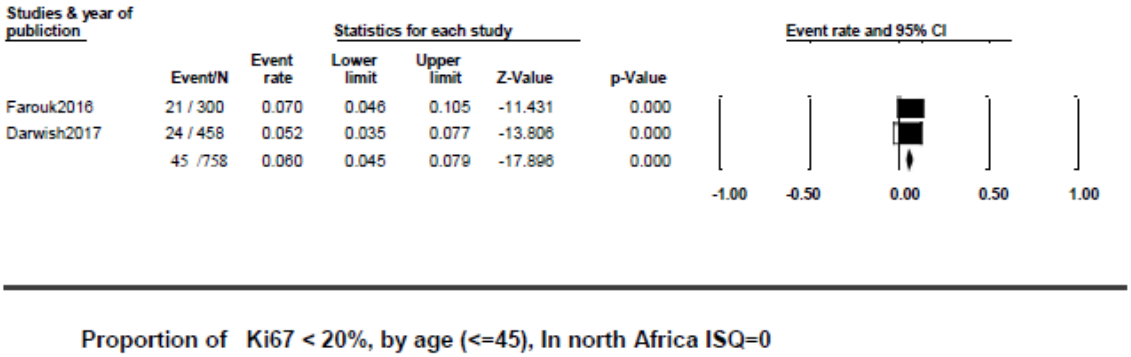

Figure 9: Proportion of KI67<20% By age (<=45), In North Africa I^2=0

4.2.3 Prevalence of Clinical Characteristics on African Population with Breast Cancer:

4.2.3.1 Breast Cancer Grade Status:

The most commonly diagnosed grade status was grade II equal to 45% (pooled prevalence) CI:] 35,53[(Figure 11). Grade III BC cases were reported at 33% CI:]27 ,40[Whereas grade I BC cases was lowest reported 7% CI:] 4,9[. **(Figure 10)**

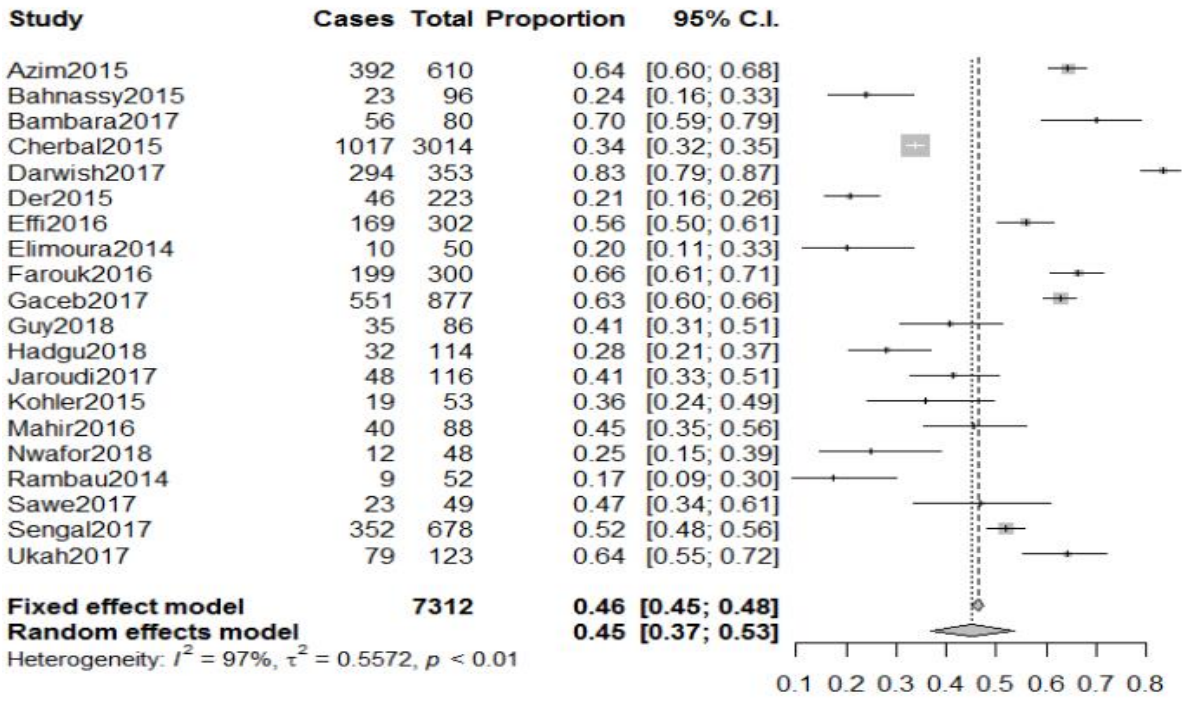

Figure 10: Prevalence of Grade II Breast Cancer in Africa –Studies published April /2014 2018

4.2.3.2 Breast Cancer Stage Status:

The commonly diagnosed BC clinical stage was early stage (stage I & II) corresponding to 33% CI:]21 ,47[(Figure 13) followed by stage III estimated at 31% CI]24,39[. The proportion of Stage IV (Late stage) was reported as the lowest percentage (16%) CI:]7,33[**(Figure 11)**

4.2.3.3 Breast Cancer Histological Status:

Breast cancer histological types reported were categorized into three types. Ductal Carcinoma, Lobular carcinoma and others. The most commonly diagnosed BC histological types were Ductal carcinoma which ranged from 49% to 96% across specific studies where the pooled prevalence was estimated to 84% CI (78,89) with I^2 98 (Figure 9). The proportion of BC ductal carcinoma was estimated at 89% with $I^2$84 among sub-Saharan women population aged >45 years [85,71,11,63,54,74,75,76,77]. The pooled proportion of Ductal Carcinoma in north Africa in the women population aged > 45 was estimated to 59%with 99ISQ [70,57,61,66].The proportion of BC ductal carcinoma in Sub-Saharan Africa was estimated at 76% with I^2 90 in age group <=45 years [83,84,59,80] **. (Figure 12)**Lobular carcinoma and other BC histological types were reported at pooled proportion of 7% CI:]4, 13[and 9%, CI]6, 13[respectively (Table 2).

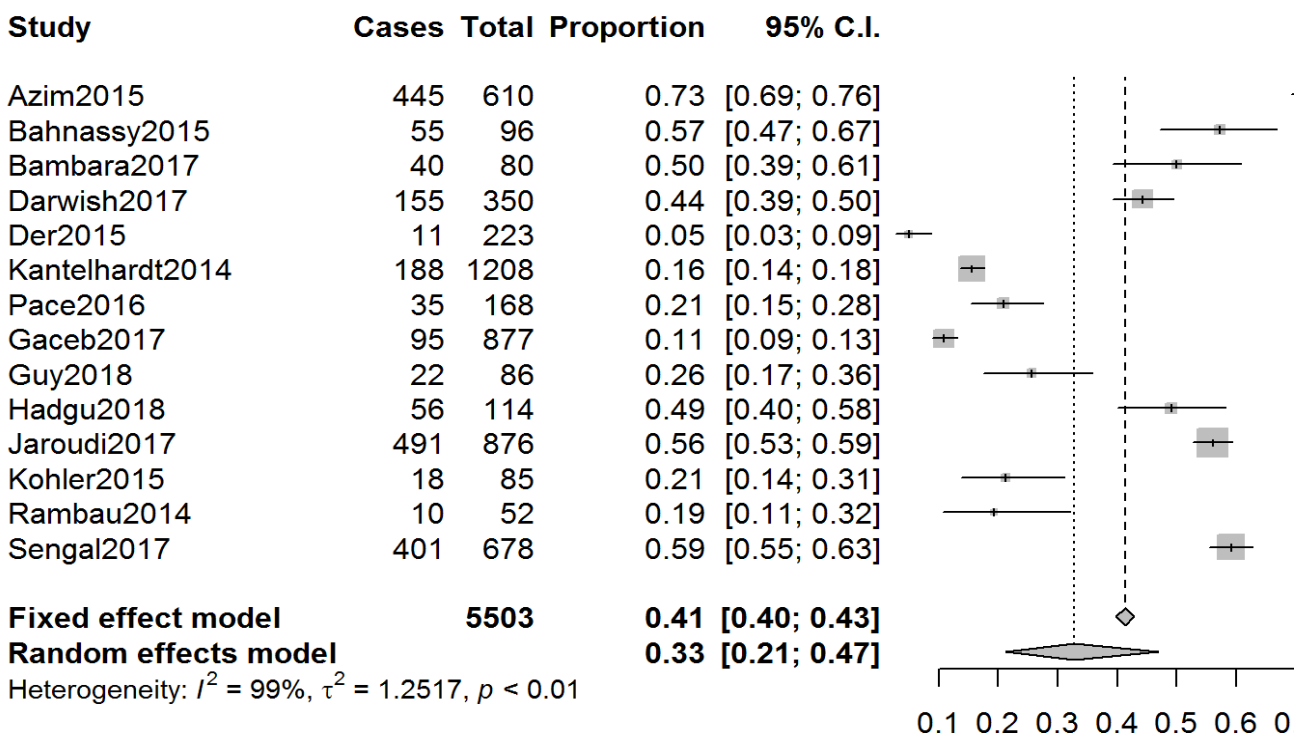

Figure 11: Prevalence of BC diagnosed in early clinical stage (I&II) in Africa –Studies published April /2014-2018

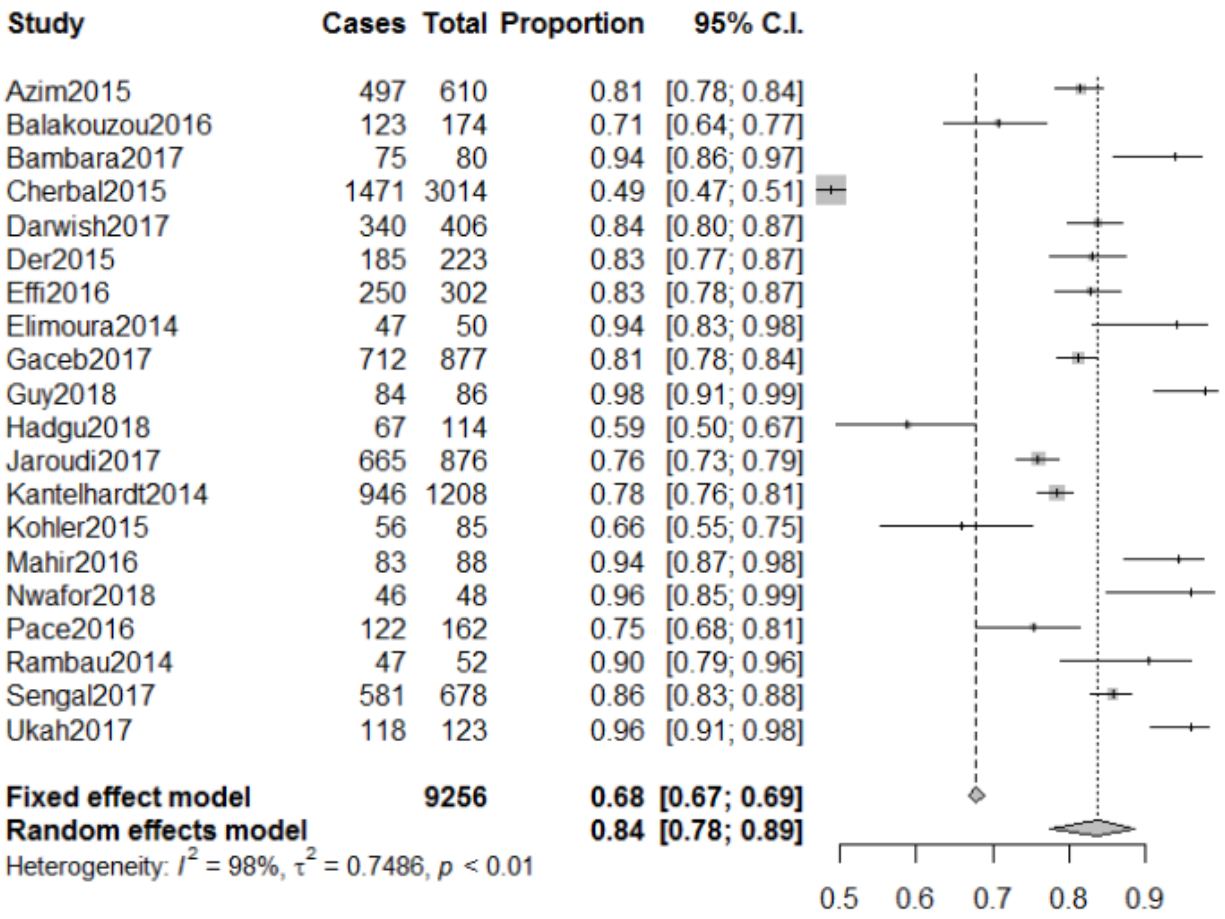

Figure 12: Prevalence of Ductal Carcinoma in Africa –Studies published April /2014-2018

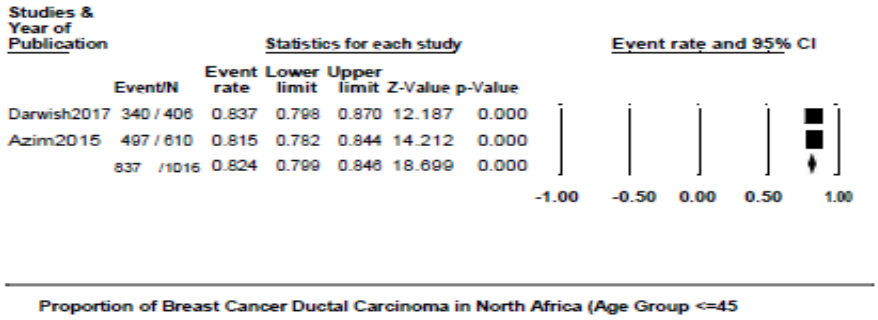

Figure 13: Prevalence of Ductal Carcinoma in North Africa –Studies published April /2014-2018

4.3 Factors Associated with Breast Cancer Molecular subtypes and clinical characteristics

4.3 .1 Association of Age and Breast Cancer Grade Status and TBNC Expression

The women population in Northern Africa aged >45 Years diagnosed with BC at Grade II are 28.63 Times likely to express TNBC compared to those diagnosed with BC at grade I (OR: 28.63 [17.38,47.16] (**Figure 14)**[66,58,67]**.**

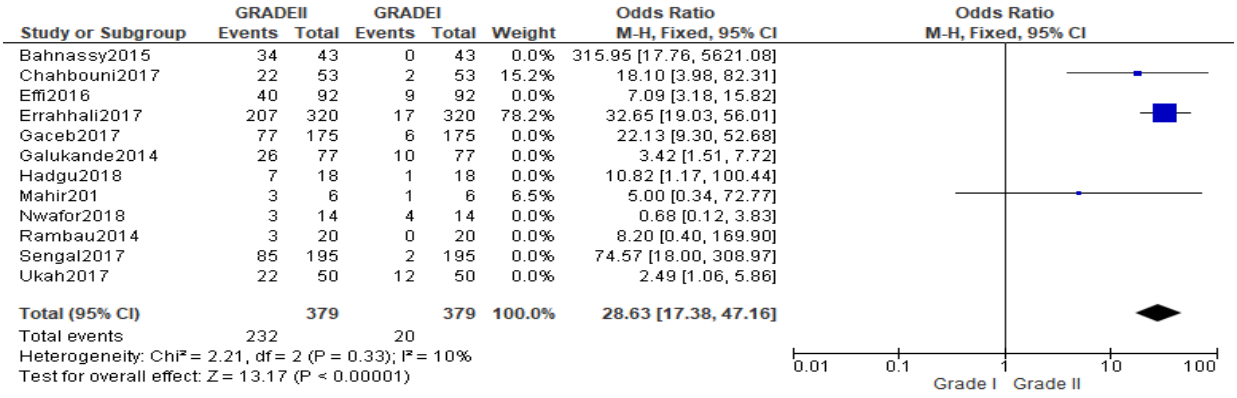

Figure 14: Association of BC Grades (II &I) with TNBC Expression BY Age >45 In Northern Africa studies published from April 2014 to 2018

4.3.4 Association of Breast Cancer Status and HER2 Overexpression

The population in Northern Africa aged >45 diagnosed with BC at Grade III were 12.36 times likely to overexpress HER2 compared to those with the same age but with Grade I BC (OR:12.36 [6.35,24.07][67,78,66] **.(Figure 15)**

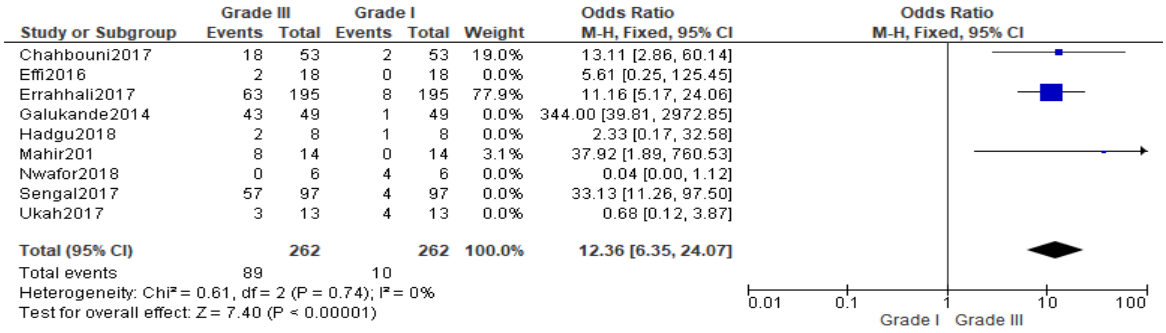

Figure 15: Association of Grade (III & I) and HER2 Overexpression in Northern Africa Age>45 studies published from April 2014 to 2018

women in northern Africa aged >45 diagnosed with BC grade II were 46 times likely to express HER Overexpression compared to those with the same age at Grade I (OR 46 [23,91]) (**Figure 16).**

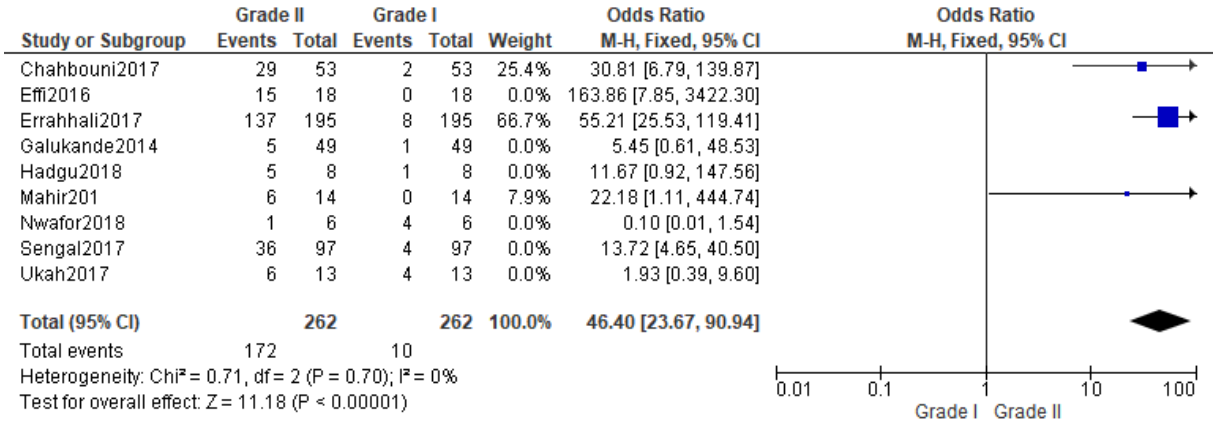

Figure 16: Association of BC Grades (II &I) with Age status in HER2 Overexpression (BY Age>45 in Northern Africa) Studies published April /2014-2018

CHAPITER V:

Discussion

In the present review, we found that luminal A (29%) subtype was the most prevalent followed by TNBC (28%) subtype, Luminal B subtypes (23%), and HER2-enriched (11%). Our findings reveal that Luminal A was more prevalent at older age (among women aged >45) estimated at 31 % in north Africa compared to Sub-Saharan Africa (27%).our findings are comparable to the distribution seen in the western countries where in Europe, North America, Asia and middle eastern countries, 30– 70% of breast cancers are luminal A tumor. [86,87] The current review reveals that luminal B pooled prevalence was estimated at 23%. Our review reported luminal B in North Africa among women aged >45 estimated at 26 %. We have not been able to calculate the luminal B proportion among women aged <=45 is North Africa due to the limited number of primary studies. The review also revealed the proportion of Luminal B among women aged >45 years estimated at 13% in Sub-Saharan Africa whereas the proportion in women aged <=45 years was estimated at 16%. We observed that Luminal B was more prevalent in older age in Africa and it was commonly expressed in North Africa. However, in sub-Saharan Africa Luminal B was more prevalent at young age which agrees with findings from Studies in the west where literature reveals a drop in luminal B subtypes as patients' age increase with the increase of luminal A incidence,in other words , in western countries , age distribution at diagnosis is seen where incidence of the more aggressive phenotype luminal B peaks at earlier ages whereas luminal A type peaks at older ages[88]

Literature reveals that Women with TNBC have lower disease free survival and overall survival in many African American studies[89,90]. Our review revealed the pooled proportion of TNBC or basal like was estimated at 28% and was higher compared to Asian White American and European populations, where the TN represents 10-20% of breast cancer (European countries 11.8–12%, China 12.9%, and the white, Hispanic and Asian ethnic groups of the US population

9–13%) [91,92,93,94,95,96]. The review also reported that in Northern Africa the proportion of TNBC OR Basal like among women aged >45 was estimated at 19% where as those <=45 the proportion was estimated at 16% which was comparable to the prevalence of TNBC in Asian, white American and European populations where the TN represents 10-20% of breast cancer. On the side of sub-Saharan Africa our findings reported the pooled proportion of TNBC among women age >45 years estimated at 39% which was higher compared to the prevalence in North Africa and compared to the proportion of TNBC patients (Caucasian women) in Europe, America and in Chinese women according to Reports from Europe, America and China which show that proportion of TNBC subtype varies from 11.39 to 16%[97,98,99]. It is of note that the proportion of TNBC subtype in our review is higher than that in African-American patients (20 to 26.4%) [100,101]. The high proportion of TNBC subtype in African women compared to Caucasian women, European ancestry could be linked to environmental factors and to genetic elements of African population[102]. This review add to the existing evidence that breast cancer in sub-Saharan Africa is characterized by aggressive disease, advanced stage at presentation and with a significant proportion among young women[92,103] . Some studies suggest that these disparities may be explained by genetic differences such as unidentified founder mutations in breast cancer[104,105,106] . Studies to explore gene mutation patterns may explain such differences [107,108,109].TNBC are known to have poor clinical, pathologic and molecular prognosis and more aggressive clinical course when compared to Lumina A subtype.[110,111]. Other researchers have also shown that young black women were more likely than nonblack women to have ER negative or TN breast cancers.[112]

The current review reported HER2 Overexpression at 11% (Figure 6). HER 2 Overexpression in North Africa among women aged >45 was estimated at 10 % where as those aged <=45 was estimated to 14%. The findings revealed that in Sub-Saharan Africa the proportion of HER 2 Overexpression among women aged >45 years was estimated at 8% whereas the proportion in

women aged <=45 years was estimated at 15%. HER2 enriched was generally, higher than that in European countries (3–8%). [91,92,93,9495,96] Present review has shown HER2 enriched at lower proportion compared to the rate in white Americas , African Americans, which is about 17%, 19% respectively [113]. These findings are in agreement with the literature data which reported 10-30% of HER2 positive in invasive breast cancer, indicating that HER2 status remains stable in breast carcinoma (Gullick and Srinivasan, 1998; Beltjens et al., 2015). The HER2 overexpression was more prevalent at young age (<=45) in Africa. Further studies are suggested in Young women population to understand why HER2 is overexpressed in young population compared to old age. we observed a significant association between breast cancer grade status and HE2 Overexpression in North African population of older age where by women aged (>45) diagnosed at BC Grade III status were 12 times more likely to overexpress HER2 than those diagnosed at BC grade I. The current review demonstrated that the most commonly diagnosed Breast cancer grade was grade II estimated at (45%). The Grade II in North Africa among women aged >45 was estimated at 55 % where as those aged <=45 was estimated to 74%. In Sub-Saharan Africa the proportion of GRADE II among women aged <=45 years was estimated at 27% whereas the proportion in women aged >45 years was estimated at 44%. The observation here is that grade II was more prevalent at older age in north Africa which is contrary to sub-Sahara Africa where it was prevalent at younger age. Grade III was more prevalent at young age in Sub-Sahara Africa compared to North Africa where Grade III was more prevalent at older age .These findings call for special attention to young population in Sub-Sahara Africa by introducing BC early screening interventions taking into consideration grade status as an important diagnostic factor associated with expression of molecular subtypes, particularly in advanced grade where women diagnosed with BC Grade III at the age <=45 years are 9.55 times likely to express TNBC or basal like compared to those in grade I in Sub-Sahara Africa . In addition, it was observed that women at grade II aged <=45

years were 7 times more likely to overexpress HER 2 compared to those diagnosed with lower grade. In northern Africa women aged >45 years diagnosed with grade II were 28 times more likely express TNBC compared to those at lower grade (I). In Addition, the same population at grade II were 46 times more likely to overexpress HER2 compared to those diagnosed at lower grade I. It is of note that management of Breast cancer should take into consideration the role of grade status and molecular subtypes in the prognosis and treatment of breast cancer in Africa. The findings also revealed that the most commonly diagnosed BC clinical stage was early stage I & II corresponding to 33% followed by stage III estimated at 31%. We observe a positive change as the early stage cases I & II were highly reported compared to late stages in the past five years which may be due to the improvement of BC prevention and management strategies in Africa. However , When we compare our findings with western findings, Africa still represent a high percentage of late stage (Stage III BC disease) compared to the prevalence of Stage III in western countries [114,115,116] . The main reasons of this difference we observed is due to limited awareness of Breast cancer and diagnostic capacity which is still scarce in Africa. On the other side, according to the review published in 2017 on BC stage it highlighted a high proportion of BC at late stage among Africa women due to the fact it included studies published before our review period[117] .But the findings agree with our review as it showed a decline of BC late stage over years among African women . The Breast cancer histological types commonly diagnosed in Africa was ductal carcinoma corresponding to 84%. Many authors agreed that invasive ductular carcinoma is the most breast cancer in African and in European women[118,119].This also agrees with international distribution of breast cancer types, worldwide where the invasive ductal carcinoma is the most common breast cancer[120].The review findings estimated the pooled proportion of ER+ at 50%, and in Sub-Sahara Africa the proportion of ER+ expression among women aged <=45 years was estimated at 26% which was low compared to the prevalence among women aged >45 years old (39%) .The review also

reported the proportion of ER+ estimated at 69% in north Africa, whereas the pooled prevalence in <=45 was 58%. The observation here is that ER + was generally more prevalent at Older age in Africa. Endocrine therapy for ER may be the best option therapy in Africa as recommended by other studies.[41](Example of endocrine treatments such as tamoxifen, and selective ER degraders such as fulvestrant, and aromatase inhibitors (AIs). The findings also revealed the pooled proportion of PR+ estimated at 49%, the subgroup analysis of the review by geographical location showed the prevalence of PR+ in north Africa estimated at 55% where as in Sub-Sahara Africa was estimated at 40%. This shows that the PR+ was more prevalent in NA than SA. The findings also revealed ER+ or PR+ pooled proportion estimated at 50% (the pooled prevalence of ER+ or PR + in sub-Sahara among women aged <=45 was estimated at 60% 11.939 ISQ)[68,84]The findings also revealed that the KI67 Proliferation marker overexpression (>20) was estimated at 60% [73,75] and subgroup analysis revealed that in Sub-Sahara Africa, the pooled prevalence of KI67 overexpression was estimated at 80% among women aged >45 years whereas in northern Africa the KI67 over expression was reported at 59% among women aged > 45 years. literature reveals that positivity and intensity of Ki67 proliferation marker indicate bad prognosis[121] .Unexpectedly, the current review shows that the overexpression of proliferation marker was more prevalent at older age in Sub-Sahara Africa compared to North Africa .

The strengths of this review include the use of earlier studies published between 2014-2018 comprising (13114 women with breast cancer) which provided the current status of distribution of breast cancer molecular subtypes and clinical pathological characteristics within past 5 years. second strength is the consideration of studies which reported the association of molecular subtypes and proliferation markers with clinical pathological characteristics which enable to study the association of grade status and molecular subtypes expression. Another strength is that we used broader search terms which enabled us obtaining relevant papers

included in the review. Another strength of this review, is the extended review by including the data on the KI67 proliferation marker which was not included in the previous reviews. Another strength of this review is the use of subgroup analysis which lead to the reduction of heterogeneity among included studies and hence increased the certainty of the findings.

The main limitation of the review is that Only 12 sub-Saharan countries out of 49 countries were represented in the review (i.e., Rwanda, Nigeria, Ghana, Kenya, Tanzania, Ethiopia, Republic of Congo, Ivory coast, Malawi, Eritrea and Sudan, Burkina Faso) and most studies were from Nigeria, Ethiopia and RDC. In addition, only 4 countries represented north Africa (Morocco, Egypt, Algeria and Saudi Arabia) with a predominance of the studies from Morocco and Egypt .Due to limited studies, we failed to calculate the proportion of KI67 over expression among women at young age (<45 years) .In addition we failed to calculate the proportion of ER+ or PR+ in North Africa , as well as the proportion of TNBC among women aged <=45 in Sub-Sahara Africa due to limited number of primary studies . As it is stated by previous studies, few countries in Africa were able to determine molecular subtypes status of the patients due to limited resources and hence downgraded the diagnosis and treatment of breast cancer on the continent of Africa. Therefore, Most of the studies have based on the convenience samples and only 4 out of 27 studies included in the review were conducted on population based context .In addition, more than half of the total studies included in review (17 studies) had a sample size which is lower than 300 which may have caused publication bias and most of those studies represented the sub-Sahara region (Tanzania-Rambau ,Nigeria – Nwafor,Ukah, ,DRC-Guy, Malawi, Rwanda ,Ethiopia-Hadgu ,Ghana ,Sudan ,Burkinafaso, Central Africa Republic Bangui,Kenya (Sawe), Cote d'Ivoire and Republic of Congo (Islamy2015).Differences in clinical and laboratory analytical procedures across studies may have contributed to differences per geographical location. Our review was limited by language as only studies published in English were included in the review. Limitation of our review

also include use of sample which may not have been properly stored as most of our studies were retrospective studies with low quality samples caused by antigen degradation of archival materials[122123124].Therefore, the quality of the samples may have influenced the high frequency of hormone receptor negativity observed in our review. In addition, limited resource capacity of histopathological diagnosis may have affected our findings. Including studies with small sample size, use of a retrospective clinical data collection and lack of evaluation for HER2+ equivocal results using fluorescent in-situ hybridization (FISH) and not performing Ki67 as a marker of proliferative index in some of the studies may have affected our results Furthermore, not all BC patients were evaluated for Hormone receptors in health facilities, this might have affected our inferences.[74] . In the current review , we did not differentiate TNBC and basal like breast cancer because the majority of basal like cancers are also triple negative and the majority of TNBC (80%) also basal like[125] .However , we admit that this may have affected our inferences as the science through clinical micro assay and immuno-histochemical data already confirmed the difference between TNBC and Basal like[126] . Hospital based studies may not be representative of the entire population which also may have affected our results. The funnel plots standard error by logit event provide evidence of publication bias for studies with small sample sizes which reported on molecular subtypes status such as Luminal A, Luminal B, TNBC, ER, + and KI67 Overexpression, HER2 Overexpression. For example, on luminal A show that the majority of the studies with large sample size had standard error <0.05. However, it is also noted that studies with small sample sizes had a very large standard error which may have contributed to the asymmetric distribution leading to the conclusion that the studies with small sample size haven't been published and therefore a publication bias was observed. Funnel plot precision by logit event rate for Luminal A demonstrated that most of the studies included in the review had a confidence interval less than or beyond but closer to 10. For example, show that only 3 studies out of 16 had CI above 10. This observation was the

same in other subtypes where for example 2 out of 15 studies had confidence interval above 10 for Luminal B, and one study had a CI above 10 for KI67, 3 out of 17 studies for TNBC and 3 studies out of 13 were above 10 for ER+ whereas for HER2 Overexpression only one studies out of 14 studies had CI above 10. This generally lead to the conclusion that the publication bias observed was due to studies with small sample size and asymmetric distribution may not have affected the level of precision for our findings.

CHAPITER VI

Conclusion

This review complements the existing evidence which provided a strong evidence that the distribution of breast cancer molecular subtypes is not slightly different from the ones in Western population. However, it also adds an evidence that the TNBC is highly expressed in

sub-Sahara Africa compared to other regions of Africa. Furthermore, this review also adds a strong evidence on the association of grade status and expression of molecular subtypes particularly Luminal B, TNBC and HER2 Overexpression on the continent of Africa. It also contributes to the evidence that KI67 overexpress at old age (>45 years) and less expressed at the young age.

Recommendation/Policy Implication:

1. More population studies using the more rigorous ASCO/CAP guidelines for quantified hormone receptor expression is necessary particularly in exploring TNBC or Basal like status among patients diagnosed with BC at Younger age.
2. Integration of Molecular subtypes receptor testing in Routine management of BC diseases to be given a high priority in order to increase Diseases survival rate among African indigenous population.
3. Routine use of tamoxifen (anti hormonal therapy) without prior receptor status testing should be avoided as it may lead to the waste of resources if it happens to have HER2 Overexpression and TNBC breast cancer cases in African setting.

   Role of proliferation markers such as KI67 in the prognosis and treatment of Breast cancer on the continent of Africa should be taken into consideration for proper follow up and treatment of Breast cancer patients in Africa .
4. Studies exploring status of KI67 proliferation marker at young age are also suggested in African population in order to establish strong mechanisms for patient follow up and treatment response.
5. Understanding the pattern and function of immune cell infiltrates in TNBC tumors of African women may guide in identifying the critical immune cells that could be therapeutic targets in this population.

6. Studies to understand the immune response generated by the tumors are suggested in order to understand which immunotherapy treatment options would be relevant to treat these tumors.
7. Further studies are suggested to test if African breast cancer patients may be carriers for BRCA-1 mutation and that may explain the variability in aggressiveness and the disease outcome as well as variability in molecular features across the continent.
8. Availability of Trastuzumab to African BC Patients with luminal B is recommended as they can benefit from both hormonal therapy and trastuzumab,
9. Establishment of policy and protocols for use of Trastuzumab on African BC patients with enriched HER-2 is suggested .
10. Breast cancer Grade status may be a promising indicator in the treatment of breast cancer based on molecular subtypes status particularly TNBC or Basal and HER2 overexpression and Luminal B.
11. special attention on the sub-Saharan African population is recommended especially at the age >45 in order to increase their survival rate as the TNBC was highly observed in this population (33%) compared to North Africa.
12. women population in North Africa, aged >45 Years with advanced BC grade may be given special attention as they are at risk of expressing TNBC.

13. More efforts in increasing access to cost effective therapeutic interventions tailored to African population is encouraged.
14. Including Ki-67 in the standard pathological assessment could help to identify and treat aggressive tumors as early as possible as well introducing proper follow up of patient outcome as positivity of Ki67 proliferation marker indicate bad prognosis. Therefore , Ki67 proliferation marker may be used as a key indicator in the follow up of patient

outcome particularly in sub-Sahara Africa where It is over proliferated at (80%) among women of >45 years old.

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APPENDICES

ANNEX 1 -HORMONE RECEPTORS

	Event	**Event rate**	**Confidence Interval**		**Z Value**	**P value**
			Lower Limit	**Upper limit**		
ER+(N : 2023/4309)						
Hadgu2018	74 /114	0.649	0.557	0.649	0.731	**0.002**
Darwish2017	193/286	0.675	0.618	0.675	0.727	**0.000**
Sengal2017	309/678	0.456	0.419	0.456	0.493	**0.021**
Nwafor2015	26/257	0.101	0.070	0.101	0.144	**0.000**
Azim 2015	395/610	0.648	0.609	0.648	0.684	**0.000**
Rambau2014	17/52	0.327	0.214	0.327	0.464	**0.015**
Kantelhardt2014	352/1208	0.291	0.266	0.291	0.318	**0.000**
Elmoula2014	27/50	0.540	0.402	0.540	0.672	**0.572**
Rasmy2014	233/280	0.832	0.784	0.832	0.872	**0.000**
Farouk2016	147/300	0.490	0.434	0.490	0.546	**0.729**
Effi2016	169/302	0.560	0.503	0.560	0.615	**0.039**
Sawe2017	29/49	0.592	0.451	0.592	0.719	**0.201**
Ukah2017	52/123	0.423	0.339	0.423	0.512	**0.088**
Pooled statistics	2023/4309	**0.501**	0.391	0.501	0.611	**0.983**

PR+ (N: 1629/3334)						
Hadgu2018	49/114	0.430	0.342	0.522	-1.494	0.135
Darwish2017	180/287	0.627	0.570	0.681	4.261	0.000
Sengal2017	267/678	0.394	0.358	0.431	-5.488	0.000
Nwafor2015	24/257	0.093	0.063	0.136	-10.603	0.000
Rambau2014	22/52	0.423	0.297	0.560	-1.105	0.269
Azim2015	324/610	0.531	0.491	0.570	1.538	0.124
Rasmy2014	198/280	0.707	0.651	0.440	6.713	0.000
Elmoula2014	15/50	0.300	0.190	0.757	0.672	0.006
Kantelhardt2014	162/232	0.517	0.636	0.573	2.746	0.584

Farouk2016	155/300	0.698	0.460	0.754	0.577	0.000
Effi2016	148/302	0.490	0.434	0.546	5.866	0.730
Sawe2017	19/49	0.388	0.263	0.529	-0.345	0.119
Ukah2017	46/123	0.374	0.293	0.463	-2.765	0.006
Pooled statistics	1490/6409	**0.496**	0.478	0.514	-0.444	0.657
ER+ or PR+ (N: 741/1553)						
Bahnassy2015	53/96	0.552	0.452	0.648	1.019	0.308
Pace2016	107/168	0.637	0.562	0.706	3.503	0.000
Farouk2016	176/300	0.587	0.530	0.641	2.987	0.003
Mahir2016	68/88	0.773	0.674	0.848	4.811	0.000
Sengal2017	314/678	0.463	0.426	0.501	-1.918	0.055
Der2015	23/223	0.103	0.070	0.150	-9.823	0.000
Pooled statistics	741/1553	**0.501**	0.347	0.656	0.018	0.985

ER- or PR- (N: 688/1457)						
Pace2016	107/168	0.310	0.244	0.383	-4.808	0.000
Farouk2016	176/300	0.413	0.359	0.470	-2.987	0.003
Mahir2016	68/88	0.227	0.152	0.326	-4.811	0.000
Sengal2017	314/678	0.534	0.496	0.571	1.766	0.078
Der2015	23/223	0.233	0.182	0.293	-7.517	0.000
Pooled statistics	688/1457	**0.427**	0.401	0.454	-5.358	0.000
>20% KI67 Proliferation marker (N 1396)						
Sawe2017	43/49	.878	0.753	0.944	4.519	0.000
Mahir2016	32/88	0.364	0.270	0.469	-2.525	0.012
Rambau2014	39/52	0.750	0.616	0.849	3.430	0.001
Gaceb2017	530/877	0.604	0.572	0.636	6.134	0.000
Elmoula2014	29/50	0.580	0.441	0.708	1.126	0.260
Rasmy2014	177/280	0.632	0.574	0.687	4.369	0.000
Pooled statistics	**850** /1396	**0.605**	**0.579**	**0.631**	**7.669**	**0.000**
<20% **KI67 Proliferation marker (2154)**						
Sawe2017	6/49	0.122	0.056	0.247	-3.910	0.000
Mahir2016	25/88	0.284	0.200	0.342	-3.856	0.000

Rambau2014	13/52	0.250	0.151	0.384	-3.430	0.001
Gaceb2017	347/877	0.396	0.364	0.428	-6.134	0.000
Elmoula2014	21/50	0.420	0.292	0.559	-1.126	0.260
Farouk2016	21/300	0.052	0.046	0.105	-11.431	0.000
Rasmy2014	103/280	0.368	0.313	0.426	-4.369	0.000
Darwish2017	24/458	0.052	0.035	0.077	-13.806	0.000
Pooled statistics	560/2154	**0.209**	**0.118**	**0.342**	**-3.856**	**0.000**

ANNEX 2- PROPORTION OF MOLECULAR SUBTYPES

Studies	Event	**Event rate**	**Confidence Interval**		**Z Value**	**P value**
			Lower Limit	**Upper limit**		
Luminal A (N : 2672/6867)						
Bambara2017	4/11	0.364	0.143	0.661	-0.893	**0.372**
Darwish2018	129/458	0.282	0.242	0.325	-9.013	**0.000**
Effi2016	148/302	0.490	0.434	0.546	-0.345	**0.730**
Gaceb 2017	279/877	0.318	0.288	0.350	-10.515	**0.000**
Cherbal2015	1525/3014	0.506	0.488	0.524	0.656	**0.512**
Sengal2017	196/678	0.289	0.256	0.324	-10.622	**0.000**
Chahbouni2017	119/390	0.305	0.261	0.353	-7.484	**0.000**

Galukande2014	83/226	0.396	0.307	0.432	-3.942	**0.000**
Nwafor2018	19/48	0.081	0.269	0.539	-1.433	**0.152**
Der2015	18/223	0.439	0.051	0.124	-9.896	**0.000**
Ukah 2017	54/123	0.346	0.354	0.528	-1.349	**0.177**
Rambau 2014	18/52	0.143	0.230	0.484	-2.182	**0.029**
Sawe 2017	7/49	0.032	0.070	0.271	-4.389	**0.000**
Farouk2016	7/216	0.402	0.016	-8.839	-8.839	**0.000**
Mahir2016	21/88	0.292	0.161	0.338	-4.639	**0.000**
Hadgu2018	45/112	0.364	0.315	0.495	-2.065	**0.039**
Pooled statistics		**0.282**	0.231	0.360	-5.550	0.000
Luminal B (N: 1490/6409)						
Bambara2017	2/11	0.182	0.046	0.507	-1.924	0.054
Effi2016	29/302	0.096	0.068	0.135	-11.480	0.000
Chahbouni 2017	163/390	0.418	0.370	0.468	-3.226	0.001
Ukah2017	6/123	0.049	0.022	0.104	-7.096	0.000
Sawe2017	20/49	0.408	0.281	0.549	-1.278	0.201
Mahir2016	47/88	0.534	0.430	0.635	0.639	0.523
Hadgu2018	30/112	0.268	0.194	0.357	-1.924	0.000
Gaceb2017	371/877	0.423	0.391	0.456	-4.712	0.000

Cherbal2015	593/3014	0.197	0.183	0.211	-4.540	0.000
Sengal2017	68/678	0.100	0.080	0.125	-30.702	0.000
Galukande2014	13/226	0.058	0.034	0.097	-17.161	0.000
Nwafor2018	9/48	0.188	0.101	0.323	-9.788	0.000
Der2015	23/223	0.103	0.070	0.150	-3.965	0.000
Rambau2014	9/52	0.173	0.093	0.300	-9.823	0.000
Farouk2016	107/216	0.495	0.429	0.562	-4.267	0.892
Pooled statistics	**1490/6409**	**0.212**	0.148	0.295	-5.858	0.000
HER2 Overexpression (N: 2023/6258)						
Hadgu2018	11/112	0.098	0.055	0.169	-6.983	0.000
Darwish2017	55/458	0.120	0.093	0.153	-13.855	0.000
Gaceb2017	52/877	0.059	0.045	0.077	-19.333	0.000
Cherbal2015	269/3014	0.089	0.080	0.100	-36.357	0.000
Sengal2017	85/678	0.125	0.102	0.152	-16.749	0.000
Galukande2014	49/226	0.217	0.168	0.275	-7.956	0.000

Nwafor2018	6/48	0.125	0.057	0.252	-4.459	0.000
Rambau2014	5/52	0.096	0.041	0.211	-4.763	0.000
Farouk2016	45/216	0.208	0.159	0.268	-7.968	0.000
Bambara2017	2/11	0.182	0.046	0.507	-1.924	0.054
Effi2016	18/302	0.060	0.038	0.093	-11.350	0.000
Ukah2017	13/123	0.106	0.062	0.174	-7.282	0.000
Sawe2017	4/49	0.082	0.031	0.198	-4.639	0.000
Mahir2016	14/88	0.159	0.097	0.251	-5.713	0.000
Pooled statistics	2023/6258	**0.114**	0.090	0.145	-14.799	**0.000**
Basal Like or Triple Negative (TNBC) (N : 1692/7728)						
Bambara2017	8/11	0.727	0.414	0.910	**1.449**	**0.147**
Darwish2018	24/459	0.052	0.035	0.077	**-13.818**	**0.000**
Effi2016	92/302	0.305	0.255	0.359	**-6.601**	**0.000**
Gaceb2017	175/877	0.200	0.174	0.227	**-16.441**	**0.000**
Cherbal2015	627/3014	0.208	0.194	0.223	**-29.790**	**0.000**

Sengal2017	182/678	0.268	0.236	0.303	**-11.568**	**0.000**
Chahbouni2017	53/390	0.136	0.105	0.174	**-12.518**	**0.000**
Galukande2014	77/226	0.341	0.282	0.405	**-4.703**	**0.000**
Bahnassy2015	43/96	0.448	0.352	0.548	**-1.019**	**0.308**
Nwafor2018	14/48	0.407	0.181	0.434	**-2.794**	**0.005**
Der2015	130/223	0.132	0.517	0.646	**2.466**	**0.014**
Ukah2017	50/123	0.385	0.323	0.495	**-2.062**	**0.039**
Jaroudi2017	116/876	0.367	0.112	0.157	**-18.857**	**0.000**
Rambau2014	18/52	0.264	0.263	0.522	**-1.649**	**0.099**
Sawe2017	57/96	0.068	0.245	0.509	**-1.834**	**0.067**
Farouk2016	6/48	0.407	0.209	0.327	**-6.645**	**0.000**
Mahir2016	20/88	0.132	0.031	0.144	**-6.183**	**0.000**
Pooled statistics	1692/7728	**0.264**	0.209	0.328	-6.535	0.000

ANNEX 3-TUMOR GRADE STATUS

Studies	Event	**Event rate**	**Confidence Interval**		**Z Value**	**P value**
			Lower Limit	**Upper limit**		
Grade I (N: 468/**7538)**						
Farouk 2016	9/300	0.030	0.016	0.057	**-10.271**	**0.000**
Hadgu2018	7/114	0.061	0.030	0.123	**-6.990**	**0.000**
Darwish2017	1/353	0,003	0.000	0.020	**-5.855**	**0.000**
Gaceb2017	74/877	0.084	0.068	0.105	**-19.626**	**0.000**
Cherbal2015	177/3014	0.059	0.051	0.068	**-35.810**	**0.000**
Sengal2017	30/678	0.044	0.031	0.063	**-16.453**	**0.000**
Galukande2014	16/226	0.071	0.044	0.112	**-9.927**	**0.000**
Kohler2015	8/53	0.151	0.077	0.274	**-4.502**	**0.000**
Nwafor2015	17/48	0.354	0.233	0.498	**-13.874**	**0.047**
Der2015	20/223	0.090	0.059	0.135	**-7.133**	**0.000**
Azim2015	14/610	0.023	0.014	0.038	**-4.696**	**0.000**
Jaroudi2017	9/116	0.078	0.041	0.142	**-3.853**	**0.000**
Rambau2014	3/52	0.058	0.019	0.164	**-5.863**	**0.000**

Elimoura2014	1/50	0.020	0.003	0.129	**-11.018**	**0.000**
Bambara2017	5/80	0.063	0.026	0.142	**-5.258**	**0.000**
Guy2018	4/86	0.047	0.018	0.117	**-5823**	**0.000**
Effi2016	41/302	0.136	0.102	0.179	**-4.582**	**0.000**
Mahir2016	2/88	0.023	0.006	0.086	**-5.388**	**0.000**
Ukah2017	27/123	0.220	0.155	0.301	**-10.271**	**0.000**
Sawe2017	3/49	0.061	0.020	0.173	**-6.990**	**0.000**
Bahnassy2015	9/300	0.021	0.005	0.079	**-5.855**	**0.000**
Pooled statistics			**0.067**	**0.049**		0.090
-15.740	**0.000**					
Grade II (N: 3463/7538)						
Farouk 2016	199/300	0.663	0.608	0.715	5.551	0.000
Hadgu2018	32/114	0.281	0.206	0.370	-4.515	0.000
Darwish2017	294/353	0.833	0.790	0.868	11.258	0.000
Gaceb2017	551/877	0.628	0.596	0.355	7.511	0.000
Cherbal2015	1017/3014	0.337	0.321	0.557	-17.516	0.000
Sengal2017	352/678	0.519	0.482	0.313	0.998	0.318
Galukande2014	57/226	0.252	0.200	0.495	-7.096	0.000

Kohler2015	19/53	0.358	0.242	0.390	-2.032	0.042
Nwafor2015	12/48	0.250	0.148	0.264	-3.296	0.001
Der2015	46/223	0.206	0.158	0.680	-8.142	0.000
Azim2015	392/610	0.643	0.604	0.505	6.945	0.000
Jaroudi2017	48/116	0.414	0.328	0.300	-1.715	0.065
Rambau2014	9/52	0.173	0.093	0.333	2.067	0.000
Elimoura2014	10/50	0.200	0.111	0.790	-0.852	0.000
Bambara2017	56/80	0.700	0.591	0.513	3.111	0.001
Guy2018	35/86	0.407	0.309	0.615	0.428	0.086
Effi2016	169/302	0.560	0.503	0.559	-4.830	0.039
Mahir2016	40/88	0.455	0.354	0.722	5.551	0.394
Ukah2017	79/123	0.642	0.554	0.608	-4.515	0.002
Sawe2017	23/49	0.469	0.335	0.335	11.258	0.668
Bahnassy2015	23/96	0.240	0.165	0.715	7.511	0.000
Pooled statistics			**0.439**	**0.359**	**0.522**	**-1.437** **0.151**
Grade III (N: 1976/**7538)**						
Farouk 2016	92/300	0.663	0.608	0.715	5.551	0.000
Hadgu2018	39/114	0.342	0.261	0.434	-3.312	0.001
Darwish2017	58/353	0.164	0.129	0.207	-11.324	0.000

Gaceb2017	250/877	0.285	0.256	0.316	-12.293	0.000
Cherbal 2015	544/3014	0.180	0.167	0.195	-31.946	0.000
Sengal2017	294/678	0.434	0.397	0.471	-3.446	0.001
Galukande2014	149/226	0.659	0.595	0.718	4.703	0.000
Kohler2015	26/53	0.491	0.360	0.623	-0.137	0.891
Nwafor2015	14/48	0.292	0.181	0.434	-2.794	0.005
Der 2015	50/223	0.224	0.174	0.284	-7.731	0.000
Azim 2015	89/610	0.146	0.120	0.176	-15.407	0.000
Jaroudi 2017	59/116	0.509	0.418	0.598	0.186	0.853
Rambau2014	40/52	0.769	0.636	0.864	3.658	0.000
Elmoura 2014	31/50	0.620	0.480	0.743	1.680	0.093
Bambara 2017	19/80	0.238	0.157	0.343	-4.440	0.000
Guy 2018	47/86	0.547	0.441	0.648	0.861	0.389
Effi 2016	63/302	0.209	0.166	0.258	-9.415	0.000
Mahir 2016	45/88	0.511	0.408	0.614	0.213	0.831
Bahnassy 2015	15/96	0.156	0.096	0.243	-5.999	0.000
Ukah2017	33/123	0.268	0.197	0.353	-4.930	0.000
Sawe 2017	19/49	0.388	0,263	0.529	5.551	0.119
Pooled statistics			**0.366**	**0.287**		**0.454**
-2.949	**0.003**					

ANNEX 4-TUMOR STAGE STATUS

Studies	Event	**Event rate**	**Confidence Interval**		**Z Value**	**P value**
			Lower Limit	**Upper limit**		
Early stage (I&II) (N :2047/5729)						
Bambara2017	40/80	0.500	0.392	0.608	0.000	1.000
Guy2018	22/86	0.256	0.175	0.358	-4.321	0.000
Bahnassy2015	55/96	0.573	0.472	0.668	1.424	0.155
Hadgu2018	56/114	0.491	0.401	0.582	-0.187	0.851
Darwish2017	155/350	0.443	0.392	0.495	-2.133	0.033
Sengal2017	401/678	0.591	0.554	0.628	4.735	0.000
Galukande2014	25/226	0.111	0.076	0.159	-9.829	0.000
Kohler2015	18/85	0.212	0.138	0.311	-4.951	0.000
Der2015	11/223	0.049	0.028	0.087	-9.568	0.000
Azim2015	445/610	0.730	0.693	0.763	10.885	0.000
Jarroudi2017	491/876	0.561	0.527	0.593	3.573	0.000
Rambau2014	10/52	0.192	0.107	0.322	-4.078	0.000
Pace2016	35/168	0.208	0.154	0.276	-7.027	0.000
Kantelhardt2014	188/1208	0.156	0.136	0.177	-21.307	0.000
Gaceb2017	95/877	0.108	0.089	0.131	-19.401	0.00

Pooled statistics		**0.308**	**0.199**			**0.443**
-2.722	**0.006**					
Stage III (N: 1693/5809)						
	23/80	0.288	0.199	0.396	-3.674	0.000
Bambara2017	64/86	0.744	0.642	0.825	4.321	0.000
Guy2018	41/96	0.427	0.332	0.528	-1.424	0.155
Bahnassy2015	36/114	0.316	0.237	0.407	-1.602	0.000
Hadgu2018	160/350	0.457	0.406	0.510	-13.298	0.109
Darwish2017	155/678	0.229	0.199	0.262	-4.829	0.000
Sengal2017	76/226	0.336	0.278	0.400	-6.110	0.000
Galukande2014	7/85	0.082	0.040	0.163	-9.792	0.000
Kohler2015	14/223	0.063	0.038	0.103	-14.643	0.000
Der2015	105/610	0.172	0.144	0.204	-12.269	0.000
Azim2015	250/876	0.285	0.256	0.316	1.649	0.000
Jarroudi2017	32/52	0.615	0.478	0.737	-1.079	0.099
Rambau2014	77/168	0.458	0.384	0.534	-8.428	0.281
Pace2016	456/1208	0.377	0.351	0.405	-16.490	0.000
Kantelhardt2014	174/877	0.198	0.173	0.226	-3.674	0.000

Gaceb2017	23/80	0.288	0.199	0.396	4.321	0.000
Pooled statistics		**0.311**	**0.248**		**0.383**	**-**
4.924	**0.000**					
Stage IV (N: 862/3786)						
Hadgu2018	4/114	0.035	0.013	0.090	-6.511	0.000
Darwish2017	32/350	0.091	0.065	0.126	-12.382	0.000
Sengal2017	88/678	0.130	0.107	0.157	-16.651	0.000
Galukande2014	10/226	0.044	0.024	0.080	-9.499	0.000
Kohler2015	11/85	0.129	0.073	0.219	-5.899	0.000
Pace2016	52/168	0.310	0.244	0.383	-4.808	0.000
Kanteldhardt2014	143/1208	0.118	0.101	0.138	-22.545	0.000
Gaceb2017	505/877	0.576	0.543	0.608	4.474	0.000
Bambara2017	17/80	0.213	0.136	0.316	-4.793	0.000
Pooled statistics		**0.144**	**0.065**		**0.288**	**-**
3.975	**0.000**					

ANNEX 5. HISTOLOGICAL TYPES

Studies	Event	**Event rate**	**Confidence Interval**		**Z Value**	**P value**
			Lower Limit	**Upper limit**		
Ductal Carcinoma (N :6713 /9482)						
Hadgu2018	67/114	0.588	0.495	0.674	1.863	0.062
Darwish2017	340/406	0.837	0.798	0.870	12.187	0.000
Gaceb2017	712/877	0.812	0.785	0.836	16.923	0.000
Cherbal2015	1471/3014	0.488	0.470	0.506	-1.311	0.190
Sengal2017	581/678	0.857	0.829	0.881	16.320	0.000
Galukande2014	198/226	0.876	0.826	0.913	9.688	0.000
Kohler2015	56/85	0.659	0.552	0.751	2.876	0.004
Nwafor2015	46/48	0.958	0.848	0.990	4.341	0.000
Der2015	185/223	0.830	0.774	0.873	8.887	0.000
Azim2015	497/610	0.815	0.782	0.844	14.212	0.000
Ukah2017	118/123	0.959	0.906	0.983	6.924	0.000
Jaroudi2017	665/876	0.753	0.730	0.786	14.528	0.000
Rambau2014	47/52	0.904	0.789	0.959	4.763	0.000
Pace2016	122/162	0.753	0.681	0.813	6.120	0.000
Balakouzou2016	123/174	0.707	0.635	0.770	5.286	0.000
Elmoula2014	47/50	0.940	0.830	0.981	4.621	0.000
Kantelhardt2014	946/1208	0.783	0.759	0.805	18.390	0.000
Bambara2017	75/80	0.939	0.858	0.974	5.863	0.000
Mahir2016	83/88	0.943	0.871	0.976	6.101	0.000
Effi2016	250/302	0828	0.781	0.866	10.302	0.000
Guy2018	84/86	0.977	0.912	0.994	5.224	0.000
Pooled statistics 8.228 0.000			**0.840**	**0.780**		**0.887**
Lobular Carcinoma (N :590 /9270)						
Der 2015	**12/223**	**0.054**	**0.031**	**0.092**	**-9.661**	**0.000**
Azim2015	**111/610**	**0.182**	**0.153**	**0.215**	**-14.323**	**0.000**
Ukah2017	**3/123**	**0.024**	**0.008**	**0.073**	**-6.311**	**0.000**
Jaroudi2017	**52/876**	**0.059**	**0.046**	**0.077**	**-19.323**	**0.000**
Rambau2014	**3/52**	**0.019**	**0.019**	**0.164**	**-4.696**	**0.000**
Pace2016	**3/162**	**0.013**	**0.006**	**0.056**	**-6.813**	**0.000**
Belakouzou2016	**23/174**	**0.023**	**0.089**	**0.191**	**-8.407**	**0.000**
Kantelhardt2014	**59/1208**	**0.043**	**0.038**	**0.063**	**-22.242**	**0.000**
Bambara2017	**1/80**	**0.012**	**0.002**	**0.083**	**-4.342**	**0.000**
Mahir2016	**2/88**	**0.037**	**0.006**	**0.086**	**-5.258**	**0.000**
Effi2016	**13/302**	**0.098**	**0.025**	**0.073**	**-10.939**	**0.000**

Guy2018	**1/86**	**0.051**	**0.002**	**0.078**	**-4.417**	**0.000**
Darwish2017	**15/406**	**0.043**	**0.022**	**0.060**	**-12.393**	**0.000**
Gaceb 2017	**86/877**	**0.062**	**0.080**	**0.120**	**-19.543**	**0.000**
Cherbal2015	**154/3014**	**0.106**	**0.044**	**0.060**	**-35.318**	**0.000**
Sengal2017	**29/678**	**0.054**	**0.030**	**0.061**	**-16.376**	**0.000**
Galukande2014	**14/226**	**0.182**	**0.037**	**0.102**	**-9.848**	**0.000**
Kohler2015	**9/85**	**0.106**	**0.056**	**0.191**	**-6.052**	**0.000**
Pooled statistics		**0.056**	**0.041**	**0.076**	**-16.704**	**0.000**
Others (**N :719**/8616**)**						
Hadgu2018	31/114	0.272	0.198	0.361	-4.679	0.000
Darwish2017	51/406	0.126	0.097	0.182	-12.957	0.000
Gaceb2017	79/877	0.090	0.073	0.111	-19.608	0.000
Cherbal2015	55/3014	0.018	0.014	0.024	-29.285	0.000
Sengal 2017	66/678	0.097	0.077	0.122	-17.190	0.000
Galukande2014	12/226	0.053	0.030	0.091	-9.712	0.000
Der2015	26/223	0.117	0.081	0.166	-9.705	0.000
Jaroudi2017	98/876	0.112	0.093	0.135	19.328	0.000
Rambau2014	2/52	0.038	0.010	0.141	-4.464	0.000
Belakouzou2016	9/174	0.052	0.027	0.096	-8.497	0.000
Pace2016	32/162	0.198	0.143	0.266	-7.104	0.000
Elmoula2014	2/50	0.040	0.010	0.146	-4.404	0.000
Kantelhardt2014	208/1208	0.172	0.152	0.195	-20.604	0.000
Effi2016	39/302	0.129	0.096	0.172	-11.123	0.000
Mahir2016	3/88	0.034	0.011	0.100	-5.692	0.000
Bambara2017	5/80	0.063	0.026	0.142	-5.863	0.000
Guy2018	1/86	0.012	0.002	0.078	-4.417	0.000
Pooled statistics		**0.084**	**0.059**			**0.119**
-11.985	**0.00**					

ANNEX 6- CRITICAL APPRAISAL RESULTS

Citation	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Total score**
Jarroudi 2017.	U	Y	U	Y	Y	Y	Y	Y	Y	7
Bahnassy. 2015.	U	U	U	Y	Y	Y	Y	U	U	4
Balekouzou 2016.	U	U	U	Y	Y	Y	Y	Y	Y	6
Bambara. 2017.	Y	Y	U	Y	Y	Y	Y	U	U	6
Cherbal 2015.	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
Darwish 2017.	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
Der 2015.	Y	Y	U	Y	Y	Y	Y	Y	Y	8
Effi 2016.	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
Errahhali 2017.	U	U	U	Y	Y	Y	Y	Y	N	5
Farouk 2016.	U	Y	Y	Y	Y	Y	Y	Y	Y	8
Gaceb 2018.	Y	Y	Y	Y	Y	Y	Y	Y	U	9
Hadgu 2018.	U	Y	U	Y	Y	Y	Y	Y	N	6

Islami 2015.	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
Kohler 2015.	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
Guy 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
Nwafor 2015.	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
Pace 2016.	Y	Y	Y	Y	Y	Y	Y	Y	U	8
Kantelhardt 2017.	Y	Y	Y	Y	Y	Y	Y	Y	U	8
Azim 2015.	Y	U	Y	Y	Y	Y	Y	Y	U	8
Mahir2016	U	U	U	Y	Y	Y	Y	Y	Y	6
Rasmy 2015.	Y	Y	U	Y	Y	Y	Y	Y	Y	8
Chahbouni2017.	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
Ukah 2017.	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
Kantelhardt 2014.	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
Rambau 2014.	Y	Y	U	Y	Y	Y	Y	Y	U	7
Elmoula 2014.	U	U	U	Y	Y	Y	Y	N	Y	5
Sawe 2017.	Y	Y	U	Y	Y	Y	Y	Y	U	7

%	71.42	78.57	57.14	100.0	100.0	100.0	100.0	89.28	64.28	

ANNEX .7-CHARACTERISTICS OF INCLUDED STUDIES

Annex 8-Search Strategy

1. Triple Negative Breast Neoplasms"[Mesh]
2. OR
3. "Unilateral Breast Neoplasms"[Mesh]
4. OR
5. "Inflammatory Breast Neoplasms"[Mesh]
6. Search "Triple Negative Breast Neoplasms"[Mesh] OR "Unilateral Breast Neoplasms"[Mesh] OR "Inflammatory Breast Neoplasms"[Mesh]: **3402**
7. Search Breast cancer [tiab]: **237518**
8. Search Breast neoplasm [tiab]: **608**
9. "Triple Negative Breast Neoplasms"[Mesh]
10. OR
11. "HER2-neu-derived peptide (780-786)" [Supplementary Concept])
12. OR
13. "Receptors, Estrogen"[Mesh])
14. "Ki-67 Antigen"[Mesh])
15. OR
16. "Receptors, Progesterone"[Mesh]
17. Search ((("Triple Negative Breast Neoplasms"[Mesh] OR "HER2-neu-derived peptide (780-786)" [Supplementary Concept]) OR "Receptors, Estrogen"[Mesh]) OR "Ki-67 Antigen"[Mesh]) OR "Receptors, Progesterone"[Mesh]: **67103**
18. Search Prevalence[tiab): 536275

19. Search "Clinical pathology"[tiab]: **3007**

20. "Prevalence"[Mesh]

21. OR

22. "Epidemiology"[Mesh]

23. OR

24. "epidemiology" [Subheading]

25. Search "Prevalence"[Mesh] OR "Epidemiology"[Mesh] OR "epidemiology" [Subheading]: **1996093**

26. "Pathology, Clinical"[Mesh]: **5093**

27. "Africa"[Mesh]

28. OR

29. "Africa South of the Sahara"[Mesh]

30. OR

31. "South Africa"[Mesh]

32. OR

33. "Africa, Western"[Mesh]

34. OR

35. "Africa, Southern"[Mesh]

36. OR

37. "Africa, Northern"[Mesh]

38. OR

39. "Africa, Eastern"[Mesh]

40. OR

41. "Africa, Central"[Mesh]

42. "Namibia"[Mesh]

43. OR

44. "Mozambique"[Mesh]

45. Search "Africa"[Mesh] OR "Africa South of the Sahara"[Mesh] OR "South Africa"[Mesh] OR "Africa, Western"[Mesh] OR "Africa, Southern"[Mesh] OR "Africa, Northern"[Mesh] OR "Africa, Eastern"[Mesh] OR "Africa, Central"[Mesh] OR "Namibia"[Mesh] OR "Mozambique"[Mesh]: **236005**

46. "Triple Negative Breast Neoplasms"[Mesh]

47. OR

48. "Unilateral Breast Neoplasms"[Mesh]

49. OR

50. "Inflammatory Breast Neoplasms"[Mesh]))

51. OR

52. Breast cancer [tiab])

53. OR

54. Breast neoplasm [tiab])

55. OR

56. "Triple Negative Breast Neoplasms"[Mesh]

57. OR

58. "HER2-neu-derived peptide (780-786)" [Supplementary Concept])

59. OR

60. "Receptors, Estrogen"[Mesh])

61. OR

62. "Ki-67 Antigen"[Mesh])

63. OR

64. "Receptors, Progesterone"[Mesh])

65. Search ((((("Triple Negative Breast Neoplasms"[Mesh] OR "Unilateral Breast Neoplasms"[Mesh] OR "Inflammatory Breast Neoplasms"[Mesh])) OR Breast cancer [tiab]) OR Breast neoplasm [tiab]) OR ((((("Triple Negative Breast Neoplasms"[Mesh] OR "HER2-neu-derived peptide (780-786)" [Supplementary Concept]) OR "Receptors, Estrogen"[Mesh]) OR "Ki-67 Antigen"[Mesh]) OR "Receptors, Progesterone"[Mesh]): **282140**
66. Prevalence [tiab
67. OR
68. "Clinical pathology"[tiab])
69. OR
70. "Prevalence"[Mesh]
71. OR
72. "Epidemiology"[Mesh]
73. OR
74. "epidemiology" [Subheading]
75. OR
76. "Pathology, Clinical"[Mesh]
77. Search (((Prevalence[tiab)) OR "Clinical pathology"[tiab]) OR ("Prevalence"[Mesh] OR "Epidemiology"[Mesh] OR "epidemiology" [Subheading])) OR "Pathology, Clinical"[Mesh]: **2249008**
78. "Africa"[Mesh]
79. OR
80. "Africa South of the Sahara"[Mesh]
81. OR
82. "South Africa"[Mesh]

83. OR

84. "Africa, Western"[Mesh]

85. OR

86. "Africa, Southern"[Mesh]

87. OR

88. "Africa, Northern"[Mesh]

89. OR

90. "Africa, Eastern"[Mesh]

91. OR

92. "Africa, Central"[Mesh]

93. OR

94. "Namibia"[Mesh]

95. OR

96. "Mozambique"[Mesh]

97. AND

98. "Triple Negative Breast Neoplasms"[Mesh]

99. OR

100. Unilateral Breast Neoplasms"[Mesh]

101. OR

102. "Inflammatory Breast Neoplasms"[Mesh]

103. OR

104. Breast cancer [tiab]

105. OR

106. Breast neoplasm [tiab])

107. OR

108. "Triple Negative Breast Neoplasms"[Mesh]

109. OR

110. "HER2-neu-derived peptide (780-786)" [Supplementary Concept])

111. OR

112. "Receptors, Estrogen"[Mesh])

113. OR

114. "Ki-67 Antigen"[Mesh]

115. "Receptors, Progesterone"[Mesh]

116. AND

117. Prevalence[tiab

118. OR

119. "Clinical pathology"[tiab]

120. "Prevalence"[Mesh]

121. OR

122. "Epidemiology"[Mesh]

123. OR

124. "epidemiology" [Subheading]))

125. OR

126. "Pathology, Clinical"[Mesh])

127. Search (("Africa"[Mesh] OR "Africa South of the Sahara"[Mesh] OR "South Africa"[Mesh] OR "Africa, Western"[Mesh] OR "Africa, Southern"[Mesh] OR "Africa, Northern"[Mesh] OR "Africa, Eastern"[Mesh] OR "Africa, Central"[Mesh] OR "Namibia"[Mesh] OR "Mozambique"[Mesh])) AND (((("Triple Negative Breast Neoplasms"[Mesh] OR "Unilateral Breast Neoplasms"[Mesh] OR "Inflammatory Breast Neoplasms"[Mesh])) OR Breast cancer [tiab]) OR Breast neoplasm [tiab]) OR

((((("Triple Negative Breast Neoplasms"[Mesh] OR "HER2-neu-derived peptide (780-786)" [Supplementary Concept]) OR "Receptors, Estrogen"[Mesh]) OR "Ki-67 Antigen"[Mesh]) OR "Receptors, Progesterone"[Mesh]))) AND ((((Prevalence[tiab)) OR "Clinical pathology"[tiab]) OR ("Prevalence"[Mesh] OR "Epidemiology"[Mesh] OR "epidemiology" [Subheading])) OR "Pathology, Clinical"[Mesh]): **5723**

128. "Africa"[Mesh]
129. OR
130. "Africa South of the Sahara"[Mesh]
131. OR
132. "South Africa"[Mesh]
133. OR
134. "Africa, Western"[Mesh]
135. OR
136. "Africa, Southern"[Mesh]
137. OR
138. "Africa, Northern"[Mesh]
139. OR
140. "Africa, Eastern"[Mesh]
141. OR
142. "Africa, Central"[Mesh]
143. OR
144. "Namibia"[Mesh]
145. OR
146. "Mozambique"[Mesh]
147. AND

148. "Triple Negative Breast Neoplasms"[Mesh]

149. OR

150. "Unilateral Breast Neoplasms"[Mesh]

151. OR

152. "Inflammatory Breast Neoplasms"[Mesh]

153. OR

154. Breast cancer [tiab])

155. OR

156. Breast neoplasm [tiab]

157. OR

158. "Triple Negative Breast Neoplasms"[Mesh]

159. OR

160. "HER2-neu-derived peptide (780-786)" [Supplementary Concept])

161. OR

162. "Receptors, Estrogen"[Mesh])

163. OR

164. "Ki-67 Antigen"[Mesh]

165. OR

166. "Receptors, Progesterone"[Mesh]

167. Prevalence[tiab

168. OR

169. "Clinical pathology"[tiab]

170. OR

171. "Prevalence"[Mesh]

172. OR

173. "Epidemiology"[Mesh]

174. OR

175. "epidemiology" [Subheading]

176. OR

177. "Pathology, Clinical"[Mesh]

178. Search ((("Africa"[Mesh] OR "Africa South of the Sahara"[Mesh] OR "South Africa"[Mesh] OR "Africa, Western"[Mesh] OR "Africa, Southern"[Mesh] OR "Africa, Northern"[Mesh] OR "Africa, Eastern"[Mesh] OR "Africa, Central"[Mesh] OR "Namibia"[Mesh] OR "Mozambique"[Mesh])) AND (((((("Triple Negative Breast Neoplasms"[Mesh] OR "Unilateral Breast Neoplasms"[Mesh] OR "Inflammatory Breast Neoplasms"[Mesh])) OR Breast cancer [tiab]) OR Breast neoplasm [tiab]) OR ((((("Triple Negative Breast Neoplasms"[Mesh] OR "HER2-neu-derived peptide (780-786)" [Supplementary Concept]) OR "Receptors, Estrogen"[Mesh]) OR "Ki-67 Antigen"[Mesh]) OR "Receptors, Progesterone"[Mesh]))) AND ((((Prevalence[tiab)) OR "Clinical pathology"[tiab]) OR ("Prevalence"[Mesh] OR "Epidemiology"[Mesh] OR "epidemiology" [Subheading])) OR "Pathology, Clinical"[Mesh]) **Filters: Humans**: **4835**

179. Search ((("Africa"[Mesh] OR "Africa South of the Sahara"[Mesh] OR "South Africa"[Mesh] OR "Africa, Western"[Mesh] OR "Africa, Southern"[Mesh] OR "Africa, Northern"[Mesh] OR "Africa, Eastern"[Mesh] OR "Africa, Central"[Mesh] OR "Namibia"[Mesh] OR "Mozambique"[Mesh])) AND (((((("Triple Negative Breast Neoplasms"[Mesh] OR "Unilateral Breast Neoplasms"[Mesh] OR "Inflammatory Breast Neoplasms"[Mesh])) OR Breast cancer [tiab]) OR Breast neoplasm [tiab]) OR ((((("Triple Negative Breast Neoplasms"[Mesh] OR "HER2-neu-derived peptide (780-786)" [Supplementary Concept]) OR "Receptors, Estrogen"[Mesh]) OR "Ki-67

Antigen"[Mesh]) OR "Receptors, Progesterone"[Mesh]))) AND ((((Prevalence[tiab)) OR "Clinical pathology"[tiab]) OR ("Prevalence"[Mesh] OR "Epidemiology"[Mesh] OR "epidemiology" [Subheading])) OR "Pathology, Clinical"[Mesh]) **Filters: Humans; English: 3941**

180. ((("Africa"[Mesh] OR "Africa South of the Sahara"[Mesh] OR "South Africa"[Mesh] OR "Africa, Western"[Mesh] OR "Africa, Southern"[Mesh] OR "Africa, Northern"[Mesh] OR "Africa, Eastern"[Mesh] OR "Africa, Central"[Mesh] OR "Namibia"[Mesh] OR "Mozambique"[Mesh])) AND (((((("Triple Negative Breast Neoplasms"[Mesh] OR "Unilateral Breast Neoplasms"[Mesh] OR "Inflammatory Breast Neoplasms"[Mesh])) OR Breast cancer [tiab]) OR Breast neoplasm [tiab]) OR ((((("Triple Negative Breast Neoplasms"[Mesh] OR "HER2-neu-derived peptide (780-786)" [Supplementary Concept]) OR "Receptors, Estrogen"[Mesh]) OR "Ki-67 Antigen"[Mesh]) OR "Receptors, Progesterone"[Mesh]))) AND ((((Prevalence[tiab)) OR "Clinical pathology"[tiab]) OR ("Prevalence"[Mesh] OR "Epidemiology"[Mesh] OR "epidemiology" [Subheading])) OR "Pathology, Clinical"[Mesh]) **Filters: Publication date from 2014/04/16 to 2018/07/31; Humans; English: 759**

ANNEX.9-Figures Publication Bias Funnel Plot of standard error

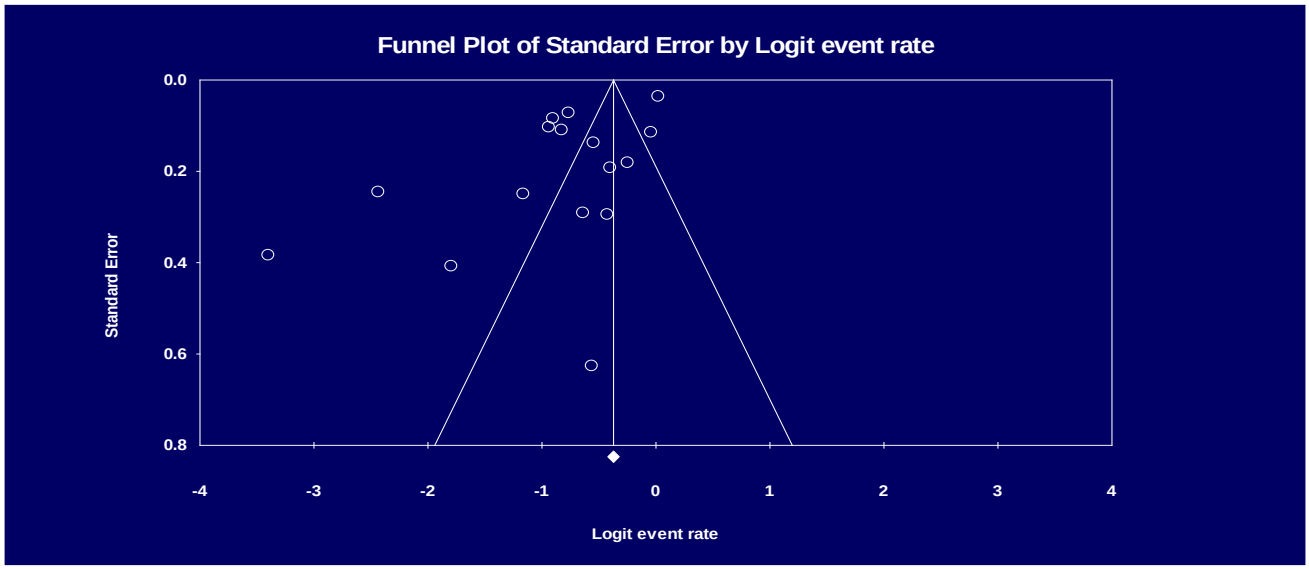

Figure 17: Funnel Plot of standard error by Logit event rate for Luminal A

ANNEX.10-Figures Publication Bias Funnel Plot of precision by Logit event rate

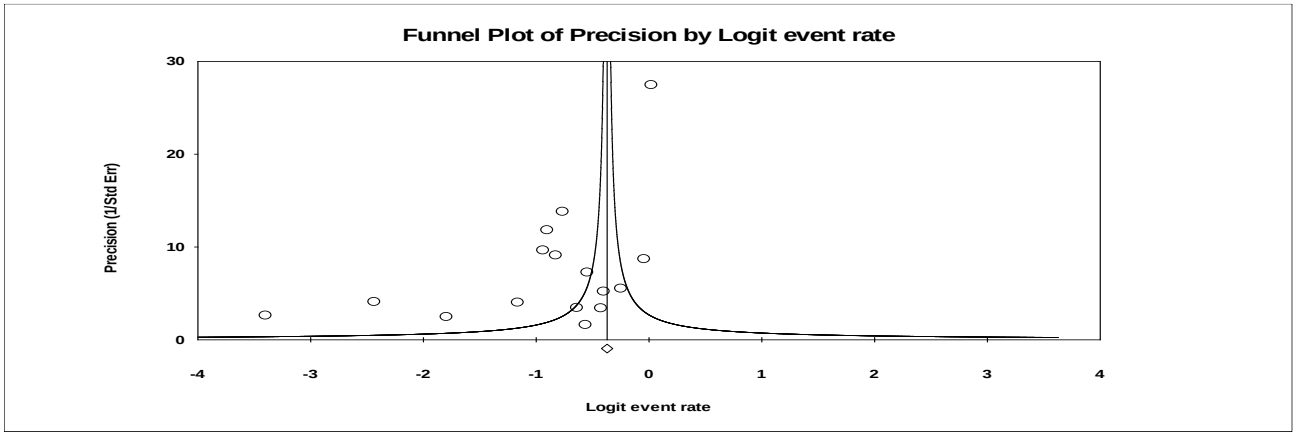

Figure 18: Funnel Plot of precision by Logit event rate for Luminal A