



# Receptor-Defined Subtypes of Breast Cancer in Indigenous Populations in Africa: A Systematic Review and Meta-Analysis

Amanda Eng<sup>1,2</sup>, Valerie McCormack<sup>3</sup>, Isabel dos-Santos-Silva<sup>1\*</sup>

**1** Department of Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, United Kingdom, **2** Centre for Public Health Research, Massey University, Wellington, New Zealand, **3** Section of Environment and Radiation, International Agency for Research on Cancer, Lyon, France

## Abstract

**Background:** Breast cancer is the most common female cancer in Africa. Receptor-defined subtypes are a major determinant of treatment options and disease outcomes but there is considerable uncertainty regarding the frequency of poor prognosis estrogen receptor (ER) negative subtypes in Africa. We systematically reviewed publications reporting on the frequency of breast cancer receptor-defined subtypes in indigenous populations in Africa.

**Methods and Findings:** Medline, Embase, and Global Health were searched for studies published between 1st January 1980 and 15th April 2014. Reported proportions of ER positive (ER+), progesterone receptor positive (PR+), and human epidermal growth factor receptor-2 positive (HER2+) disease were extracted and 95% CI calculated. Random effects meta-analyses were used to pool estimates. Fifty-four studies from North Africa ( $n = 12,284$  women with breast cancer) and 26 from sub-Saharan Africa ( $n = 4,737$ ) were eligible. There was marked between-study heterogeneity in the ER+ estimates in both regions ( $I^2 > 90\%$ ), with the majority reporting proportions between 0.40 and 0.80 in North Africa and between 0.20 and 0.70 in sub-Saharan Africa. Similarly, large between-study heterogeneity was observed for PR+ and HER2+ estimates ( $I^2 > 80\%$ , in all instances). Meta-regression analyses showed that the proportion of ER+ disease was 10% (4%–17%) lower for studies based on archived tumor blocks rather than prospectively collected specimens, and 9% (2%–17%) lower for those with  $\geq 40\%$  versus those with  $< 40\%$  grade 3 tumors. For prospectively collected samples, the pooled proportions for ER+ and triple negative tumors were 0.59 (0.56–0.62) and 0.21 (0.17–0.25), respectively, regardless of region. Limitations of the study include the lack of standardized procedures across the various studies; the low methodological quality of many studies in terms of the representativeness of their case series and the quality of the procedures for collection, fixation, and receptor testing; and the possibility that women with breast cancer may have contributed to more than one study.

**Conclusions:** The published data from the more appropriate prospectively measured specimens are consistent with the majority of breast cancers in Africa being ER+. As no single subtype dominates in the continent availability of receptor testing should be a priority, especially for young women with early stage disease where appropriate receptor-specific treatment modalities offer the greatest potential for reducing years of life lost.

Please see later in the article for the Editors' Summary.

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**Abbreviations:** CISH, chromogenic in situ hybridization; ER, estrogen receptor; FISH, fluorescent in situ hybridization; FFPE, formalin-fixed paraffin-embedded; HER2, human epidermal growth factor-2; HR, hormone receptor; IHC, immunohistochemistry; PR, progesterone receptor; prop, proportion of receptor-positive tumors; SISH, silver in situ hybridization.

\* Email: isabel.silva@lshtm.ac.uk

## Introduction

Breast cancer is the most common female malignancy in Africa, being the cancer with the first or second highest incidence and/or mortality in most African countries (Figure 1). Although breast cancer incidence rates are lower in Africa than in the rest of the world, mortality rates in certain African countries (e.g., Nigeria, Egypt, Ethiopia) are among the highest worldwide [1], reflecting the relatively poor survival from the disease in the continent. Different breast cancer subtypes are classified in the clinical setting by estrogen (ER), progesterone (PR), and human epidermal growth factor-2 (HER2) receptor status. These receptors are a fundamental characteristic of the epidemiology of this malignancy [2], as its aetiology and incidence trends are receptor-status specific, and they are also a major determinant of treatment options, disease outcomes, and survival [3].

ER-positive (ER+) tumors typically have a better prognosis and are more receptive to hormonal treatment [4]. In white (i.e., European ancestry) women, ER+ tumors predominate, with 79% of breast tumors in US-born white women being ER+ (calculated amongst women with known ER-status) [5]. The proportion of ER+ tumors is lower among US-born black (i.e., of African ancestry) women (61% are ER+, all ages combined) [5,6], but the extent to which this is also reflected in Africa is not well-established. Some studies [7,8] have reported a markedly higher proportion of ER-negative (ER-) or basal-like breast cancers in indigenous populations in Africa, which may contribute to the poor survival from this malignancy, but others suggest that the relative frequency of the different subtypes in the continent may not differ substantially to that seen elsewhere [9,10].

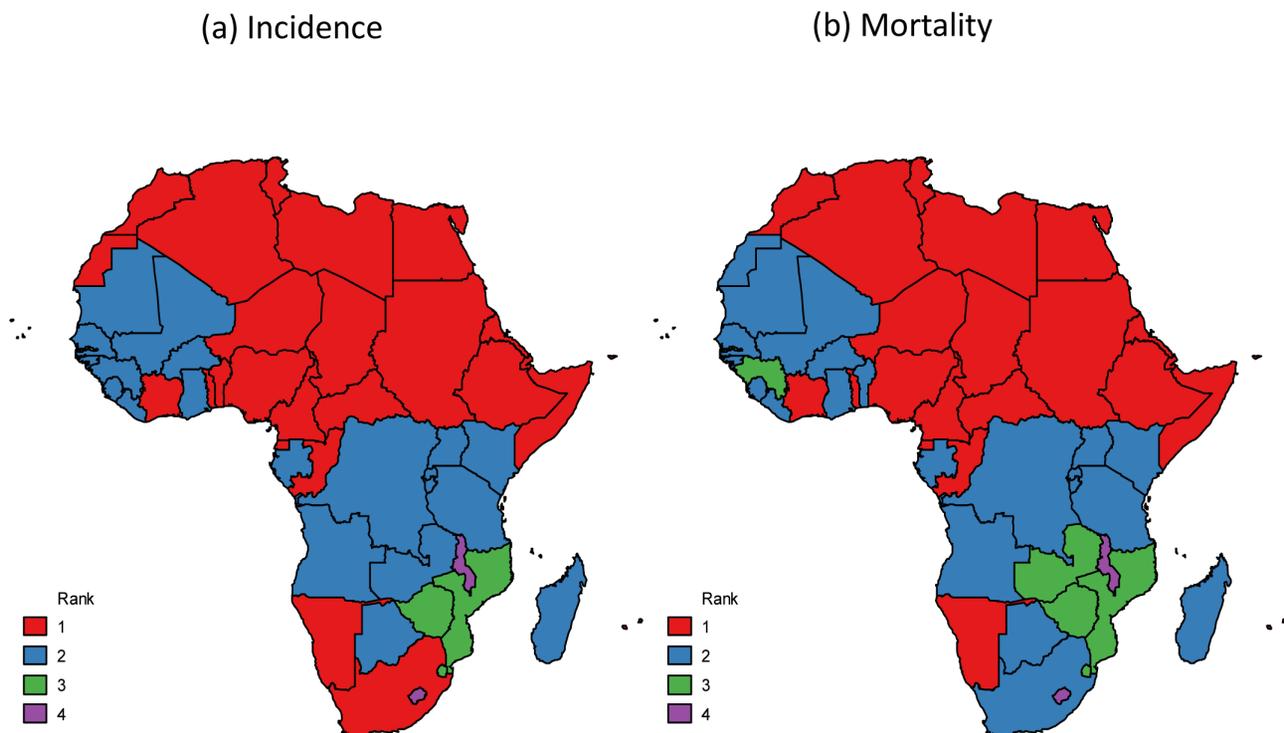
Knowledge of the relative frequency of breast cancer subtypes in Africa would be of relevance for several reasons. Firstly, if the distribution of receptor status is greatly different in Africa than elsewhere, the differing contribution of genetic and environmental risk factors to such a difference would need to be investigated, as is debated for ethnic differences in the US [11]. Secondly, where tumor receptor status is not routinely ascertained, the need for introducing it would be more urgent if one subtype does not greatly dominate and all subtypes are present. The latter scenario would call for the introduction of receptor testing to be prioritised, especially for patients who would have the prospect of good survival if given the appropriate treatment. Knowledge of the distribution of tumor receptor subtypes in Africa would also be of relevance globally as the continent would provide a better setting to study any subtypes that are rare elsewhere, but may be common there.

In the absence of large standardized multi-country studies of breast cancer subtypes in Africa, a rigorous systematic review of previously published studies will provide the timeliest answer to the debate on the receptor status distribution in Africa. Herein, we systematically review all studies that have reported receptor status of breast cancer in indigenous African populations and assess sources of between-study heterogeneity in prevalence estimates based on more than 17,000 women with breast cancer.

## Methods

### Search Methodology

The PRISMA guidelines (Text S1) were used to develop the study protocol (Text S2). We conducted a search of Medline,



**Figure 1. Breast cancer ranking among women for (a) incidence and (b) mortality, Africa, 2012 [1].**  
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**Table 1.** Characteristics of the participating studies: North Africa (54 studies).

First Author, Year [Ref]	Country	Study Design	Sample Size	Method For ER And/Or PR	Criteria For ER/PR Positivity	HER2-Testing: Y/N	Method(S) For HER2	Criteria For HER2-Positivity	ER Quality Score	PR Quality Score	HER2Quality Score
Ismaili 2014-IBC [68]	Morocco	Consecutive case series	64	NK	NK	Y	NK	NK	15	15	13
Tazzite 2013 [44]	Morocco	Convenient case series	570	NK (ER and PR extracted from MR)	NK	N	n/a	n/a	12	12	17
Bennis 2012 [34]	Morocco	Convenient case series	366	IHC (ER: Immunotech, clone 1D5; PR: Immunotech, clone 10A9)	≥10% nuclei staining	Y	IHC (Dako, clone A0485)	Score 3+, score 2+ and FISH+	17	17	17
Bouffal et al, 2010 [26]	Morocco	Convenient case series	451	NK (ER and PR extracted from MR)	NK	N <sup>a</sup>	n/a	n/a	13	13	13
Bouzid 2013 [64]	Tunisia	Consecutive case series	99	NK; HR <sup>b</sup> reported	NK	N	n/a	n/a	15	15	15
Ben Gacem 2012 [21]	Tunisia	Convenient case series	94	IHC (ER and PR, NOS)	≥10% nuclei staining	Y	IHC (NOS)	Score ≥2+	18	18	17
Karray-Chouayekh 2011 [32]	Tunisia	Convenient case series	80	IHC: ER (Dako, clone 1D5, 1:25); PR (Dako, clone Pgr636, 1:50)	>5% nuclei staining	Y	IHC (Dako, clone 124, 1:100)	Score 3+ (intense and complete membrane staining in >30% cells)	13	13	12
Hamrita 2011 [23]	Tunisia	Convenient case series	287	NK (ER and PR extracted from MR)	NK	N	n/a	n/a	12	12	12
Karray-Chouayekh 2010 [41]	Tunisia	Convenient case series	78	IHC (ER: Dako, clone 1D5, 1:25; PR: Dako, clone Pgr636, 1:50)	>5% nuclei staining	Y	IHC (Dako, clone 124, 1:100)	Score 3+ (intense and complete membrane staining in >30% cells)	17	17	16
Louesiati 2010 [46]	Tunisia	Convenient case series	70	IHC (ER and PR, NOS)	NK	N	n/a	n/a	11	11	11
Marrakchi 2010 [27]	Tunisia	Convenient case series	127	NK (ER and PR)	NK	N	NK	NK	15	15	15
Abdelkrim 2010 [47]	Tunisia	Convenient case series	194	IHC (ER and PR, NOS)	≥10% nuclei staining	Y	IHC (NOS)	Score 3+ (intense and complete membrane staining in >10% cells)	19	19	18
Snoussi 2010 [22]	Tunisia	Consecutive case series	297	NK (ER extracted from MR)	NK	N	n/a	n/a	14	14	14
Kallel 2010 [53]	Tunisia	Convenient case series	133	IHC (ER: Dako, clone 1D5; PR: Dako, clone Pgr636)	>5% nuclei staining	Y	IHC (ACRIS, clone BM5084)	>5% cell staining	18	18	15
Hachana 2008 [24]	Tunisia	Convenient case series	122	IHC (ER: Dako, clone 1D5, 1:40; PR: Dako, clone Pgr636, 1:40)	≥10% nuclei staining	Y	IHC (Dako, polyclonal, 1:1000)	Score ≥2+	16	16	15

Table 1. Cont.

First Author, Year [Ref]	Country	Study Design	Sample Size	Method For ER And/Or PR	Criteria For ER/PR Positivity	HER2-Testing: Y/N	Method(S) For HER2	Criteria For HER2+Positivity	ER Quality Score	PR Quality Score	HER2Quality Score
Ben Hamida 2008 [28]	Tunisia/ France (methods reported for Tunisia only)	Convenient case series	78	IHC (ER: Novocastra, clone 6F 11.2, 1:60; PR: Dako, clone PFR636, 1:80)	≥1% nuclei staining	Y	IHC (Dako, clone AO485, 1:500)	Score ≥2+	19	19	18
Ayadi 2008 [39]	Tunisia	Convenient case series	155	IHC (ER: Dako, clone 1D5, 1:25; PR: Dako, clone Pgr636, 1:50)	Allred scoring method, NOS	Y	IHC (Dako, clone 124, 1:100)	Score 3+ (intense and complete membrane staining in >30% cells)	16	16	15
Marrakchi 2008 [35]	Tunisia	Convenient case series	80	NK (ER and PR)	NK	N	n/a	n/a	15	15	
Maleej 2008 [37]	Tunisia	Population-based	938	NK (ER and PR extracted from MR)	NK	N	n/a	n/a	13	13	
Le 2005 [30]	Tunisia/ France. (methods reported for Tunisia only)	Consecutive case series	172	NK (ER and PR)	NK	N	n/a	n/a	16	16	
Baccouche 2003 [36]	Tunisia	Convenient case series	50	IHC (ER: Dako, clone 1D5)	>20% nuclei staining	N	n/a	n/a	15		
McCarthy 2002 [19]	Tunisia	Convenient case series	66	IHC (ER: BioGenex, clone 6F 11)	>10% nuclei staining	Y	IHC (Zymed, a mix of mouse TAB250 and PAD24881 rabbit serum)	Score 3+ (intense staining in >10% cells)	16		15
Boder 2013 [63]	Libya	Convenient case series	130	NK; HR <sup>b</sup> reported	NK	N	n/a	n/a	15	15	
Ermiah 2013 [57]	Libya	Convenient case series	170	IHC (ER and PR extracted from MR)	Allred scoring method, NOS	N	n/a	n/a	19	19	
Moona 2010 [42]	Libya	Convenient case series	78	ICH (ER and PR extracted from MR)	NK	Y	ICH and FISH	NK	11	11	11
Alieidin 2014 [62]	Egypt	Consecutive case series	617	IHC or enzyme immunoassay (ER and PR extracted from MR)	NK	N	n/a	n/a	15	15	
Hirko 2013 [72,73]	Egypt	Population-based	3,060	IHC (monoclonal antibodies for ER and PR)	>1% nuclei staining	N	n/a	n/a	18	18	
Elesawy 2014 [65]	Egypt	Convenient case series	125	IHC (ER: Dako, clone 1D5, 1:50; PR: Dako, clone Pgr636, 1:50)	≥1% nuclei staining	Y	IHC (CB11, Novocastra, 1:50)	Score 3+, score 2+ and FISH+	16	16	16
Hagras 2014 [67]	Egypt	Consecutive case series	120	IHC (ER: mouse monoclonal IgG, PR: rabbit polyclonal IgG, Santa Cruz)	NK	Y	IHC (Mouse monoclonal IgG, Santa Cruz)	NK	20	20	20
Rashad 2014 [69]	Egypt	Convenient case series	80	IHC (ER and PR: monoclonal)	>10% nuclei staining	Y	IHC (mAb CB11)	Score 3+, score 2+ and FISH+	19	19	19

Table 1. Cont.

First Author, Year [Ref]	Country	Study Design	Sample Size	Method For ER And/Or PR	Criteria For ER/PR Positivity	HER2-Testing: Y/N	Method(S) For HER2	Criteria For HER2+Positivity	ER Quality Score	PR Quality Score	HER2Quality Score
El-Shinawi 2013 [66]	Egypt	Convenient case series	77	IHC (ER and PR, NOS)	>10% nuclei staining	Y	IHC (NOS)	>10% membrane staining of tumor cells	16	16	15
Hussein 2013 [52]	Egypt	Convenient case series	263	IHC (ER: Lab Vision, clone SP1; PR: Lab Vision, clone Ab-2) <sup>a</sup>	>1% nuclei staining	Y	IHC (Lab Vision Ab-17, clone e2-4001+3B5)	>30% cells staining	17	17	16
Salama 2013 [71]	Egypt	Consecutive case series	99	IHC (primary ER and PR antibodies, Labvision, thermoscientific); HR <sup>b</sup> reported	>1% nuclei staining	Y	IHC (Dako)	Score 3+	18	18	17
El-Hawary 2012 [33]	Egypt	Convenient case series	274	IHC (ER: Cell Marque, clone SP1; PR: Dako, clone Pgr636) <sup>c</sup>	Allred scoring method, NOS	Y	IHC (Cell Marque, clone CB-11)	Guidelines of the American Society of Clinical Oncology, NOS	14	14	13
Salhia 2011 [49]	Egypt	Convenient case series	203	IHC (ER: Dako K1904; PR: Dako K1904)	≥1% nuclei staining	Y	IHC (Dako, clone A0485, 1:100)	Scores ≥2+ (weak or intense complete staining of the membrane in >10% of cells)	16	16	15
Abbas 2011 [29]	Egypt	Convenient case series	129	NK (HR <sup>b</sup> extracted from MR)	NK	N	n/a	n/a	12	12	
Hussein 2011 [31]	Egypt	Convenient case series	96	NK (ER extracted from MR)	NK	N	n/a	n/a	13		
El Mongy 2010 [50]	Egypt	Consecutive case series	934	NK (ER and PR extracted from MR)	NK	N	n/a	n/a	16	16	
Hafez 2010 [59]	Egypt	Convenient case series	90	IHC <sup>d</sup> (ER and PR, NOS)	NK	N	n/a	n/a	12	12	
El-Rehim 2009 [38]	Egypt	Convenient case series	65	IHC (ER: Dako, clone 1D5, 1:80; PR: Dako, clone 636, 1:100)	Histocore based on intensity (1+ to 3+) and % of cells stained positive (0%–100%). Positive if expression rates >10%	N	n/a	n/a	17	17	
Zeeineldin 2009 [43]	Egypt	Consecutive case series	57	IHC (HR <sup>b</sup> , NOS)	>5% nuclei staining	Y	IHC (HerceptTest)	Unclear if positive for scores ≥2+, or only for scores 3+	23	23	21
Ali-Labbib 2009 [25]	Egypt	Convenient case series	50	NK (ER extracted from MR)	NK	N	n/a	n/a	16		
Marzouk 2009 [54]	Egypt	Consecutive case series	174	IHC (ER and PR, NOS)	NK	N	n/a	n/a	16	16	
Youssef 2008 [56]	Egypt	Convenient case series	65	NK (ER and PR extracted from MR)	NK	Y	NK (extracted from MR)	NK	17	17	15

Table 1. Cont.

First Author, Year [Ref]	Country	Study Design	Sample Size	Method For ER And/OR PR	Criteria For ER/PR Positivity	HER2-Testing: Y/N	Method(S) For HER2	Criteria For HER2-Positivity	ER Quality Score	PR Quality Score	HER2Quality Score
Rashed 2007 [45]	Egypt	Convenient case series	50	IHC (ER: Ventana, clone 6F11, 1:40; PR: Ventana, 1:16, 1:30)	>10% nuclei staining	Y	IHC (Ventana, clone DA485, 1:1500)	Score 3+ (intense and complete membrane staining in >10% cells)	16	16	15
Mohammad 2006 [40]	Egypt	Convenient case series	64	IHC (ER: Dako, clone 1D5; PR: Dako, clone 1A6)	>5% nuclei staining	Y	IHC (Dako, HerceptTest)	Score $\geq 2+$	15	15	14
Swellam 2004 [60]	Egypt	Convenient case series	51	Abbott enzyme immunoassay (ER and PR)	>1.5 fmol/mg protein	N	n/a	n/a	19	19	
Asaad 2003 [58]	Egypt	Convenient case series	44	NK (ER and PR extracted from IMR)	NK	N	n/a	n/a	13	13	
Abdel-Fattah 2001 [61]	Egypt	Consecutive case series	19	NK (ER and PR extracted from IMR)	NK	N	n/a	n/a	11	11	
Abu-Bedair 2000 [51]	Egypt	Convenient case series	71	Radioreceptor assay (ER: <sup>125</sup> I-radioreceptor assay kit, DSL)	Cytosols with saturable binding $\geq 10$ fmol <sup>125</sup> I-17beta-estradiol per mg protein	N	n/a	n/a	16		
Bekkouche 2013 [70]	Algeria	Consecutive case series	120	IHC (ER: 1D5, Dako code 1:575; PR: PgR636, Dako code 1630)	NK	Y	IHC (Polyclonal anti-human C-erbB2 Dako A0485)	Score 3+	17	17	17
Chaher 2012 [55]	Algeria	Convenient case series	176	IHC (ER: Thermo Scientific, clone RB-9016, 1:100; PR: Dako, clone PgR 636, 1:100)	>10% nuclear staining	Y	IHC (Ventana, clone 4B5)	Score 3+, scores 1+ or 2+, and CISH+	19	19	19
Elgaili 2010 [20]	Sudan	Population-based	48	IHC (ER: Novocastra, clone IDS, 1:25; PR: Novocastra, clone IA6, 1:40)	% of epithelial cells with positive staining scored as 0 = no, 1 = weak, 2 = moderate, and 3 = strong staining. Unclear if scores >0 were taken as positive.	N	n/a	n/a	16	16	
Awadelkarim 2008 [48]	Sudan/Italy. (Methods presented for Sudan only)	Consecutive case series	114	IHC (ER: Dako, clone 1D5, 1:100; PR: clone PgR 636, 1:100)	>5% nuclei staining	Y	IHC (Dako, polyclonal antiserum, 1:350)	Score 3+, score 2+ and FISH+	19	19	19

<sup>a</sup>HER2 testing was performed but not included in the review because it was not possible to estimate the standard error as the sample size was NK.

<sup>b</sup>Only HR+ (ER+ and/or PR+) estimates are provided.

<sup>c</sup>Only HR+ (defined as subtypes Luminal A + Luminal B) estimates are provided.

<sup>d</sup>Only the results from IHC (versus ICH) were included in the review.

AJCC, American Joint Committee on Cancer; BC, breast cancer; IBC, inflammatory breast cancer; IDC, invasive ductal carcinoma; ICH, immunocytochemistry; IgG, immunoglobulin G; MR, medical records; n/a, not applicable; NK, not given in the paper; NOS, not otherwise specified. doi:10.1371/journal.pmed.1001720.t001

**Table 2.** Characteristics of the participating studies: Sub-Saharan Africa (26 studies).

First Author, Year [Ref]	Country	Study Design	Sample Size	Method For ER And/Or PR	Criteria For ER/PR Positivity	HER2Testing: Y/N	Method(S) For HER2	Criteria For HER2+ Positivity	ER Quality Score	PR Quality Score	HER2Quality Score
Ly 2012 [84]	Mali	Consecutive case series	113	IHC (ER: Novocastra, clone 6F11 (NCL-ER 6F11), 1:50; PR: Novocastra, clone 16 (NCL-PRG312), 1:50)	>10% nuclei staining Y	Y	IHC (Dako A0485 polyclonal, 1:1000)	Score 3+ (>30% cells staining); score 2+ and FISH+	19	19	19
Togo 2010 [94]	Mali	Consecutive case series	160	NK (ER and PR extracted from MR)	NK	N	n/a	n/a	14	14	14
Ugiagbe 2012 [74]	Nigeria	Convenient case series	135	IHC (ER and PR: Dako, NOS)	>10% nuclei staining N	N	n/a	n/a	16	16	16
Agboola 2012 [76]	Nigeria/UK (Methods presented for Nigeria only)	Convenient case series	274	IHC (ER: Dako, clone 1D5, 1:200; PR: Dako, clone Pgr, 1:150)	≥1% cells stained	Y	IHC (Dako, polyclonal, 1:100)	Score 3+; score 2+ and CISH+	15	15	15
Huo 2009 [8]	Nigeria and Senegal (series 1 only) <sup>a</sup>	Consecutive case series	378	IHC (ER: NeoMarkers, SP1 clone, 1:50; PR: NeoMarkers, SP2 clone, 1:50)	Unclear (semi-quantitative score using Reiner's 4-point scale based on intensity and % of IHC reaction)	Y	IHC (Dako, HerceptTest)	"According to manufacturer's instructions (DAKO)" (sic)	18	18	16
Adebamowo 2008 [10]	Nigeria	Consecutive case series	177	IHC (ER: Zymed, clone 1D5; PR: Zymed, clone 2C5)	>10% nuclei staining Y	Y	IHC (Zymed, clone Z4881)	Score 3+ (intense and complete membrane staining in >10% of cells)	19	19	18
Iyare 2007 [75]	Nigeria	Convenient case series	102	IHC (ER and PR, NOS)	NK	Y	IHC (NOS)	NK	13	13	13
Gukas 2005 [79]	Nigeria	Consecutive case series	36	IHC (ER: Novocastra, clone ER6F11, 1:15; PR: Dako, PGR636, 1:50)	≥10% nuclei staining Y	Y	IHC (Dako, clone Polyclonal, 1:1000)	≥5% cells staining	19	19	18
Ikpatt 2003 [77]	Nigeria	Convenient case series	129	IHC (ER: Novocastra, clone CC4-5 (NCL-ER-LH2), 1:80; PR: Novocastra, clone 1A6 (NCL-PGR), 1:20)	Total score: staining intensity score (0-3)+ percentage of positive cell score (0-4). Positive: total score ≥2	N	n/a	n/a	19	19	19

Table 2. Cont.

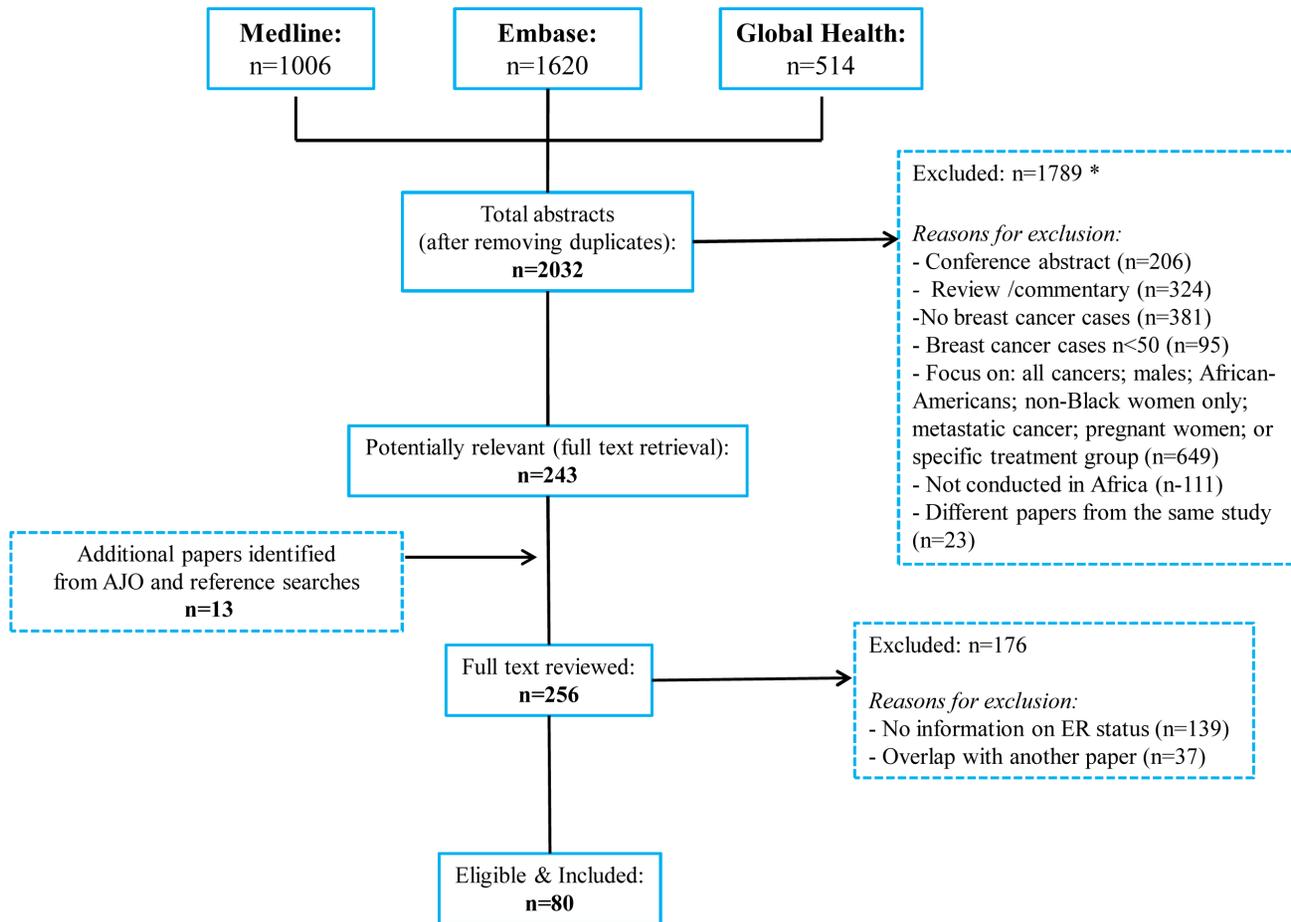
First Author, Year [Ref]	Country	Study Design	Sample Size	Method For ER And/Or PR	Criteria For ER/PR Positivity	HER2 Testing: Y/N	Method(S) For HER2	Criteria For HER2+ Positivity	ER Quality Score	PR Quality Score	HER2 Quality Score
Ohene-Yeboah 2012 [87]	Ghana	Consecutive case series	68	IHC (ER and PR: commercially available kits, NOS)	≥10% nuclei staining Y	Y	IHC (commercially available kits, NOS)	Score 3+; Score 2+ and SISH+	17	17	17
Schwartz 2013 [80]	Ghana	Convenient case series	103	IHC (ER: Dako, clone ID5, 1:50; PR: Dako, clone Pgr636, 1:50)	≥2% nuclei staining	Y	IHC (Dako, 1:100)	Score 3+ (no samples scored 2+)	16	16	15
Stark 2010 [78]	Ghana/US (Methods reported for Ghana only)	Convenient case series	75	IHC (ER: Dako, clone ID5; PR: Dako, clone Pgr636)	% of nuclei staining assessed semi-quantitatively as positive (including focal positive) or negative.	Y	IHC (Dako, HercepTest)	Score 3+ (strong complete membrane staining in >10% cells); score 1+ or 2+ and FISH+	14	12	14
Yarney 2008 [85]	Ghana	Convenient case series	74	IHC (ER and PR, NOS)	Quick score ≥3	Y	IHC (NOS)	Score 3+	13	13	12
Galukande 2013 [86]	Uganda	Consecutive case series	113	IHC (ER <sup>b</sup> : Cell Marque, clone SP-1)	≥5% nuclei staining	N <sup>b</sup>	n/a	n/a	21		
Nalwoga 2010 [83]	Uganda	Population-based series	183	IHC (ER: Dako, clone ID5, dilution 1:50; PR: Dako, clone Pgr 636, dilution 1:150)	≥10% nuclei staining	Y	IHC (Dako, clone Polyclonal, 1:500)	Scores 2+ and 3+ (>10% cells stained)	18	18	17
Bird 2008 [7]	Kenya	Consecutive case series	120	IHC (ER: Dako, clone ID5, 1:50; PR: Dako, clone MO A-HU, 1:30)	IHC score ≥1	Y	IHC (Dako, clone AO48529, 1:200)	Scores 2+ and 3+	19		16
Nyagol 2006 [82]	Kenya	Consecutive case series	158	IHC (ER: Dako, clone ID5, 1:50; PR: Dako, clone MO A-HU, 1:30)	>10% nuclei staining	Y	IHC (Dako, clone AO48529, 1:200)	Score 3+; (complete membrane staining in >10% cells); score 2+ and FISH+	18	18	18
Burson 2010 [88]	Tanzania	Convenient case series	65	IHC (ER: Dako, clone ID5, 1:100; PR: Dako, clone 636, 1:200)	Total Allred score: staining intensity score (0-3)+ percentage of positive cell score(0-5). Positive: total score > 2	N	n/a	n/a	14	14	

Table 2. Cont.

First Author, Year [Ref]	Country	Study Design	Sample Size	Method For ER And/Or PR	Criteria For ER/PR Positivity	HER2 Testing: Y/N	Method(S) For HER2	Criteria For HER2+ Positivity	ER Quality Score	PR Quality Score	HER2 Quality Score
Mbonde 2001 [81]	Tanzania	Convenient case series	60	IHC (ER and PR; Dako, NOS)	Total score: staining intensity score (0–3)+ percentage of positive cell score (0–3). Positive: total score $\geq 3$	N	n/a	n/a	15	15	15
van Bogaert 2013 [92]	South Africa	Population-based	769	IHC (ER and PR, NOS)	NK	Y	IHC (NOS)	NK	12	12	12
McCormack 2013 [9]	South Africa. (Methods reported for black women only)	Consecutive case series	957	IHC (ER and PR; Ventana, NOS)	>1% nuclei staining	Y	IHC (Ventana, NOS)	Score 3+	25	25	24
Basro 2010 [93]	South Africa	Consecutive case series	118	IHC (ER and PR, NOS)	NK	Y	IHC (NOS)	NK	17	15	13
Winters 1988 [90]	South Africa	Consecutive case series	65	Radioligand binding assay (ER)	Oestradiol binding value >3 fmol/mg of cytosol protein.	N	n/a	n/a	17		
Savage 1981 [89]	South Africa. (Methods reported for black women only)	Convenient case series	170	Radioligand binding assay (ER: DCC method)	Positive if results showed a Scatchard plot, a $K_d < 5 \times 10^{10}$ M and an oestradiol-binding value >3 fmol/mg protein	N	n/a	n/a	15		
Collings 1980 [91]	South Africa. (Methods reported for black women only)	Convenient case series	60	ERc assay (ER: DCC method)	Positive if results showed a Scatchard plot, a $K_d < 5 \times 10^{-10}$ , an oestradiol-binding value >3 fmol/mg protein and a binding index of >12%	N	n/a	n/a	19		
Emile Hasiniatsy 2014 Madagascar [95]	Madagascar	Consecutive case series	75	IHC (DAB revelation with Auto-mate Ventana Benchmark with ER or PR antibodies)	>1% nuclei staining	N	n/a	n/a	17	17	17

<sup>a</sup>Only Series 1 ( $n = 378$ ) was included in the review. Series 2 is a replicate sample ( $n = 129$ ) which was excluded because of a) potential overlap with other studies included in the review; and b) the number of ER+, PR+ and HER2+ known was not reported.

<sup>b</sup>Methods for PR and HER2 testing are provided in the paper but no estimates for these two receptors are given. AJCC, American Joint Committee on Cancer; BC, Breast cancer; IBC, inflammatory breast cancer; ICH, immunocytochemistry; MFI, medical records; n/a, not applicable; NK, not given in the paper; NOS, not otherwise specified. doi:10.1371/journal.pmed.1001720.t002



**Figure 2. Flow diagram detailing study identification, screening, and eligibility.** Many abstracts could fit into more than one exclusion category; these were allocated to the first eligible category in the order listed here. doi:10.1371/journal.pmed.1001720.g002

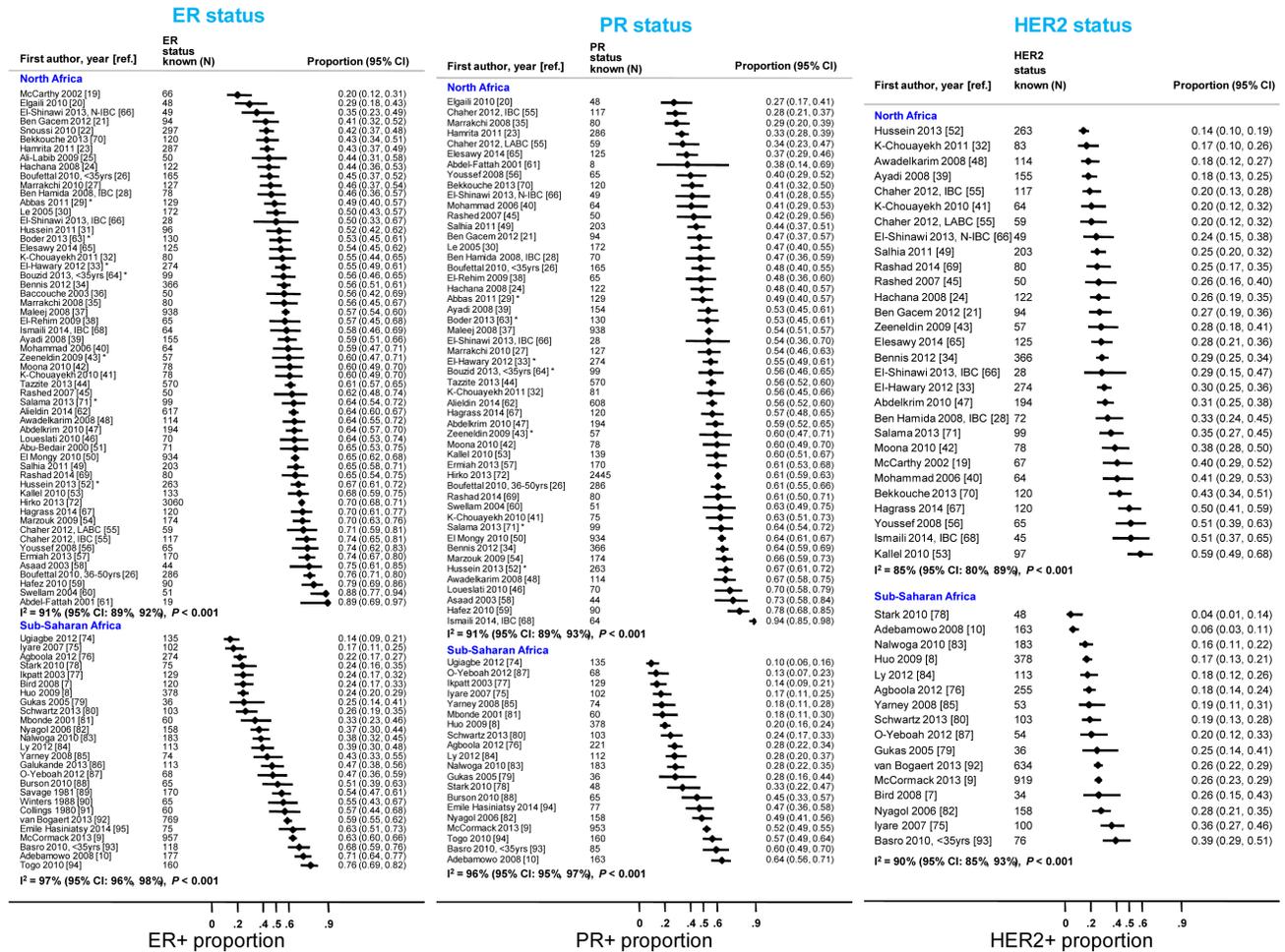
Embase, and Global Health [12] of studies published between 1st January 1980 and 15th April 2014. After an initial search using specific keywords, the search was broadened to “breast cancer” in “Africa” (with each country individually named; Text S3) in order to capture the studies where receptor status was not the focus of the paper but likely to be reported under patients’ characteristics. No language restrictions were imposed. In addition, we searched African Journals Online (AJO) and the Breast Health Global Initiative – INCTR Breast Cancer Control Library [13].

The titles and abstracts were reviewed by one author (AE) twice independently. Abstracts were excluded if the studies did not focus on breast cancer (e.g., studies of “all cancers”) or did not include women with breast cancer (e.g., surveys of attitudes towards breast screening); if they exclusively focused on: males, African-American women, metastatic breast cancer, pregnant women, or specific treatment groups; or if the total number of women with breast cancer included was <50. The latter were predominantly clinical reports or unrepresentative small case series of women with breast cancer who had been selected because of their unusual clinical or pathological characteristics (e.g., high-risk familial cases, BRCA1/2 carriers, bilateral cases, gestational breast cancers), and were also more likely to have arisen from settings where there was less quality control in laboratory procedures for fixation and immunohistochemistry (IHC). Studies were also excluded if they focused exclusively on non-black populations (e.g., white or coloured

women in South Africa). Reviews and conference proceedings were not included, but their references were cross-checked. A random sample of 80 titles/abstracts was also reviewed independently by another author (IdSS); this review revealed high between-reviewer reproducibility with no disagreements on which papers to select for full text review. The full text was retrieved for all potentially relevant papers and reviewed by the same author (AE) for reporting of receptor status. If there were multiple papers from the same study the paper with the most information on receptor status was selected for inclusion.

#### Data Extraction

The data extraction from each eligible paper was carried out independently by two reviewers (AE and IdSS or VM and IdSS) using a specifically developed and pre-tested computerised data extraction form (Text S2). Data were extracted on the number of women with breast cancer with available receptor status information, and the number of those with positive and negative tumors, as classified in the original article regardless of the criteria used to define positivity (Tables 1 and 2), for ER (ER+/ER−), PR (PR+/PR−), and HER2 (HER2+/HER2−) and, where available, for combined subtypes: luminal A (ER+ and/or PR+; HER2−), luminal B (ER+ and/or PR+; HER2+), HER2+-enriched (ER−; PR−; HER2+), and triple negative (ER−; PR−; HER2−). Information was also extracted on type of study, including study



**Figure 3. Proportion of ER+, PR+, and HER2+ disease (ranked by increasing magnitude), North and sub-Saharan Africa.** IBC, inflammatory breast cancer; LABC, non-IBC locally advanced breast cancer; N-IBC, non-inflammatory breast cancer. \*These studies provided only a combined HR estimate for tumors that were either ER+ or PR+ [33] or ER+ and/or PR+ ([29]; [43]; [52]; [63]; [64]; [71]). These HR estimates were included in both the ER+ and PR+ plots. doi:10.1371/journal.pmed.1001720.g003

design (e.g., population-based, case series based on consecutive women diagnosed with breast cancer over a defined time period, or collection based on convenience [opportunistic] samples), source of the breast cancer patients (e.g., hospital/clinic or cancer registry), sample size and study period; tumor characteristics (e.g., histological type; tumor size, stage, and grade); collection and storage conditions of the tumor specimens (e.g., fresh-frozen, formalin-fixed paraffin-embedded [FFPE] blocks); receptor testing (e.g., timing, type of assay, positivity criteria); and on demographic and reproductive-related variables (e.g., ethnicity, age, and menopausal status at diagnosis) where available. Many studies had limited information on how women with breast cancer were selected, or on the time period from tumor specimen collection to receptor testing, and the details provided in their methods section were used to obtain as informed a description as was possible. We did not attempt to contact the authors because most of the missing information was from studies published in the early years, making it difficult to establish contact and unlikely that the missing information would still be available. A few studies included a small number of men with breast cancer; these were included in the review as the papers did not provide enough information to allow

their exclusion. Disagreements were discussed by both reviewers and a consensus reached.

**Study Quality**

We adopted an approach similar to that used by the Cochrane Collaboration to develop a standardised quality assessment form for assessing the risk of bias in randomised studies [14]. We identified items within three quality domains to reflect the potential for selection bias, misclassification of receptor status, and availability of data on key correlates of receptor status. A list of items for each one of the three domains was developed. For each item, papers were allocated a score ranging from 0 (if it did not meet the criteria or if the information provided was unclear) to a maximum of 2 or 4, depending on the item, with more weight given to items in the selection bias and misclassification domains. Items in the selection bias domain included study design/case selection (score 0 if unclear; 2, if opportunistic case series; 4, if consecutive or population-based case series) and percentage of patients with known receptor status (score 0, if unclear; 2, if < 70%; 4, if ≥ 70%). Items in the misclassification domain comprised timing of tumor specimen collection (score 0, if inferred that tumor

**Table 3.** Summary of the characteristics of the 80 participating studies.

Variable	North Africa				Sub-Saharan Africa							
	ER Status	PR Status	HER2 Status	HER2 Status	ER Status	PR Status	HER2 Status	HER2 Status				
	Number of Studies	Number of Cases (%) <sup>a</sup>	Number of Studies	Number of Cases (%) <sup>a</sup>	Number of Studies	Number of Cases (%) <sup>a</sup>	Number of Studies	Number of Cases (%) <sup>a</sup>				
<b>Total</b>	54	12,284 (100)	48	11,013 (100)	27	3,324 (100)	26	4,737 (100)	20	3,310 (100)	16	3,307 (100)
<b>Country</b>												
North Africa:												
Egypt	25	6,877 (56)	22	6,025 (55)	12	1,477 (44)						
Tunisia	18	3,120 (25)	15	2,701 (25)	9	948 (29)						
Others <sup>b</sup>	11	2,287 (19)	11	2,287 (21)	6	899 (27)						
Sub-Saharan Africa:												
South Africa												
Nigeria <sup>c</sup>	6	2,139 (45)	2	1,038 (31)	3	1,629 (49)						
Others <sup>d</sup>	7	1,231 (26)	7	1,164 (35)	5	932 (28)						
Others <sup>d</sup>	13	1,367 (29)	11	1,108 (33)	8	746 (23)						
<b>Study design</b>												
Population-based (e.g., cancer registry)	3	4,046 (33)	3	3,431 (31)	0	0 (0)	2	952 (20)	1	183 (6)	2	817 (25)
Consecutive case series	13	2,886 (23)	12	2,569 (23)	6	555 (17)	13	2,538 (54)	10	2,190 (66)	9	1,931 (58)
Convenience case series	38	5,352 (44)	33	5,013 (46)	21	2,769 (83)	11	1,247 (26)	9	937 (28)	5	559 (17)
<b>Year of diagnosis<sup>e</sup></b>												
Before 2000	4	335 (3)	3	250 (2)	2	139 (4)	5	484 (10)	2	189 (6)	0	0 (0)
2001–2007	17	4,182 (34)	16	3,881 (35)	7	674 (20)	8	1,327 (28)	7	1,193 (36)	7	1,069 (32)
2008+	20	6,635 (54)	19	5,924 (54)	14	2,220 (68)	11	2,121 (45)	10	1,892 (57)	7	1,568 (47)
Not known	13	1,132 (9)	10	958 (9)	4	291 (9)	2	805 (17)	1	36 (1)	2	670 (20)
<b>Menopausal status at presentation<sup>f</sup></b>												
<60% cases were postmenopausal	30	8,856 (72)	27	7,774 (71)	13	1,292 (39)	14	1,862 (39)	12	1,492 (45)	8	992 (30)
≥60% cases were postmenopausal	2	412 (3)	2	411 (4)	1	125 (4)	4	1,142 (24)	2	1,013 (31)	1	919 (28)
Not known	22	3,016 (25)	19	2,828 (26)	13	1,907 (57)	8	1,733 (37)	6	805 (24)	7	1,396 (42)
<b>Stage at presentation</b>												
<60% cases with stage 3 and 4	19	6,865 (56)	17	6,093 (55)	7	1,054 (32)	4	1,240 (26)	4	1,203 (36)	3	1,031 (31)
≥60% cases with stage 3 and 4	12	1,148 (9)	12	1,140 (10)	7	572 (17)	9	941 (20)	6	628 (19)	4	364 (11)
Not known	23	4,271 (35)	19	3,780 (34)	13	1,698 (51)	13	2,556 (54)	10	1,479 (45)	9	1,912 (58)
<b>Tumor grade</b>												
<40% cases with grade 3	30	6,675 (54)	28	6,593 (60)	18	2,415 (73)	3	302 (6)	2	223 (7)	1	163 (5)
≥40% cases with grade 3	15	1,861 (15)	12	1,448 (13)	7	831 (25)	14	2,686 (57)	12	2,388 (72)	11	2,102 (64)

Table 3. Cont.

Variable	North Africa				Sub-Saharan Africa			
	ER Status	PR Status	HER2 Status	HER2 Status	ER Status	PR Status	HER2 Status	HER2 Status
	Number of Studies	Number of Studies	Number of Studies	Number of Studies				
	(%)*	(%)*	(%)*	(%)*	(%)*	(%)*	(%)*	(%)*
<i>Not known</i>	9	8	2	9	6	4	1,042 (32)	
<b>Storage conditions of Tumor tissue</b>								
Frozen	6	3	2	1	0	0	0 (0)	
FFPE	25	24	19	15	13	10	1,408 (43)	
Both	1	1	1	0	0	0	0 (0)	
<i>Not known</i>	22	20	5	10	7	6	1,899 (57)	
<b>Timing of Tumor tissue collection</b>								
Prospective	30	27	10	11	6	6	1,899 (57)	
Retrospective (archival material)	17	16	14	15	14	10	1,408 (43)	
<i>Not known</i>	7	5	3	0	0	0	0 (0)	

\*Percentage of the number given in the total row (percentages for each variable do not always add to 100 because of rounding errors).

<sup>b</sup>Includes four studies from Morocco (number of women with known ER, PR, and HER2 status: 1,451, 1,451, and 411, respectively), three from Libya (378, 378, 78, respectively), two from Sudan (162, 162, and 114, respectively), and two from Algeria (296, 296, and 296, respectively) (see Tables 1 and 2).

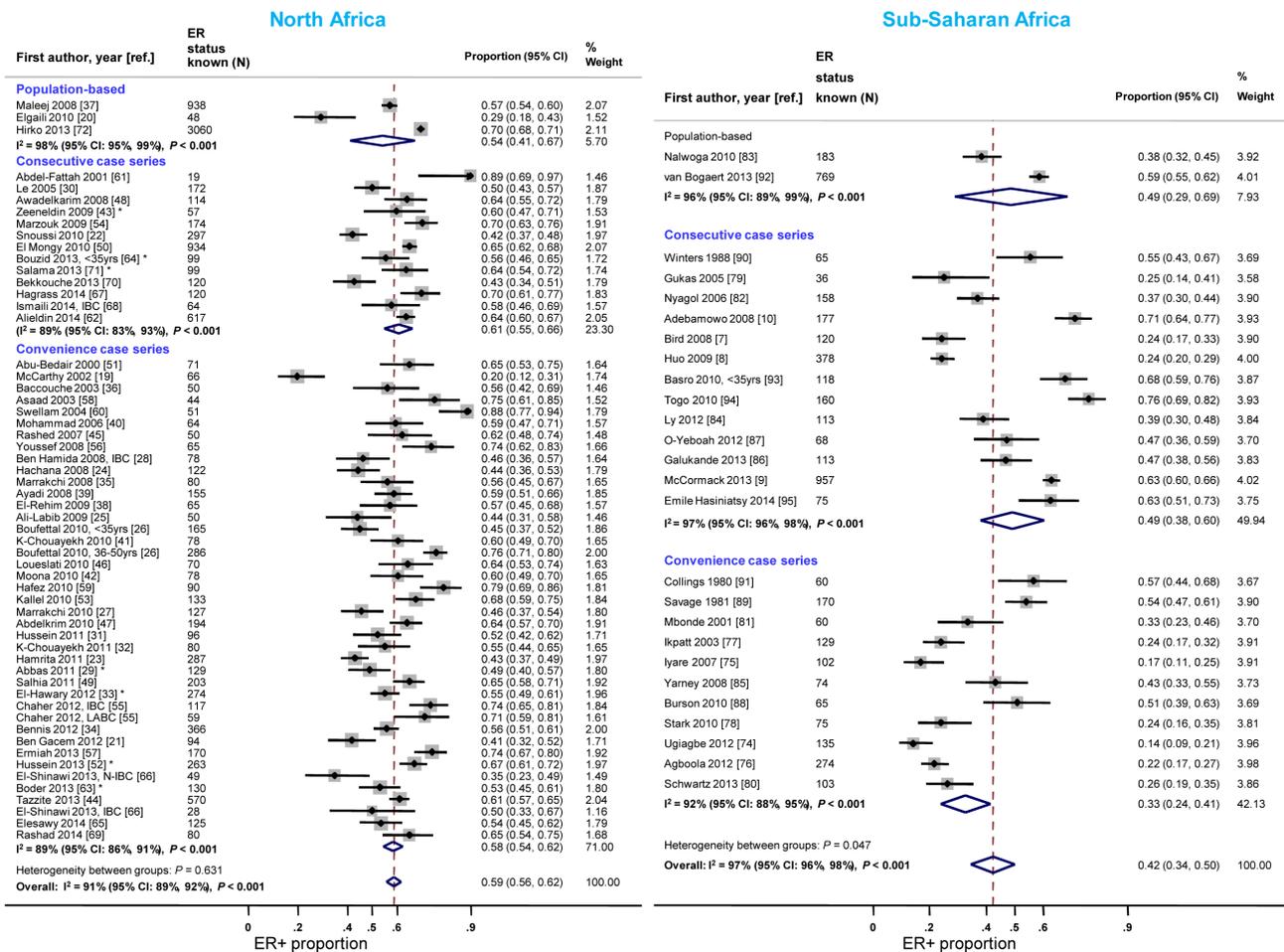
<sup>c</sup>Includes a multi-centric study [8] with several centres based in Nigeria and one in Senegal (number of women with known ER, PR, and HER2 status: 378, 378, and 378, respectively).

<sup>d</sup>Includes two studies from Mali (number of women with known ER, PR, and HER2 status: 273, 272, and 113, respectively); four from Ghana (320, 293, and 258, respectively); two from Uganda (296, 183 and 183, respectively), two from Kenya (278, 158 and 192, respectively), two from Tanzania (125, 125 and 0, respectively), and one from Madagascar (75 and 77, respectively) (see Tables 1 and 2).

<sup>e</sup>Defined according to the last year in which patient recruitment took place.

<sup>f</sup>If information on menopausal status was not available women aged >50 years at diagnosis were classified as postmenopausal.

doi:10.1371/journal.pmed.1001720.t003



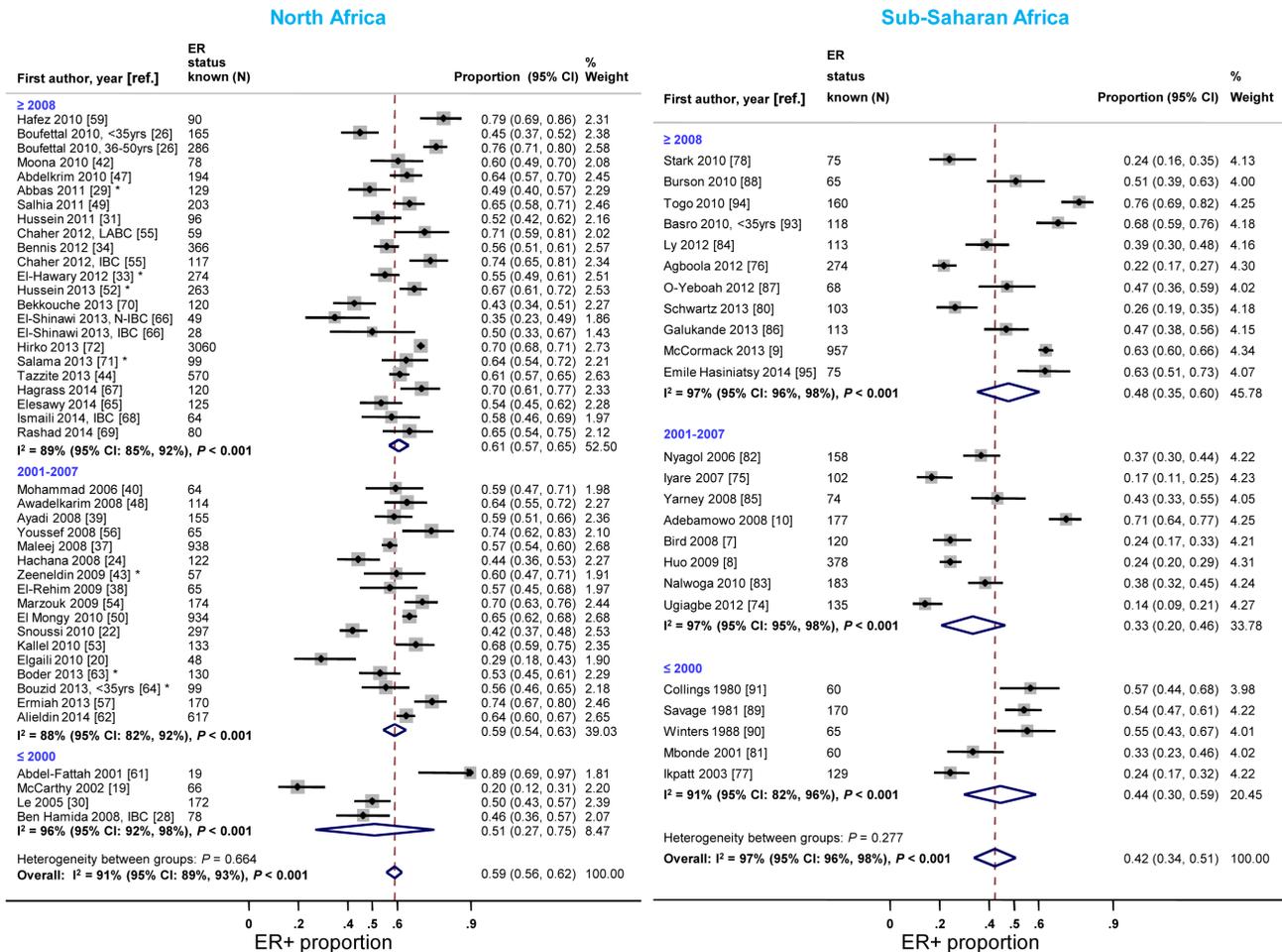
**Figure 4. Proportion of ER+ disease by study design, North and sub-Saharan Africa.** IBC, inflammatory breast cancer; N-IBC, non-inflammatory breast cancer. \*These studies provided only a combined HR estimate for tumors that were either ER+ or PR+ [33] or ER+ and/or PR+ ([29]; [43]; [52]; [63]; [64]; [71]). doi:10.1371/journal.pmed.1001720.g004

samples were collected prior to the start of treatment but this is not clearly stated—studies stating that collection was done after treatment were excluded from the review; 2, if specified that collection was done prior to treatment onset; tumor tissue storage conditions (score 0, if unclear; 2, if FFPE; 4, if frozen); timing of receptor status testing (score 2, if retrospective based on archival samples; 4, if conducted at the time of diagnosis); assay method (score 0, if not given; 2, if method described); criteria used to ascertain receptor positivity (for ER and PR: score 0, if not given; 2, if criteria described; for HER2: score 0, if not given; 1, if criteria described but fluorescent in situ hybridization [FISH] [chromogenic in situ hybridization (CISH) or silver in situ hybridization (SISH)] not used; 2, if FISH [CISH or SISH] used). The domain on correlates of receptor status comprised availability of information on age and/or menopausal status, tumor grade, and tumor stage (all scored as 0 if missing, 1 if available). The overall quality of the study was expressed as the sum of its item-specific scores. The range of possible scores was from 0 (lowest) to 25 (highest); the higher the score the higher the methodological quality of the study and, hence, the lower the risk that its findings might have been affected by bias.

Two authors (AE and IdSS) reviewed the quality of individual studies and inconsistencies discussed to reach consensus. In the analysis, we opted for simply describing the distribution of scores for studies reporting on each specific receptor, rather than using an arbitrary cut-off to define high versus low quality studies, and for examining both the contribution of the overall quality score and of specific quality criteria to between-study heterogeneity in estimates.

## Statistical Methods

As previous studies suggested differential ER+ proportions in women of African, rather than Arabic origin, results are presented separately for North Africa (i.e., Algeria, Egypt, Libya, Morocco, Sudan, Tunisia, and Western Sahara) and sub-Saharan Africa (i.e., all remaining African countries) according to their predominant population groups as defined by the United Nations [15]. For each receptor, the proportion of receptor-positive breast cancers (*prop*) was the statistic of interest, calculated as (number of receptor-positive tumors)/(*n* = number of tumors with known receptor status). Wilson score 95% CIs for this binomial *prop* were calculated and, on the basis of these, meta analyses were



**Figure 5. Proportion of ER+ disease by year of diagnosis, North and sub-Saharan Africa.** IBC: inflammatory breast cancer; LABC: non-IBC locally advanced breast cancer; N-IBC: non-inflammatory breast cancer. \*These studies provided only a combined HR estimate for tumors that were either ER+ or PR+ [33] or ER+ and/or PR+ ([29]; [43]; [52]; [63]; [64]; [71]). doi:10.1371/journal.pmed.1001720.g005

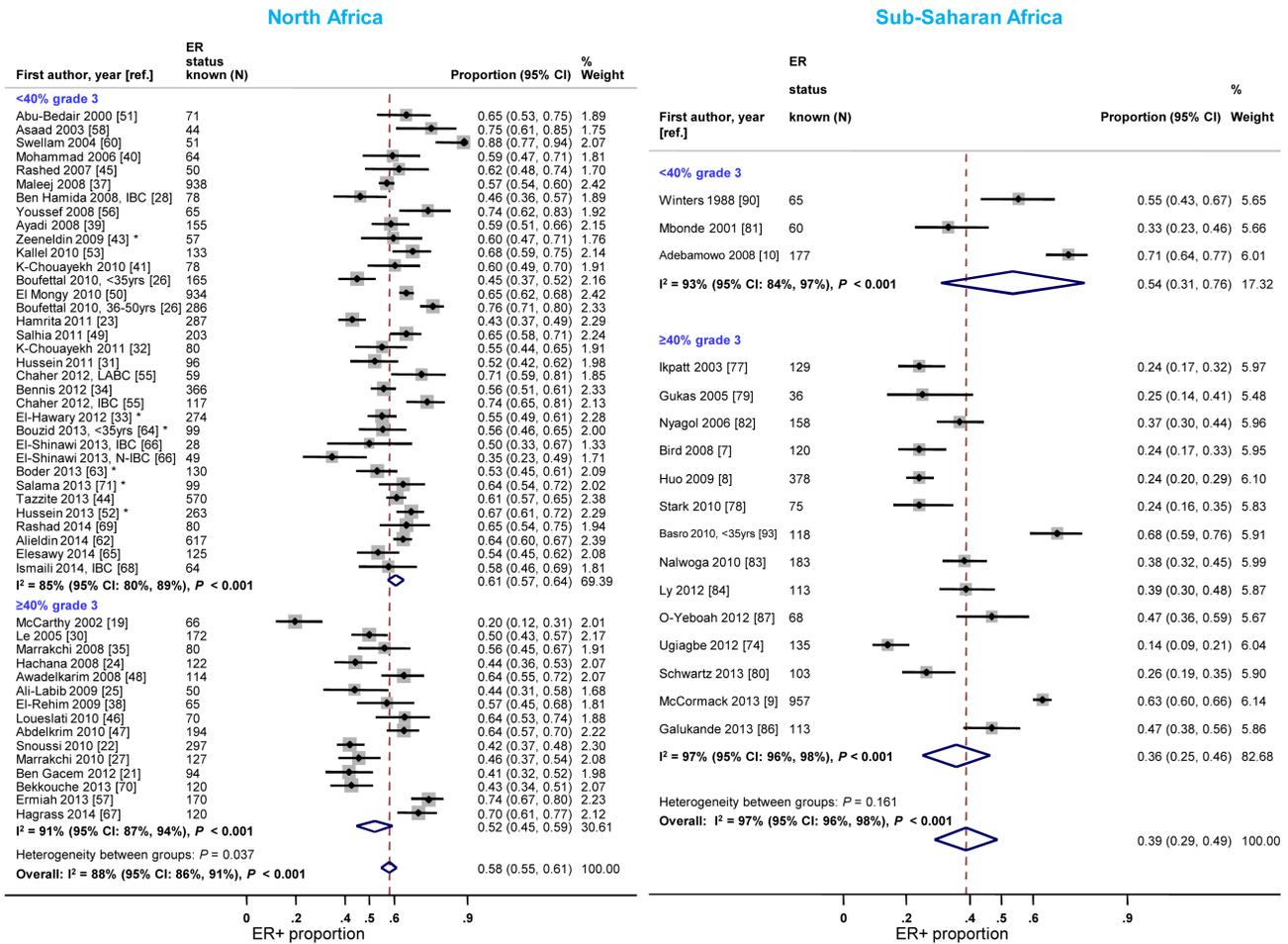
conducted in STATA version 12 (StataCorp), using the *metaprop* command to estimate pooled proportions using random effects models. Between-study heterogeneity was assessed using  $I^2$  (with its 95% CI estimated by the method of Higgins and Thomson [16]) and the  $p$ -value for heterogeneity (Cochrane's  $Q$  statistic). The  $I^2$  statistic represents the percentage of between-study variation due to heterogeneity rather than chance [17]. To examine potential sources of heterogeneity, study-specific estimates were stratified according to *a priori* defined geographical (i.e., two *ad hoc* sub-regions within North Africa—North-Eastern and North-Western—and three sub-regions in sub-Saharan Africa—Eastern, Southern, and Western—as defined by the United Nations [15]; see Results section), clinical factors (e.g., age, year, and menopausal status at diagnosis, tumor stage, and grade) and methodologically relevant variables (e.g., study design, timing of receptor testing, specimen storage conditions, study quality). Few studies provided information on reproductive-related variables except menopausal status; if data on the latter variable were not available, women aged >50 years were classified as post-menopausal. Meta-regression analyses were conducted to identify independent sources of between-study heterogeneity. These analyses necessitated an assumption of a single standard error

that was estimated as  $\sqrt{\{prop(1-prop)/n\}}$ . Funnel plots and the Egger test [18] were performed to examine whether small study bias could have affected the results.

## Results

### Characteristics of Included Studies

The systematic search in Medline, Embase, and Global Health produced 2,032 abstracts, of which 243 were identified as potentially relevant and the full text reviewed (Figure 2). A further 13 studies were identified from African Journals Online or hand-searches of bibliographic references. Eighty studies reported on ER status (no studies reported on PR or HER2 status without also reporting on ER status) and were therefore included in the review, involving a total of 17,021 women with breast cancer. Tables 1 and 2 present the characteristics of each one of the 80 participating studies. Fifty-four studies from North Africa [19–73] and 26 from sub-Saharan Africa [7–10,74–95] reported on ER status, with fewer also reporting on PR or HER2 status (Figure 3; Tables 1, 2, and 3). Eighty percent of the North African studies, corresponding to 81% of all women with breast cancer from this region, were conducted in Egypt or Tunisia; 50% of the sub-Saharan African studies,



**Figure 6. Proportion of ER+ disease by tumor grade, North and sub-Saharan Africa.** IBC, inflammatory breast cancer; N-IBC, non-inflammatory breast cancer. \*These studies provided only a combined HR estimate for tumors that were either ER+ or PR+ [33] or ER+ and/or PR+ ([43]; [52]; [63]; [64]; [71]). doi:10.1371/journal.pmed.1001720.g006

corresponding to 71% of women with breast cancer from the region, were from South Africa or Nigeria (the distribution by country is given in Table 3). Most studies had sample sizes <300 patients with known receptor status. Only four studies [9,37,50,72,73] had >900 women with breast cancer, with the largest one ( $n = 3,060$ ) also being one of the few to be based on a population-based cancer registry (an Egyptian study [72,73]). The most common method for assessing receptor status was monoclonal assays (i.e., the quantitative enzyme immunoassay and, more often, the semi-quantitative IHC approach), but ER status was ascertained by ligand binding assays (e.g., dextran-coated charcoal [DCC] method) in some earlier studies (Tables 1 and 2) [51,89–91]. FISH, CISH, or SISH to ascertain the HER2 status of specimens with an equivocal IHC score of 2+ was only performed in a few studies (Tables 1 and 2) [34,42,48,55,65,69,76,78,82,84,87].

Figure 3 shows study-specific reported proportions of ER+, PR+, and HER2+ tumors, ranked according to their magnitude, for North and sub-Saharan Africa. There was marked between-study heterogeneity in the ER+ estimates in both regions ( $I^2 > 90\%$ ), with the majority reporting proportions between 0.40 and 0.80 in North Africa and between 0.20 and 0.70 in sub-Saharan Africa. Similarly, large between-study heterogeneity was observed

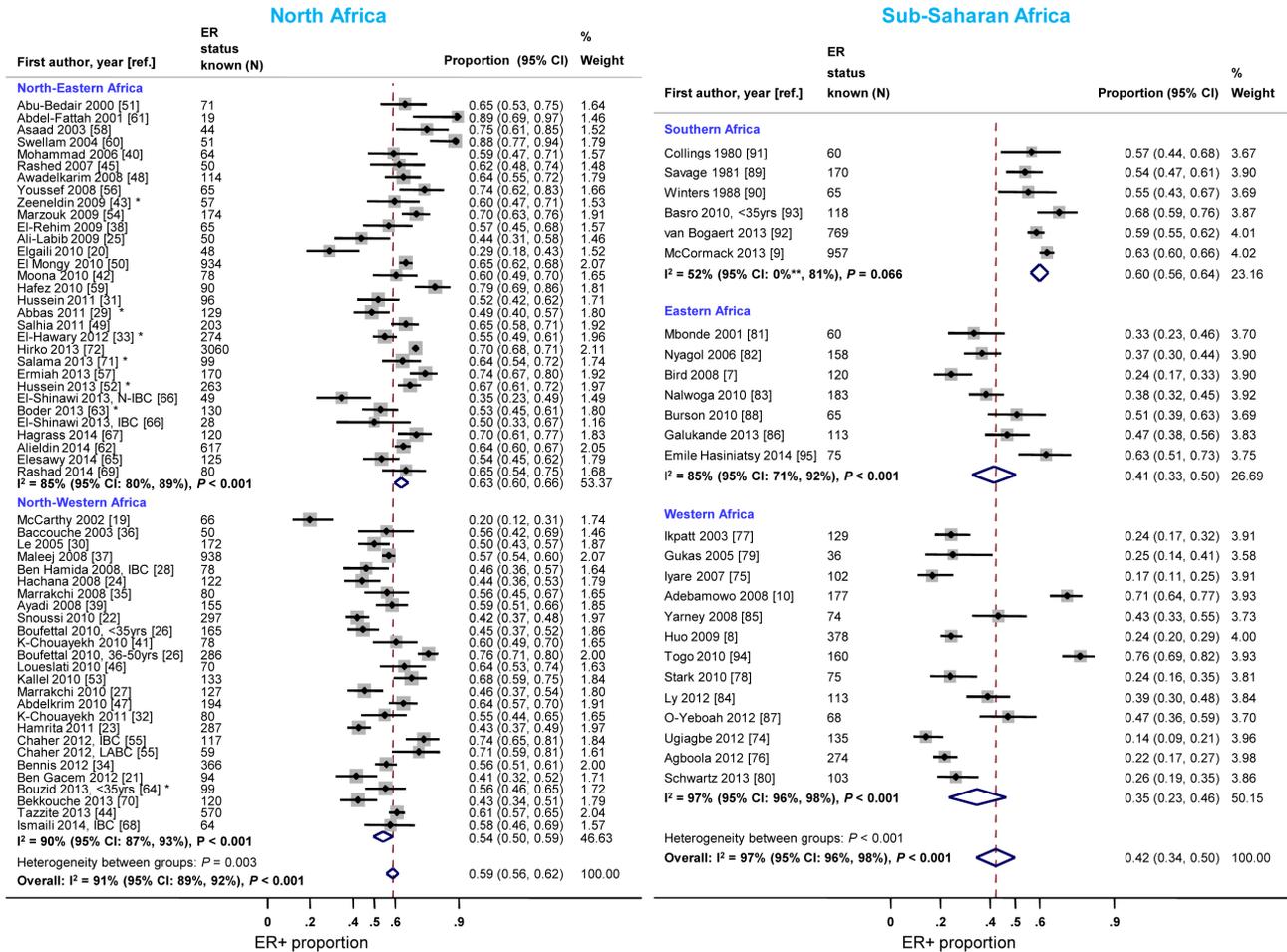
for PR+ and HER2+ estimates ( $I^2 > 80\%$ , in all instances). There were no clear differences in the reported proportions of HER2+ tumors according to whether they were classified with a IHC cut-off score of 2+/3+ or 3+ as HER2+, or whether they were, or were not, further tested with FISH, CISH, or SISH.

### Between-Study Heterogeneity

**Study design.** Case series based on convenience samples predominated in North Africa whereas roughly half of the case series in sub-Saharan Africa were consecutive (Table 3). For North African studies, there were no consistent differences in the ER+ proportion by study design; for sub-Saharan African studies, the studies that yielded the highest ER+ estimates tended to be those based on population-based or consecutive series rather than those based on convenience samples but there was still wide between-study variability among the former (Figure 4). A similar pattern was observed for PR receptor status (Figure S1). There were no clear differences by study design for HER2 status in North or sub-Saharan Africa (Figure S2).

**Year of diagnosis.** The majority of studies in both North and sub-Saharan Africa comprised women diagnosed with breast cancer after 2001 (Table 3). In each region, the study-specific ER+





**Figure 8. Proportion of ER+ disease by sub-regions within North and sub-Saharan Africa.** IBC, inflammatory breast cancer; LABC, non-IBC locally advanced breast cancer; N-IBC, non-inflammatory breast cancer. North-Western Africa: Morocco, Algeria, and Tunisia; North-Eastern Africa: Egypt, Sudan, and Libya; Eastern Africa: Kenya, Uganda, Tanzania, and Madagascar; Western Africa: Ghana, Mali, Nigeria, and Senegal; Southern Africa: South Africa. \*These studies provided only a combined HR estimate for tumors that were either ER+ or PR+ [33] or ER+ and/or PR+ ([29]; [43]; [52]; [63]; [64]; [71]). \*\*Lower limit of 95% confidence interval for I<sup>2</sup> statistic truncated at 0. doi:10.1371/journal.pmed.1001720.g008

**Timing of receptor testing and specimen storage conditions.** Reported proportions of ER+ and PR+ disease tended to be lower for studies where receptor status assays were conducted on retrospective (archival) tissue blocks than for those based on prospectively analysed specimens in sub-Saharan Africa, but not in North Africa (Figures 7 and S8). North African studies that used FFPE blocks tended to report lower ER+ (pooled prop = 0.57, 95% CI 0.52–0.62; I<sup>2</sup> = 91%; p < 0.01) and PR+ estimates (pooled prop = 0.51, 95% CI 0.46–0.55; I<sup>2</sup> = 88%; p < 0.01) than those based on frozen tissue samples (pooled ER+ prop = 0.64, 95% CI 0.52–0.76; I<sup>2</sup> = 87%, p < 0.01; pooled PR+ prop = 0.61; 95% CI 0.55–0.67; I<sup>2</sup> = 0%; p = 0.88). Virtually all sub-Saharan African studies were based on FFPE tissue blocks (Table 3). No clear patterns in the frequency of HER2+ tumors by timing of receptor testing, or specimen storage conditions, were observed within each region (e.g., pooled prop [95% CI] for prospectively collected versus archival tissue: 0.36 [0.30–0.42] versus 0.28 [0.23–0.33] in North Africa; 0.22 [0.14–0.31] versus 0.20 [0.15–0.25] in sub-Saharan Africa [I<sup>2</sup> ≥ 74% for all]; Figure S9).

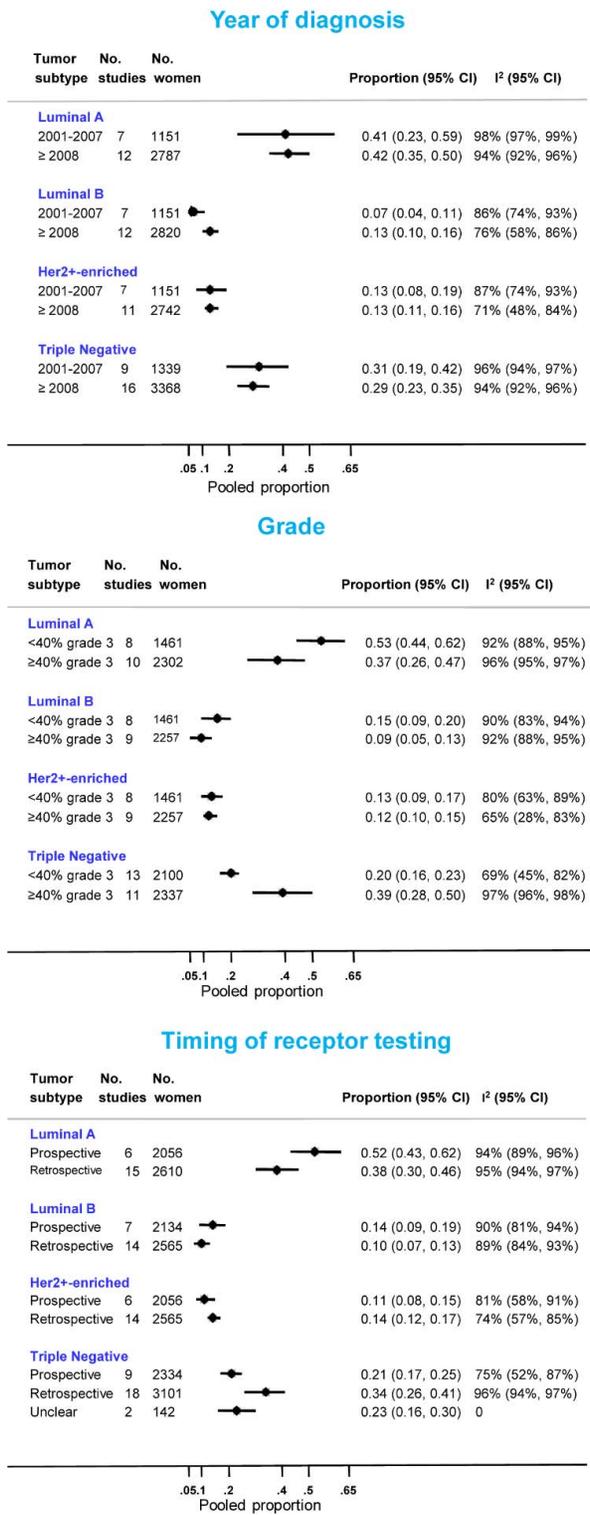
**Study quality.** The median (inter-quartile range [IQR]) quality scores for studies reporting on ER, PR, and HER2 status for North Africa were 16 (14–17), 16 (15–18), and 15 (14–17), respectively (Table 1). The corresponding estimates for sub-Saharan Africa were 17 (15–19), 17 (15–19), and 16 (14–18) (Table 2). There were no clear differences in the frequency of ER+, PR+, and HER2+ disease by study quality scores, despite the differences observed for specific individual criteria (e.g., study tissue storage conditions, timing of receptor testing) described above.

**Geographical sub-regions.** Studies from North-Eastern Africa (i.e., Egypt, Sudan, and Libya) yielded higher ER+ proportions than those conducted in North-Western Africa (i.e., Morocco, Algeria, and Tunisia) (Figure 8). There was also a gradient within sub-Saharan Africa with the highest ER+ proportions being reported by studies from Southern Africa (i.e., South Africa) and the lowest by studies from Eastern Africa (i.e., Kenya, Uganda, Tanzania, and Madagascar) and Western Africa (i.e., Ghana, Mali, Nigeria, and Senegal) (Figure 8). Similar patterns by sub-region were observed for PR+ disease except that the gradient within North Africa was smaller (Figure S10). There was no

**Table 4.** Sources of between-study heterogeneity in the proportions of ER+, PR+, and HER2+ cases from meta-regression analyses.

Variable	ER+			PR+			HER2+		
	N	Crude Absolute Difference (%)	Adjusted <sup>a</sup> Absolute Difference (%)	N	Crude Absolute Difference (%)	Adjusted <sup>a</sup> Absolute Difference (%)	N	Crude Absolute Difference (%)	Adjusted <sup>a</sup> Absolute Difference (%)
<b>Year of diagnosis<sup>b,c</sup></b>									
≤2000	9	-3.4 (-16.4 to 9.6)	-0.19 (-11.4 to 11.0)	5	-14.0 (-31.6 to 3.5)	-10.8 (-25.6 to 3.9)	2	9.4 (-25.6 to 3.9)	3.0 (-9.1 to 28.0)
2001–2007	25	0 (ref)	0 (ref)	23	0 (ref)	0 (ref)	14	0 (ref)	0 (ref)
≥2008	34	5.8 (-3.0 to 14.5)	4.7 (-2.7 to 12.2)	32	4.1 (-5.2 to 13.4)	3.9 (-9.5 to 11.6)	23	0.3 (-7.7 to 8.3)	-2.7 (-10.5 to 5.0)
<b>Age at diagnosis (y)<sup>b,d</sup></b>									
31–	21	0 (ref)	0 (ref)	18	0 (ref)	0 (ref)	11	0 (ref)	0 (ref)
47–	24	9.7 (-0.0 to 19.4)	5.4 (-3.2 to 14.1)	22	8.4 (-2.6 to 19.5)	3.8 (-5.7 to 13.3)	10	-3.0 (-13.5 to 7.6)	-6.1 (-16.9 to 4.6)
49.5+	25	13.0 (3.4–22.6)	6.7 (-2.08 to 15.4)	22	9.1 (-1.9 to 20.0)	0.1 (-9.5 to 9.6)	18	2.0 (-7.1 to 11.1)	-4.7 (-15.4 to 6.0)
<b>Grade 3<sup>b</sup></b>									
<40%	37	0 (ref)	0 (ref)	34	0 (ref)	0 (ref)	22	0 (ref)	0 (ref)
≥40%	29	-15.9 (-23.4 to -8.3)	-9.1 (-16.6 to -1.5)	24	-12.2 (-21.1 to -3.4)	-2.5 (-11.2 to 6.3)	18	-2.0 (-9.6 to 5.6)	4.4 (-4.6 to 13.4)
<b>Timing of receptor testing</b>									
Prospective	43	0 (ref)	0 (ref)	35	0 (ref)	0 (ref)	17	0 (ref)	0 (ref)
Retrospective	33	-13.6 (-20.6 to -6.6)	-10.4 (-17.3 to -3.6)	31	-12.3 (-20.4 to -4.3)	-5.6 (-13.1 to 2.0)	25	-6.0 (-13.3 to 1.3)	-8.3 (-15.7 to -0.9)
Unclear	7	5.7 (-7.0 to 18.3)	4.2 (-10.2 to 18.6)	5	5.9 (-1.0 to 21.8)	4.3 (-12.1 to 20.8)	3	-5.5 (-20.2 to 9.3)	-6.5 (-22.8 to 9.9)
<b>Region</b>									
Sub-Saharan Africa	26	0 (ref)	0 (ref)	20	0 (ref)	0 (ref)	16	0 (ref)	0 (ref)
North Africa	57 <sup>e</sup>	16.4 (9.3–23.4)	12.3 (5.1–19.6)	51 <sup>e</sup>	21.4 (13.8– 29.0)	20.0 (11.5– 28.4)	29 <sup>e</sup>	9.3 (2.6– 16.0)	10.8 (2.4– 19.1)
<i>Stratified by timing of receptor testing<sup>f</sup></i>									
<i>Prospective</i>									
Sub-Saharan Africa	11	0 (ref)	0 (ref)	6	0 (ref)	0 (ref)	6	0 (ref)	0 (ref)
North Africa	32	-0.1 (-9.3 to 9.1)	0.4 (-9.9 to 10.6)	29	10.5 (-3.9 to 24.9)	14.8 (-0.3 to 29.9)	11	13.6 (2.0– 25.2)	12.2 (-1.9 to 26.3)
<i>Retrospective</i>									
Sub-Saharan Africa	15	0 (ref)	0 (ref)	14	0 (ref)	0 (ref)	10	0 (ref)	0 (ref)





**Figure 9. Frequency of tumor subtypes by year of diagnosis, grade, and timing of receptor testing.**  
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versus a proportion of 0.83 among Italian women, but the proportion of advanced tumors was much higher for the former (Figure 10). Three studies from South Africa [9,89,91], presented remarkably consistent between-ethnic differences despite covering

a 30-year period, with all reporting smaller differences in the frequency of ER+ disease between black and white women than those described above (Figure 10), with this magnitude being broadly in line with the magnitude of the ethnic differences between black and white women in the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, US (SEER) data (data downloaded from [6] using the same methods as in [9]) (Figure 10). The pooled proportions of ER+ disease yielded by this review for North (0.59) and sub-Saharan studies (0.59) on the basis of the possibly better quality prospectively collected samples, were broadly similar to the ER+ proportion for US black women in the SEER data (0.64). Notably, when the analysis was further restricted to studies in this review with <40% grade 3 tumors, a case mix more akin to that seen in the US series, the pooled ER+ proportions for North (0.59; 95% CI 0.54–0.64) and sub-Saharan studies (0.64; 0.49–0.90; based on two studies) were similar to the ER+ proportion seen among US black women (0.64) (Figure 10).

### Small Study Bias

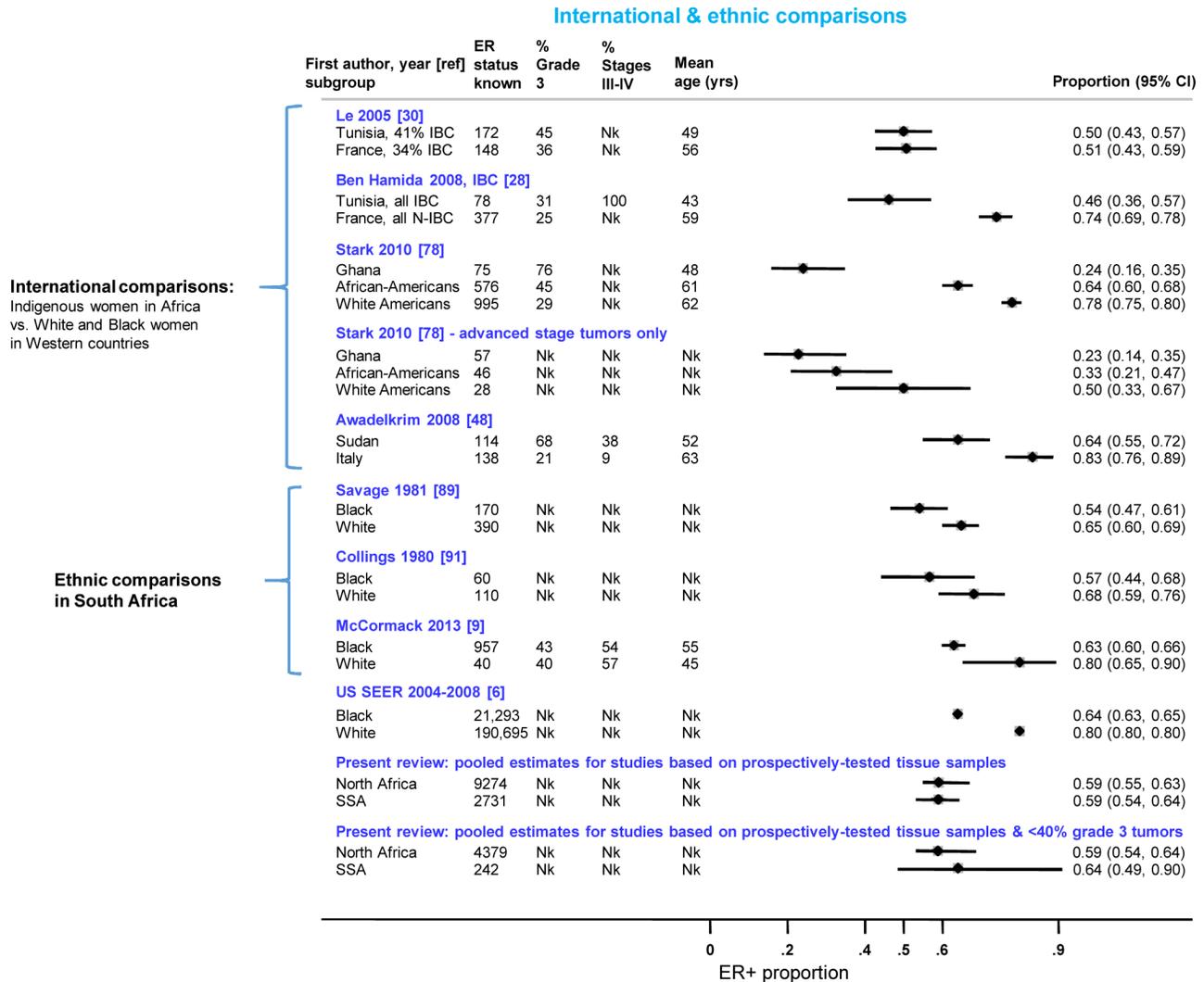
The funnel plots (Figure S12) and Egger's test for small study effects provide evidence of small study bias for North African studies only ( $p$ -values for studies reporting on ER, PR, and HER2 status:  $p = 0.004, 0.03, \text{ and } 0.01$ , respectively).

## Discussion

### Main Findings

This systematic review aimed to characterize the distribution of receptor-defined subtypes of breast cancer in indigenous populations in Africa. It highlighted the extent to which data on these receptors, which are important prognostic markers of the disease, is scarce in the continent. Nevertheless, we identified 80 studies, comprising >17,000 women with breast cancer, with information on at least ER status, thus providing the largest synthesis so far to our knowledge of breast cancer subtypes in Africa. The review revealed large between-study heterogeneity in the reported frequency of ER+ tumors, ranging approximately from 1 in 4 to 3 in 4 tumors being ER+ within each region. This heterogeneity may have arisen as a result of regional and temporal differences in the prevalence of subtype-specific risk factors, differences in tumor characteristics (e.g., grade, stage) at presentation, or artefacts caused by unrepresentative case series and varying quality in the procedures used to collect, store, and analyse tumor specimens.

The review revealed a tendency for studies based on archival tissue and/or FFPE blocks to yield lower ER+ and PR+ frequency estimates, in line with archival samples being particularly susceptible to antigen degradation [96,97]. Additionally, such archival samples tended to be from older studies where quality control on pre-analytical factors may have been suboptimal. More recent studies have demonstrated the vulnerability of hormone receptor (HR) testing to false negatives and the importance of pre-analytical factors, with errors introduced by delays, inadequate or prolonged fixation and variability in fixatives used, dehydration procedures, and quality of paraffin. The present review also found that the proportion of ER+ disease decreased with increasing tumor grade, reflecting perhaps the accelerated growth rate of ER- tumors, loss of estrogen expression in more advanced forms of the disease, and higher likelihood of false-negative results (due to difficulties in obtaining a biopsy of the original tumor). Although the observed increase in the frequency of ER+ disease over time may reflect improvements in methodology as well as the change in the tumor nuclei staining intensity score threshold for ER positivity



**Figure 10. International and ethnic comparisons in the proportion of ER+ disease.** IBC, inflammatory breast cancer; N-IBC, non-inflammatory breast cancer; Nk, information not given in the original paper; SEER, Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, US (data downloaded from [6] using the same methods as in [9]); SSA, sub-Saharan Africa. doi:10.1371/journal.pmed.1001720.g010

from  $\geq 10\%$  to  $\geq 1\%$  (following the introduction of new guidelines in 2010 [98]), they may also represent a genuine rise in ER+ disease as African women became more westernised (as illustrated by declines in fertility [99] and rises in body mass index [100,101] and, consequently, age at menarche in the continent).

A few studies in this review included international or ethnic comparisons in the distribution of ER status. None of the international studies appeared to have conducted centralized receptor status testing, with none reporting on cross-centre evaluation of comparability in measurements and quality control procedures, but each one of the three ethnic studies was conducted within a single institution and hence using the same procedures for all their participants. These comparisons consistently reported a lower frequency of ER+ tumours in indigenous women in Africa relative to Western white women, or in black relative to white women in South Africa, consistent with the well documented ethnic differences in the US. The existence of, and reasons for, the black-white differences in the US may shed light on the situation in Africa. Over

age 35 years, a higher ER+ proportion among US white than black women with breast cancer is driven by the latter group's slightly higher absolute incidence rate of triple negative disease, in combination with their much lower incidence rate of better prognosis ER+/PR+ HER2- tumors [102]. However, the magnitude of the black-white difference in the ER+ proportion has changed somewhat over time and the reasons driving these differences are much debated [11]. As risk factors are subtype-specific, ethnic differences in the prevalence of hormonal-related risk factors may contribute to ethnic differences in the incidence of the various breast cancer subtypes. Pre-menopausal obesity and higher parity may be associated with raised risk of triple-negative disease, in contrast to their protective effects on ER+ disease [103,104], and oral contraceptive use may increase more markedly the risk of triple negative disease than the risk of other subtypes [105]. Equally, or in addition, ethnic differences may derive from genetic susceptibility to triple negative or ER-negative breast cancer in some African populations [106,107].

In the present study, relative to breast cancer in Western white women, the disease in indigenous women in Africa was characterized by a younger age, an advanced stage, and a higher grade at presentation (Figure 10). Both young age and more advanced forms of the disease at presentation are associated with lower prevalence of ER+ tumors. Thus, the observed lower frequency of ER+ tumors in indigenous African women may simply reflect a much younger demographic structure of the indigenous African populations rather than a more intrinsic aggressive biology of the disease, as incidence rates at young ages are lower than among Western white women [1], as well as a tendency for late presentation due to lack of breast cancer awareness and screening activities, the unavailability of appropriate healthcare facilities, and the influence of socio-cultural and logistic factors that could limit access to health-care. In fact, our finding that the proportion of ER+ disease reported by African studies based on prospectively collected samples with predominantly low grade tumors was virtually the same as among US black women (all ~64%) argues against breast cancer being a much more biologically aggressive disease in Africa than in the West.

Two subtypes are known to be associated with particularly poor breast cancer outcomes: triple negative and HER2+-enriched tumors. Few studies provided information on these subtypes and even fewer were based on prospectively collected samples. Nevertheless, the estimates based on the latter for triple negatives (pooled *prop* = 0.21; Figure 9) were slightly above the range of frequencies usually seen in white populations (10%–16%) [2,108], but similar to that seen in US black women (e.g., 26% in [109]). The prevalence of HER2+-enriched tumors (pooled *prop* = 0.11) (Figure 9) was slightly higher than that seen in white populations [2] or US black women [109] (6%–10% for both) but similar to that reported for Chinese women [108]. However, considerable misclassification of HER2 status may have occurred as few African studies used FISH (or CISH/SISH) to ascertain the true HER2 status of tumors with an equivocal IHC score of 2+.

It is noteworthy to highlight that although between-study differences in the proportion of ER+ disease reflect the ratios of the underlying receptor-specific incidence rates (assuming no bias is present), they cannot be used to infer anything about the differences in incidence rates. The proportion of ER+ disease represents the ratio of the number of women who developed ER+ disease in a given population over a certain time period (thus, reflecting the underlying incidence rate of ER+ disease) by the total number of women who develop any type of breast cancer in the same population during the same time period (reflecting the incidence rate of ER+ and ER– disease combined). Thus, differences in the proportion of ER+ disease among women with breast cancer could arise from two populations with (i) the exact same incidence rates of ER– disease, but different incidence rates of ER+ disease, or (ii) equal incidence rates of ER+ disease, but different rates of ER– disease, or (iii) any combinations of these two. Case-only studies are unable to disentangle these different alternatives. Consequently, the findings from this review cannot be used to infer differences in the underlying incidence rates of receptor-specific disease across populations, e.g., between North and sub-Saharan Africa.

### Strengths and Limitations

Major strengths of this review are the very comprehensive and inclusive search strategy (with inclusion of African-specific journals, the use of broad search terms rather than specific keywords, and the decision not to impose any language restrictions), the large number of eligible studies (comprising >17,000 women with breast cancer), and the use of well-established methodologies to provide an unbiased

synthesis of the published evidence. The study had several weaknesses too. Firstly, the systematic review includes data from all countries in North Africa except Western Sahara, but with a predominance of studies from Egypt and Tunisia (Table 3). The proportion of sub-Saharan countries represented in the review was much smaller—only nine (i.e., South Africa, Nigeria, Senegal, Mali, Ghana, Uganda, Kenya, Tanzania, and Madagascar) out of 49 countries, albeit together these countries represent 46% of the total African female population [1]. Furthermore, no receptor status testing is performed in many of the countries not represented in the review. Secondly, the representativeness of the case series was not only compromised by the poor design of many of the participating studies, particularly those based on convenience samples, but also by the limited access to appropriate diagnostic and treatment facilities experienced by most indigenous African women affected with breast cancer. For instance, in many countries, receptor status testing in public hospital attendees is only available to those who can afford it. Thirdly, it is also possible that women with breast cancer may have contributed to more than one study. When multiple papers from the same study were identified, only the one with the most information on receptor status was included in the review. However, it was often impossible to ascertain potential overlaps in study populations, particularly among studies conducted within the same institution. This was a particular issue for Egyptian and Tunisian studies published in the early years, most of which provided a poor description of how their study populations were recruited, but sensitivity analyses including only studies in each institution whose recruitment dates did not overlap yielded similar estimates to those reported here. Fourthly, there was no suggestion that small study bias affected the results for receptor status in sub-Saharan Africa, but for North African studies, the smaller studies tended to have lower-than-average ER+ and PR+ proportions and higher-than-average HER2+ proportions. If this small study bias is real, the true ER+ and PR+ proportions would be higher and the HER2+ lower than the pooled estimates reported here. Finally, real geographical or temporal differences in the frequency of breast cancer subtypes may have been obscured by the lack of standardisation in pre-analytical and analytical procedures across studies.

### Implications

Large well-designed studies, incorporating standardised high-quality procedures for receptor testing, are required to accurately quantify the distribution of the various breast cancer subtypes across Africa. In the meantime, this systematic review provides the strongest evidence yet that the distribution of receptor-defined subtypes is not dramatically different to that found in Western populations given their younger age structure and late presentation. The availability of receptor testing should be a priority in Africa, especially for young women with early stage disease where the potential to improve survival and reduce years of life-lost is greatest. In the absence of such testing, it would be appropriate to presume that the majority of tumors are ER+.

The findings have important implications for both research needs and public health in Africa. In addition to the need for high-quality characterisation of receptor-status, etiologic studies on breast cancer in the continent need to be conducted separately by subtype, to gain a better insight into risk factors for each. For the rare subtypes, such as triple negatives, this will require collaborative efforts to provide sufficient numbers of cases. In terms of public health implications, despite relatively low incidence rates, African women have mortality rates from breast cancer that are as high as in high incidence countries [1]. If more aggressive breast tumors predominated, the potential to improve survival rates would be curtailed using current therapies.

However, the present synthesis suggests that this is not the case, and that two-thirds of women with breast cancer have a less aggressive disease form for which targeted endocrine treatments have been shown to produce good survival rates. Tamoxifen [4], in particular, may provide an effective therapeutic option because of its low cost and ease of administration. Improving prognosis for such cancers will also hinge on the ability to diagnose and commence treatment at earlier stages of the disease, which is needed across many African countries as several hospitals have over 70% of breast cancer patients being diagnosed at stage III/IV. With a majority of ER+ tumors, this less-aggressive disease is also consistent with relatively long (6–18 months) symptomatic periods reported by women prior to diagnosis. This is a time-window during which efforts to encourage earlier presentation and faster referral through health systems to treatment centres can be focussed.

## Supporting Information

**Figure S1 Proportion of PR+ disease by study design, North and sub-Saharan Africa.** IBC, inflammatory breast cancer; LABC, non-IBC locally advanced breast cancer; N-IBC, non-inflammatory breast cancer. \*These studies did not provide separate ER and PR estimates; only an HR estimate for tumors that were ER+ or PR+ [33] or ER+ and/or PR+ ([29]; [43]; [52]; [63]; [64]; [71]). (PDF)

**Figure S2 Proportion of HER2+ disease by study design, North and sub-Saharan Africa.** IBC, inflammatory breast cancer; LABC, non-IBC locally advanced breast cancer; N-IBC, non-inflammatory breast cancer. (PDF)

**Figure S3 Proportion of PR+ disease by year of diagnosis, North and sub-Saharan Africa.** IBC, inflammatory breast cancer; LABC, non-IBC locally advanced breast cancer; N-IBC, non-inflammatory breast cancer. \*These studies did not provide separate ER and PR estimates; only an HR estimate for tumors that were ER+ or PR+ [33] or ER+ and/or PR+ ([29]; [43]; [52]; [63]; [64]; [71]). (PDF)

**Figure S4 Proportion of HER2+ disease by year of diagnosis, North and sub-Saharan Africa.** IBC, inflammatory breast cancer; LABC, non-IBC locally advanced breast cancer; N-IBC, non-inflammatory breast cancer. (PDF)

**Figure S5 Proportion of ER+ disease by tumor grade for the 12 studies that provided grade-specific estimates.** \*Grade 1 tumors ( $n = 17$ ) were excluded; \*\*grade 1 tumors ( $n = 5$ ) were excluded. (PDF)

**Figure S6 Proportion of PR+ disease by tumor grade, North and sub-Saharan Africa.** IBC, inflammatory breast cancer; LABC, non-IBC locally advanced breast cancer; N-IBC, non-inflammatory breast cancer. \*These studies did not provide separate ER and PR estimates; only an HR estimate for tumors that were ER+ or PR+ [33] or ER+ and/or PR+ ([43]; [52]; 2013 [63]; [64]; [71]). (PDF)

**Figure S7 Proportion of HER2+ disease by tumor grade, North and sub-Saharan Africa.** IBC, inflammatory breast

cancer; LABC, non-IBC locally advanced breast cancer; N-IBC, non-inflammatory breast cancer. (PDF)

**Figure S8 Proportion of PR+ disease by timing of receptor testing, North and sub-Saharan Africa.** IBC, inflammatory breast cancer; LABC, non-IBC locally advanced breast cancer. \*These studies did not provide separate ER and PR estimates; only an HR estimate for tumors that were ER+ or PR+ [33] or ER+ and/or PR+ ([29]; [43]; [52]; 2013 [63]; [64]; [71]). (PDF)

**Figure S9 Proportion of HER2+ disease by timing of receptor testing, North and sub-Saharan Africa.** IBC, inflammatory breast cancer; LABC, non-IBC locally advanced breast cancer. (PDF)

**Figure S10 Proportion of PR+ disease by sub-region within North and sub-Saharan Africa.** IBC, inflammatory breast cancer; LABC, non-IBC locally advanced breast cancer. North-Western Africa: Morocco, Algeria, and Tunisia; North-Eastern Africa: Egypt, Sudan, and Libya; Eastern Africa: Kenya, Uganda, Tanzania, and Madagascar; Western Africa: Ghana, Mali, Nigeria, and Senegal; Sothorn Africa: South Africa. \*These studies provided only a combined HR estimate for tumors that were either ER+ or PR+ [33] or ER+ and/or PR+ ([29]; [43]; [52]; 2013 [63]; [64]; [71]). \*\*Lower limit of 95% confidence interval for  $I^2$  statistic truncated at 0. (PDF)

**Figure S11 Proportion of HER2+ disease by sub-region within North and sub-Saharan Africa.** IBC, inflammatory breast cancer; LABC, non-IBC locally advanced breast cancer. North-Western Africa: Morocco, Algeria, and Tunisia; North-Eastern Africa: Egypt, Sudan, and Libya; Eastern Africa: Kenya, Uganda, Tanzania, and Madagascar; Western Africa: Ghana, Mali, Nigeria, and Senegal; Sothorn Africa: South Africa. \*Lower limit of 95% confidence interval for  $I^2$  statistic truncated at 0. (PDF)

**Figure S12 Funnel plots (with pseudo 95% confidence limits) for published ER+, PR+, and HER2+ studies, North and sub-Saharan Africa.** (PDF)

**Alternative Language Abstract S1 French and Portuguese translations of the title and abstract by VM and IdSS, respectively.** (DOCX)

**Text S1 PRISMA checklist of items to include when reporting a systematic review.** (DOC)

**Text S2 Protocol of the systematic review.** (DOCX)

**Text S3 Terms used in the literature search.** (DOCX)

## Author Contributions

Performed the experiments: AE VM IdSS. Analyzed the data: AE VM IdSS. Wrote the first draft of the manuscript: AE IdSS. Contributed to the writing of the manuscript: AE VM IdSS. ICMJE criteria for authorship read and met: AE VM IdSS. Agree with manuscript results and conclusions: AE VM IdSS. Literature search: AE. Data extraction: AE IdSS VM.

## References

- International Agency for Research on Cancer (2012) GLOBOCAN 2012. Available: <http://globocan.iarc.fr/>. Accessed 17 April 2014.
- Yang XR, Chang-Claude J, Couch EL, Couch FJ, Nevanlinna H, et al. (2011) Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. *J Natl Cancer Inst* 103: 250–263.
- Blows FM, Driver KE, Schmidt MK, Broeks A, van Leeuwen FE, et al. (2010) Subtyping of breast cancer by immunohistochemistry to investigate a relationship between subtype and short and long term survival: a collaborative analysis of data for 10,159 cases from 12 studies. *PLoS Med* 7: e1000279.
- Davies C, Godwin J, Gray R, Clarke M, Cutter D, et al. (2011) Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 378: 771–784.
- Jemal A, Fedewa SA (2012) Is the prevalence of ER-negative breast cancer in the US higher among Africa-born than US-born black women? *Breast Cancer Res Treat* 135: 867–873.
- Surveillance Epidemiology and End Results (SEER) Program (Available: [www.seer.cancer.gov/](http://www.seer.cancer.gov/)) SEER\*Stat Database: Incidence, SEER 17 Regs Research Data+Hurricane Katrina Impacted Louisiana Cases, Nov 2010 Sub (1973–2008 varying), Linked To County Attributes. 2010. Total U.S., 1969–2009 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch released April 2011 (updated 10/28/2011). Ref Type: Report
- Bird PA, Hill AG, Houssami N (2008) Poor hormone receptor expression in East African breast cancer: evidence of a biologically different disease? *Ann Surg Oncol* 15: 1983–1988.
- Huo D, Ikpatt F, Khramtsov A, Dangou JM, Nanda R, et al. (2009) Population differences in breast cancer: Survey in indigenous african women reveals over-representation of triple-negative breast cancer. *J Clin Oncology* 27: 4515–4521.
- McCormack VA, Joffe M, van den Berg E, Broeze N, dos Santos Silva I, et al. (2013) Breast cancer receptor status and stage at diagnosis in over 1,200 consecutive public hospital patients in Soweto, South Africa: a case series. *Breast Cancer Res* 15: R84.
- Adebamowo CA, Famooto A, OgunDIRAN TO, Aniagwu T, Nkwodimma C, et al. (2008) Immunohistochemical and molecular subtypes of breast cancer in Nigeria. *Breast Cancer Res Treat* 110: 183–188.
- Krieger N, Chen JT, Waterman PD (2011) Temporal trends in the black/white breast cancer case ratio for estrogen receptor status: disparities are historically contingent, not innate. *Cancer Causes Control* 22: 511–514.
- Global Health (2014) Available: <http://www.cabi.org/publishing-products/online-information-resources/global-health/>.
- Lodge M, Corbex M (2011) Establishing an evidence-base for breast cancer control in developing countries. *Breast* 20 Suppl 2: S65–69.
- The Cochrane Collaboration Cochrane Handbook for Systematic Reviews of Interventions 2009. Available: <http://handbook.cochrane.org/>
- United Nations (2013) United Nations Composition of macro geographical (continental) regions, geographical sub-regions, and selected economic and other groupings. Available: <http://unstats.un.org/unsd/methods/m49/m49regin.htm>. Accessed 10 December 2013.
- Higgins J, Thompson S (2002) Quantifying heterogeneity in a meta-analysis. *Stat Med* 21: 1539–1558.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. *BMJ* 327: 557–560.
- Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315: 629–634.
- McCarthy NJ, Yang X, Linnoila IR, Merino MJ, Hewitt SM, et al. (2002) Microvessel density, expression of estrogen receptor alpha, MIB-1, p53, and c-erbB-2 in inflammatory breast cancer. *Clin Cancer Res* 8: 3857–3862.
- Elgaili EM, Abuidris DO, Rahman M, Michalek AM, Mohammed SI (2010) Breast cancer burden in central Sudan. *Int J Womens Health* 2: 77–82.
- Ben Gacem R, Hachana M, Ziadi S, Ben Abdelkarim S, Hidar S, et al. (2012) Clinicopathologic significance of DNA methyltransferase 1, 3a, and 3b overexpression in Tunisian breast cancers. *Hum Pathol* 43: 1731–1738.
- Snoussi K, Mahfoudh W, Bouaouina N, Fekih M, Khairi H, et al. (2010) Combined effects of IL-8 and CXCR2 gene polymorphisms on breast cancer susceptibility and aggressiveness. *BMC Cancer* 10: 283.
- Hamrita B, Ben Nasr H, Gabbouj S, Bouaouina N, Chouchane L, et al. (2011) Apolipoprotein A1 –75 G/A and +83 C/T polymorphisms: susceptibility and prognostic implications in breast cancer. *Mol Biol Rep* 38: 1637–1643.
- Hachana M, Trimeche M, Ziadi S, Amara K, Gaddas N, et al. (2008) Prevalence and characteristics of the MMTV-like associated breast carcinomas in Tunisia. *Cancer Lett* 271: 222–230.
- Ali-Labib R, El-Monem F (2009) Hypermethylation of the tumour suppressor RASSF1A gene in malignant and benign breast tissues from Egyptian patients. *The Egyptian Journal of Biochemistry & Molecular Biology* 27: 83–100.
- Boufettal H, Noun M, Samouh N (2010) [Breast cancer in young patient in Morocco]. *Cancer Radiother* 14: 698–703.
- Marrakchi R, Khadimallah I, Ouerhani S, Gamoudi A, Khoms F, et al. (2010) Expression of WISP3 and RhoC genes at mRNA and protein levels in inflammatory and noninflammatory breast Cancer in Tunisian patients. *Cancer Invest* 28: 399–407.
- Ben Hamida A, Labidi IS, Mrad K, Charafe-Jauffret E, Ben Arab S, et al. (2008) Markers of subtypes in inflammatory breast cancer studied by immunohistochemistry: prominent expression of P-cadherin. *BMC Cancer* 8: 28.
- Abbas H, Salem AAS, Salem MAE, Binziad S, Gamal B (2011) Breast cancer: radiotherapy at the South Egypt Cancer Institute. *Gastric and Breast Cancer* 10: 180–186.
- Le MG, Arriagada R, Contesso G, Cammoun M, Pfeiffer F, et al. (2005) Dermal lymphatic emboli in inflammatory and noninflammatory breast cancer: A French-Tunisian joint study in 337 patients. *Clin Breast Cancer* 6: 439–445.
- Hussein YM, Gharib AF, Etewa RL, El-Shal AS, Abdel-Ghany ME, et al. (2011) The melanoma-associated antigen-A3, -A4 genes: relation to the risk and clinicopathological parameters in breast cancer patients. *Mol Cell Biochem* 351: 261–268.
- Karray-Chouayekh S, Trifa F, Khabir A, Boujelbene N, Sellami-Boudawara T, et al. (2011) Methylation status and overexpression of COX-2 in Tunisian patients with ductal invasive breast carcinoma. *Tumour Biol* 32: 461–468.
- El-Hawary AK, Abbas AS, Elsayed AA, Zalata KR (2012) Molecular subtypes of breast carcinoma in Egyptian women: clinicopathological features. *Pathol Res Pract* 208: 382–386.
- Bennis S, Abbas F, Akasbi Y, Znati K, Joutei KA, et al. (2012) Prevalence of molecular subtypes and prognosis of invasive breast cancer in north-east of Morocco: retrospective study. *BMC Research Notes* 5: 436.
- Marrakchi R, Ouerhani S, Benammar S, Rouissi K, Bouhaha R, et al. (2008) Detection of cytokeratin 19 mRNA and CYFRA 21-1 (cytokeratin 19 fragments) in blood of Tunisian women with breast cancer. *Int J Biol Markers* 23: 238–243.
- Baccouche S, Daoud J, Frikha M, Mokdad-Gargouri R, Gargouri A, et al. (2003) Immunohistochemical Status of p53, MDM2, bcl2, bax, and ER in Invasive Ductal Breast Carcinoma in Tunisian Patients. *Ann N Y Acad Sci* 1010: 752–763.
- Maalej M, Hentati D, Messai T, Kochbati L, El May A, et al. (2008) Breast cancer in Tunisia in 2004: a comparative clinical and epidemiological study. *Bull Cancer* 95: E5–9.
- El-Rehim D, Ali M (2009) Aberrant expression of beta-catenin in invasive ductal breast carcinomas. *Journal of the Egyptian National Cancer Institute* 21: 185–195.
- Ayadi L, Khabir A, Amouri H, Karray S, Dammak A, et al. (2008) Correlation of HER-2 over-expression with clinico-pathological parameters in Tunisian breast carcinoma. *World J Surg Oncol* 6: 112.
- Mohammad AM, Abdel HA, Abdel AM, Ahmed AM, Wael T, et al. (2006) Expression of cyclooxygenase-2 and 12-lipoxygenase in human breast cancer and their relationship with HER-2/neu and hormonal receptors: impact on prognosis and therapy. *Indian J Cancer* 43: 163–168.
- Karray-Chouayekh S, Trifa F, Khabir A, Boujelbene N, Sellami-Boudawara T, et al. (2010) Aberrant methylation of RASSF1A is associated with poor survival in Tunisian breast cancer patients. *J Cancer Res Clin Oncol* 136: 203–210.
- Moona MS, Alarabi RAR, Hussain A, Ahmad M, Mehdi I (2010) The study of ER (Oestrogen Receptor), PR (Progesterone Receptor) and HER-2/neu status in patients with breast cancer. *Jamahiriya Medical Journal* 10: 141–143.
- Zeeneldin AA, Mohamed AM, Abdel HA, Taha FM, Goda IA, et al. (2009) Survival effects of cyclooxygenase-2 and 12-lipoxygenase in Egyptian women with operable breast cancer. *Indian J Cancer* 46: 54–60.
- Tazzite A, Joughadi H, Saiss K, Benider A, Nadifi S (2013) Relationship between family history of breast cancer and clinicopathological features in moroccan patients. *Ethiop J Health Sci* 23: 150–157.
- Rashed MM, Ragab NM, Galal MK (2007) The association of HER-2/neu over-expression in relation to p53 nuclear accumulation, hormonal receptor status and common clinico-pathological prognostic parameters in a series of Egyptian women with invasive ductal carcinoma. *European Journal of General Medicine* 4: 73–79.
- Loueslati BY, Troudi W, Cherni L, Rhomdhane KB, Mota-Vieira L (2010) Germline HVR-II mitochondrial polymorphisms associated with breast cancer in Tunisian women. *Genet Mol Res* 9: 1690–1700.
- Abdelkrim SB, Trabelsi A, Missaoui N, Beizig N, Bdioui A, et al. (2010) Distribution of molecular breast cancer subtypes among Tunisian women and correlation with histopathological parameters: A study of 194 patients. *Pathol Res Pract* 206: 772–775.
- Awadelkarim KD, Arizzi C, Elamin EOM, Hamad HMA, Blasio Pd, et al. (2008) Pathological, clinical and prognostic characteristics of breast cancer in Central Sudan versus Northern Italy: implications for breast cancer in Africa. *Histopathology* 52: 445–456.
- Salhia B, Tapia C, Ishak EA, Gaber S, Berghuis B, et al. (2011) Molecular subtype analysis determines the association of advanced breast cancer in Egypt with favorable biology. *BMC Womens Health* 11.
- El Mongy M, El Hossieny H, Haggag F, Fathy R (2010) Clinico-pathological study and treatment results of 1009 operable breast cancer cases: Experience of

- NCI Cairo University, Egypt. *Chinese-German Journal of Clinical Oncology* 9: 409–415.
51. Abu-Bedair FA, El-Gamal BA, Ibrahim NA, El-Aaser AA (2000) Hormonal profiles and estrogen receptors in Egyptian female breast cancer patients. *Tumori* 86: 24–29.
  52. Hussein O, Mosbah M, Farouk O, Farag K, El-Saed A, et al. (2013) Hormone receptors and age distribution in breast cancer patients at a university hospital in northern Egypt. *Breast Cancer: Basic and Clinical Research* 7: 51–57.
  53. Kallel I, Kharrat N, Al-fadhly S, Rebai M, Khabir A, et al. (2010) HER2 polymorphisms and breast cancer in Tunisian women. *Genet Test Mol Biomarkers* 14: 29–35.
  54. Marzouk D, Gaafary M, Damaty S, Sabbour S, Mecky F, et al. (2009) Breast cancer and hormonal intake among Egyptian females. *Eur J Oncol* 14: 37–51.
  55. Chaher N, Arias-Pulido H, Terki N, Qualls C, Bouzid K, et al. (2012) Molecular and epidemiological characteristics of inflammatory breast cancer in Algerian patients. *Breast Cancer Res Tr* 131: 437–444.
  56. Youssef N, Hewedi I, Raboh N (2008) Immunohistochemical expression of survivin in breast carcinoma: relationship with clinicopathological parameters, proliferation and molecular classification. *Journal of the Egyptian National Cancer Institute* 20: 348–357.
  57. Ermiah E, Buhmeida A, Khaled BR, Abdalla F, Salem N, et al. (2013) Prognostic value of bcl-2 expression among women with breast cancer in Libya. *Tumour Biol* 34: 1569–1578.
  58. Asaad NY, Kandil MAEH, Shaban MI (2003) Prognostic significance of maspin expression in breast carcinoma. *Cancer Mol Biol* 10: 1937–1951.
  59. Hafez N, Tahoun N (2010) Assessment of the reliability of immunocytochemical detection of estrogen and progesterone receptors status on the cytological aspirates of breast carcinoma. *Journal of the Egyptian National Cancer Institute* 22: 217–225.
  60. Swellam M, Ismail M, Eissa S, Hamdy M, Mokhtar N (2004) Emerging role of P53, Bcl-2 and telomerase activity in Egyptian breast cancer patients. *IUBMB Life* 56: 483–490.
  61. Abdel-Fattah M, Lotfy NS, Bassili A, Anwar M, Mari E, et al. (2001) Current treatment modalities of breast-cancer patients in Alexandria, Egypt. *Breast* 10: 523–529.
  62. Alieldin NH, Abo-Elazm OM, Bilal D, Salem SE, Gouda E, et al. (2014) Age at diagnosis in women with non-metastatic breast cancer: Is it related to prognosis? *Journal of the Egyptian National Cancer Institute* 26: 23–30.
  63. Boder J, Abdalla F, Elfagieh M, Buhmeida A, Collan Y (2013) Proliferative activity in Libyan breast cancer with comparison to European and central African patients. *BioMed Research International* 2013.
  64. Bouzid N, Lahmar R, Tebra S, Bouaouina N (2013) Breast cancer in woman younger than 35 years in Tunisia: Retrospective study about 124 cases. [French] *Cancer du sein chez la femme jeune de moins de 35 ans en Tunisie: etude retrospective a propos de 124 cas. Gynecologie Obstetrique Fertilité* 41: 356–360.
  65. Elesawy BH, Abd El Hafez A, Shawky AEA, Arafa M (2014) Immunohistochemistry-based subtyping of breast carcinoma in Egyptian women: a clinicopathologic study on 125 patients. *Ann Diagn Pathol* 18: 21–26.
  66. El-Shinawi M, Mohamed HT, El-Ghonaimy EA, Tantawy M, Younis A, et al. (2013) Human cytomegalovirus infection enhances NF- $\kappa$ B/p65 signaling in inflammatory breast cancer patients. *PLoS ONE* 8: e55755.
  67. Hagrass HA, Pasha HF, Shaheen MA, Abdel Bary EH, Kassem R (2014) Methylation status and protein expression of RASSF1A in breast cancer patients. *Mol Biol Rep* 41: 57–65.
  68. Ismaili N, Elyaaakoubi H, Bensouda Y, Errihani H (2014) Demographic, clinical, pathological, molecular, treatment characteristics and outcomes of nonmetastatic inflammatory breast cancer in Morocco: 2007 and 2008. *Experimental Hematology and Oncology* 3.
  69. Rashad YA, Elkhodary TR, El-Gayar AM, Eissa LA (2014) Evaluation of serum levels of HER2, MMP-9, nitric oxide, and total antioxidant capacity in Egyptian breast cancer patients: correlation with clinico-pathological parameters. *Scientia Pharmaceutica* 82: 129–145.
  70. Bekkouche Z, Guedouar Y, Ben Ali F, El Kebir FZ (2013) Characteristics of triple-negative breast carcinomas in west Algeria. [French] *Caractéristiques des carcinomes mammaires triple-négatifs dans l'Ouest-algerien. Journal Africain du Cancer* 5: 155–161.
  71. Salama A, El-Fendy H, Talaat S, Bayomi B, Amin A (2013) Prognostic value of immunohistochemical stratification of invasive duct carcinoma of the breast. *Chinese-German Journal of Clinical Oncology* 12: P265–P272.
  72. Hirko KA, Soliman AS, Hablas A, Seifeldin IA, Ramadan M, et al. (2013) Trends in breast cancer incidence rates by age and stage at diagnosis in gharbiah, Egypt, over 10 years (1999–2008). *Journal of Cancer Epidemiology* 2013.
  73. Dey S, Soliman AS, Hablas A, Seifeldin IA, Ismail K, et al. (2010) Urban-rural differences in breast cancer incidence by hormone receptor status across 6 years in Egypt. *Breast Cancer Res Treat* 120: 149–160.
  74. Ugiagbe EE, Obaseki DE, Oluwasola AO, Olu-Eddo AN, Akhiwu WO (2012) Frequency of distribution of oestrogen and progesterone receptors positivities in breast cancer cases in Benin-City, Nigeria. *Nigerian Postgraduate Medical Journal* 19: 19–24.
  75. Iyare F (2007) Immunohistochemical characteristics of breast cancers in South East Nigeria. *Ebonyi Medical Journal* 6: 9–12.
  76. Agboola AJ, Musa AA, Wanangwa N, Abdel-Fatah T, Nolan CC, et al. (2012) Molecular characteristics and prognostic features of breast cancer in Nigerian compared with UK women. *Breast Cancer Res Treat* 135: 555–569.
  77. Ikpat OF, Ndoma-Egba R (2003) Oestrogen and progesterone receptors in Nigerian breast cancer: relationship to tumour histopathology and survival of patients. *Cent Afr J Med* 49: 122–126.
  78. Stark A, Kleer CG, Martin I, Awuah B, Nsiah-Asare A, et al. (2010) African ancestry and higher prevalence of triple-negative breast cancer: findings from an international study. *Cancer* 116: 4926–4932.
  79. Gukas ID, Jennings BA, Mandong BM, Igun GO, Girling AC, et al. (2005) Clinicopathological features and molecular markers of breast cancer in Jos, Nigeria. *West Afr J Med* 24: 209–213.
  80. Schwartz T, Stark A, Pang J, Awuah B, Kleer CG, et al. (2013) Expression of aldehyde dehydrogenase 1 as a marker of mammary stem cells in benign and malignant breast lesions of Ghanaian women. *Cancer* 119: 488–494.
  81. Mbonde MP, Amir H, Aklsen LA, Kitinya JN (2001) Expression of oestrogen and progesterone receptors, Ki-67, p53 and BCL-2 proteins, cathepsin D, urokinase plasminogen activator and urokinase plasminogen activator-receptors in carcinomas of the female breast in an African population. *East Afr Med J* 78: 360–365.
  82. Nyagol J, Nyong'o A, Byakika B, Muchiri L, Cocco M, et al. (2006) Routine assessment of hormonal receptor and her-2/neu status underscores the need for more therapeutic targets in Kenyan women with breast cancer. *Anal Quant Cytol Histol* 28: 97–103.
  83. Nalwoga H, Arnes JB, Wabinga H, Aklsen LA (2010) Expression of aldehyde dehydrogenase 1 (ALDH1) is associated with basal-like markers and features of aggressive tumours in African breast cancer. *Br J Cancer* 102: 369–375.
  84. Ly M, Antoine M, Dembele AK, Levy P, Rodenas A, et al. (2012) High incidence of triple-negative tumors in sub-saharan Africa: a prospective study of breast cancer characteristics and risk factors in Malian women seen in a Bamako university hospital. *Oncology* 83: 257–263.
  85. Yarney J, Vanderpuye V, Clegg Lamptey JN (2008) Hormone receptor and HER-2 expression in breast cancers among Sub-Saharan African women. *Breast J* 14: 510–511.
  86. Galukande M, Wabinga H, Mirembe F, Karamagi C, Asea A (2013) Difference in risk factors for breast cancer by ER status in an indigenous African population. *ISRN Oncology* 1.
  87. Ohene-Yeboah M, Adjei E (2012) Breast cancer in Kumasi, Ghana. *Ghana Medical Journal* 46: 8–13.
  88. Burson AM, Soliman AS, Ngoma TA, Mwaiselage J, Ogweyo P, et al. (2010) Clinical and epidemiologic profile of breast cancer in Tanzania. *Breast Dis* 31: 33–41.
  89. Savage N, Levin J, De Moor NG, Lange M (1981) Cytosolic oestrogen receptor content of breast cancer tissue in blacks and whites. *S Afr Med J* 59: 623–624.
  90. Winters Z, Mammell A, Esser JD (1988) Breast cancer in black South Africans. *S Afr J Surg* 26: 69–70.
  91. Collings JR, Levin J, Savage N (1980) Racial differences in oestrogen receptor and peroxidase status of human breast cancer tissue. *S Afr Med J* 57: 444–446.
  92. Van Bogaert IJ (2013) Breast cancer molecular subtypes as identified by immunohistochemistry in South African black women. *Breast Journal* 19: 210–211.
  93. Basro S, Apffelstaedt JP (2010) Breast cancer in young women in a limited-resource environment. *World J Surg* 34: 1427–1433.
  94. Togo A, Kante L, Dembele BT, Traore A, Diakite I, et al. (2010) Breast cancer in Bamako hospitals: epidemiologic and diagnostic aspects. *Medecine d'Afrique Noire* 57: 249–253.
  95. Emile Hasiniatsy NR, Vololonantainaina CR, Rabarikoto HF, Razafimanjato N, Ranoharison HD, et al. (2014) First results of hormone receptors' status in Malagasy women with invasive breast cancer. *Pan African Medical Journal* 17.
  96. Khoury T, Sait S, Hwang H, Chandrasekhar R, Wilding G, et al. (2009) Delay to formalin fixation effect on breast biomarkers. *Mod Pathol* 22: 1457–1467.
  97. Wasielewski R, Hasselmann S, Ruschoff J, Fissler-Eckhoff A, Kreipe H (2008) Proficiency testing of immunohistochemical biomarker assays in breast cancer. *Virchows Arch* 453: 537–543.
  98. Hammond ME, Hayes DF, Wolff AC, Mangu PB, Temin S (2010) American society of clinical oncology/college of american pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Oncol Pract* 6: 195–197.
  99. Moultrie TA, Sayi TS, Timaeus IM (2012) Birth intervals, postponement, and fertility decline in Africa: a new type of transition? *Popul Stud (Camb)* 66: 241–258.
  100. Pelletier D, Rahn M (1998) Trends in body mass index in developing countries. *Food Nutr Bull* 19: 223–238.
  101. James P (2004) Obesity: the worldwide epidemic. *Clin Dermatol* 22: 276–280.
  102. Clarke C, Keegan T, Yang J, Press D, Kurian A, et al. (2012) Age-specific incidence of breast cancer subtypes: understanding the black-white crossover. *J Natl Cancer Inst* 104: 1094–1101.
  103. Vona-Davis L, Rose D, Hazard H, Howard-McNatt M, Adkins F, et al. (2008) Triple-negative breast cancer and obesity in a rural Appalachian population. *Cancer Epidemiol Biomarkers Prev* 17: 3319–3324.
  104. Phipps A, Chlebowski R, Prentice R, McTiernan A, Wactawski-Wende J, et al. (2011) Reproductive history and oral contraceptive use in relation to risk of triple-negative breast cancer. *J Natl Cancer Inst* 103: 470–477.

105. Dolle J, Daling J, White E, Brinton L, Doody D, et al. (2009) Risk factors for triple-negative breast cancer in women under the age of 45 years. *Cancer Epidemiol Biomarkers Prev* 18: 1157–1166.
106. Palmer J, Ruiz-Narvaez E, Rotimi C, Cupples L, Cozier Y, et al. (2013) Genetic susceptibility loci for subtypes of breast cancer in an African American population. *Cancer Epidemiol Biomarkers Prev* 22: 127–134.
107. Ruiz-Narvaez E, Rosenberg L, Rotimi C, Cupples L, Boggs D, et al. (2010) Genetic variants on chromosome 5p12 are associated with risk of breast cancer in African American women: the Black Women's Health Study. *Breast Cancer Res Treat* 123: 525–530.
108. Su Y, Zheng Y, Zheng W, Gu K, Chen Z, et al. (2011) Distinct distribution and prognostic significance of molecular subtypes of breast cancer in Chinese women: a population-based cohort study. *BMC Cancer* 11: 292.
109. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, et al. (2006) Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA* 295: 2492–2502.

## Editors' Summary

**Background.** Breast cancer is the commonest female tumor in Africa and death rates from the disease in some African countries are among the highest in the world. Breast cancer begins when cells in the breast acquire genetic changes that allow them to grow uncontrollably and to move around the body. When a breast lump is found (by mammography or manual examination), a few cells are collected from the lump (a biopsy) to look for abnormal cells and to test for the presence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) on the cells. The hormones estrogen and progesterone promote the growth of normal breast cells and of ER+ and PR+ breast cancer cells. HER2 also controls the growth of breast cells. The receptor status of breast cancer is a major determinant of treatment options and prognosis (likely outcome). ER+ tumors, for example, are more receptive to hormonal therapy and have a better prognosis than ER– tumors, whereas HER2+ tumors, which make large amounts of HER2, are more aggressive than HER2– tumors. Breast cancer is treated by surgically removing the lump or the whole breast (mastectomy) if the tumor has already spread, before killing any remaining cancer cells with chemotherapy or radiotherapy. In addition, ER+, PR+, and HER2+ tumors are treated with drugs that block these receptors (including tamoxifen and trastuzumab), thereby slowing breast cancer growth.

**Why Was This Study Done?** ER+ tumors predominate in white women but the proportion of ER+ tumors among US-born black women is slightly lower. The frequency of different receptor-defined subtypes of breast cancer in indigenous populations in Africa is currently unclear but policy makers need this information to help them decide whether routine receptor status testing should be introduced across Africa. Because receptor status is a major determination of treatment options and outcomes, it would be more important to introduce receptor testing if all subtypes are present in breast cancers in indigenous African women and if no one subtype dominates than if most breast cancers in these women are ER+. In this systematic review (a study that uses pre-defined criteria to identify all the research on a given topic) and meta-analysis (a statistical approach that combines the results of several studies), the researchers examine the distribution of receptor-defined breast cancer subtypes in indigenous populations in Africa.

**What Did the Researchers Do and Find?** The researchers identified 54 relevant studies from North Africa involving 12,284 women with breast cancer (mainly living in Egypt or Tunisia) and 26 studies from sub-Saharan Africa involving 4,737 women with breast cancer (mainly living in Nigeria or South Africa) and used the data from these studies to calculate the proportions of ER+, PR+, and HER2+ tumors (the number of receptor-positive tumors divided by the number of tumors with known receptor status) across Africa. The proportion of ER+ tumors varied markedly between

studies, ranging between 0.40 and 0.80 in North Africa and between 0.20 and 0.70 in sub-Saharan Africa. Among prospectively collected samples (samples collected specifically for receptor-status testing; studies that determined the receptor status of breast cancers using stored samples reported a lower proportion of ER+ disease than studies that used prospectively collected samples), the overall pooled proportions of ER+ and triple negative tumors were 0.59 and 0.21, respectively.

**What Do These Findings Mean?** Although these findings highlight the scarcity of data on hormone receptor and HER2 status in breast cancers in indigenous African populations, they provide new information about the distribution of breast cancer subtypes in Africa. Specifically, these findings suggest that although slightly more than half of breast cancers in Africa are ER+, no single subtype dominates. They also suggest that the distribution of receptor-defined breast cancer subtypes in Africa is similar to that found in Western populations. The accuracy of these findings is likely to be affected by the low methodological quality of many of the studies and the lack of standardized procedures. Thus, large well-designed studies are still needed to accurately quantify the distribution of various breast cancer subtypes across Africa. In the meantime, the current findings support the introduction of routine receptor testing across Africa, especially for young women with early stage breast cancer in whom the potential to improve survival and reduce the years of life lost by knowing the receptor status of an individual's tumor is greatest.

**Additional Information.** Please access these websites via the online version of this summary at <http://dx.doi.org/10.1371/journal.pmed.1001720>.

- This study is further discussed in a *PLOS Medicine* Perspective by Sulma i Mohammed
- The US National Cancer Institute (NCI) provides comprehensive information about cancer (in English and Spanish), including detailed information for patients and professionals about breast cancer including an online booklet for patients
- Cancer Research UK, a not-for profit organization, provides information about cancer; its detailed information about breast cancer includes sections on tests for hormone receptors and HER2 and on treatments that target hormone receptors and treatments that target HER2
- Breastcancer.org is a not-for-profit organization that provides up-to-date information about breast cancer (in English and Spanish), including information on hormone receptor status and HER2 status
- The UK National Health Service Choices website has information and personal stories about breast cancer; the not-for profit organization Healthtalkonline also provides personal stories about dealing with breast cancer