

## Review Article

# The Landscape of Randomised Controlled Trials of Therapies in Breast Cancer in Low and Middle Income Countries

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**Objectives.** The objectives of this study were to identify the randomised controlled trials in breast cancer occurring in low and middle income countries (LMICs) generally and within Sub-Saharan Africa specifically, to describe the current status and identify opportunities for further research in these areas. **Materials and Methods.** Data for this study were obtained from ClinicalTrials.gov. The search term “Breast Cancer Research” was used, and relevant information extracted and analysed. **Results.** 2414 trials were identified, of which 1099 were eligible for inclusion. 69 of these trials occurred in LMICs. Of the 52 LMICs globally, 30% were participating in breast cancer research. Of the 17 LMICs in Africa, 77% are situated in Sub-Saharan Africa; 23% were participating in breast cancer research, which accounted for 9% of total Sub-Saharan African studies. **Conclusion.** This study provides current evidence for the need for breast cancer research in LMICs globally and within Sub-Saharan Africa. Within LMIC regions where research is active, the type and numbers of studies are unevenly distributed. High quality research within such areas should be encouraged as the results may have both local and global applications, particularly in the provision of affordable health care.

## 1. Introduction

In 2012, women from less developed countries were less than half as likely to develop breast cancer by the age of 75 compared to those from more developed countries (8% v 3.3%), yet almost just as likely to die from breast cancer (1.6% v 1.2%) (see Figures 1 and 2) [1]. Safe and effective therapies continue to be developed; however their escalating cost means they are increasingly becoming out of reach of the patients who need them. Howard et al. [2] emphasised this trend by calculating the average launch price of anticancer drugs from 1995 to 2013, adjusted for inflation and health benefits. They found an increase of 10% annually—an average of \$8,500 per year. Considering that it is estimated that by 2020 70% of the twenty million new cancer cases will occur in countries that collectively have only five percent of the global resources for cancer control [3], this trend will have global repercussions. Lower to middle income countries (LMICs) will be at the epicentre of the eruption that occurs when the high cost of treatment, coupled with increasing incidence rates, collides with a lack of access and ability to pay,

unless suitable alternatives can be found. Such alternatives have to provide affordable, simple, and widely accessible solutions. Furthermore, in order to achieve global equality in long term breast cancer incidence and mortality, more evidence-based research addressing particular circumstances in LMICs themselves is required. This will generate the highest level of evidence in breast cancer research in LMICs to be produced. Factors influencing incidence, access to treatment, and mortality are to be identified and solutions formulated and scrutinised based upon these constraints, rather than continuing the expensive and evidence-poor culture of implementing effective treatment methods identified in high income countries (HICs) [4].

We have prepared an overview of randomised controlled trials currently being run in LMICs, in order to identify areas where further research is needed.

## 2. Materials and Methods

A descriptive analysis was performed of all of the trials with one or more locations in an LMIC. Data was extracted from

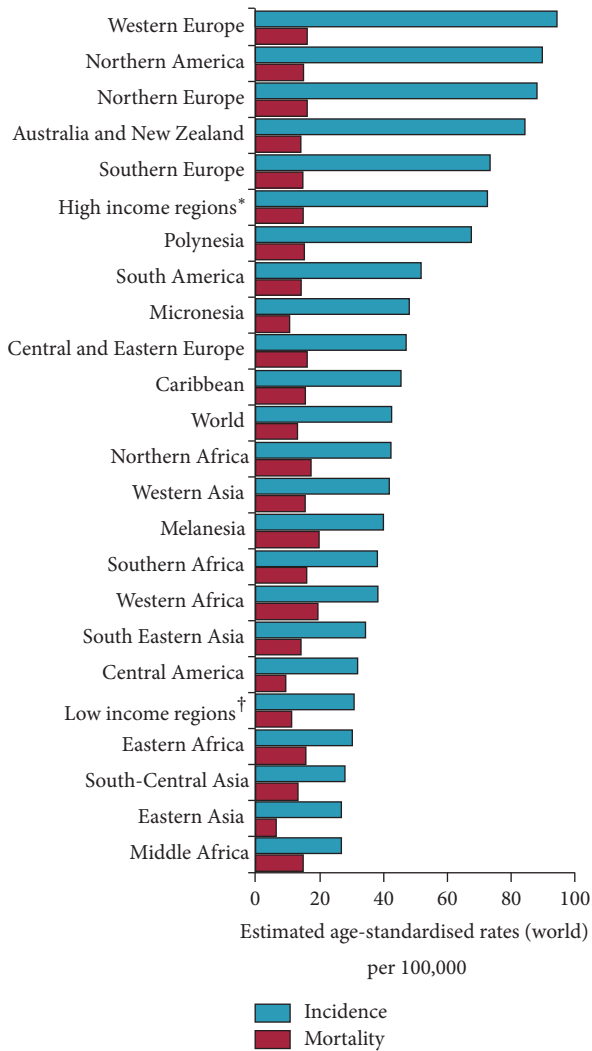


FIGURE 1: Global breast cancer incidence and mortality in women in 2012. Estimated age-standardised rates for breast cancer incidence (blue bar) and mortality (red bar) in females are shown for global regions, high income regions, low income regions, and the world. Reproduced with permission from Abenaa M Brewster, Mariana Chavez-MacGregor, and Powel Brown. \* includes all regions of Europe, Northern America, Australia, New Zealand, and Japan. † includes all regions of Africa, Asia (excluding Japan), Latin America, the Caribbean, and Federated States of Micronesia.

ClinicalTrials.gov, a publicly available database of clinical trials [5]. On 29 August 2016 the search term “Breast Cancer Research” was applied to the 223,969 trials registered on ClinicalTrials.gov. The search results were downloaded onto a spreadsheet for tabulation and analysis. Trials with a withdrawn status and those that did not specify that they were randomised were excluded.

LMICs were grouped into the geographical regions South Asia, South East Asia, East Asia, Middle East, North Asia, Pacifica, Africa, South America, Central America, North America, and Europe as defined by clinicaltrials.gov, the US Congress definition of Sub-Saharan Africa was used (Table 1). South Sudan was not distinguished from Sudan

in the clinicaltrials.gov database. For regional analysis, each region was selected on the website and the studies for each LMIC within a region were downloaded. Withdrawn trials and trials that did not specify a randomised status were excluded. Trials were crosschecked using NCT numbers to remove duplicates (trials listed twice or those which occurred in more than one LMIC).

Intraregional analysis, using the spreadsheets described above, was conducted on regions with a large number of trials occurring in that region, to identify intraregional distribution of trials within LMICs. Duplicate entries were removed from the number of trials tabulated within each LMIC in South Asia, South East Asia, North Asia, and Africa. For interventional analysis, the regional spreadsheets were used to determine the number of trials using each intervention. The data extracted for each trial included the recruitment status, study results, conditions, interventions, sponsor/collaborators, gender, age groups, phases, enrolment, source of funding, study type, first received, start date, completion date, results first received, and primary outcome.

### 3. Results

Of the initial 2414 trials, 1099 fit the criteria for inclusion in the analysis. Trials that did not specify that they were randomised or that had the recruitment status “withdrawn” were excluded. 1315 trials were excluded. Trial names and ClinicalTrials.gov identification numbers of all included trials are listed in the Appendix.

**3.1. Global Results (Tables 2 and 3).** Of the 1099 trials included in the analysis, 69 (6.3%) occurred in one or more LMICs. Lower to middle income countries were identified 104 times for these 69 trials.

Of the 52 LMICs identified by the World Bank (Table 1), 30.8% (16) had breast cancer research located within them. 5 (9.6%) are located in South Asia, 7 (13.5%) are located in South East Asia, 1 (1.9%) is in East Asia, 3 (5.8%) are located in the Middle East, 6 (11.5%) are located in North Asia, 7 (13.5%) are in Pacifica, 17 (32.7%) are in Africa, 1 (1.9%) is in South America, 4 (7.7%) are in Central America, and 1 (1.9%) is in Europe (Table 2). No LMICs are located in North America.

The percentage of LMICs that contained active breast cancer research in each region was identified as 60% in South Asia (3), 42.9% (3) in South East Asia, 0% in East Asia, 0% in the Middle East, 16.7% (1) in North Asia, 0% in Pacifica, 35.3% (6) in Africa, 100% (1) in South America, 50% (2) in Central America, and 0% in Europe (Table 3).

**3.2. Intraregional Analysis.** 35 breast cancer research trials were located at 37 sites amongst the 3 LMICs of South Asia (India, Pakistan, and Bangladesh). Of the 37 sites, 34 (91.9%) were located in India, 2 (5.4%) were located in Pakistan, and 1 (2.7%) was located in Bangladesh. 12 breast cancer research trials were located at 16 sites amongst the 3 active LMICs in South East Asia (Philippines, Vietnam, and Indonesia). Of the 16 sites, 12 (75%) were located in the Philippines, 2 (12.5%) in Vietnam, and 2 (12.5%) in Indonesia. 25 breast

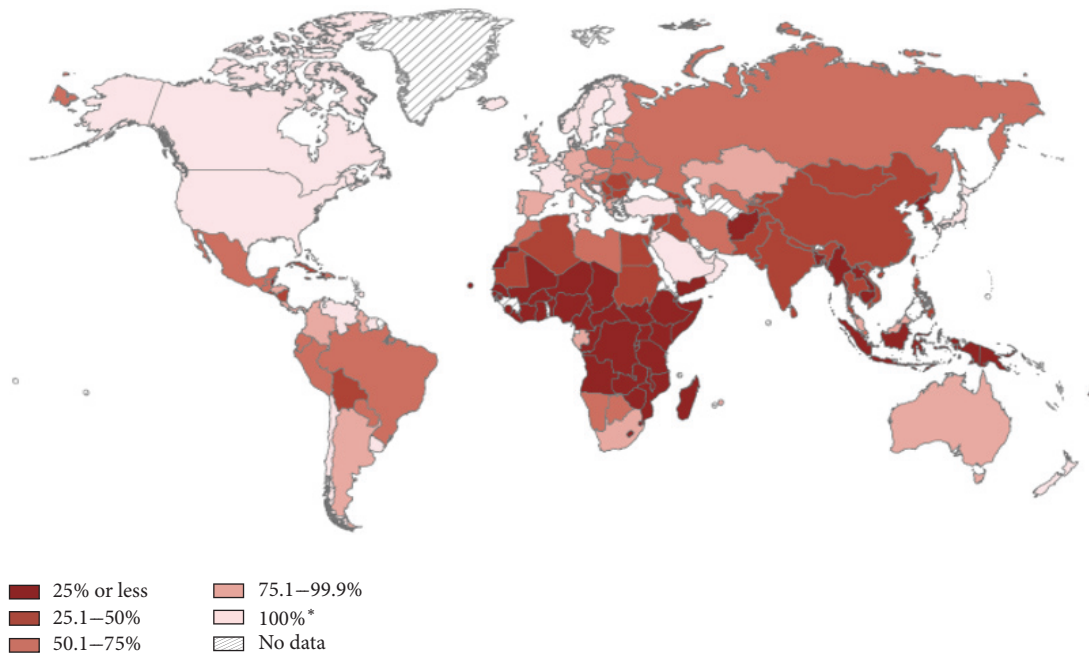


FIGURE 2: Global cancer statistics regarding the estimated percentage of patients with access to radiotherapy, 2012. Reproduced with permission from Volume 65, Issue 2, pages 87–108, 4 FEB 2015. \* refers to countries where 100% of the population can access radiotherapy or countries where radiotherapy is greater in supply than demand, despite possible regional differences in access to radiotherapy within the country. Source: The Cancer Atlas, second edition, as obtained from the International Atomic Energy Agency.

TABLE 1: Lower-middle income economies as defined by the World Bank. LMICs are categorized regionally based upon clinicaltrials.gov regional definitions. Countries written in italic font participate in RCTs in breast cancer research. Countries denoted with \*\* are members of Sub-Saharan Africa (US Congress definition).

Africa	South East Asia	East Asia
Cabo Verde**	<i>Indonesia</i>	Mongolia
Cameroon**	Lao PDR	
Congo, Rep.**	Myanmar	Middle East
Cote d'Ivoire**	<i>Philippines</i>	Syrian Arab Republic
Djibouti**	<i>Vietnam</i>	West Bank and Gaza
<i>Egypt, Arab Rep.</i>	Timor-Leste	Yemen, Rep.
<i>Ghana</i> **	Cambodia	
<i>Kenya</i> **		Pacific
Lesotho**	South Asia	Kiribati
Mauritania**	<i>Bangladesh</i>	Micronesia, Fed. Sts.
<i>Morocco</i>	Bhutan	Papua New Guinea
<i>Nigeria</i> **	<i>India</i>	Samoa
Sao Tome and Principe**	<i>Pakistan</i>	Solomon Islands
Sudan**	Sri Lanka	Vanuatu
Swaziland**		Tonga
Tunisia	South America	
Zambia**	<i>Bolivia</i>	Europe
		Kosovo
North Asia	Central America	<i>Ukraine</i>
Armenia	<i>El Salvador</i>	
Kyrgyz Republic	<i>Guatemala</i>	
Tajikistan	Honduras	
Uzbekistan	Nicaragua	
Moldova		

TABLE 2: *The proportion of global LMICs per region.* The proportion of LMICs in each region out of the total number of LMICs globally (52) was calculated to determine the distribution of LMICs globally.

Regions	Total regional LMICs	Proportion of global LMICs per region (%)
South Asia	5	9.6
South East Asia	7	13.5
East Asia	1	1.9
North Asia	6	11.5
Africa	17	32.7
South America	1	1.9
Central America	4	7.7
Europe	1	1.9
Middle East	3	5.8
Pacifica	7	13.5

TABLE 3: *The proportion of breast cancer research active LMICs per region.* The proportion of LMICs in each region undertaking breast cancer research was calculated to determine the distribution of research within each region.

Regions	Active research LMICs	Active research LMICs within region (%)
South Asia	3	60.0
South East Asia	3	42.9
East Asia	0	0.0
North Asia	1	16.7
Africa	6	35.3
South America	1	100.0
Central America	2	50.0
Europe	0	0.0
Middle East	0	0.0
Pacifica	0	0.0

cancer research trials were located at 25 LMIC sites in North Asia; all 25 were located in Ukraine.

15 breast cancer research trials were located at 21 sites amongst the 6 active LMICs of Africa (Morocco, Tunisia, Egypt, Kenya, Ghana, and Nigeria). Of the 21 sites, 3 were located in Morocco (14.3%), 1 was in Tunisia (4.8%), 12 were in Egypt (57.1%), 1 was in Kenya (4.8%), 1 was in Ghana (4.8%), and 3 were in Nigeria (14.3%).

3.3. *LMIC Breast Cancer Research Intervention (Table 4).* Intervention is categorised by clinicaltrials.gov as radiation, biological, behavioural, drug, other, or combinations of these options. For LMICs in each region, breast cancer research using drug intervention was the most common, representing at least 33.3% of the total breast cancer research in each region alone, and in combination with other categories; research containing a drug intervention represented 100% of the research in South East Asia and North Asia and 67% of the total breast cancer research in Central America, whilst only 20% of African breast cancer research on LMICs was

not involving a drug intervention. Regions with the largest numbers of breast cancer research trials occurring in LMICs (Africa, South Asia, and North Asia) exhibited intervention with a large focus around the drug intervention type (60.0%, 68.6%, and 65.4%, resp.) with all other intervention types evenly distributed at a low frequency. Regions with fewer LMIC breast cancer research trials (Central America and East Asia) exhibited a more even distribution of intervention type; however this was still heavily focused around the drug intervention type. South America exhibited no drug or associated drug intervention, with 100% of its intervention focused on device and other intervention.

3.4. *Sub-Saharan Africa.* Of the 44 total countries that make up Sub-Saharan Africa, 4 (9%) have studies located within them (Nigeria, Kenya, Ghana, and South Africa).

Of the 17 LMICs in Africa (Table 1), 13 (76.5%) are located in Sub-Saharan Africa (Table 1); 3 of these countries (23.1%) contain breast cancer research.

Of the total 54 studies located at sites in Sub-Saharan Africa, 5 (9.3%) are located in LMICs, with the remaining 49 (90.7%) located in South Africa.

Of the 6 LMICs where research is undertaken in Africa, 60% (3) are located in Sub-Saharan Africa. They account for 23.8% (5) of the total LMIC sites in Africa, and 4 (26.6%) of the total LMIC studies in Africa. The remaining three African LMICs are located in North Africa (Egypt, Tunisia, and Morocco). These accounted for 16 (76.2%) of the total sites, and 11 (73.3%) of the total studies in LMICs in Africa.

## 4. Discussion

Our results show that, of the 1099 trials included in the analysis, 70 (6.4%) occurred in an LMIC, across 104 LMIC sites. Studies are unevenly distributed amongst regions: less than one-third of LMICs are undertaking breast cancer research globally, and in the Middle East, Pacifica, East Asia, and Europe there is no breast cancer research occurring in LMICs, despite Pacifica accounting for 13.5% of the world's LMICs.

Although some regions, such as South Asia, have a high percentage of breast cancer research in LMICs (60%), there is evidence that this is monopolised by one country. For example, 92% of the current breast cancer research studies located in LMICs in South Asia are undertaken in India where the healthcare expenditure per capita for 2012 is approximately double (1.7 and 2.2 times) that of Pakistan and Bangladesh, respectively [1]. A similar situation was found in Africa, where three North African LMICs (Egypt, Tunisia, and Morocco) are collectively responsible for 76% (16 of 21) of the total LMIC studies located in Africa.

Despite making up 44 of the 51 African countries, Sub-Saharan Africa is hugely lacking in breast cancer research. Sub-Saharan LMICs currently account for only 9.3% of the total studies located in Africa. Equally, only 4 (9%) of all Sub-Saharan African countries are undertaking breast cancer research trials. Furthermore, the distribution of total research within Sub-Saharan Africa is distorted; for example, South Africa undertakes 91% of the total 54 Sub-Saharan African

TABLE 4: *Types of intervention for RCTs in breast cancer research in LMICs in each region.* The percentage for each intervention was calculated. North America and East Asia are not included due to no LMICs being present in these regions.

Intervention	South America (%)	Central America (%)	North Asia (%)	South East Asia (%)	South Asia (%)	Africa (%)
Total number of studies	1	3	25	12	35	15
Procedure	0.0	0.0	0.0	0.0	0.0	6.7
Radiation	0.0	0.0	0.0	0.0	2.9	13.3
Other	0.0	0.0	0.0	0.0	2.9	0.0
Biological	0.0	0.0	3.8	0.0	2.9	0.0
Behavioural	0.0	0.0	0.0	0.0	2.9	0.0
Drug	0.0	33.3	65.4	58.3	68.6	60.0
Drug and radiation	0.0	0.0	0.0	0.0	2.9	0.0
Drug and procedure	0.0	0.0	11.5	33.3	2.9	13.3
Drug and procedure and radiation	0.0	0.0	0.0	0.0	2.9	0.0
Drug and procedure and other	0.0	0.0	0.0	0.0	2.9	0.0
Drug and Other	0.0	33.3	7.7	8.3	2.9	0.0
Drug and biological	0.0	0.0	11.5	0.0	5.7	6.7
Drug and behavioural	0.0	0.0	0.0	0.0	0.0	0.0
Procedure and biological	0.0	33.3	0.0	0.0	0.0	0.0
Device and other	100.0	0.0	0.0	0.0	0.0	0.0

studies, despite having a breast cancer mortality rate 2.1 times that of Kenya, 4 times that of Ghana, and less than one-third (29%) that of Nigeria, and a health care expenditure per capita for 2012 15.5 times that of Kenya, 7.6 times that of Ghana, and 7 times that of Nigeria.

As identified by Elzawawy [6], national cancer control programs may be present in LMICs; however they are global solutions implemented in countries with local challenges, causing limited accessibility and affordability. Chemotherapeutic-protocols from high income countries cannot be used in low income countries due to the lack of supportive care facilities and trained personnel. Less intensive, less toxic, and less expensive protocols are needed [7]. Equally, radiotherapy is highly inaccessible to most patients in Africa. Access averages 0.89 machines per million inhabitants compared to 8.9 per million in high income countries [8]; 29 out of 52 African countries have no facilities at all [9].

As highlighted by Elzawawy [6], clinical trials in LMICs take place within the economic, social, and logistical constraints to healthcare found in these regions, which means that research outcomes from trials here are applicable to populations facing similar challenges in high income countries. At a local level, research would enable local challenges to be identified and specific, realistic interventions to be designed. Research in LMICs could help to ensure global targets are met, such as the 80% availability of affordable basic technologies and essential medicines set by the WHO for 2020.

The repurposing of medications could also help to reach these targets, by providing a simple, cheap, effective alternative that is scientifically robust as well as realistic in the treatment of breast cancer. For example, the analgesic ketorolac, a relatively inexpensive nonsteroidal anti-inflammatory

drug, given perioperatively is associated with a significantly superior disease-free survival in the first few years after surgery [10]. A simple treatment such as this would also be applicable to populations who, despite living in HICs, cannot afford therapies that are more expensive. Akinyemiju et al. [11] found that more than half of the African-American women diagnosed with breast cancer studied received no radiation or surgery as the first course of treatment despite 35% of cases being diagnosed at stages III or IV.

Furthermore, regions such as Africa can provide large groups of patients with a high prevalence of specific subtypes and stages of breast cancer for research and clinical trials. These populations are less prevalent in HICs, making studies in these populations very difficult and expensive. The research outcomes from such studies could be hugely beneficial to women worldwide. For example, African female populations present a higher proportion of triple-negative, hormone receptor negative tumours at a later stage. Research in these populations could provide a better understanding of type-specific cancers but also have applications in HICs with large populations of African ancestry. For example, in the USA, the lifetime risk of African-American women developing triple-negative breast cancer is almost double that of other races [11] and accounts for 20% of the breast cancer mortality rate in the USA despite only a 12% prevalence.

As discussed by Akinyemiju et al. [11], clinical trials conducted in LMICs need to have clear guidance regarding ethical conduct. Such trials must demonstrate an ethical control arm and maintain a local aim, with the potential of global extrapolation. With this in mind, it is ethical for the control arm to be placebo-based, so that potential value treatments are compared to no treatment rather than the ideal treatment, which by definition is too expensive and logistically convoluted to be accessed in the local community.

It is crucial that this methodology for testing potential treatments must only be used if such treatments can realistically be implemented in the testing community. However, to maintain long term viability, trials in LMICs must be appropriately balanced between being ethical, beneficial to those undertaking them and the wider community and yet realistic in these aims, to maintain economic viability for the sponsors.

Greater research capacity in LMICs would also benefit from and enable the formation of long term research collaborations between institutions in HICs and LMICs. Such collaborations have been successfully established and maintained in other research areas such as the Harvard University and Universite' Cheikh Anta Diop of Dakar, Senegal collaboration regarding HIV/AIDS, and are beneficial to both HICs and LMICs, HICs providing greater access to grant funding, and models for research and infrastructure for LMICs, which in turn provide regional disease experience and knowledge, grant access, experienced public health officials, alternative demographics, and affordable treatments for HICs [12]. Greater breast cancer research in LMICs would provide the opportunity for such collaborations between LMICs and HICs to take place, stimulating both further research in LMICs, and the production of greater clinical and translational research, which has the potential to enhance global understanding of breast cancer and, crucially, provide affordable treatments.

## 5. Conclusions

Clearly there is insufficient research in LMICs globally. Less than one-third of LMICs participate in randomised controlled trials of breast cancer research; increasing the research undertaken in LMICs is fundamental if affordable, simple, and widely accessible healthcare treatments are to be discovered. Research in such regions will benefit the countries themselves by providing realistic treatment solutions that work around the constraints currently facing them. It can also provide affordable options to people globally who struggle to access treatments, which are rapidly increasing in price and complexity, making them an unrealistic and inaccessible option. In addition, LMICs enable research into specific subtypes of disease presenting at later stages. LMICs provide a research environment which, if harnessed, could produce solutions to not only the healthcare problems faced in these regions, but problems faced by people globally.

## Appendix

List of trials from ClinicalTrials.gov used in this study (see Supplementary Material available online at <https://doi.org/10.1155/2017/4259704>).

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## References

- [1] World Health Organization, *GLOBOCAN 2012*, 2015.
- [2] D. H. Howard, P. B. Bach, E. R. Berndt, and R. M. Conti, "Pricing in the market for anticancer drugs," *Journal of Economic Perspectives*, vol. 29, no. 1, pp. 139–162, 2015.
- [3] K. Sikora, "Developing a global strategy for cancer," *European Journal of Cancer*, vol. 35, no. 14, pp. 1870–1877, 1999.
- [4] M. M. Demment, K. Peters, J. A. Dykens et al., "Developing the evidence base to inform best practice: a scoping study of breast and cervical cancer reviews in low- and middle-income countries," *PLoS ONE*, vol. 10, no. 9, Article ID e0134618, 2015.
- [5] U.S. National Institutes of Health, ClinicalTrials.gov, 2015, <https://clinicaltrials.gov>.
- [6] A. M. Elzawawy, "Could African and low- and middle-income countries contribute scientifically to global cancer care?" *Journal of Global Oncology*, vol. 1, no. 2, pp. 49–53, 2015.
- [7] S. Mostert, F. Njuguna, G. Olbara et al., "Corruption in health-care systems and its effect on cancer care in Africa," *The Lancet Oncology*, vol. 16, no. 8, pp. e394–e404, 2015.
- [8] D. Rodin, D. Jaffray, R. Atun, F. M. Knaul, and M. Gospodarowicz, "The need to expand global access to radiotherapy," *The Lancet Oncology*, vol. 15, no. 4, pp. 378–380, 2014.
- [9] M. Abdel-Wahab, J.-M. Bourque, Y. Pynda et al., "Status of radiotherapy resources in Africa: an international atomic energy agency analysis," *The Lancet Oncology*, vol. 14, no. 4, pp. e168–e175, 2013.
- [10] M. Retsky, R. Rogers, R. Demicheli et al., "NSAID analgesic ketorolac used perioperatively may suppress early breast cancer relapse: particular relevance to triple negative subgroup," *Breast Cancer Research and Treatment*, vol. 134, no. 2, pp. 881–888, 2012.
- [11] T. Akinyemiju, J. X. Moore, and S. F. Altekruze, "Breast cancer survival in African-American women by hormone receptor subtypes," *Breast Cancer Research and Treatment*, vol. 153, no. 1, pp. 211–218, 2015.
- [12] V. Prasad, H. Kumar, and S. Mailankody, "Ethics of clinical trials in low-resource settings: lessons from recent trials in cancer medicine," *Journal of Global Oncology*, vol. 2, no. 1, pp. 1–3, 2016.

## Appendix

### ClinicalTrials.gov trials used in this study

NCT02429427	NCT01609790	NCT01149083	NCT00828139	NCT00408408	NCT00086762
NCT02393833	NCT01602380	NCT01131195	NCT00789581	NCT00390455	NCT00082641
NCT02352779	NCT01594398	NCT01104935	NCT00785291	NCT00390169	NCT00079248
NCT02338310	NCT01593020	NCT01101438	NCT00770809	NCT00382070	NCT00078832
NCT02297412	NCT01579552	NCT01098955	NCT00769470	NCT00382018	NCT00077168
NCT02278900	NCT01572727	NCT01097642	NCT00769379	NCT00378703	NCT00077090
NCT02224261	NCT01557478	NCT01097278	NCT00721409	NCT00377156	NCT00075764
NCT02170415	NCT01547741	NCT01091428	NCT00698815	NCT00376597	NCT00074152
NCT02154776	NCT01530607	NCT01086605	NCT00684983	NCT00365105	NCT00072462
NCT02152462	NCT01527487	NCT01084057	NCT00656786	NCT00355381	NCT00072293
NCT02150148	NCT01515800	NCT01081262	NCT00644228	NCT00345072	NCT00072020
NCT02137837	NCT01515124	NCT01077154	NCT00630032	NCT00337103	NCT00070564
NCT02116530	NCT01508273	NCT01074970	NCT00613275	NCT00331773	NCT00070499
NCT02104830	NCT01504789	NCT01073865	NCT00602459	NCT00326898	NCT00066703
NCT02058615	NCT01498289	NCT01068522	NCT00601900	NCT00324805	NCT00066690
NCT02042443	NCT01492101	NCT01064635	NCT00588770	NCT00321048	NCT00063882
NCT02015806	NCT01485926	NCT01049425	NCT00581256	NCT00313170	NCT00053898
NCT02004834	NCT01479244	NCT01017601	NCT00569127	NCT00310180	NCT00052910
NCT01942135	NCT01478477	NCT01015833	NCT00567580	NCT00301925	NCT00052156
NCT01940016	NCT01452399	NCT01009918	NCT00567554	NCT00301457	NCT00052130
NCT01913990	NCT01446159	NCT01008150	NCT00556374	NCT00295620	NCT00045032
NCT01910350	NCT01434342	NCT01007942	NCT00556218	NCT00294996	NCT00041119
NCT01907880	NCT01421472	NCT00999804	NCT00553410	NCT00289263	NCT00039546
NCT01900730	NCT01411787	NCT00981305	NCT00553358	NCT00287898	NCT00033683
NCT01881230	NCT01381874	NCT00976573	NCT00532727	NCT00282035	NCT00030758
NCT01876238	NCT01376349	NCT00976131	NCT00530868	NCT00274469	NCT00025688
NCT01874184	NCT01355393	NCT00971009	NCT00524277	NCT00265941	NCT00005970
NCT01867866	NCT01349322	NCT00954174	NCT00520975	NCT00265850	NCT00005957
NCT01835158	NCT01346761	NCT00948701	NCT00513292	NCT00253422	NCT00005886
NCT01822314	NCT01306032	NCT00946712	NCT00507923	NCT00248287	NCT00005581
NCT01800422	NCT01299038	NCT00945607	NCT00499603	NCT00229697	NCT00004935
NCT01783444	NCT01296893	NCT00942357	NCT00493870	NCT00217737	NCT00004179
NCT01764022	NCT01293032	NCT00942331	NCT00486668	NCT00204490	NCT00004067
NCT01741883	NCT01275677	NCT00929084	NCT00470236	NCT00204477	NCT00003857
NCT01740427	NCT01266642	NCT00927433	NCT00463489	NCT00203372	NCT00003680
NCT01712009	NCT01237067	NCT00925652	NCT00454805	NCT00186602	NCT00003679
NCT01705691	NCT01231204	NCT00909818	NCT00453154	NCT00134056	NCT00003678
NCT01688973	NCT01224678	NCT00904033	NCT00451555	NCT00130533	NCT00003612
NCT01658943	NCT01219075	NCT00887536	NCT00433589	NCT00129389	NCT00003418
NCT01647607	NCT01204125	NCT00877500	NCT00433511	NCT00126581	NCT00002851
NCT01642251	NCT01198158	NCT00876395	NCT00433420	NCT00118846	NCT00001806
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