Uptake of Guidelines for Breast Cancer in Low and Middle-resource Countries

From Research to Implementation

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Abstract

Uptake of Guidelines for Breast Cancer in Low and Middle-resource Countries

From Research to Implementation

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Background: Breast cancer (BC) is the most common cancer killer in women worldwide and the burden of disease is currently higher in Low and Middle Resource Countries (LMRCs) than in more developed regions. Recognizing this, The Breast Health Global Initiative (BHGI) developed evidence-based, resource-stratified BC guidelines for LMRCs. **Purpose:** To evaluate how these guidelines have been used in the global health literature as a proxy for potential impact. **Methods:** We conducted a systematic review and citation analysis to identify and analyze documents referencing the guidelines by region, topic and purpose. **Findings** Of the 776 documents included for analysis, 71% were published by authors or groups external to BHGI, and 57.8% of all documents were focused on LMRCs. The frequency of publications has progressively increased, with early detection being the most common theme referenced. More than 67.2% referenced the guidelines to support and idea related with the management of the disease while only 6% used them to support an implementation process. **Conclusion:** These guidelines have been disseminated worldwide and have been used increasingly in the global

health literature during the last decade. However, it is fundamental to develop better implementation strategies to promote their uptake into routine practices in LMRCs.

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List of acronyms and abbreviations

FHCRC	Fred Hutchinson Cancer Research center
BHGI	Breast Health Global initiative
LMRCs	Low and middle-resource countries
HRCs	High-resource countries
HIEs	High-income economies
BC	Breast Cancer
NCDs	Non-communicable diseases

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Dedication

To Luisfer my loved mentor, accomplice and husband.

To Juan Pablo and Juliana, my inspiration and my model of spontaneity, adaptation, strength and continuum learning.

To all professionals, activist and people working to control the burden of disease and improve the quality of life of people affected with breast cancer worldwide.

I. Introduction

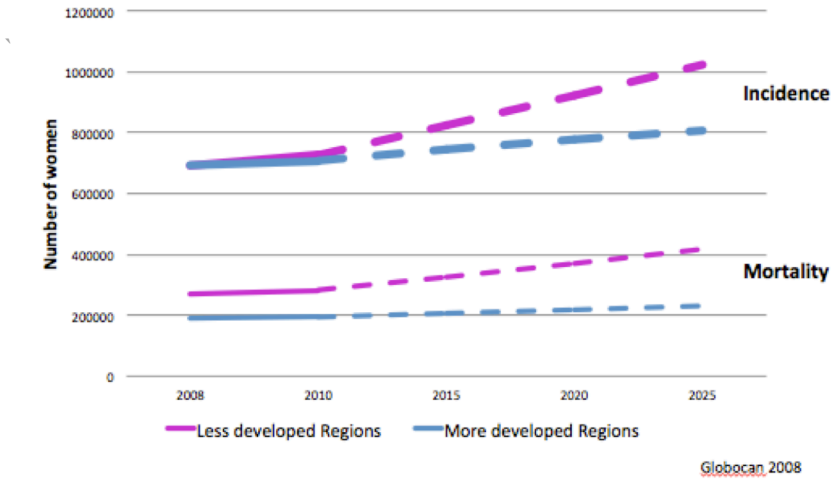
Breast Cancer in Low- and Middle-Resource Countries (LMRCs)

Breast cancer is a major global public health problem and represents the most common cancer killer of women worldwide [1]. With an estimated global incidence of 1.38 million new cancer cases diagnosed per year, breast cancer accounted for 23% of all total cancer cases and almost 14% of the total cancer deaths in women in 2008 [2].

Historically, breast cancer incidence rates have been higher in more developed regions compared to less developed regions, with large variations between them. For instance, while incidence rates were 19.0 cases per 100,000 in Eastern Africa in 2008, in Western Europe these rates were 90.0 cases per 100,000 in the same year [2]. This may be result of low attention to non-communicable diseases (NCDs), deficiencies in information systems, or low screening rates in low and middle resource countries (LMRCs), among other causes. Because of these historical trends, breast cancer has been considered a disease of the developed world. However, incidence rates in less developed regions have been gradually increasing over time and are projected to represent the majority of the burden during the next decade [3] [see Figure 1].

These increasing trends in breast cancer are primarily due to the growing population and increased life expectancy, as well as the adoption of western lifestyles in LMRCs [4]. In addition, 75% of the breast cancer cases in these countries are diagnosed in late clinical stages; therefore, the case fatality rates are much higher compared with rates in most developed countries [5]. It is estimated that such cases could grow to represent a 60% share of the breast cancer deaths worldwide [4].

Figure 1: Estimated breast cancer incidence and mortality



Breast Cancer Clinical Guidelines

Significant initiatives and scientific advances for effective breast cancer management have occurred in recent years. Many different organizations around the world have published comprehensive, evidence-based guidelines outlining optimal approaches for early detection, diagnosis, and treatment of breast cancer. These guidelines are important not only for knowledge dissemination but also for implementation into clinical practice [6] and national cancer control programs [7]. However, most of these guidelines define optimal breast care and services such as screening mammography and treatment with state-of-the-art chemical agents. Because of the scarcity of health care resources in less developed countries, it is often unrealistic for those nations to implement such complicated and expensive procedures. Consequently, there is a critical deficit of programs for early detection, diagnosis, and treatment resulting in particularly poor breast health outcomes in much of the developing world [8].

Background: The Breast Health Global Initiative

The experience of reducing mortality and improving breast cancer outcomes in more developed countries, suggests that there may be opportunities to reverse the adverse breast cancer trends in LMRCs. In order to do that, it is necessary to develop and implement more practical, applicable, and cost-effective initiatives [8]. This was the position taken by the Seattle-based Breast Health Global Initiative (BHGI), an international alliance co-sponsored by the Fred Hutchinson Cancer Research Center in Seattle, WA, and the Susan G. Komen For The Cure organization, located in Dallas, TX. The BHGI holds that fundamental and progressive practices in early detection, diagnosis, and treatment for breast cancer can be integrated within existing health care systems in LMRCs. Over the past decade, BHGI has provided evidence-based, resource stratified, and culturally appropriate guidelines to facilitate this process and ultimately improve breast health outcomes in LMRCs.

Since 2002, the BHGI has held five international summits (2002, 2005, 2007, 2010, and 2012), bringing together experts from around the world to develop a consensus panel process on appropriate resource-stratified breast cancer care and management. The panels focus on what is feasible within an LMRC's existing health system and provide guidelines based on those resources. Over time, through these summits, the BHGI has developed evidence-based, resource-stratified, and culturally appropriate guidelines along the continuum of breast cancer. During the first two summits the authors developed the resource-stratified guidelines, and in the third summit (2007) the authors outlined effective implementation strategies as well as key process metrics to assess the success of that implementation [9]. The guidelines were published in a series of journals since 2003, the year following the first summit.

The most important and differential characteristics of these guidelines are that 1) they are

comprehensive, since they address the areas of early detection, diagnosis and pathology, treatment, and health care systems, and 2) they are resource sensitive, as they are outlined using a four-tiered resource setting framework (basic, limited, enhanced and maximal), [see appendix 1].

Rationale and study question

The BHGI breast cancer guidelines aim to define best practices in LMRCs and transfer to the global community, alternatives for breast cancer management [10]. To date and since the first publication of the guidelines, there has not been an overall assessment of the amount of attention that has been paid to the BHGI guidelines in low and middle-income countries.

In this study, we conducted a systematic review and citation analysis to assess how the BHGI guidelines have been recognized and used in the global health literature as a proxy for potential impact.

Research question:

How are the BHGI Breast Cancer Guidelines being addressed and/or used by low and middle-resource countries in the global health literature?

Specific questions:

1. To what extent along the time continuum have the guidelines been referenced?
2. What guideline topics have been most commonly referenced?
3. For which geographical regions have the guidelines been referenced?
4. For what purposes have the guidelines been referenced?

II. Methods

This review used as the core documents 15 guidelines that were the products of the first three BHGI global summit consensus conferences held in 2002, 2005, and 2007. Every summit had a particular and different purpose as well as the guidelines product of these sessions. The first three summits specifically focused on the development and definition of BC resource-stratified guidelines for LMRCs and were therefore the most relevant to this study. The last two summits were not included in this analysis because they used a different approach, their products were different, and also because in order to identify ongoing trends, it is necessary to wait some time for manuscripts to be disseminated and reviewed after their publication.

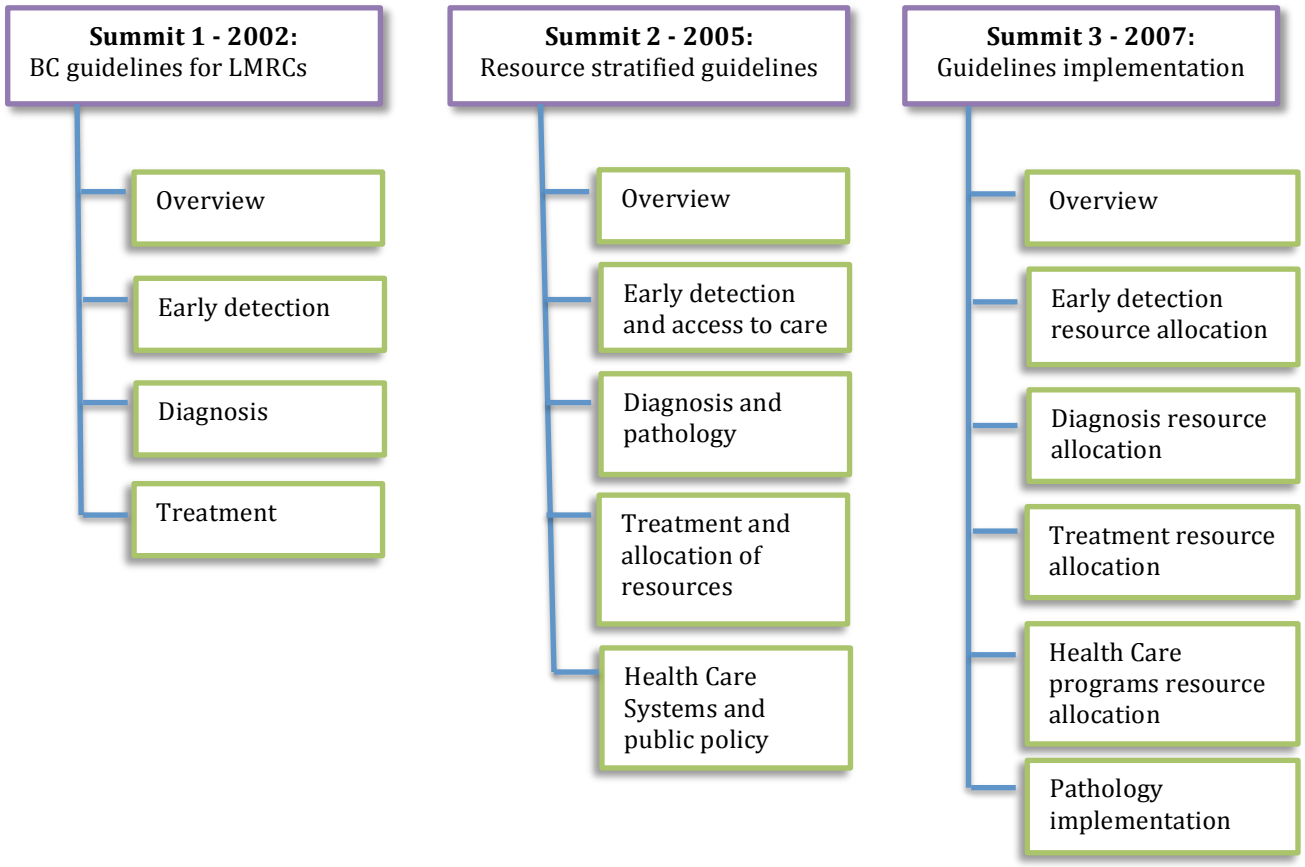
The first evidence-based guidelines were a product of the first BHGI summit held in Seattle in 2002. These guidelines outlined general recommendations for enhancement in breast health services and breast health care disparities in LMRCs and addressed early detection, diagnosis and treatment of breast cancer [11], [12], [13], [14].

Later, in 2005 during the second summit held in Maryland, a group of experts from around the world as well as different international organizations working in cancer and breast health, discussed and reviewed the previous published guidelines and updated them through the introduction of a resource stratification approach, where recommendations were stratified by four levels of resources available - basic, limited, enhanced, and maximal - to help countries in prioritizing resource allocation in their fight against breast cancer. In addition these guidelines expanded their coverage including the area of health care systems and public policy [10], [15], [16], [17], [18].

The goal of the third summit held in 2007 in Budapest, was to address implementation guidelines in LMRCs. On the same basis of resource stratification, the experts and organizations

participating debated key issues and identified effective strategies for guideline implementation as well as well as outlined key process metrics to measure the success of that implementation [9], [19], [20], [21], [22], [23]. See in Figure 2 the distribution of these guidelines by summit and by topic.

Figure 2: 15 Core guidelines object of the study by summit and topic



See appendix 2 for further description of each summit and guideline

Literature search strategy and selection

Between January and July 2013, we performed a comprehensive search in four online databases: Medline, Scopus, Web of Science, and Google Scholar to identify all documents that have referenced the guidelines since 2003. We used different databases in order to cover journal

articles published in different countries, and languages, as well as to include other documents beyond academic articles. We included all articles and documents published between 2003 and 2012 in different journal sections, as well as technical reports recovered in the data collection process. Since the investigator is fluent in English and Spanish, as well as proficient in Portuguese, all articles written in those three languages were included. Documents and books that did not have the full online version available were omitted, due to concerns over access.

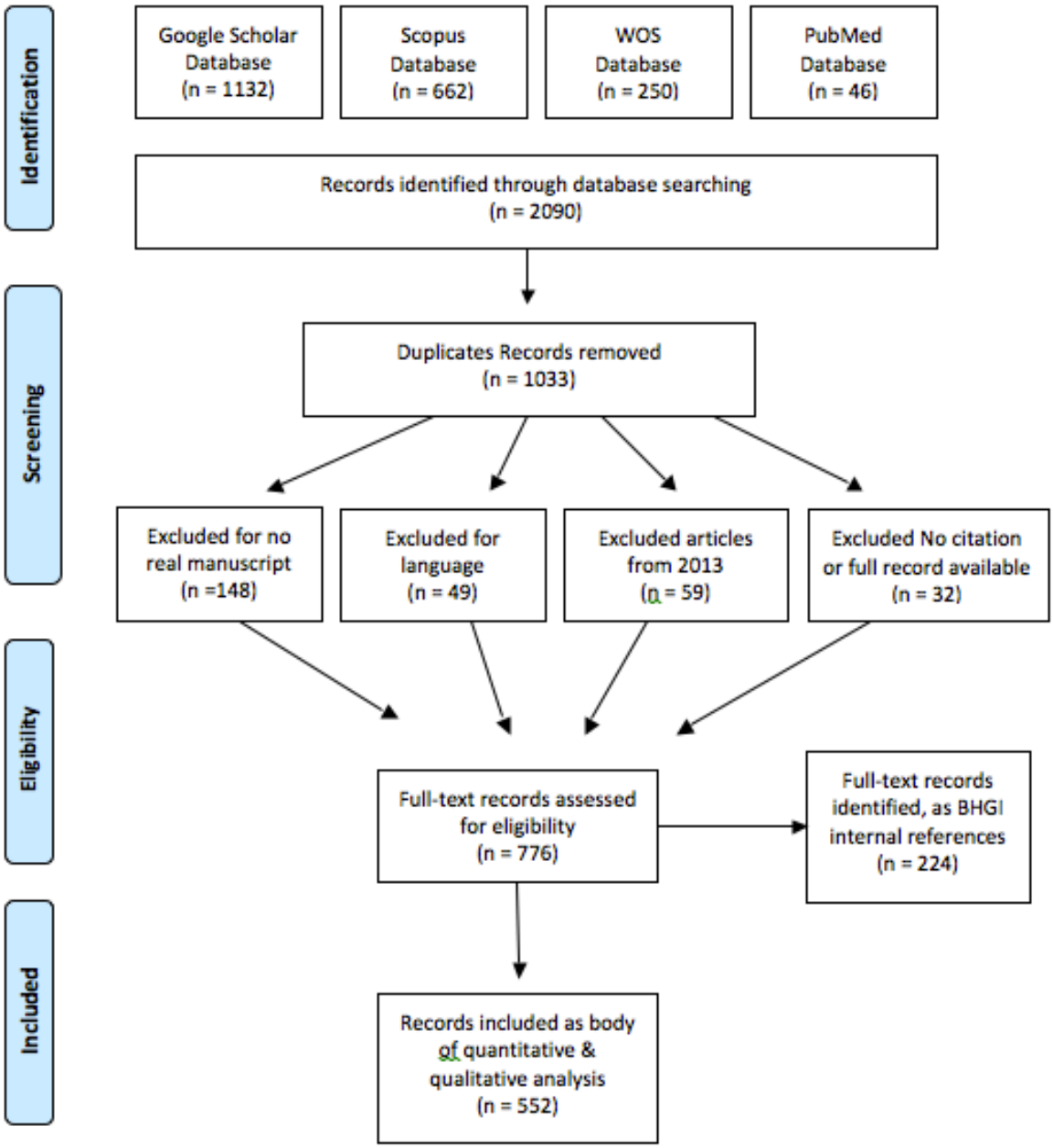
Our search strategy retrieved 2097 documents that were screened for eligibility. After collecting these documents, we removed 1033 duplicates, and 288 documents that did not meet our inclusion criteria. Finally 776 full text records were assessed for eligibility. See Figure 3 for the detailed description of the search and selection process.

Data extraction and analysis

We collected key information from each record into an Excel file, where items were coded as follows: authors, journal, year, document type (e.g., original articles, review articles, and conference papers), affiliated institution, and country/region of the study population. In addition, we extracted more detailed information such as abstract, purpose of the study and the specific citation(s) of the guidelines in order to assess how the guidelines were used.

For the data analysis we conducted quantitative and qualitative analysis, using descriptive statistics as well as content analysis to add details to our quantitative findings. For the quantitative analysis we used descriptive statistics to determine frequency and distribution of the number of references by 1) internal (BHGI-related) versus external authors, 2) regions and countries in which the articles were focused, and 3) topic of the guideline referenced: early detection, diagnosis and pathology, treatment, health care systems, and overview (summary of the overall guidelines and disease management).

Figure 3: PRISMA Flow Diagram describing the different literature search and selection stages



Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For the qualitative analysis we conducted a content analysis of every citation along with the abstract and purpose of the study. We identified three general themes or categories and then categorized every citation into one of these three categories:

1. **General reference**: the guidelines were referenced to support general ideas, primarily related to the epidemiology of the disease.
2. **Analytical tool:** the guidelines were referenced to support a specific idea related to breast cancer management and suggested that it should be used to determine a course of action.
3. **Framework for implementation:** the guideline was actually referenced to support an intervention as a framework for the implementation process around breast cancer management within an institution, country, or region.
4. **Others:** citations that did not fit in any of the three categories were grouped into this category.

Where classification was problematic the other authors (Benjamin Anderson, Beti Thompson) reviewed the article to reach consensus.

III. Findings

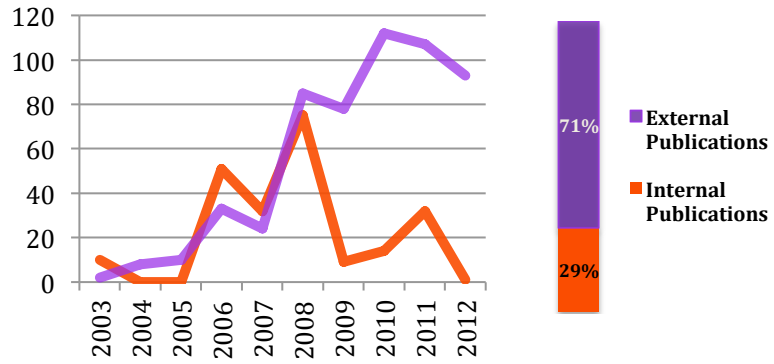
A total of 776 records found during our data collection process met our inclusion criteria and were included for analysis. The data collected from each article was coded manually, and analyzed from different perspectives but following the logic of our research questions.

Extent of documents referencing the guidelines

Initially, we found an important number of articles referencing the guidelines that were products of the BHGI group itself. This means that their authors were leaders from the BHGI. We classified these documents as 'internal publications'. From the total records included in our analysis, 224 documents (29%) were internal publications and 552 (71%) were 'external publications' written by authors outside of the BHGI. Appendix 3 summarizes the number of internal and external publications that reference the guidelines by summit and topic.

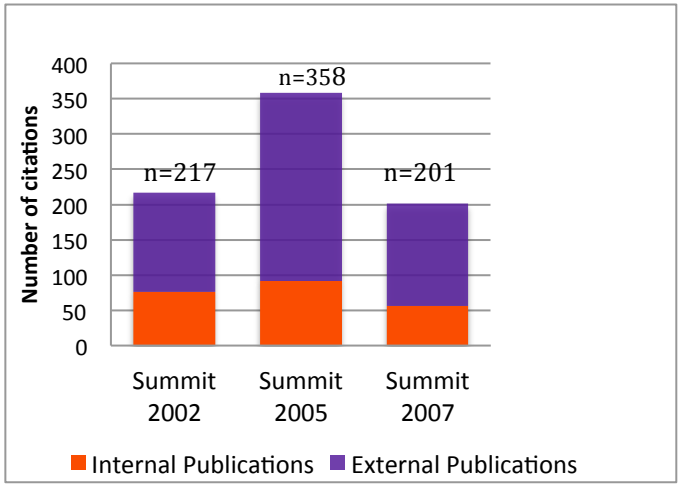
When we analyzed this data over the time, we observed that external publications have referenced the guidelines progressively since they were first published. There is also a clear trend over time toward increasing external references while decreasing internal references [see Figure 4].

Figure 4: Extent of citations - Internal versus external references



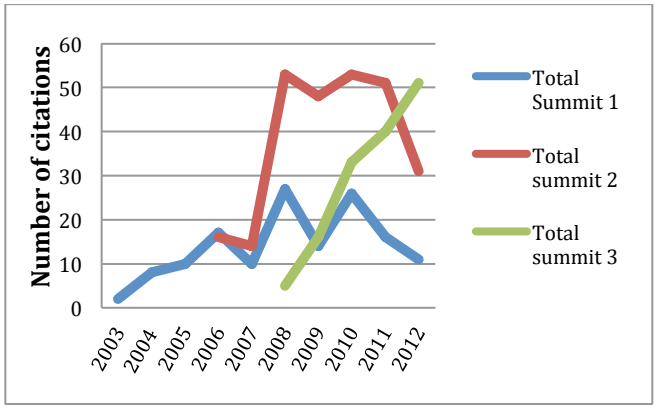
If we disaggregate the records referencing the guidelines by summit, we found that a large majority 46% (n=358) reference the guidelines produced during the second summit [see Figure 5].

Figure 5: Extent of citations – Internal & external references by summit



In addition, in looking at the number of external references only by summit over time, we observed that after the publication of each group of guidelines, they began to be referenced in the literature very quickly and continued to be used for the next decade with only small decreases over time. For the guidelines produced in the first summit, the overall number of citations varied significantly by year but was usually fewer than 25 records per year. The number of records referencing the guidelines from summit 2 showed sharp growth after two years of their publication and remained almost stable with an average of 50 records per year between 2008 and 2011 before decreasing in 2012 to 31 articles. Finally, the numbers of records citing the third group of guidelines, published in 2008, have shown progressive and sustainable growth overtime, although more moderated than the previous guidelines [see Figure 6].

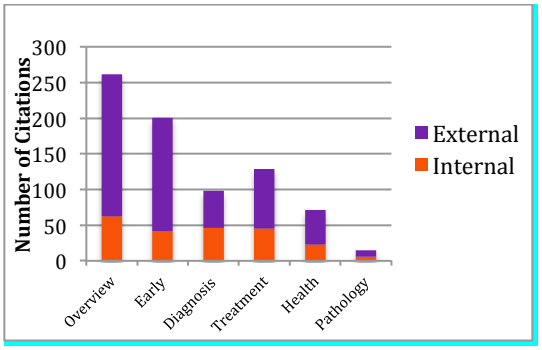
Figure 6: Extent of citations –references (external only) by summit over time



Documents by Topic

Looking at the trends in the extent of citations by topic of the guidelines, we found that the numbers of internal publications were similar at referencing early detection (n=42), treatment (n= 45) and diagnosis guidelines (n=46), and slightly higher at referencing the overview guidelines (n=62). Of the external publications, 65% of the records are focused on the overviews and early detection guidelines (overview: 36.2%, n= 200 and early detection 28.8%, n=159), followed by treatment (15.2%, n=84), diagnosis (9.4% n=52), and health care system guidelines (8.7%, n=48). Pathology as an independent topic was included in the third summit and its use in the literature still remains low (1.6%, n=9) [see Figure 7].

Figure 7: Extent of citations by topic of the guideline



Countries & Regions Referencing the Guidelines

Using the World Bank geographical region classification, we categorized all the external publications referencing the guidelines according to the country or region object of study. Almost 57.8% of all documents specifically refer to less developed countries and regions, and only 9.4% refer to high-income economies. The remaining 32.8% are documents that were not concentrated in a particular region, and we called them non-country specific. Among the non-country specific records, 33.7% of them stated "low and middle-resource countries" as the object of their study. Figures 8 and 9 illustrate the distribution of records referencing the guidelines by region.

Figure 8: Percentage of external publications referencing the guidelines by regions

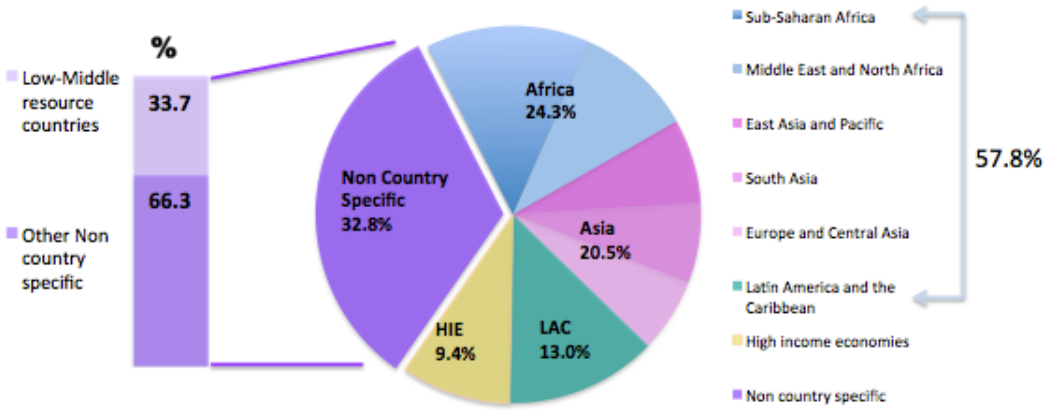


Figure 9: Detailed frequency of external records referencing the guidelines by regions

Regions	#	%	Predominant countries
Sub-Saharan Africa	78	14.1	Nigeria, South Africa
Middle East and North Africa	56	10.1	Iraq, Egypt
East Asia and Pacific	40	7.2	China, Malaysia
South Asia	38	6.9	Pakistan, India
Europe and Central Asia	35	6.3	Turkey
Latin America and the Caribbean	72	13.0	Brazil, Colombia, Mexico
High income economies	52	9.4	---
Non country specific	181	32.8	---

The detailed regional analysis illustrates that Sub-Saharan Africa is the most frequently referenced region in the records included in our analysis (14.1%), followed by Latin America and the Caribbean region (13.0%) and Middle East and North Africa (10.1%). By looking at the detail(s) for specific countries, Figure 9 shows the predominant countries by region.

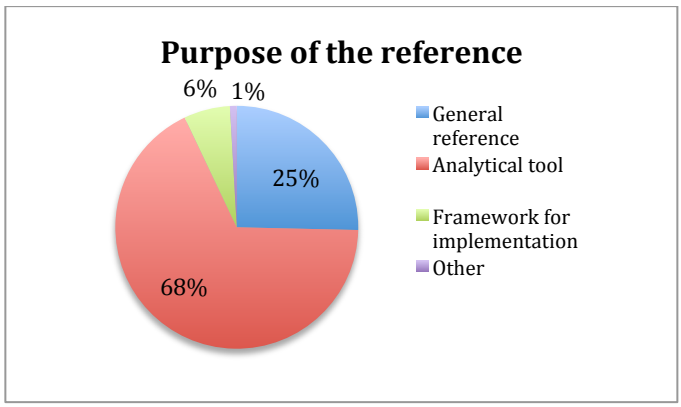
Purposes of Guideline Citation in the Literature

From the content and citation analysis, we found that 68% of the records are referencing the guidelines as an analytic tool. In these documents, the authors recognize that some concepts outlined in the guidelines related with the management of the disease are important and suggest that they might be used to determine a course of action, but they have not yet used them to support an implementation process. For instance, they might reference the guidelines to promote breast self-awareness, clinical breast examination (CBE), and resource-adapted mammographic screening as fundamental steps in early detection of breast cancer or maybe to highlight the positive financial impact of adequate pathology services in morbidity, but yet not use these recommendations as part of an actual initiative or practice in a particular setting.

Only 6% of the records referenced the guidelines as a framework for implementation supporting a specific intervention or action.

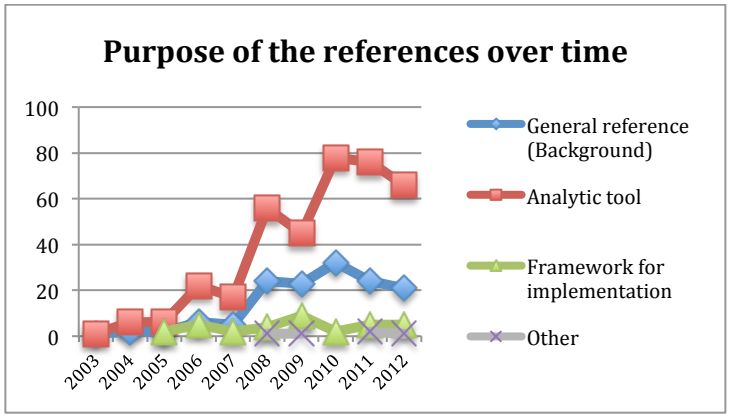
On the other hand it is important to note that 25% of the records referenced the guidelines to support general ideas; mostly supporting epidemiological data in the context of the disease. [see Figure 10].

Figure 10: Content and citation analysis, purpose of the use of the guidelines



By looking at the purpose of the citation over time, Figure 11 illustrates a rapid progression in the use of the guidelines as analytic tool while the use of the guidelines as an implementation framework has remained low with a very slight growth in the last years.

Figure 11: Content and citation analysis over time



IV. Discussion of Findings

International clinical guidelines are important tools for guiding decisions and standardizing medical care. However, the uptake of most clinical guidelines represents a challenge for LMRCs in particular, as resources are not available for highly technically advanced procedures. The BHGI resource-stratified guidelines for breast cancer represent an opportunity toward improving breast health care and cancer control in such countries. This systematic review provides an overview of how these guidelines have been referenced in the global health literature as an initial effort to assess their uptake and use in LMRCs.

Dissemination and utility of BHGI guidelines

These findings suggest that there has been an important amount of attention of the BHGI guidelines in the global health literature. The number of documents referencing the guidelines are clearly increasing, although there have been some variations over time. This is true for most of the guidelines, including the first group of guidelines published in 2003. This growth communicates the dissemination and utility of these guidelines, and may be used as a proxy for initial assessments of potential impact in the settings where these guidelines are used or implemented.

Most of the articles included in our research referenced the guidelines that were produced at the second summit. During this summit, the authors discussed and introduced the concept of resource stratification. This concept has become the basis for the BHGI guidelines, where the authors define the basic elements of a breast health program and using a tier system offer pathways for quality and results improvement based on the level of resources available in countries [24]. Four levels of resources are defined - basic, limited, enhanced and maximal. For each level, the guidelines provide recommendations for addressing breast cancer early detection,

diagnosis, treatment by stage, and health care systems with the ultimate goal of facilitating governments and health program managers to make better decisions for resource prioritization in breast cancer programs in LMRCs [8]. The resource stratification concept seems to have represented an important tool for LMRCs, since numerous articles in our review highlighted it. In fact, some articles have adopted it for internal practices. For instance, recent work by Murillo et al (2008) on a pilot program for implementing early detection of breast cancer in Colombia speaks to the use of the BHGI guidelines to move from a limited to an enhanced scenario for early detection of breast cancer in Colombia [25].

It is not surprising that the majority of records identified in this review referenced the overviews and early detection guidelines. On the one hand, the overviews offer a summary of the complete recommendations in different areas of breast cancer management, facilitating the reader to find the most important recommendations in one same document. However, it may also speak of the level of detail that the reader is seeking from these guidelines. On the other hand, early detection has become a fundamental component in breast cancer management. There has been strong evidence supporting not only the positive impact of early detection on breast cancer morbidity and mortality but also, the implications that diagnosis of breast cancer in early stages has in costs and complexity of the management of the disease [12] [16]. This represents an outstanding opportunity for LMRCs where the scarcity of resources make it fundamental to make cost effective decisions for NCDs avoiding to drain resources from other public health priorities. It is certainly essential for LMRCs investment in early detection research and programs; however, it is also necessary to focus on developing effective diagnosis and treatment strategies.

Our findings also suggest that little attention has been placed on health care system guidelines. Elements such as resource allocation, organizational and management capacity, and institutional buy-in of the health care system, as well as political willingness are fundamental for planning, delivering and measuring effective breast health services within a public health system [16]. Of course, integrating these elements into a existing health care system will not be an easy task and cannot be addressed as a breast health isolated issue. Yet, breast cancer health care systems guidelines can provide a framework for facilitating professionals, patients, advocates, and decision makers strengthening health care systems and ultimate improving breast health outcomes.

Uptake in LMRCs

As it is the main intention of the BHGI to focus its efforts towards LMRCs, the majority of articles referencing the guidelines were either conducted, or concentrated on these economic disadvantaged regions. Sub-Sahara Africa, predominantly Nigeria and South Africa are the countries that have referenced the guidelines most frequently. It is interesting that along with epidemiological and management of breast cancer studies our research found that from this region, many studies make special emphasis in knowledge awareness and cultural perceptions of breast cancer. Some examples are:

1. "Nurses practices and knowledge of breast self-examination in selected hospitals, Bayelsa State, Nigeria" by Adika V.O. et al 2012;
2. "Knowledge and Practice of Breast Self Examination among Female Students in a Sub Saharan African University" by Obaikol R. et al, 2010; and
3. "An Exploration of rural and urban Kenyan women's knowledge and attitudes regarding breast cancer and breast cancer early detection measures" by Muthoni A. et al, 2010.

Studying awareness and cultural perceptions of breast cancer is important since it represents one of the first steps in LMRCs for preventing late diagnosis of the disease.

Latin America and the Caribbean region were the second regions most commonly utilizing the guidelines in global health literature. However, in this region we did not find many documents related with awareness and cultural perception of breast cancer, but instead most of the articles were concentrated in specific topics related with clinical management of the disease such as early detection, diagnosis and treatment.

Some regions in Asia have also demonstrated significant use of the BHGI guidelines. In fact, three Asian Oncology Summits in 2009, 2010 and 2012 have been held, where Asian experts, along with some international advisors, used the BHGI resource-stratified guidelines model as a framework for developing not only their own breast cancer guidelines, but also guidelines for other types of cancers predominant in the region [26], [27], [28]. Acknowledging the diversity in ethnicity and cultures as well as the inequalities in infrastructure, resources and development between regions and countries in Asia, health care leaders in the region have discussed and established recommendations for breast, cervical, colorectal, and hepatocellular cancer for the four levels of resources described originally by the BHGI [29].

More than 90% of the countries referencing the guidelines were middle-income countries (lower-middle and upper-middle). This is not surprising, as in these countries the patterns of disease have recently shifted from infectious diseases to NCDs, such as breast cancer and, consequently, more attention has been placed in these diseases during the last decade. Although survival rates are higher in MRCs than in LRCs, middle-income economies still face enormous challenges for cancer control; late-stage presentation of cancer remains common; and there are

still enormous inequalities in access to care and breast health outcomes among these countries [30]. However MRCs also have tremendous opportunities for improvement, some of them are:

1) Consistent economic growth and social transformation
2) Previous experiences in cancer control programs since several years ago
3) Access to universal health coverage in most of the countries, although with significant shortcomings. [30], [31].

Slowly towards implementation

Finally, guidelines are important tools for bridging the gap between knowing and doing. They usually aim to provide a guide for program implementation. However, our findings suggest that implementation of the BHGI guidelines or some of their recommendations remain a challenge for more LMRCs. Most articles in this review cited the guidelines to acknowledge their relevance and support an idea suggesting a course of action, but not actually implementing the activities. Only few documents referenced the guidelines as a framework for an implementation process, such as Murillo et al. (2008) in their paper "Pilot implementation of breast cancer early detection programs in Colombia" [25] or Wong et al. (2009) in "Management of HER2-positive breast cancer in Asia: consensus statement from the Asian Oncology Summit 2009" [32]. In these articles, the authors used the BHGI guidelines as a framework to develop their own country guidelines.

The way the guidelines are outlined, by level of resources, not only helps governments and health decision-makers with prioritizing resource allocation but also provides a model that can actually be implemented even in resource-limited settings. This offers the possibility to start with the basics and scale up according with the resources available [9]. In addition, the international summit held in 2007 was specifically focused in addressing guideline

implementation by providing strategies to overcome barriers for such process in LMRCs. With these two elements, and the growing number of articles acknowledging the BHGI guidelines, it is likely that in coming years we will see an increase in the number of articles referencing the guidelines to support interventions. After all it is the hope of the BHGI that other international organizations and countries will take notice, and disseminate and implement these guidelines according to specific needs in countries to reduce mortality and improve the outcomes of breast cancer worldwide.

V. Conclusion

Study Limitations

This review relied on online published studies and the availability of them using the method outlined in the search strategy as well as the inclusion criteria. Thus, we may be missing relevant country experiences, using the BHGI breast cancer guidelines as references that have not been published or are outside of the scope of this study. We tried to minimize this by including some documents published in gray literature, such as country reports, editorials, review articles and other non-academic articles.

Since we conducted an analysis from different perspectives, dependent on the research avenue we took, there might be some document overlap.

The verification mechanism for the categorization of the references was concentrated only in citations that were identified as complex.

The use of citation analysis as a proxy for potential impact of the research is based on the assumption that citations are a way of giving credit and recognizing the value of a specific work. However, this impact is not demonstrated in this study [33], [34].

Main contributions

1. This research will inform the BHGI, as well as other breast health care initiatives and stakeholders about the potential impact, application, and trends in the use of clinical breast cancer guidelines in less developed countries.
2. In addition, this work provides insights about the level of uptake of the guidelines in LMRCs, and thereby reveals opportunities to drive guideline implementation.
3. It also provides valuable information for future directions for efforts aimed to address breast cancer issues in low and middle-income countries.

4. Conducting an extensive and systematic review such as this, also offers the opportunity to identify strengths and gaps in the body of literature where more studies are needed.

Conclusion

The burden of breast cancer in LMRCs is increasing rapidly, but the experience in more developed countries can be used to reduce mortality and control the disease in these countries. The evidence based and resources-stratified BHGI guidelines provide an opportunity to inform health care providers and decision makers, and to influence the uptake of knowledge into clinical practice even when resources are limited. These guidelines have been disseminated worldwide and their presence in the global health literature has grown during the last decade. However, it is fundamental to develop better implementation strategies to promote the uptake of these guidelines and other evidence-based recommendations into routine practices, and ultimately improve breast cancer outcomes in LMRCs.

Future directions

Although it is important for LMRCs to invest in early detection research and programs; it is fundamental to capitalize simultaneously on diagnosis, treatment and healthcare systems since all of these areas are complementary and necessary to impact breast health outcomes.

The mere development and dissemination of guidelines does not necessarily result in implementation in clinical practice. The journey continues; we need to continue looking for better implementation strategies in ways that are measurable and serve as example to other countries, with the ultimate goal of narrowing the gap between knowing and doing, and be able to make this a global phenomenon.

It is important to conduct similar studies in the future, to evaluate the trends in the use of the BHGI guidelines over longer period of time. It is also very valuable to conduct case studies to analyze and understand the level of uptake of the guidelines within its real-life context.

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Appendices

Appendix 1: Summary tables from the BHGI resource stratified guidelines

		LEVEL OF AVAILABLE RESOURCES			
		BASIC	**LIMITED**	**ENHANCED**	**MAXIMAL**
EARLY DETECTION	Public Education and Awareness	• Development of culturally sensitive, linguistically appropriate local education programs for target populations to teach value of early detection, breast cancer risk factors and breast health awareness (education + self-examination)	• Culturally and linguistically appropriate targeted outreach/ education encouraging CBE for age groups at higher risk administered at district/provincial level using healthcare providers in the field	• Regional awareness programs regarding breast health linked to general health and women's health programs	• National awareness campaigns regarding breast health using media
	Detection Methods	• Clinical history and CBE	• Diagnostic breast US +/- diagnostic mammography in women with positive CBE • Mammographic screening of target group[3]	• Mammographic screening every 2 years in women ages 50-69[3] • Consider mammographic screening every 12-18 months in women ages 40-49[3]	• Consider annual mammographic screening in women ages 40 and older • Other imaging technologies as appropriate for high-risk groups[2]
	Evaluation Goal	• Breast health awareness regarding value of early detection in improving breast cancer outcome	• Downsizing of symptomatic disease	• Downsizing and/ or downstaging of asymptomatic disease in women in highest yield target groups	• Downsizing and/ or downstaging of asymptomatic disease in women in all risk groups
DIAGNOSIS	Clinical	• History • Physical examination • CBE • Tissue sampling for cancer diagnosis (cytologic or histologic) prior to initiation of treatment	• US-guided FNAB of sonographically suspicious axillary nodes • Sentinel lymph node (SLN) biopsy with blue dye[4]	• Image guided breast sampling • Preoperative needle localization under mammo and/or US guidance • SLN biopsy using radiotracer[4]	
	Imaging and Lab Tests	See footnote 4	• Diagnostic breast US • Plain chest & skeletal radiography • Liver US • Blood chemistry profile[4] • CBC[4]	• Diagnostic mammography • Specimen radiography • Bone scan, CT scan • Cardiac function monitoring	• PET scan, MIBI scan, breast MRI, BRCA 1/2 testing • Mammographic double reading
	Pathology	• Pathology diagnosis obtained for every breast lesion by any available sampling procedure • Pathology report containing appropriate diagnostic and prognostic/predictive information to include tumor size, lymph node status, histologic type and tumor grade • Process to establish hormone receptor status possibly including empiric assessment of response to therapy[5] • Determination and reporting of TNM stage	• Determination of ER status by IHC[5] • Determination of margin status, DCIS content, presence of LVI • Frozen section or touch prep SLN analysis[6]	• Measurement of HER-2/ neu overexpression or gene amplification[5] • Determination of PR status by IHC	• IHC staining of sentinel nodes for cytokeratin to detect micrometastases • Pathology double reading Gene profiling tests

			LEVEL OF AVAILABLE RESOURCES			
TREATMENT			BASIC	LIMITED	ENHANCED	MAXIMAL
STAGE I	Local-regional treatment	Surgery	Modified radical mastectomy	Breast conserving surgery[2] Sentinel lymph node (SLN) biopsy with blue dye[3]	SLN biopsy using radiotracer[3] Breast reconstruction surgery	
		Radiation Therapy			Breast-conserving whole-breast irradiation as part of breast-conserving therapy[1]	
	Systemic treatment	Chemotherapy		Classic CMF[3] AC, EC, or FAC[3]	Taxanes	Growth factors Dose-dense chemotherapy
		Endocrine Therapy	Oophorectomy in premenopausal women Tamoxifen[4]		Aromatase inhibitors LH-RH agonists	
		Biological therapy		See footnote 5	Trastuzumab for treating HER-2/neu positive disease[5]	
STAGE II	Local-regional treatment	Surgery	Modified radical mastectomy	Breast c onserving surgery[2] Sentinel lymph node (SLN) biopsy with blue dye[3]	SLN biopsy using radiotracer[3] Breast reconstruction surgery	
		Radiation Therapy	See footnote 6	Postmastectomy irradiation of chest wall and regional nodes for high-risk cases[6]	Breast-conserving whole-breast irradiation as part of breast-conserving therapy[1]	
	Systemic treatment	Chemotherapy	Classic CMF[3] AC, EC, or FAC[3]		Taxanes	Growth factors Dose-dense chemotherapy
		Endocrine Therapy	Oophorectomy in premenopausal women Tamoxifen[4]		Aromatase inhibitors LH-RH agonists	
		Biological therapy		See footnote 5	Trastuzumab for treating HER-2/neu positive disease[5]	

			LEVEL OF AVAILABLE RESOURCES			
TREATMENT			BASIC	LIMITED	ENHANCED	MAXIMAL
LOCALLY ADVANCED	Local-regional treatment	Surgery	Modified radical mastectomy		Breast conserving surgery Breast reconstruction surgery	
		Radiation Therapy	See footnote 1	Postmastectomy irradiation of chest wall and regional nodes[1]	Breast-conserving whole-breast irradiation as part of breast-conserving therapy	
	Systemic treatment (Adjuvant and neoadjuvant)	Chemotherapy	Preoperative chemotherapy with AC, EC, FAC, or CMF[2]		Taxanes	Growth factors Dose-dense chemotherapy
		Endocrine Therapy	Oophorectomy in premenopausal women Tamoxifen[3]		Aromatase inhibitors LH-RH agonists	
		Biological therapy		See footnote 4	Trastuzumab for treating HER-2/neu positive disease[4]	
METASTASIC & RECURRENT	Local-regional treatment	Surgery	Total mastectomy for ipsilateral breast tumor recurrence after breast conserving surgery			
		Radiation Therapy		Palliative radiation therapy		
	Systemic treatment	Chemotherapy		Classic CMF[2] Anthracycline monotherapy or in combination[2]	Sequential single agent or combination chemotherapy Trastuzumab Lapatinib	Bevacizumab
		Endocrine Therapy	Oophorectomy in premenopausal women Tamoxifen[3]		Aromatase inhibitors	Fulvestrant
		Biological therapy	Nonopioid and opioid analgesics and symptom management		Bisphosphonates	Growth factors

Appendix 2: Description of the 15 guidelines object of study

Guideline	Summary - Description
Summit 1: The purpose of the Global Summit Consensus Conference was to begin a process to develop guidelines for improving breast health care in countries with limited resources—those with either low- or medium-level resources based on WHO criteria. (2002 Global summit consensus) Published 2003	
1. Overview of breast health care guidelines for countries with limited resources	Findings and conclusions of the three panels that during the 2002 Global Summit Consensus Conference developed guidelines for achieving "priority actions" in breast cancer care.
2. Early Detection of Breast Cancer in Countries with Limited Resources	Early detection, What it entails, Elements for succeeding
3. Diagnosis of Breast Cancer in Countries with Limited Resources	Diagnosis benefits, limitations, Recommendations Clinical and Pathologic diagnosis description
4. Treatment of Breast Cancer in Countries with Limited Resources	Conditions and fundamental elements for treatment Different therapies - Prognosis versus stages Requirements in terms of human and economic resources
Summit 2: The 2005 BHGI panels outlined a stepwise, systematic approach to health care improvement using a tiered system of resource allotment into four levels—basic, limited, enhanced, and maximal - based on the contribution of each resource toward improving clinical outcomes. (2005 Global summit consensus) Published 2006	
5. Breast Cancer in Limited-Resource Countries: An Overview of the Breast Health Global Initiative 2005 Guidelines	Summary of the four consensus panels in the BHGI summit 2005 which aimed to update and expand on the BHGI Guidelines published in 2003, with a stepwise, systematic approach to health care improvement using a tiered system of resource allotment into four levels—basic, limited, enhanced, and maximal—based on the contribution of each resource toward improving clinical outcomes.
6. Breast Cancer in Limited-Resource Countries: Early Detection and Access to Care	1) Early detection methods by level of resources (Basic, Limited, Enhanced, Maximal). 2) Recommendations and considerations for early detection programs 3) Implementation of Evaluation Programs
7. Breast Cancer in Limited-Resource Countries: Diagnosis and Pathology	Reaffirmed the recommendations from 2002 summit and additionally stratified diagnostic and pathology methods into four levels of resources
8. Breast Cancer in Limited-Resource Countries: Treatment and Allocation of Resources	Evidence-based guidelines for systematically prioritizing cancer therapies across the entire spectrum of resource levels for stages Justification for recommendations.
9. Breast Cancer in Limited-Resource Countries: Health Care Systems and Public Policy	1) Factors, barriers, and challenges facing by health care ministries to create and support health care programs that can improve BC outcomes. 2) Recommendations for health care systems. 3) Benefits of the stratified framework outlining for policy makers

Summit 3: The objective of this third Global Summit was to address resource allocation, specifically focusing on guideline implementation in LMCs. (2007 Global summit consensus) Published 2008	
10. Guideline implementation for breast healthcare in low-income and middle-income countries: Overview of the Breast Health Global Initiative Global Summit 2007	Summary of the third BHGI Global Summit held in 2007 whose goal was to expand broad BHGI resource stratified guidelines to identify effective implementation strategies and to measure the success of that implementation through the identification of key process metrics.
11. Guideline implementation for breast healthcare in low-and middle-income countries: Early detection resource allocation	Address the implementation of BHGI guidelines for the early detection of disease as they related to resource allocation (Diff levels) for public education and awareness, cancer detection methods, and evaluation goals, as well as specify process metrics.
12. Guideline implementation for breast healthcare in low- and middle-income countries: Diagnosis resource allocation	Reviewed diagnosis guideline tables and discussed core implementation issues and process indicators based on the resource stratification guidelines.
13. Guideline implementation for breast healthcare in low- and middle-Income countries: Treatment resource allocation	1) Implementation of treatment guidelines 2) Therapy checklist including strengths, weaknesses, and required resources 3) Recommendations
14. Guideline implementation for breast healthcare in low- and middle-income countries: Breast healthcare program resource allocation	Description of the issues and questions related to Health Care Systems that are important to consider when designing, implementing, and measuring the performance of a Breast Care Program. (Human resources, System resources, Insurance systems, pharmaceutical delivery Economic metrics and modeling, tools for decision making. Process metrics for Breast Healthcare programs by level of resources
15. Breast pathology guideline implementation in low- and middle-income countries	Address the specific needs and concerns related to breast pathology program implementation in LMCs. Specific recommendations and justification

Appendix 3: Number of internal and external publications referencing every guideline

Guideline	Total publications #	Internal publications #	Internal publications %	External publications #	External publications %
Summit 2002					
1. Overview	61	25	41.0	36	59.0
2. Early Detection	74	16	21.6	58	78.4
3. Diagnosis	31	18	58.1	13	41.9
4. Treatment	51	17	33.3	34	66.7
Total summit 2002	**217**	**76**	**35.0**	**141**	**65.0**
Summit 2005					
5. Overview	117	25	21.4	92	78.6
6. Early Detection	89	17	19.1	72	80.9
7. Diagnosis and Pathology	48	18	37.5	30	62.5
8. Treatment and Allocation of Resources	53	17	32.1	36	67.9
9. Health Care Systems and Public Policy	51	15	29.4	36	70.6
Total summit 2005	**358**	**92**	**25.7**	**266**	**74.3**
Summit 2007					
10. Overview	84	12	14.3	72	85.7
11.Implementation - Early detection resource allocation	38	9	23.7	29	76.3
12. Implementation - Diagnosis resource allocation	19	10	52.6	9	47.4
13. Implementation - Treatment resource allocation	25	11	44.0	14	56.0
14. Implementation Healthcare programs resource allocation	20	8	40.0	12	60.0
15. Implementation - Breast pathology	15	6	40.0	9	60.0
Total summit 2007	**201**	**56**	**27.9**	**145**	**72.1**
Grand Total	**776**	**224**	**28.9**	**552**	**71.1**