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TOPIC HIGHLIGHT

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Challenges to the early diagnosis and treatment of breast cancer in developing countries

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Abstract

This critical review of the literature assembles and compares available data on breast cancer clinical stage, time intervals to care, and access barriers in different countries. It provides evidence that while more than 70% of breast cancer patients in most high-income countries are diagnosed in stages Ⅰ and Ⅱ, only 20%-50% patients in the majority of low- and middle-income countries are diagnosed in these earlier stages. Most studies in the developed world show an association between an advanced clinical stage of breast cancer and delays greater than three months between symptom discovery and treatment start. The evidence assembled in this review shows that the median of this interval is 30-48 d in high-income countries but 3-8 mo in low- and middle-income countries. The longest delays occur between the first medical consultation and the beginning of treatment, known as the provider interval. The little available evidence suggests that access barriers and quality deficiencies in cancer care are determinants of provider delay in low- and middle-income countries. Research on specific access barriers and deficiencies in quality of care for the early diagnosis and treatment of breast cancer is practically non-existent in these countries, where it is the most needed for the design of cost-effective public policies that strengthen health systems to tackle this expensive and deadly disease.

Key words: Breast cancer; Early diagnosis; Delays; Time intervals; Clinical stage; Access; Health care delivery

Core tip: This review assembles the available data on breast cancer clinical stage for 10 high-income and 13 low-income countries and the time intervals from symptom discovery to cancer diagnosis and treatment for 33 countries. Most breast cancer patients in low-income countries suffer very long delays and are diagnosed in advanced stages. The scant available evidence for low and middle-income countries suggests that access barriers and quality deficiencies in cancer care are determinants of these delays.

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INTRODUCTION

The World Bank classifies countries according to their gross national income as low income, lower-middle income, higher-middle income and high income. Low- and middle-income countries (LMICs) are also sometimes referred to as "developing" economies, while high-income countries (HICs) are referred to as "developed"[1]. The term does not imply either that all developing countries

Table 1 Countries with the highest breast cancer incidence and mortality rates[3]

Country	Incidence rate	Country	Mortality rate
1 Belgium	111.9	1 Fiji	28.4
2 Denmark	105	2 Bahamas	26.3
3 France	104.5	3 Nigeria	25.9
4 The Netherlands	99	4 Pakistan	25.2
5 Bahamas	98.9	5 New Caledonia	24.4
6 Iceland	96.3	6 Armenia	24.2
7 United Kingdom	95	7 Lebanon	24.0
8 Barbados	94.7	8 Trinidad and Tobago	23.5
9 United States	92.9	9 Ethiopia	23.0
10 Ireland	92.3	10 Uruguay	22.7
11 French Polynesia	92.2	11 Barbados	22.1
12 Germany	91.6	12 Serbia	22.0
13 Italy	91.3	13 Jordan	21.8
14 Finland	89.4	14 Syria	21.5
15 Luxembourg	89.1	15 Somalia	20.6
16 New Caledonia	87.6	16 Afghanistan	20.6
17 Australia	86	17 Eritrea	20.5
18 Malta	85.9	18 French Polynesia	20.4
19 New Zealand	85	19 Montenegro	20.2
20 Switzerland	83.1	20 Guyana	20.1
21 Israel	80.5		
22 Sweden	80.4		

Incidence and mortality rates are number of cases and number of deaths, respectively, per 100000 women. Both measures are age-standardized.

are actually in the process of developing or that those in the developed group have necessarily reached some final stage of development[1]. For global health care, this classification provides a useful framework to assess how the countries' available resources should be allocated to address the most relevant health issues[2].

Breast cancer is the most frequent cancer in women worldwide, with 1.67 million new cases diagnosed in 2012[3]. It is also the leading cause of cancer death among women, with approximately 500000 annual deaths[3]. The highest incidence rates occur in the most developed regions of the world, with 74.1 new cases per 100000 women in comparison to the 31.3 new cases per 100000 observed in less-developed regions[3]. Nevertheless, the mortality rates are actually higher in developing countries. Table 1 presents the countries with the highest breast cancer incidence rates (above 80 per 100000 women) and those with the highest mortality rates (above 20 per 100000 women) in 2012. As shown, the majority of countries with the top incidence rates are high-income countries (HICs), while the majority of those with the highest mortality rates are low- and middle-income countries (LMICs).

Cancer survival data are extremely scarce for developing countries, but the few data available are in line with the observed incidence/mortality differences. The 5-year survival rates for breast cancer are much worse for low- and low-middle income countries such as Gambia (12%), Algeria (38.8%), India (52%) and Brazil (58.4%) in comparison to HICs such as the United States of America (83.9%), Sweden (82.0%), Japan (81.6%) and Australia (80.7%)[4,5].

The higher breast cancer mortality rates in LMICs are thought to be due to diagnosis in advanced stages and access barriers to medical care[6]. The limited data available for developing countries have made it difficult to determine how many more cases of advanced breast cancer are actually diagnosed in LMICs than in HICs. Even more rare are data from LMICs on time to care and access barriers. The purpose of this review was to assemble and compare the available data on the clinical stage, time intervals and access barriers across different countries to identify the main challenges in the early treatment of breast cancer in developing countries.

A critical review of the literature was conducted of quantitative studies published in English, Spanish, or Portuguese in the last 15 years that reported breast cancer clinical stage, time intervals and/or access and quality barriers associated with delayed cancer care. The PubMed and SciELO electronic databases were searched for "breast cancer" combined with each of the following terms: "clinical stages", "survival", "delay", "time intervals", "help seeking behavior", "access", "barriers"; plus one of the subsequent terms: "developing countries", "limited resource", "low income" or "middle income". For data on clinical stage, Google searches were also performed, using the terms "breast cancer" and "clinical stages". Additionally, references from relevant studies were used to trace other studies. The search was updated to December 2013. All articles relevant to clinical stage, time intervals and access and quality barriers were included, as they are scarce, particularly those performed in developing countries, which were the most relevant to this analysis.

This review presents information on clinical stage, which was collected from 20 studies or registries providing data for 10 HICs and 13 LMICs. Evidence on the time intervals to care is summarized for 33 studies that

gathered data for 10 HICs and 23 LMICs. Finally, the data from 26 studies on access barriers to care are presented, of which only three studies took place in LMICs.

ADVANCED CLINICAL STAGE OF BREAST CANCER IN LMICs

The clinical stage at breast cancer diagnosis remains one of the most important prognostic factors of survival[7]. The most accepted classification is the TNM staging system developed by the American Joint Committee on Cancer (AJCC)[8]. The estimated 3-year survival rates for high-income countries such as Canada, Sweden, Norway, Denmark and the United Kingdom are between 99.3 and 100.0% for patients diagnosed in stage Ⅰ, 91.5% to 96.4% for stage Ⅱ, between 69.0% and 83.0% for stage Ⅲ, and 27.4% to 41.8% for distantly spread disease (stage Ⅳ)[9]. Another staging classification that is sometimes used is that proposed by the United States National Cancer Institute of Surveillance, Epidemiology, and End Results (SEER) Program. This system considers three stages: (1) localized, for tumors confined to the breast with no extension to the lymph nodes (equivalent to TNM stages Ⅰ and ⅡA); (2) regional, when breast cancer has disseminated to the regional lymph nodes (equivalent to stages ⅡB, ⅢA, ⅢB and ⅢC); and (3) distant, when cancer has spread to distant organs (TNM stage Ⅳ)[10]. The reported 5-year survival rates for 317340 patients who were diagnosed between 2003 and 2009 in the United States SEER regions were 98.6% for localized stage cancer patients, 84.4% for regional stage patients and 24.3% for distant stage patients[10].

Table 2 summarizes the clinical stage data reported for different countries. As shown, while the majority of breast cancers are diagnosed in localized stages in HICs, most are detected in regionally spread stages in LMICs. In HICs, more than 70% of breast cancer patients are diagnosed in stages Ⅰ and Ⅱ; Sweden and Norway have proportions above 90%. In contrast, in LMICs, only between 20 and 60% of patients are diagnosed in these earlier stages, while between 30 and 80% are diagnosed in stages Ⅲ and Ⅳ. The exceptions in the table are Porto Alegre in Brazil and white women in South Africa, who behave similar to women in developed countries, with 70% and 68% of breast cancer cases detected in stages Ⅰ and Ⅱ, respectively. The data presented for the different regions or subpopulations in Brazil, South Africa and India reveal tremendous disparities within each of these countries. Similar differences have been reported in the United States, the United Kingdom and other developed countries and have been shown to be a result of socioeconomic disparities, as will be discussed in detail later on. These inequities are revealed in this table only for these particular cases because the data available for developing countries come from country-regions or even hospitals, while the data for most HICs were gathered through national registries and thus constitute a single measure for the entire population.

The question remains as to why cancer patients are diagnosed in such advanced stages in developing countries. Research on this matter is scarce. Most study findings in the developed world show an association of advanced clinical stage of breast cancer with delays greater than three months between symptom discovery and treatment start (total delay)[11-13]. Additionally, delays greater than three months are associated with reduced survival[12,13]. A reasonable explanation of the relationship between delay and survival is that delay influences disease progression, which in turn affects survival. This hypothesis is supported by studies in which the association between delay and survival disappears once clinical stage is controlled for[12,14].

TIME INTERVALS FOR BREAST CANCER CARE

Traditionally, breast cancer total delay has been defined as more than three months between symptom discovery and the beginning of cancer treatment and has been classified in two types: patient delay and provider delay[15-18]. Patient delay refers to the lengthening of the interval between the discovery of symptoms and the first medical consultation, and the most accepted threshold to establish it is three months. Provider delay is that which takes place between the first medical consultation and the beginning of definitive treatment, and the threshold used to define it is highly variable between studies. Table 3 summarizes the data for the total, patient and provider intervals reported in different countries. The median lengths of the intervals are reported when available and, in the absence of medians, some mean intervals and/or percentages of delays greater than three months are reported.

Diverse classifications and names of the provider interval have been used. The most commonly used are the diagnosis and treatment interval classifications. The diagnosis interval is that from the first medical consultation to the confirmation of a cancer diagnosis. The treatment interval is the time between diagnosis and the beginning of oncologic treatment. Two other classifications have also been used: (1) the doctor (from first consultation with the primary physician to the first investigation of cancer) and system (from the first investigation to the beginning of cancer treatment) intervals; and (2) the referral (from the first medical consultation with the primary physician to the patient's referral to the specialist) and specialist care (from the patient's referral to the beginning of cancer treatment) intervals[19]. These two last classifications (doctor/system, and referral/specialist) are rarely used, although the names are commonly used interchangeably in reference to the provider interval. They have been properly used only in health systems with well-organized primary and secondary care services, such as those of the United Kingdom and Denmark. They would be extremely difficult to measure in the context of fragmented health services or a lack of registries and electronic medical records, as is the case for the majority of developing countries. For the sake of clarity, despite the delay

Table 2 Clinical stage of breast cancer patients by country-summary from the literature

	Year(s)	TNM staging system				SEER staging system		
		I	II	III	IV	Localized	Regional	Distant
High-income Countries:								
Australia[9]	2000-2007	-	-	-	-	55.9	38.1	6.0
Canada[9]	2000-2007	41.0	38.1	13.3	7.6	-	-	-
Denmark[9]	2000-2007	29.3	47.2	15.8	7.7	-	-	-
Germany (Saarland)[11]	1996-1998	-	-	-	-	52.0	44.0	4.0
Northern Ireland[91]	2006	30.4	43.6	19.6	6.4	-	-	-
Norway[9]	2000-2007	43.4	47.1	3.8	5.7	-	-	-
Saudi Arabia[92]	2004	-	-	-	-	27.8	56.2	16.0
Sweden[9]	2000-2007	45.2	46.5	5.3	3.0	-	-	-
United Kingdom[9]	2000-2007	40.0	45.4	9.2	5.4	-	-	-
United States[10]	2002-2008	-	-	-	-	62.3	32.6	5.1
Low and middle-income countries:								
Brazil								
Goias[93]	2002-2009	14.7	36.1	27.9	21.3	-	-	-
Porto Alegre[94]	1975-1997	16.0	54.0	19.0	11.0	-	-	-
Sao Paulo[94]	1979-1989	11.0	22.0	53.0	14.0	-	-	-
Colombia (Bogota)[95]	2006-2007	-	-	-	-	26.4	68.2	5.4
Egypt (South Cancer Inst.)[96]	2001-2008	11.0	39.0	25.0	25.0	-	-	-
Egypt (Gharbiah)[97]	1999-2008	-	-	-	-	25.2	60.3	14.5
India[98]								
Mumbai	1995	7.8	57.4	28.4	5.9	-	-	-
Trivandrum	1996	4.4	42.3	40.5	12.8	-	-	-
Chennai		1.0	23.0	52.0	24.0	-	-	-
Iraq (Kurdistan)[99]	2006-2008	4.9	53.3	31.8	9.9	-	-	-
Jordan[100]	2009	29.0	30.0	23.0	10.0			
Libya[22]	2008-2009	9.0	25.5	54.0	11.5	-	-	-
Malaysia (East Coast and Kuala Lumpur)[26]	2005-2007	5.2	38.7	44.8	11.3	-	-	-
Mexico								
INCAN[101]-uninsured pop.	2007	10.2	36.4	40.9	12.5	-	-	-
IMSS[102]-insured pop.	2002	13.8	39.6	33.9	12.7	-	-	-
Nigeria (Lagos)[103]	2009-2010	5.5	15.4	62.7	16.4	-	-	-
Peru (Lima)[94]	1985-1997	9.0	42.0	33.0	16.0	-	-	-
South Africa[104]								
Whites	1970-1997	30.8	38.0	18.8	11.9	-	-	-
Blacks		5.4	16.9	41.6	36.1	-	-	-
Thailand[36]	2009	12.0	38.0	41.0	9.0	-	-	-

Data are population-based, except for the following countries where data is hospital-based: Brazil, Colombia, Egypt, India, Iraq, Libya, Malaysia, Mexico, Nigeria, Peru, South Africa and Thailand. All percentages were corrected to exclude Non-Staged cancers.

nomenclature used in each study, the terms presented in Table 3 are those that correspond to the definition that was used. When this was not possible, only the definition is shown and not the term used by the researchers.

To further complicate things, a wide range of methods has been used to measure time points and intervals, with the majority of existing studies lacking methodological rigor[20,21]. As a result, research findings are not easily comparable between studies and countries. Nevertheless, to obtain a rough idea of the differences in intervals of care between developing and developed countries, data from all the retrieved studies were included.

Among HICs, the median total intervals range between 30 and 48 d, and more than 60% of patients begin treatment less than 3 mo after symptom discovery (Table 3). In comparison, the median total intervals for LMICs are between 5.5 mo (Malaysia) and 8 mo (Brazil), and for countries with available data (Brazil, Libya, Mexico and Malaysia), it is striking that fewer than 30% of patients start treatment in less than three months after abnormal screening or symptom discovery[22-27].

The median patient interval is between 7 and 16 d for HICs and between 10 d and 3 mo for LMICs. The lengthiest median patient intervals have been reported for Iran (3 mo), Egypt (2.7 mo) and Malaysia (2 mo)[26,28,29]. Among countries that report mean instead of median intervals, including Eastern European countries, India and Ethiopia, the average patient interval is between 24 d (Hungary) and 1.5 mo (India) for all except Ethiopia, which reports a striking 18-mo patient interval mean.

Finally, available provider intervals or subintervals are also presented in Table 3. It is hard to compare these because of the diverse definitions used. The full provider interval is only reported for one HIC, Germany, with a median duration of 15 d. In contrast, the median provider intervals in LMICs, which are available only for Brazil, Colombia, Mexico and Turkey, range between 2.6 mo and 6.5 mo. The median diagnosis intervals for the HICs of France and the United States are 7 and 32 d, respectively, while that for the LMIC Brazil is 6.5 mo[24,30,31]. Notably,

Table 3 Time intervals for breast cancer care-findings from the literature

Country (region)	Year	*n*	Total interval			Patient interval		Provider/system intervals			
			Definition	Median/ mean[1]	> 3 mo (%)	Median/ mean[1]	> 3 mo (%)	Reported interval	Definition	Median/ mean[1]	> 3 mo (%)
High-income countries											
Canada (Quebec)[105]	1992-1998	29606	-	-	-	-	-	Treatment	1st diagnostic study to surgery.	42 d	17.1
Canada[106]	1996	4465	-	-	-	-	-	Diagnosis	Abnormal screening to diagnosis	31 d	-
France[30]	2003	1494	1st abnormal screening to treatment start	34 d	-	-	-	Diagnosis	Abnormal screening to diagnosis	7 d	-
								Treatment	Diagnosis to treatment start	27 d	-
Germany (Saarland)[11,107,108]	1996-1998	380	Symptom discovery or abnormal screening to diagnosis	-	26.1	16 d	17.4	Provider	1st consultation to treatment start	15 d	11.0
Italy (Campania)[56]	1998-1999	644	Symptom discovery to surgery	-	35.0	-	20.0	-	1st medical consultation to hospital admission	-	11.0
Italy (Campania and Apulia)[109]	2004-2006	959	-	-	-	-	-	Diagnosis	1st consultation to diagnosis	-	60.0
Nether-lands[110]	1996-2002	1503	-	-	-	-	-	Diagnosis	Screening to diagnosis	-	6.5
North Ireland[91]	2006	759	-	-	-	-	-	Treatment	Diagnosis to treatment start	15 d	-
Scotland[111]	2005-2007	1250	-	-	-	7 d	-	Referral	1st consultation to referral	1 d	-
							-	Specialist	Referral by GP to 1st consultation by specialist	18 d	-
Spain (Catalonia)[112]	2001-2002	266	-	-	-	-	-	Treatment	Diagnosis to treatment start	35 d	-
United Kingdom[113]	1999-2000	25627	Symptom discovery to diagnosis	30 d	-	9 d	-	-	GP referral to diagnosis	11 d	-
United States[31]	1991-1995	1659	Abnormal screening to treatment start	48 d	22.9	-	-	Diagnosis	1st abnormal screening to diagnosis	32 d	-
								Treatment	Diagnosis to treatment start.	10 d	-
United States[54]	1995-2005	246957	-	-	-	-	-	Treatment	Diagnosis to treatment start	23 d	-
United States (California)[114]	2003-2005	921 low income women	Symptom discovery to biopsy		39.0	-	-	-	-	-	-
United States (North Carolina)[115]	2000-2002	1786	-	-	-	-	-	Treatment	Diagnosis to treatment start	22 d	-
Middle-income countries											
Brazil (Brasilia)[25]	2010	250	Symptom discovery to treatment	7.5 mo	88.8	-	29.9	Provider	1st consultation to treatment start	-	77.6
Brazil (Rio)[24]	2004	104	Symptom discovery to diagnosis	8 mo	-	1 mo	-	Diagnosis	1st consultation to diagnosis	6.5 mo	80.0

Bulgaria[23]	2011	448	Symptom discovery to treatment	3.9 mo[1]	-	1.2 mo[1]	-	Provider	1st consultation to treatment start	3.1 mo[1]	-
Colombia[95,116]	2006-2007	852	-	-	-	-	20.3	Provider	1st consultation to treatment start	4.5 mo	31.0
Croatia[23]	2011	167	Symptom discovery to treatment	3.4 mo[1]	-	1.2 mo[1]		Provider	1st consultation to treatment start	2.6 mo[1]	-
Egypt[29]	2010	163	-	-	-	2.7 mo	-	-	1st consultation to hospital arrival	18 d	-
Ethiopia[117]	2008	69	-	-	-	18 mo[1]	-	-	-	-	-
Haiti[118]	2012	90	-	-	-	1 wk	42.0	-	-	-	-
Hungary[23]	2011	167	Symptom discovery to treatment	4.0 mo[1]	-	24 d[1]	-	Provider	1st consultation to treatment start	3.6 mo[1]	-
India[23]	2011	207	Symptom discovery to treatment	7.4 mo[1]	-	1.5 mo[1]	-	Provider	1st consultation to treatment start	6.2 mo[1]	-
Iran[28]	2000-2001	200	-	-	-	3 mo	42.5	-	-	-	-
Latvia[23]	2011	111	Symptom discovery to treatment	4.4 mo[1]	-	1.5 mo[1]	-	Provider	1st consultation to treatment start	3.3 mo[1]	-
Libya[22]	2008-2009	200	Symptom discovery to diagnosis	-	70.0	-	54.5	-	-	-	-
Lithuania[23]	2011	368	Symptom discovery to treatment	3.0 mo[1]	-	1.2 mo[1]	-	Provider	1st consultation to treatment start	2.1 mo[1]	-
Malaysia[26]	2005-2007	328	Symptom discovery to diagnosis	5.5 mo	72.6	2 mo	43.3	-	-	-	-
Mexico[34]	2008	32	Symptom discovery to treatment start	7.5 mo		10 d		Diagnosis	1st consultation to diagnosis	2.8 mo	
Mexico[27]	2010-2011	384	Abnormal mammogram or symptom discovery to treatment start	7.8 mo	90.0	11 d	20.6	Provider	1st consultation to treatment start	4.7 mo	73.7
Nigeria[103]	2009-2010	201	-	-	-	-	81.0	-	-	-	-
Poland[23]	2011	557	Symptom discovery to treatment	2.9 mo[1]	-	25 d[1]	-	Provider	1st consultation to treatment start	2.4 mo[1]	-
Romania[23]	2011	271	Symptom discovery to treatment	6.4 mo[1]	-	1.5 mo[1]	-	Provider	1st consultation to treatment start	7.4 mo[1]	-
Russia[23]	2011	718	Symptom discovery to treatment	3.9 mo[1]	-	1.2 mo[1]	-	Provider	1st consultation to treatment start	3.1 mo[1]	-
Slovakia[23]	2011	154	Symptom discovery to treatment	3.3 mo[1]	-	1.0 mo[1]	-	Provider	1st consultation to treatment start	2.7 mo[1]	-
Serbia[23]	2011	663	Symptom discovery to treatment	3.2 mo[1]	-	1.1 mo[1]	-	Provider	1st consultation to treatment start	2.3 mo[1]	-
Thailand[35]	1994-1996	94	-	-	-	1 mo	26.6	Provider	1st medical consultation to hospital admission	1 mo	24.4
Thailand[36]	2009	109	-	-	-	12 d	17.0.	Provider	1st consultation to treatment start	21 d	42.0
Turkey[23]	2011	694	Symptom discovery to treatment	3.4 mo[1]	-	1.2 mo[1]	-	Provider	1st consultation to treatment start	2.6 mo[1]	-

[1]These correspond to mean intervals, instead of medians. Patient interval is not defined in the table because studies coincide in the accepted definition: symptom discovery or abnormal screening to first medical consultation.

the median patient interval in LMICs is between 1.4 and 12.9 times longer than that observed in HICs, and the diagnosis interval is between 3.8 and 27.9 times longer. The patient interval prolongation is primarily influenced by the patients' help-seeking behavior, which varies according to different socioeconomic and cultural factors. In turn, the delayed provider intervals most likely reflect access barriers and quality deficiencies in cancer care in the LMIC health systems, as has been observed in some of the few available studies[32-36].

ACCESS BARRIERS AND QUALITY OF CARE DEFICIENCIES ASSOCIATED WITH DELAYED BREAST CANCER TREATMENT

Access to health care is a multidimensional concept that has been defined as the "degree of fit" between a patient's socioeconomic characteristics, the health system, and health services organization[37], and it includes both financial and non-financial dimensions[38-41]. Five different components of access have been described: affordability, acceptability, accessibility, accommodation, and availability[37]. Availability refers to the adequacy of the supply of health providers, facilities and services in relation to the patients' health needs. Accessibility is the relationship between the geographical location of services and that of patients (*e.g.*, transportation resources, travel time, distance and cost). Accommodation is the relationship between the manner in which the supply resources are organized to accept patients (*e.g.*, operation hours, appointment systems, telephone services), the patients' ability to accommodate these factors, and the patients' perceptions of their appropriateness. Affordability is the relationship between

Table 4 Studies of access or quality of care barriers related to provider delay

Access or quality barriers	Studies		
	Country	Year of publication	Sample size
Low socioeconomic status	England[47]	2005	19760
	Canada[48]	2007	696
Ethnic minorities	United States[31]	2000	1659
	United States[51]	2004	831
	United States[54]	2011	246957
Lack of health insurance	United States[54]	2011	246957
Patient's old age	United States[54]	2011	246957
Patient's young age	England[55]	1999	36222
	Italy[56]	2001	644
	Scotland[57]	2004	1069
	Scotland[58]	2004	5283
	England[47]	2005	19760
Travel time to hospital	Thailand[36]	2013	180
Distance from hospital	Thailand[36]	2013	180
Long waiting times to get medical appointments	Mexico[33]	2011	125
Consulting 3 or more different health services before arrival to a cancer center	Mexico[33]	2011	125
Type of first health service contacted	Thailand[35]	2000	94
Medical specialty of first provider consulted	Italy[56]	2001	644
Medical errors in initial diagnosis, screening interpretation or pathology review	United States[31]	2000	1659
	England[64]	2000	1004
	Thailand[35]	2000	94
	United States[65]	2002	454
	Scotland[58]	2004	5283
	Netherlands[119]	2004	153969
	Canada[48]	2007	696
	Mexico[33]	2011	125

the prices of services and the patients' ability to pay and/or existing health insurance. Finally, acceptability refers to the patients' beliefs, perceptions and attitudes in regard to the characteristics of health personnel and facilities (*e.g.*, doctor's gender or ethnicity, clinic type), as well as the health personnel's attitudes about the acceptable personal characteristics of the patients.

Table 4 summarizes different factors related to access or quality of care deficiencies that have been associated with breast cancer provider delay. As shown, there is little research on this matter, and the vast majority of studies have taken place in developed countries. Furthermore, the predominating focus has been to quantify associations between the patients' socio-demographic characteristics and delays, without exploration of specific access and quality of care issues that could explain these relationships.

Socioeconomic status (SES) has long been linked to morbidity, mortality, illness behavior, health services utilization and access to care[42-44]. SES differences in health are embedded in the larger problem of health disparities associated with social disadvantage[44]. As SES decreases, breast cancer clinical stage has been shown to increase and 5-year survival rates to decline[45,46]. These associations have been confirmed for several measures of SES, including income, education and occupation. SES has a direct impact on the access dimension of affordability[37]. Therefore, a plausible explanation for the disparities of breast cancer clinical stage and survival is that people with low SES suffer longer provider delays than people with high SES, as documented[47,48], most likely because they face access barriers to health care that remain to be identified and are most likely specific to each health system.

The relationship between ethnicity and provider delay may also be mediated by lower socioeconomic status and reduced access to medical care. Black people in the United States have poorer breast cancer survival rates than whites (79.1% *vs* 91.7%), and these gaps persist within clinical stages[10]. These ethnic disparities in breast clinical stage have been shown to dissolve when controlling for socioeconomic position[49,50]. Additionally, the relationship between ethnicity and provider delay has been shown to disappear when poverty and insurance status are controlled for[51]. Moreover, a study that examined the influence of ethnicity, socioeconomic position and gender on an individual's perception of the need for and urgency or seeking health care found that Black respondents and respondents from lower socio-economic groups were at least as likely to report immediate health care seeking as White respondents and those from higher socio-economic groups[52]. These findings suggest that the ethnicity differences observed in provider delay are very likely due to socioeconomic disparities that influence access to care.

Access to health insurance is also related to socioeconomic position and has long been known to be one of the most relevant enabling factors for health care utilization[39,53]. Therefore, it is not surprising that lack of health

insurance is related to provider delay for breast cancer care[54]. This might be particularly important in countries with fragmented systems, where the uninsured population has access to only certain types of health services (availability and accommodation) and/or has to pay out-of-pocket for each consultation, medical study and treatment (affordability).

The relationship between age and delay is very interesting. Older age has been found to be associated with patient delay in several studies[11,17], while younger age has been linked with provider delay[47,55-58]. Several mechanisms have been proposed to explain the association between older age and patient delay. Studies conducted in developed countries have suggested that older women may attribute early breast cancer symptoms to other comorbid conditions or to normal aging[11,16]. Likewise, older women may be more fatalistic, thinking they have lived long enough[16]. Study findings have also confirmed that delay in these older patients could be a consequence of negative attitudes toward seeing their general practitioner and fears about the consequences of the diagnosis and treatment of cancer[59]. The relationship between older age and provider delay has been less studied, and the plausible mechanisms of this relationship have not been explained[54]. Nevertheless, some of the mechanisms discussed for patient delay might also occur after the first medical consultation has taken place, when the patient might decide to postpone studies and/or the beginning of treatment. Another possible mechanism includes the tendency for older people to be affected simultaneously by other chronic conditions in addition to cancer, such as hypertension or diabetes. In these cases, the physician might postpone cancer treatment until the other comorbidities are stable. Yet another mechanism that is particularly relevant for developing countries is that older women may face more access barriers to health care because of unemployment and its consequences on the lack of health insurance and socioeconomic problems.

The relationship between young patient age and provider delay is most likely a consequence of medical errors. The majority of studies that have found a significant association between young age and delay have failed to explore the mechanisms behind this relationship[47,60]. Some studies, however, have suggested that young age increases the difficulty of a medical diagnosis[58]. The sensitivity of mammography has been found to be significantly lower in young women than older women (68 *vs* 91 percent), and tumors have been found to be more ill-defined for palpation because of background mammary density or a diffuse growth pattern[61]. Additionally, the suspicion of a cancer diagnosis may be less common among young patients than their older counterparts[55]. The presentation of breast cancer is highly unlikely in women younger than 40 years, with an estimated risk for a 30-year-old woman of 0.44 to develop a breast cancer in the next 10 years in comparison with a risk of 3.84 for a 70-year-old woman[10]. To further complicate things, breast benign conditions such as fibroadenoma and cysts are very common in young women[62,63].

Travel time to the hospital, distance from the patient's home to the hospital, long waiting times for medical appointments and the consultation of 3 or more different health services before arriving at a cancer hospital reflect different dimensions of access to care: accommodation, availability and affordability[37]. The study of these types of specific access barriers is scarce and much needed in developing countries where delays for cancer treatment and other life-threatening conditions are very common. For each country's health system, and even each health service within countries and country regions, specific access barriers need to be identified in order to address them and improve time to care.

Finally, the associations found between provider delay and type of first health service contacted, the medical specialty of the first provider that was consulted and medical errors all reflect differences in the quality of care that patients receive. Medical errors in relation to provider delay have been studied in terms of the primary care physician's failure to suspect cancer at the initial consultation[33,35], false-negative interpretations of mammography[31,48,64,65] and false-negative biopsy interpretations[48,64]. The relationships reported between the specialty of the first doctor consulted and provider delay as well as that of the primary care physician's failure to suspect cancer highlight the relevance of the role of the first medical professional consulted. This is very pertinent for developing countries, where highly specialized human resources are scarce and the first contact for the majority of the population is a general physician, that is, a recently graduated medical doctor (NOT a specialist in General Medicine). The majority of these doctors have never seen breast cancer and are typically not familiar with breast cancer screening and diagnostic guidelines.

IMPLICATIONS FOR PUBLIC POLICY IN LMICs

As the limited available data for LMICs presented here show, breast cancer is being treated in very advanced stages after long intervals of time. This is most likely because patients in these countries face significant access barriers to quality health care. The situation may be even worse for countries in which there are no data available. As Indraneel Mittra well points out in his interesting discussion about the global applicability of cancer screening recommendations, "the real unresolved problem of cancer control in developing countries is how to make accessible to the population at large the minimum level of cancer care that will reduce mortality and suffering[66]". A common proposed solution is to enhance early detection through mammography screening. However, as I will argue, this is most likely not the right path to follow for LMICs.

Organized population-based mammography programs have been adopted as the gold standard of early detection in the majority of HICs. Many LMICs are

trying to follow this example, even if they lack the infrastructure and human and financial resources to implement programs of this magnitude. Therefore, they are typically ending up with opportunistic screening mammography programs that are not only inequitable[67], more expensive and less effective than organized screening[68,69] but also make it harder to assure test quality and access to adequate diagnosis and treatment[70].

In recent years, the benefit of screening mammography has been seriously questioned[71-74]. There is evidence from several HICs that most of the reductions in breast cancer mortality that have occurred since the national mammographic screening programs began are not attributable to mammographic screening but to improved adjuvant therapy[75-81]. A recent Cochrane Systematic Review showed no effect of screening on either cancer mortality after 10 years or on all-cause mortality after 13 years[74]. Additionally, over-diagnosis and consequent over-treatment have been reported to occur in approximately 30% of screen-detected breast cancers[82,83].

If the benefit of screening mammography is questionable in HICs, it should be more so in LMICs. The World Health Organization has suggested that for a mammography screening program to be effective in the reduction of mortality, it needs to cover at least 70% of the population at risk[84], which is a very difficult coverage to reach, even for HICs. Furthermore, for HICs, it has been estimated that for every 2000 women 50 years and older screened throughout 10 years, one breast cancer death will be avoided, and 10 healthy women who would not have been diagnosed if there had not been screening will be treated unnecessarily; more than 200 women will experience distress because of false-positive findings, and approximately half of them will undergo an unnecessary biopsy[74,85]. These estimations were calculated considering HIC incidence rates and under the assumption that screening reduces breast cancer mortality in 15% of patients and has a 30% rate of over-diagnosis and unnecessary treatment. Considering that the incidence of breast cancer in LMICs is much lower and that the peak incidence occurs at a younger age, the benefits of screening mammography in LMICs are likely to be lower than in HICs, while the costs required to establish an organized screening program are most likely unaffordable for many LMICs[70]. Some screening mammography pilot programs in LMICs have actually been shown to be ineffective and unsustainable on a larger scale because of a lack of resources[86,87].

In the context I have presented here for breast cancer care in LMICs, with most breast cancer cases diagnosed at advanced stages and long times to diagnosis and treatment due to access barriers and substandard quality of care, the benefit of a screening program is even more questionable. Screening is useless if access to adequate diagnosis and treatment cannot be assured. The Breast Health Global Initiative Guidelines recommend that a population-based screening mammography program should not be implemented until access to the basic cancer diagnosis and treatment resources is guaranteed[88].

A more cost-effective strategy could be early diagnosis or down-staging, which has been endorsed for LMICs by the World Health Organization and the Breast Health Global Initiative[84,86,89]. The early diagnosis approach consists of the promotion of the awareness of early signs and symptoms among the public, the education of first-line health professionals and improved referral procedures to facilitate the prompt and adequate diagnosis and treatment of breast cancer in early stages.

A successful example of a down-staging program was performed in Malaysia[90]. The program consisted of training 400 first-line health personnel in hospitals and rural clinics to improve their skills in early detection and of raising public awareness through visual information and sensitization by trained health personnel. After four years of program implementation, late-stage (Ⅲ and Ⅳ) breast cancer cases were reduced from 60% to 35%[90].

Although there is still not sufficient evidence regarding the benefits of down-staging programs, the World Health Organization and the Breast Health Global Initiative Guidelines recommend them as the most basic breast cancer early detection strategy to implement and strengthen in low-resource settings before moving on to consider mammography screening[84,86,89]. After reviewing the evidence of advanced clinical stage and prolonged times to treatment in LMICs, it is evident that much more than just screening remains to be done to improve breast cancer mortality rates. There are serious problems in access to health services, the strength of the first level of care for the early detection of symptomatic patients, the regulation of establishments where breast imaging tests are performed, and the faulty or absent delineation of referral pathways to cancer care. Programs directed at improving these problems, which are widespread in LMICs, are likely to be much more cost-effective and have an impact in a shorter term than attempting to establish population-wide mammography screening programs in low-resource settings.

CONCLUSION

This review assembled sufficient evidence to argue that the lower breast cancer survival rates observed for LMICs in comparison to HICs are due to diagnosis in much more advanced stages. Although there is scant information on the length of care intervals, which are incomparable in many cases, the presented data provide sufficient evidence to state that breast cancer patients in LMICs suffer long diagnosis and treatment delays, and this is most likely why they present in such advanced stages. In contrast to what has usually been assumed, the greatest delays in LMICs are not attributable to patients delaying care. The longest delays appear to occur after the first medical consultation has taken place, and they are likely the result of access barriers and substandard quality of care. Research on access barriers and quality of care for the diagnosis and treatment of breast cancer is practi-

cally non-existent for LMICs, where it is most needed. To strengthen the capacity of each country's health system(s) and health services for the early diagnosis and treatment of cancer, specific barriers need to be identified throughout the entire cancer care trajectory. Such knowledge could enable individualized designs of public policies and programs for each country, region, city or even health facility that are likely to be more effective and affordable for LMICs than attempting to implement expensive and complex screening mammography programs, which are currently proving to be more harmful than beneficial, even in HICs.

REFERENCES

1 **The World Bank.** How we classify countries. Available from: URL: http://data.Worldbank.Org/about/country-classifications

2 **Anderson BO**, Jakesz R. Breast cancer issues in developing countries: an overview of the Breast Health Global Initiative. *World J Surg* 2008; **32**: 2578-2585 [PMID: 18283512 DOI: 10.1016/S1470-2045(11)70031-6]

3 **Ferlay J,** Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Globocan 2012 v1.0. Cancer Incidence and Mortality Worldwide. IARC Cancer Base No. 11 [internet]. Lyon, France: Iinternational Agency for Research on Cancer, 2013

4 **Coleman MP**, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, Baili P, Rachet B, Gatta G, Hakulinen T, Micheli A, Sant M, Weir HK, Elwood JM, Tsukuma H, Koifman S, E Silva GA, Francisci S, Santaquilani M, Verdecchia A, Storm HH, Young JL. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008; **9**: 730-756 [PMID: 18639491 DOI: 10.1016/S1470-2045(08)70179-7]

5 **Sankaranarayanan R**, Swaminathan R, Brenner H, Chen K, Chia KS, Chen JG, Law SC, Ahn YO, Xiang YB, Yeole BB, Shin HR, Shanta V, Woo ZH, Martin N, Sumitsawan Y, Sriplung H, Barboza AO, Eser S, Nene BM, Suwanrungruang K, Jayalekshmi P, Dikshit R, Wabinga H, Esteban DB, Laudico A, Bhurgri Y, Bah E, Al-Hamdan N. Cancer survival in Africa, Asia, and Central America: a population-based study. *Lancet Oncol* 2010; **11**: 165-173 [PMID: 20005175 DOI: 10.1016/S1470-2045(09)70335-3]

6 **Anderson BO,** Jakesz R. Breast cancer issues in developing countries: An overview of the Breast Health Global Initiative. *World J Surg* 2008; **32**: 2578-2585 [DOI: 10.1007/s00268-007-9454-z]

7 **Burstein HJ,** Harris JR, Morrow M. Malignant tumors of the breast. In: DeVita VT, editor. Lawrence TS and Rosenberg SA Cancer: Principles and practice of oncology. USA: Lippincott, Williams and Wilkins, 2011

8 **Edge SB,** Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti AE. AJCC Cancer Staging Manual. 7th ed. Springer, 2010

9 **Walters S,** Maringe C, Butler J, Rachet B, Barrett-Lee P, Bergh J, Boyages J, Christiansen P, Lee M, Warnberg F, Allemani C, Engholm G, Fornander T, Gjerstorff ML, Johannesen TB, Lawrence G, McGahan CE, Middleton R, Steward J, Tracey E, Turner D, Richards MA, Coleman MP. Breast cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK, 2000-2007: A population-based study. *Br J Cancer* 2013; **108**: 1195-1208 [DOI: 10.1038/bjc.2013.6]

10 **Howlader N,** Noone A, Krapcho M, Neyman N, Aminou R, Altekruse S, Kosary C, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner M, Lewis D, Chen H, Feuer E, Cronin Ke. SEER Cancer Statistics Review, 1975-2009 (vintage 2009 populations). Bethesda, MD: National Cancer Institute, 2012

11 **Arndt V**, Stürmer T, Stegmaier C, Ziegler H, Dhom G, Brenner H. Patient delay and stage of diagnosis among breast cancer patients in Germany -- a population based study. *Br J Cancer* 2002; **86**: 1034-1040 [PMID: 11953844 DOI: 10.1038/sj.bjc.6600209]

12 **Richards MA**, Smith P, Ramirez AJ, Fentiman IS, Rubens RD. The influence on survival of delay in the presentation and treatment of symptomatic breast cancer. *Br J Cancer* 1999; **79**: 858-864 [PMID: 10070881 DOI: 10.1038/sj.bjc.6690137]

13 **Richards MA**, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ. Influence of delay on survival in patients with breast cancer: a systematic review. *Lancet* 1999; **353**: 1119-1126 [PMID: 10209974 DOI: 10.1016/S0140-6736(99)02143-1]

14 **Vernon SW**, Tilley BC, Neale AV, Steinfeldt L. Ethnicity, survival, and delay in seeking treatment for symptoms of breast cancer. *Cancer* 1985; **55**: 1563-1571 [PMID: 3978551 DOI: 10.1002/1097-0142(19850401)55]

15 **Torti RA**, Winship T. Culpability for delay in the treatment of breast cancer. *Med Ann Dist Columbia* 1963; **32**: 132-133 [PMID: 13993746]

16 **Facione NC**. Delay versus help seeking for breast cancer symptoms: a critical review of the literature on patient and provider delay. *Soc Sci Med* 1993; **36**: 1521-1534 [PMID: 8327915 DOI: 10.1016/0277-9536(93)90340-A]

17 **Ramirez AJ**, Westcombe AM, Burgess CC, Sutton S, Littlejohns P, Richards MA. Factors predicting delayed presentation of symptomatic breast cancer: a systematic review. *Lancet* 1999; **353**: 1127-1131 [PMID: 10209975]

18 **Unger-Saldaña K**, Infante-Castañeda C. Delay of medical care for symptomatic breast cancer: a literature review. *Salud Publica Mex* 2009; **51** Suppl 2: s270-s285 [PMID: 19967283 DOI: 10.1590/S0036-36342009000800018]

19 **Olesen F**, Hansen RP, Vedsted P. Delay in diagnosis: the experience in Denmark. *Br J Cancer* 2009; **101** Suppl 2: S5-S8 [PMID: 19956163 DOI: 10.1038/sj.bjc.6605383]

20 **Neal RD**. Do diagnostic delays in cancer matter? *Br J Cancer* 2009; **101** Suppl 2: S9-S12 [PMID: 19956171 DOI: 10.1038/sj.bjc.6605384]

21 **Weller D,** Vedsted P, Rubin G, Walter FM, Emery J, Scott S, Campbell C, Andersen RS, Hamilton W, Olesen F, Rose P, Nafees S, van Rijswijk E, Hiom S, Muth C, Beyer M, Neal RD. The Aarhus statement: Improving design and reporting of studies on early cancer diagnosis. *Br J Cancer* 2012; **106**: 1262-1267 [DOI: 10.1038/bjc.2012.68]

22 **Ermiah E,** Abdalla F, Buhmeida A, Larbesh E, Pyrhönen S, Collan Y. Diagnosis delay in Libyan female breast cancer. *BMC Res Notes* 2012; **5**: 452 [PMID: 22909280 DOI: 10.1186/1756-0500-5-452]

23 **Jassem J,** Ozmen V, Bacanu F, Drobniene M, Eglitis J, Lakshmaiah KC, Kahan Z, Mardiak J, Pienkowski T, Semiglazova T, Stamatovic L, Timcheva C, Vasovic S, Vrbanec D, Zaborek P. Delays in diagnosis and treatment of breast cancer: a multinational analysis. *Eur J Public Health* 2013 Sep 12; Epub ahead of print [PMID: 24029456 DOI: 10.1093/eurpub/ckt131]

24 **Rezende MC**, Koch HA, Figueiredo Jde A, Thuler LC. [Factors leading to delay in obtaining definitive diagnosis of suspicious lesions for breast cancer in a dedicated health unit in Rio de Janeiro]. *Rev Bras Ginecol Obstet* 2009; **31**: 75-81 [PMID: 19407912]

25 **Barros ÂF**, Uemura G, de Macedo JL. [Interval for access to treatment for breast cancer in the Federal District, Brazil]. *Rev Bras Ginecol Obstet* 2013; **35**: 458-463 [PMID: 24337058]

26 **Norsa'adah B**, Rampal KG, Rahmah MA, Naing NN, Biswal BM. Diagnosis delay of breast cancer and its associated factors in Malaysian women. *BMC Cancer* 2011; **11**: 141 [PMID: 21496310 DOI: 10.1186/1471-2407-11-141]

27 **Unger-Saldaña K**, Peláez-Ballestas I, Infante-Castañeda C. Development and validation of a questionnaire to assess delay in treatment for breast cancer. *BMC Cancer* 2012; **12**: 626 [PMID: 23272645 DOI: 10.1186/1471-2407-12-626]

28 **Harirchi I**, Ghaemmaghami F, Karbakhsh M, Moghimi R, Mazaherie H. Patient delay in women presenting with advanced breast cancer: an Iranian study. *Public Health* 2005; **119**: 885-891 [PMID: 15913679]

29 **Mousa SM**, Seifeldin IA, Hablas A, Elbana ES, Soliman AS. Patterns of seeking medical care among Egyptian breast cancer patients: relationship to late-stage presentation. *Breast* 2011; **20**: 555-561 [PMID: 21807518 DOI: 10.1016/j.breast.2011.07.001]

30 **Molinié F**, Leux C, Delafosse P, Ayrault-Piault S, Arveux P, Woronoff AS, Guizard AV, Velten M, Ganry O, Bara S, Daubisse-Marliac L, Tretarre B. Waiting time disparities in breast cancer diagnosis and treatment: a population-based study in France. *Breast* 2013; **22**: 810-816 [PMID: 23473773 DOI: 10.1016/j.breast.2013.02.009]

31 **Caplan LS**, May DS, Richardson LC. Time to diagnosis and treatment of breast cancer: results from the National Breast and Cervical Cancer Early Detection Program, 1991-1995. *Am J Public Health* 2000; **90**: 130-134 [PMID: 10630153]

32 **Unger-Saldaña K,** Infante-Castañeda CB. Breast cancer delay: A grounded model of help-seeking behaviour. *Soc Sci Med* 2011; **72**: 1096-1104 [DOI: 10.1016/j.socscimed.2011.01.022]

33 **Unger-Saldaña K,** Infante-Castañeda C. Is breast cancer delay really the patient's fault? In: Deng M, Raia F and Vaccarella M, editors. Relational Concepts in Medicine. Oxford, United Kingdom: Interdisciplinary Net, 2011

34 **Bright K**, Barghash M, Donach M, de la Barrera MG, Schneider RJ, Formenti SC. The role of health system factors in delaying final diagnosis and treatment of breast cancer in Mexico City, Mexico. *Breast* 2011; **20** Suppl 2: S54-S59 [PMID: 21371885 DOI: 10.1016/j.breast.2011.02.012]

35 **Thongsuksai P**, Chongsuvivatwong V, Sriplung H. Delay in breast cancer care: a study in Thai women. *Med Care* 2000; **38**: 108-114 [PMID: 10630725 DOI: 10.1097/00005650-200001000-00012]

36 **Poum A**, Promthet S, Duffy SW, Parkin DM. Factors associated with delayed diagnosis of breast cancer in northeast Thailand. *J Epidemiol* 2014; **24**: 102-108 [PMID: 24335087 DOI: 10.2188/jea.JE20130090]

37 **Penchansky R**, Thomas JW. The concept of access: definition and relationship to consumer satisfaction. *Med Care* 1981; **19**: 127-140 [PMID: 7206846 DOI: 10.1097/00005650-198102000-00001]

38 **Donabedian A.** Aspects of medical care administration: Specifying requirements for health care. Cambridge, Mass: Harvard University Press, 1973

39 **Aday LA**, Andersen R. A framework for the study of access to medical care. *Health Serv Res* 1974; **9**: 208-220 [PMID: 4436074]

40 **Pescosolido B.** Beyond rational choice: The social dynamics of how people seek help. *Am J Sociol* 1992; **97**: 1096-1138 [DOI: 10.1086/229863]

41 **Kullgren JT**, McLaughlin CG. Beyond affordability: the impact of nonfinancial barriers on access for uninsured adults in three diverse communities. *J Community Health* 2010; **35**: 240-248 [PMID: 20127505 DOI: 10.1007/s10900-010-9230-0]

42 **McKinlay J.** The help-seeking behaviour of the poor. In: Kosa J and Zola IK (editors). Poverty and health. Cambridge, Massachusetts: Harvard University Press, 1975: 224-273

43 **Mechanic D.** Illness behavior: An overview. In: McHugh S and Vallis TM Illness behavior: A multidisciplinary model. New York Plenum, 1986

44 **Adler NE**, Stewart J. Preface to the biology of disadvantage: socioeconomic status and health. *Ann N Y Acad Sci* 2010; **1186**: 1-4 [PMID: 20201864 DOI: 10.1111/j.1749-6632.2009.05385.x]

45 **Yabroff KR**, Gordis L. Does stage at diagnosis influence the observed relationship between socioeconomic status and breast cancer incidence, case-fatality, and mortality? *Soc Sci Med* 2003; **57**: 2265-2279 [PMID: 14572836]

46 **Rutqvist LE**, Bern A. Socioeconomic gradients in clinical stage at presentation and survival among breast cancer patients in the Stockholm area 1977-1997. *Int J Cancer* 2006; **119**: 1433-1439 [PMID: 16596647 DOI: 10.1002/ijc.21949]

47 **Neal RD**, Allgar VL. Sociodemographic factors and delays in the diagnosis of six cancers: analysis of data from the "National Survey of NHS Patients: Cancer". *Br J Cancer* 2005; **92**: 1971-1975 [PMID: 15900296]

48 **Bairati I**, Jobin E, Fillion L, Larochelle M, Vincent L. Determinants of delay for breast cancer diagnosis. *Cancer Detect Prev* 2007; **31**: 323-331 [PMID: 17935908]

49 **Farley TA**, Flannery JT. Late-stage diagnosis of breast cancer in women of lower socioeconomic status: public health implications. *Am J Public Health* 1989; **79**: 1508-1512 [PMID: 2817162 DOI: 10.2105/AJPH.79.11.1508]

50 **Bradley CJ**, Given CW, Roberts C. Race, socioeconomic status, and breast cancer treatment and survival. *J Natl Cancer Inst* 2002; **94**: 490-496 [PMID: 11929949 DOI: 10.1093/jnci/94.7.490]

51 **Gwyn K**, Bondy ML, Cohen DS, Lund MJ, Liff JM, Flagg EW, Brinton LA, Eley JW, Coates RJ. Racial differences in diagnosis, treatment, and clinical delays in a population-based study of patients with newly diagnosed breast carcinoma. *Cancer* 2004; **100**: 1595-1604 [PMID: 15073845 DOI: 10.1002/cncr.20169]

52 **Adamson J**, Ben-Shlomo Y, Chaturvedi N, Donovan J. Ethnicity, socio-economic position and gender--do they affect reported health-care seeking behaviour? *Soc Sci Med* 2003; **57**: 895-904 [PMID: 12850114]

53 **Wang Y**, Wang J, Maitland E, Zhao Y, Nicholas S, Lu M. Growing old before growing rich: inequality in health service utilization among the mid-aged and elderly in Gansu and Zhejiang Provinces, China. *BMC Health Serv Res* 2012; **12**: 302 [PMID: 22947369 DOI: 10.1186/1472-6963-12-302]

54 **Bilimoria KY**, Ko CY, Tomlinson JS, Stewart AK, Talamonti MS, Hynes DL, Winchester DP, Bentrem DJ. Wait times for cancer surgery in the United States: trends and predictors of delays. *Ann Surg* 2011; **253**: 779-785 [PMID: 21475020 DOI: 10.1097/SLA.0b013e318211cc0f]

55 **Sainsbury R**, Johnston C, Haward B. Effect on survival of delays in referral of patients with breast-cancer symptoms: a retrospective analysis. *Lancet* 1999; **353**: 1132-1135 [PMID: 10209976 DOI: 10.1016/S0140-6736(99)02374-0]

56 **Montella M**, Crispo A, D'Aiuto G, De Marco M, de Bellis G, Fabbrocini G, Pizzorusso M, Tamburini M, Silvestra P. Determinant factors for diagnostic delay in operable breast cancer patients. *Eur J Cancer Prev* 2001; **10**: 53-59 [PMID: 11263591 DOI: 10.1097/00008469-200102000-00006]

57 **Robertson R**, Campbell NC, Smith S, Donnan PT, Sullivan F, Duffy R, Ritchie LD, Millar D, Cassidy J, Munro A. Factors influencing time from presentation to treatment of colorectal and breast cancer in urban and rural areas. *Br J Cancer* 2004; **90**: 1479-1485 [PMID: 15083172 DOI: 10.1038/sj.bjc.6601756601753]

58 **Barber MD**, Jack W, Dixon JM. Diagnostic delay in breast cancer. *Br J Surg* 2004; **91**: 49-53 [PMID: 14716793 DOI: 10.1002/bjs.4436]

59 **Burgess CC**, Potts HW, Hamed H, Bish AM, Hunter MS, Richards MA, Ramirez AJ. Why do older women delay presentation with breast cancer symptoms? *Psychooncology* 2006; **15**: 962-968 [PMID: 16511900 DOI: 10.1002/pon.1030]

60 **Partridge AH**, Hughes ME, Ottesen RA, Wong YN, Edge SB, Theriault RL, Blayney DW, Niland JC, Winer EP, Weeks JC, Tamimi RM. The effect of age on delay in diagnosis and stage of breast cancer. *Oncologist* 2012; **17**: 775-782 [PMID: 22554997 DOI: 10.1634/theoncologist.2011-0469]

61 **Lannin DR**, Harris RP, Swanson FH, Edwards MS, Swanson MS, Pories WJ. Difficulties in diagnosis of carcinoma of the breast in patients less than fifty years of age. *Surg Gynecol Obstet* 1993; **177**: 457-462 [PMID: 8211596 DOI: 10.1097/00006254-199404000-00017]

62 **Amin AL**, Purdy AC, Mattingly JD, Kong AL, Termuhlen PM. Benign breast disease. *Surg Clin North Am* 2013; **93**: 299-308 [PMID: 23464687 DOI: 10.1016/j.suc.2013.01.001]

63 **Ferrara A**. Benign breast disease. *Radiol Technol* 2011; **82**: 447M-462M [PMID: 21572066]

64 **Jenner DC**, Middleton A, Webb WM, Oommen R, Bates T. In-hospital delay in the diagnosis of breast cancer. *Br J Surg* 2000; **87**: 914-919 [PMID: 10931028 DOI: 10.1046/j.1365-2168.2000.01460.x]

65 **Goodson WH**, Moore DH. Causes of physician delay in the diagnosis of breast cancer. *Arch Intern Med* 2002; **162**: 1343-1348 [PMID: 12076232]

66 **Mittra I**. Screening for breast cancer: is it globally applicable? *Nat Clin Pract Oncol* 2008; **5**: 60-61 [PMID: 18059392 DOI: 10.1038/ncponc1019]

67 **Palència L**, Espelt A, Rodríguez-Sanz M, Puigpinós R, Pons-Vigués M, Pasarín MI, Spadea T, Kunst AE, Borrell C. Socioeconomic inequalities in breast and cervical cancer screening practices in Europe: influence of the type of screening program. *Int J Epidemiol* 2010; **39**: 757-765 [PMID: 20176587 DOI: 10.1093/ije/dyq003]

68 **de Gelder R**, Bulliard JL, de Wolf C, Fracheboud J, Draisma G, Schopper D, de Koning HJ. Cost-effectiveness of opportunistic versus organised mammography screening in Switzerland. *Eur J Cancer* 2009; **45**: 127-138 [PMID: 19038540 DOI: 10.1016/j.ejca.2008.09.015]

69 **Bordoni A**, Probst-Hensch NM, Mazzucchelli L, Spitale A. Assessment of breast cancer opportunistic screening by clinical-pathological indicators: a population-based study. *Br J Cancer* 2009; **101**: 1925-1931 [PMID: 19861962 DOI: 10.1038/sj.bjc.6605378]

70 **Corbex M,** Burton R, Sancho-Garnier H. Breast cancer early detection methods for low and middle income countries, a review of the evidence. *Breast* 2012; **21**: 428-434 [DOI: 10.1016/j.breast.2012.01.002]

71 **Zahl PH**, Maehlen J, Welch HG. The natural history of invasive breast cancers detected by screening mammography. *Arch Intern Med* 2008; **168**: 2311-2316 [PMID: 19029493 DOI: 10.1001/archinte.168.21.2311]

72 **Jørgensen KJ**. Mammography screening is not as good as we hoped. *Maturitas* 2010; **65**: 1-2 [PMID: 19939593 DOI: 10.1016/j.maturitas.2009.10.008]

73 **Bleyer A**, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med* 2012; **367**: 1998-2005 [PMID: 23171096 DOI: 10.1056/NEJMoa1206809]

74 **Gøtzsche PC**, Jørgensen KJ. Screening for breast cancer with mammography. *Cochrane Database Syst Rev* 2013; **6**: CD001877 [PMID: 23737396 DOI: 10.1002/14651858.CD001877.pub5]

75 **Beral V**, Hermon C, Reeves G, Peto R. Sudden fall in breast cancer death rates in England and Wales. *Lancet* 1995; **345**: 1642-1643 [PMID: 7783561 DOI: 10.1016/S0140-6736(95)90151-5]

76 **Blanks RG**, Moss SM, McGahan CE, Quinn MJ, Babb PJ. Effect of NHS breast screening programme on mortality from breast cancer in England and Wales, 1990-8: comparison of observed with predicted mortality. *BMJ* 2000; **321**: 665-669 [PMID: 10987769 DOI: 10.1136/bmj.321.7262.665]

77 **Peto R**, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25% in year 2000 at ages 20-69 years. *Lancet* 2000; **355**: 1822 [PMID: 10832853 DOI: 10.1016/S0140-6736(00)02277-7]

78 **Jørgensen KJ**, Zahl PH, Gøtzsche PC. Breast cancer mortality in organised mammography screening in Denmark: comparative study. *BMJ* 2010; **340**: c1241 [PMID: 20332505 DOI: 10.1136/bmj.c1241]

79 **Kalager M**, Zelen M, Langmark F, Adami HO. Effect of screening mammography on breast-cancer mortality in Norway. *N Engl J Med* 2010; **363**: 1203-1210 [PMID: 20860502 DOI: 10.1056/NEJMoa1000727]

80 **Burton RC**, Bell RJ, Thiagarajah G, Stevenson C. Adjuvant therapy, not mammographic screening, accounts for most of the observed breast cancer specific mortality reductions in Australian women since the national screening program began in 1991. *Breast Cancer Res Treat* 2012; **131**: 949-955 [PMID: 21956213 DOI: 10.1007/s10549-011-1794-6]

81 **Autier P**, Boniol M, Gavin A, Vatten LJ. Breast cancer mortality in neighbouring European countries with different levels of screening but similar access to treatment: trend analysis of WHO mortality database. *BMJ* 2011; **343**: d4411 [PMID: 21798968 DOI: 10.1136/bmj.d4411]

82 **Jørgensen KJ**, Gøtzsche PC. Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends. *BMJ* 2009; **339**: b2587 [PMID: 19589821 DOI: 10.1136/bmj.b2587]

83 **Jørgensen KJ**. Systematic review: Mammography reduces breast cancer mortality in women aged 39-69 years; but harms may outweigh benefits in women under 50. *Evid Based Med* 2010; **15**: 62-63 [PMID: 20436133 DOI: 10.1136/ebm1045]

84 **WHO.** Early detection. Cancer control: Knowledge into action who guide for effecrtive programmes (module 3). World Health Organization, 2007

85 **Welch HG**. Overdiagnosis and mammography screening. *BMJ* 2009; **339**: b1425 [PMID: 19589820 DOI: 10.1136/bmj.b1425]

86 **Yip CH**, Smith RA, Anderson BO, Miller AB, Thomas DB, Ang ES, Caffarella RS, Corbex M, Kreps GL, McTiernan A. Guideline implementation for breast healthcare in low- and middle-income countries: early detection resource allocation. *Cancer* 2008; **113**: 2244-2256 [PMID: 18837017 DOI: 10.1002/cncr.23842]

87 **Harford JB**. Breast-cancer early detection in low-income and middle-income countries: do what you can versus one size fits all. *Lancet Oncol* 2011; **12**: 306-312 [PMID: 21376292 DOI: 10.1016/S1470-2045(10)70273-4]

88 **Anderson BO**, Shyyan R, Eniu A, Smith RA, Yip CH, Bese NS, Chow LW, Masood S, Ramsey SD, Carlson RW. Breast cancer in limited-resource countries: an overview of the Breast Health Global Initiative 2005 guidelines. *Breast J* 2006; **12** Suppl 1: S3-15 [PMID: 16430397]

89 **Harford JB**, Otero IV, Anderson BO, Cazap E, Gradishar WJ, Gralow JR, Kane GM, Niëns LM, Porter PL, Reeler AV, Rieger PT, Shockney LD, Shulman LN, Soldak T, Thomas DB, Thompson B, Winchester DP, Zelle SG, Badwe RA. Problem solving for breast health care delivery in low and middle resource countries (LMCs): consensus statement from the Breast Health Global Initiative. *Breast* 2011; **20** Suppl 2: S20-S29 [PMID: 21376593 DOI: 10.1016/j.breast.2011.02.007]

90 **Devi BC**, Tang TS, Corbex M. Reducing by half the percentage of late-stage presentation for breast and cervix cancer over 4 years: a pilot study of clinical downstaging in Sarawak, Malaysia. *Ann Oncol* 2007; **18**: 1172-1176 [PMID: 17434897 DOI: 10.1093/annonc/mdm105]

91 **Carney P**, Gavin A, O'Neill C. The role of private care in the interval between diagnosis and treatment of breast cancer in Northern Ireland: an analysis of Registry data. *BMJ Open* 2013; **3**: e004074 [PMID: 24302511 DOI: 10.1136/bmjopen-2013-004074]

92 **Al-Eid HS,** Omer-Arteh S. Cancer incidence report saudi arabia 2004. Saudi Arabia: Main Office, National Cancer Registry, 2008

93 **Freitas R**, Siqueira LB, Carrijo EN, Lacerda RP, Paulinelli RR, Rahal RM, Oliveira LF. Temporal variation of breast cancer surgical treatment in a university hospital in Brazil's

Central West region. *Rev Col Bras Cir* 2013; **40**: 180-185 [PMID: 23912363]
94 **Schwartsmann G**. Breast cancer in South America: challenges to improve early detection and medical management of a public health problem. *J Clin Oncol* 2001; **19**: 118S-124S [PMID: 11560986]
95 **Piñeros M**, Sánchez R, Cendales R, Perry F, Ocampo R. Patient delay among Colombian women with breast cancer. *Salud Publica Mex* 2009; **51**: 372-380 [PMID: 19936550 DOI: 10.1590/S0036-36342009000500004]
96 **Salem AA**, Salem MA, Abbass H. Breast cancer: surgery at the South egypt cancer institute. *Cancers* (Basel) 2010; **2**: 1771-1778 [PMID: 24281200 DOI: 10.3390/cancers2041771]
97 **Hirko KA**, Soliman AS, Hablas A, Seifeldin IA, Ramadan M, Banerjee M, Harford JB, Chamberlain RM, Merajver SD. Trends in Breast Cancer Incidence Rates by Age and Stage at Diagnosis in Gharbiah, Egypt, over 10 Years (1999-2008). *J Cancer Epidemiol* 2013; **2013**: 916394 [PMID: 24282410 DOI: 10.1155/2013/916394]
98 **Chopra R**. The Indian scene. *J Clin Oncol* 2001; **19**: 106S-111S [PMID: 11560984]
99 **Majid RA**, Mohammed HA, Saeed HM, Safar BM, Rashid RM, Hughson MD. Breast cancer in Kurdish women of northern Iraq: incidence, clinical stage, and case control analysis of parity and family risk. *BMC Womens Health* 2009; **9**: 33 [PMID: 20003359 DOI: 10.1186/1472-6874-9-33]
100 **Tarawneh M,** Nimri O, Arkoob K, Zaghal MAL. Jordan cancer registry. Jordan: Ministry of Health, 2009
101 **Mohar A**, Bargalló E, Ramírez MT, Lara F, Beltrán-Ortega A. [Available resources for the treatment of breast cancer in Mexico]. *Salud Publica Mex* 2009; **51** Suppl 2: s263-s269 [PMID: 19967282]
102 **Knaul FM**, Arreola-Ornelas H, Velázquez E, Dorantes J, Méndez O, Avila-Burgos L. [The health care costs of breast cancer: the case of the Mexican Social Security Institute]. *Salud Publica Mex* 2009; **51** Suppl 2: s286-s295 [PMID: 19967284]
103 **Ibrahim NA**, Oludara MA. Socio-demographic factors and reasons associated with delay in breast cancer presentation: a study in Nigerian women. *Breast* 2012; **21**: 416-418 [PMID: 22381153 DOI: 10.1016/j.breast.2012.02.006]
104 **Vorobiof DA**, Sitas F, Vorobiof G. Breast cancer incidence in South Africa. *J Clin Oncol* 2001; **19**: 125S-127S [PMID: 11560987]
105 **Mayo NE**, Scott SC, Shen N, Hanley J, Goldberg MS, MacDonald N. Waiting time for breast cancer surgery in Quebec. *CMAJ* 2001; **164**: 1133-1138 [PMID: 11338798]
106 **Olivotto IA**, Gomi A, Bancej C, Brisson J, Tonita J, Kan L, Mah Z, Harrison M, Shumak R. Influence of delay to diagnosis on prognostic indicators of screen-detected breast carcinoma. *Cancer* 2002; **94**: 2143-2150 [PMID: 12001110 DOI: 10.1002/cncr.10453]
107 **Arndt V**, Stürmer T, Stegmaier C, Ziegler H, Dhom G, Brenner H. Socio-demographic factors, health behavior and late-stage diagnosis of breast cancer in Germany: a population-based study. *J Clin Epidemiol* 2001; **54**: 719-727 [PMID: 11438413]
108 **Arndt V**, Stürmer T, Stegmaier C, Ziegler H, Becker A, Brenner H. Provider delay among patients with breast cancer in Germany: a population-based study. *J Clin Oncol* 2003; **21**: 1440-1446 [PMID: 12697864 DOI: 10.1200/JCO.2003.08.071]
109 **Crispo A**, Montella M, Barba M, Schittulli F, De Marco MR, Grimaldi M, Quaranta M, Serravezza G, Savastano C, Botti G, La Vecchia C, D'Aiuto G. Association between mode of breast cancer detection and diagnosis delay. *Breast* 2009; **18**: 382-386 [PMID: 19879761 DOI: 10.1016/j.breast.2009.10.001]
110 **Duijm LE**, Groenewoud JH, de Koning HJ, Coebergh JW, van Beek M, Hooijen MJ, van de Poll-Franse LV. Delayed diagnosis of breast cancer in women recalled for suspicious screening mammography. *Eur J Cancer* 2009; **45**: 774-781 [PMID: 19046632 DOI: 10.1016/j.ejca.2008.10.020]
111 **Sham JS**, Wei WI, Kwan WH, Chan CW, Choi PH, Choy D. Fiberoptic endoscopic examination and biopsy in determining the extent of nasopharyngeal carcinoma. *Cancer* 1989; **64**: 1838-1842 [PMID: 2790697 DOI: 10.1038/sj.bjc.6605397]
112 **Pérez G**, Porta M, Borrell C, Casamitjana M, Bonfill X, Bolibar I, Fernández E. Interval from diagnosis to treatment onset for six major cancers in Catalonia, Spain. *Cancer Detect Prev* 2008; **32**: 267-275 [PMID: 18789609]
113 **Allgar VL**, Neal RD. Delays in the diagnosis of six cancers: analysis of data from the National Survey of NHS Patients: Cancer. *Br J Cancer* 2005; **92**: 1959-1970 [PMID: 15870714]
114 **Farman AG**, Gould AR. Case no. 19: pitted leukoplakia of the tongue. *Ky Dent J* 1988; **40**: 19-20 [PMID: 3163388 DOI: 10.1089/jwh.2010.2105]
115 **McLaughlin JM,** Anderson RT, Ferketich AK, Seiber EE, Balkrishnan R, Paskett ED. Effect on survival of longer intervals between confirmed diagnosis and treatment initiation among low-income women with breast cancer. *J Clin Oncol* 2012; **30**: 4493-4500 [DOI: 10.1200/JCO.2012.39.7695]
116 **Piñeros M**, Sánchez R, Perry F, García OA, Ocampo R, Cendales R. [Delay for diagnosis and treatment of breast cancer in Bogotá, Colombia]. *Salud Publica Mex* 2011; **53**: 478-485 [PMID: 22282140]
117 **Moore SS**, Thompson EO, Nash AR. Oestrogen sulfotransferase: isolation of a high specific activity species from bovine placenta. *Aust J Biol Sci* 1988; **41**: 333-341 [PMID: 3270501 DOI: 10.1155/2012/908547]
118 **Dye TD**, Bogale S, Hobden C, Tilahun Y, Deressa T, Reeler A. Experience of initial symptoms of breast cancer and triggers for action in ethiopia. *Int J Breast Cancer* 2012; **2012**: 908547 [PMID: 22315692 DOI: 10.1155/2013/206367]
119 **Sharma K**, Costas A, Damuse R, Hamiltong-Pierre J, Pyda J, Ong CT, Shulman LN, Meara JG. The Haiti Breast Cancer Initiative: Initial Findings and Analysis of Barriers-to-Care Delaying Patient Presentation. *J Oncol* 2013; **2013**: 206367 [PMID: 23840209]

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