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Patient delays and system delays in breast cancer treatment in developed and developing countries

O atraso de paciente e atraso de sistema no tratamento do câncer de mama nos países desenvolvidos e em desenvolvimento

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Abstract *Delays in treating breast cancer have been associated with a more advanced stage of the disease and a decrease in patient survival rates. The scope of this integrative review was to analyze the main causal factors and types of patient and system delays. The underlying causal factors of delays were compared among studies conducted in developing and developed countries. Of the 53 studies selected, 24 were carried out in developing countries and 29 in developed countries, respectively. Non-attribution of symptoms to cancer, fear of the disease and treatment and low educational level were the most frequent causes of patient delay. Less comprehensive health insurance coverage, older/younger age and false negative diagnosis tests were the three most common causal factors of system delay. The effects of factors such as age were not decisive per se and depended mainly on the social and cultural context. Some factors caused both patient delay and system delay. Studies conducted in developing countries identified more causal factors of patient delay and had a stronger focus on patient delay or the combination of both. Studies conducted in developed countries had a stronger focus on aspects of system delay during treatment and guidance of breast cancer patients in the health care system.*

Key words *Breast cancer, Delay, Treatment, Developing countries, Developed countries*

Resumo *O atraso no tratamento de câncer de mama foi associado com o aumento do palco da doença e a diminuição da sobrevida do paciente. O objetivo desta revisão integrativa foi a analise dos principais fatores causais e dos tipos de atraso. Sendo estes comparados entre estudos de países em desenvolvimento e desenvolvidos. Dos 53 estudos selecionados, 24 eram de países em desenvolvimento e 29 de países desenvolvidos, respectivamente. A não atribuição dos sintomas ao câncer, o medo e a menor escolaridade foram as causas mais citadas do atraso de paciente ao tratamento. Seguro menos abrangente, idade e testes diagnósticos falsos negativos foram às causas mais comuns identificadas do atraso do sistema. O efeito de vários fatores como o fator idade, dependeu principalmente do contexto social e cultural. Alguns fatores causaram tanto atraso relacionado ao paciente quanto ao sistema. Os estudos dos países em desenvolvimento identificaram mais fatores causais do atraso relacionado ao paciente, focando mais forte neste referido fator ou na combinação com o de sistema. Enquanto estudos de países desenvolvidos enfocaram com maior frequência aspectos do atraso de sistema durante o tratamento e a orientação de pacientes no sistema de saúde.*

Palavras chave *Câncer de mama, Atraso, Tratamento, Países em desenvolvimento, Países desenvolvidos*

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Introduction

Breast cancer is the most common type of cancer among women worldwide, with about 1.67 million new cases diagnosed in the year 2012[1,2].The incidence of breast cancer is still high in developed countries, but the global burden of the disease is progressively shifting to developing countries[1,2]. More than 70% of breast cancer patients in developed countries are diagnosed at stages I and II, whereas in low and middle-income countries, only 20-60% of patients are diagnosed in early stages of the disease[3]. Breast cancer stage represents an important prognostic factor and advanced stage is associated with decreased time of disease-free survival and increased mortality rates[4,5]. The mortality-to-incidence ratio of developing countries tended to be lower, compared to that of developed countries, largely due to the fact that patients have the disease at more advanced stages[6,7]. Furthermore, previous studies have shown that care delay associated with increased stage had a negative effect on the survival of breast cancer patients and were more common among patients in developing countries[3,4,8,9].

In literature, care delay has been subdivided in patient delay (PD) and health care system (SD) delay[3,10]. According to Lee Caplan (2014), PD is a delay in seeking medical attention after self-discovering a potential breast cancer symptom, whereas SD is a delay within the health care system[10]. PD was mainly defined as a time gap >3 month between symptom detection and first medical consultation[3]. The socio-economic and cultural background of patients can contribute to PD[3,10]. Furthermore, symptomatology experience, ethnic origin, beliefs or perceptions that affect attitudes of patients represent important causal factors of PD[3,10-12]. SD can refer to access barriers, like long distance to treating health care centers, or no availability of specialized centers and intrinsic problems of an established health care system, like disease management, problems in obtaining or scheduling diagnostic tests and communication problems between patients and physicians[3,10,11,13]. Furthermore, to reduce SD, health services must fit with the socio-economic and cultural or ethnic background of patients[3,11].

Despite the existence of vast literature about breast cancer care delays only few authors have compared studies conducted at different regions of the world. Review articles are mainly focused on care delays and its outcomes in developing countries[3,8]. Little is known about differences of study objectives and the causal factors of PD and SD, identified by authors of distinct regions of the world. The present integrative review addressed on four main questions: 1. What are the main causal factors of PD and SD in literature? 2. What are the methods applied to analyse the contribution of causal factors on PD and SD? 3. Which types of SD are analysed in literature? 4. If care delays and their adjacent causes are different among developing and developed countries.

Method

An integrative review of care delay associated with breast cancer was conducted. The research methodology was performed according to established criteria[14]. The operational steps were conducted as followed: Definition of exclusion and inclusion criteria and database; selection of studies; extraction of information and categorization; Analysis and interpretation of data; Interpretation of results; Synthesis and resume of results. The search was conducted in the following databases: *Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS); National Library of Medicine (MEDLINE), PubMed* and in the repository *Scientific Electronic Library Online (SciELO)*.

Terms "treatment delay", "provider delay", "system delay" and "patient delay" are commonly used in public health literature, but were not identified in *Medical Subject Headings (MeSH; http://www.nlm.nih.gov/mesh/MBrowser.html)* of the U. S. National Library of Medicine. Terms "breast cancer" and "delayed diagnosis" were selected from *MeSH*. A much more common term in literature was "diagnostic delay". As shown in the results and discussion section, the term "diagnostic delay" was not very well defined. To identify a broader range of articles about any kind of care delay, the term "delayed diagnosis" was substituted by "delay". Therefore, the term "breast cancer" was used in combination with "delay" in English, Spanish ("Cáncer de mama" and "atraso") and Portuguese ("Câncer de mama" and "atraso").

The search was conducted on October 22, 2014. To establish an internal quality control, all procedure of literature selection was performed twice independently by each of the two authors. Application of search terms in *MEDLINE* led to the identification of 2390 articles. When filter "10 years" was applied, this number reduced to 731 articles. Additional application of filter "free full text" led to the identification of 299 articles. In

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the *SciELO* database, 18 articles were identified and in the *LILACS* database, no article that met criteria of both search terms in any of the three languages was identified.

Finally, 317 articles were used for further analysis. To identify articles that met selective criteria, title and abstract were analysed. The following inclusion criteria were applied: original research article or research communication, available for free and published over the last five years, in English, Spanish or Portuguese. Articles identified in more than one database, articles about breast cancer that did not deal with care delays and review articles were excluded from the study. For further method categorization, result and discussion sections were read and analysed. According to previous studies, PD was defined as a delay of medical consultation caused by the patients behaviour[3,10]. The term SD was applied in the case of any delay caused by the health care system. In the case of factors associated to PD and SD, only factors that were identified two or more times were included and factors identified only by one study were excluded. This was justified by the fact that in the case of factors like "smoking" that was identified only one time by a single study, authors did not explain any possible causal relationship with PD and/or SD.

In accordance with the International Monetary Fund (2014), the following were defined as developing economies[15]: Brazil, Cameron, Colombia, Egypt, India, Iran, Lybia, Malaysia, Nigeria, Pakistan, Poland, Thailand, Tunisia and Turkey (Table 1).

All statistical analysis was performed on Prism™ software vers.6 (GraphPad, La Jolla, California, USA). The χ^{2} Test was performed to analyse categorized variables.

Results and discussion

All together 53 studies were identified that originated from 22 different countries (Table 1). Of the 53 studies, 24 were from developing and 29 from developed countries, respectively (Table 1). Single studies originated from Australia, Denmark, Estonia, China (Hong Kong), Iran, Libya, Nigeria, Pakistan, Poland, South Korea, Thailand, Turkey and Egypt (Table 1). More than one study was carried out in Brazil (N = 2), Cameroon (N = 2), Tunisia (N = 2), India (N = 2), Colombia (N = 3), United Kingdom (N = 3), Malaysia (N = 6) and the USA (N = 21). With exception of one Brazilian study written in Portuguese, a Colombian study written in Spanish and a study carried out in Tunisia written in French, all the other 50 studies were written in English (Table 1)[16-18].

Many contributions in the form of articles, such as those carried out in Malaysia and USA could indicate a greater interest of researchers in delay issues in these countries. Alternatively, the distribution of contributions by countries may not reflect the real frequency of publications within the last five years: Contributions were not included in the present research if they were not published in open access journals or if they were published in journals that are not registered in the examined databases. Therefore, exclusion criteria could have led to a bias in the number of contributions from single countries. This is a serious limitation of the present study and results should be interpreted with care.

Methodological background of studies

The most prominent methodological approach (N = 28) to obtain data about PD and SD was interview (Table 1). Of these 28 studies, 20 were exclusively based on interviews, whereas eight studies used additionally medical records or other registered data (Table 1). Several qualitative studies (N = 7) including small sample numbers, < 20 persons applied in-depth-interview (Table 1). Furthermore, of these 28 studies, four were based on telephone interviews (Table 1)[19-22]. Questionnaires were applied in five studies and in one case, it was combined with registered data (Table 1)[23-27]. Of the 53 studies, 18 collected data exclusively of medical records or other source of recorded data (Table 1). Several of these authors obtained increased numbers of data from breast cancer patients, that varied from 21.818 to 147.682 by the usage of large data bases as source for sampling (Table 1)[28-31]. One study was based on lecture of media and the other on discussed theories, concepts and models of care delay without sampling data (Table 1)[32,33].

Several studies (N = 18) applied descriptive methods without any significance test (Table 1). Most studies were based on < 30 samples (N = 11) and 30 to 50 (N = 4), and only three were based on studies ≥ 100 samples (Table 1)[16,27,34]. All in-depth-interviews belonged to this group of studies.

Other studies (N = 12) applied univariate methods, mainly using χ^{2} Test or Fisher's exact test to analyse categorized variables and the t-Test to analyse continuous variables. Máslach et al.[35], for example, compared time delays between

Table 1. References, by quantity of publications per country and alphabetical name of the country. Sample size, sampling and analytical method and type of analyzed delay are shown for each of the 53 references. Studies from developing countries were highlighted in grey.

Reference	Country and Language*	Sample size	Method		Type of delay
			Sampling	Analysis	
Beattie, 2009[36]	Australia	30	Interview	Descriptive	P; S
Hansen et al., 2011[37]	Denmark	159	Interview / Reg. Data	Univariate	P; S
Innos et al., 2013[38]	Estonia	703	Interview	Multivariate	P
Yau et al., 2010[24]	China (Hong Kong)	158	Quest.	Univariate	P; S
Rastad et al., 2012[39]	Iran	10	In-depth-interview	Descriptive	P; S
Ermiah et al., 2012[40]	Libya	200	Interview	Univariate	P; S
Ukwenya et al., 2008[41]	Nigeria	111	Interview / Med. Rec.	Univariate	P; S
Memon et al., 2013[42]	Pakistan	100	Interview	Univariate	P
Máslach et al., 2013[35]	Poland	499	Med. Rec. / Reg. Data	Univariate	S
Yun et al., 2012[28]	South Korea	147.682	Reg. Data	Multivariate	S
Poum et al., 2014[43]	Thailand	180	Interview	Multivariate	P
Ozmen et al., 2014[23]	Turkey	1031	Quest.	Multivariate	P; S
Barros et al., 2013[17]	Brazil; Portuguese	250	Interview	Univariate	P; S
Soares et al., 2012[44]	Brazil	288	Med. Rec.	Multivariate	S
Price et al., 2012[45]	Cameroon	50	Interview	Descriptive	P; S
Ngowa et al., 2011[34]		531	Med. Rec. / Reg. Data	Descriptive	P
Schairer et al., 2013[46]	Egypt and Tunisia	74	Reg. Data	Univariate	P
Landolsi et al., 2010[16]	Tunisia; French	160	Interview	Descriptive	P; S
Bodapati e Badu, 2013[27]	India	10	In-depth-interview	Descriptive	P
Chintamani et al., 2011[67]		100	Quest.	Descriptive	P; S
Ceballos-Garcia and Giraldo-Mora, 2011[18]	Colombia; Spanish	13	Interview	Descriptive	P
Piñeros et al., 2011[48]	Colombia	1106	Interview / Med. Rec.	Univariate	S
Pineros et al., 2009[49]		1106	Interview / Med. Rec.	Multivariate	P
Quaife et al., 2014[19]	United Kingdom	6965	Tel. Inter.	Multivariate	P
Lim, 2011[32]		-	-	Descriptive	P
Rajan et al., 2011[50]		36	Reg. Data	Descriptive	P
Ghazali et al., 2013[51]	Malaysia	250	Interview / Med. Rec.	Multivariate	P
Muhamad et al., 2012[52]		11	In-depth-interview	Descriptive	P
Norsa'adah et al., 2012[53]		12	In-depth-interview	Descriptive	P; S
Norsa'adah et al., 2011[54]		328	Interview / Med. Rec.	Multivariate	P; S
Taib et al., 2011[55]		19	In-depth-interview	Descriptive	P
Yusoff et al., 2011[56]		16	In-depth-interview	Descriptive	P; S

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patients from rural and urban regions. Crowley et al.[57] compared the time gap from diagnosis to start of adjuvant hormone therapy among patients of Afro-American, Hispanic and Caucasian ethnicity. In these studies, each factor potentially contributing to care delay was analysed as a univariate variable, regardless of all the other study variables. To identify independent factors and to establish a model that could explain PD or SD, most authors (N = 23) adopted multivariate regression models (Table 1). Multivariate logistic regression models were applied on dichotomized data comparing two groups: Ghazali et al.[51] for example, determined PD as a time gap of > 3 month from symptom discovery to first medical consultation. The authors first categorized patients into two groups, those with delay > 3 month and those with no delay (≤ 3 month)[51]. After identification of significant factors by univariate analysis (χ^{2} Test), a multivariate logistic regression model was established to explain PD based on martial status (divorced or single *vs.* married), ethnicity (Chinese *vs.* Malay or Indian) and breast self examination (not performed *vs.*

Table 1. continuation

Reference	Country and Language*	Sample size	Method		Type of delay
			Sampling	Analysis	
Bustami et al., 2014[58]	United States of America	3071	Reg. Data	Multivariate	S
Crowley et al., 2014[57]		113	Med. Rec. / Reg. Data	Univariate	P; S
Thind et al., 2014[20]		924	Tel. Inter.	Multivariate	S
Fedewa et al., 2010[29]		107.587	Reg. Data	Multivariate	S
Bourdeanu et al., 2013[59]		40	Quest.	Descriptive	P; S
McGee et al., 2013[60]		601	Interview / Med. Rec.	Multivariate	S
Fayanju et al., 2013[26]		52	Interview	Multivariate	P
Ramirez et al., 2013[61]		260	Med. Rec.	Multivariate	S
Sharma et al., 2013[62]		90	Reg. Data	Multivariate	P
Sheppard et al., 2013[22]		359	Tel. Inter. / Med. Rec.	Multivariate	P, S
Black and Woods-Giscombé, 2012[33]		Social media	Lecture of media	Descriptive	P
Bleicher et al., 2012[30]		72.586	Reg. Data	Multivariate	S
Vandergrift et al., 2012[63]		6622	Reg. Data	Multivariate	S
Karliner et al., 2012[25]		4027	Reg. Data / Quest.	Univariate	S
Partridge et al., 2012[31]		21.818	Reg. Data	Multivariate	P
Simon et al., 2012[64]		2234	Reg. Data	Multivariate	S
Heisey et al., 2011[65]		14	In-depth-interview	Descriptive	P
Maly et al., 2011[21]		921	Tel. Inter.	Multivariate	P, S
Simmons et al., 2011[66]		12	Reg. Data	Descriptive	P; S
Wujcik et al., 2009[67]		4336	Reg. Data	Multivariate	S
Lobb et al., 2010[68]		2252	Reg. Data	Univariate	S

Abbreviations: E= English; Reg. Data= Registered data of a database; Tel. Inter.= Telephone interview; Med. Rec.= Medical records; P= Patient delay; Quest.= Questionnaire; S= System delay. * English, if not differently indicated.

performed)[51]. These approaches were exemplary for most studies aimed at identifying the main factors that affect PD and/or SD and multivariate regression models were standard to identify independent causal variables of PD and SD.

The association between advanced stage of breast cancer and care delays is well established in literature[3,10]. In several studies, PD was associated with or identified as a causal factor of advanced stage of breast cancer[26,31,40,49-51,53]. In a study carried out in Tunisia, PD and also long distances to health care centres contributed to advanced stage of the disease[16]. Soares et al.[44], showed that SD, caused by increased length of time between clinical suspicion and diagnostic confirmation, was associated with advanced stage of breast cancer.

Most studies have focused on breast cancer patients for sampling, but there were also some exceptions: In a study carried out in Malaysia, the authors investigated the preference of patients for western or traditional medicine and interviewed 11 breast cancer survivors[52]. Telephone interviews were applied to 6965 women in England, who were not breast cancer patients[19]. The authors used a validated questionnaire named "Awareness and Beliefs about Cancer Measure (ABC)" to analyse causal factors of PD[19]. Black and Woods-Giscombé[33], used the narratives of non-patients to apply a gender-specific, culturally responsive stress process framework to identify the reasons why Afro Americans, compared to women of other ethnic groups, have more often PD.

These publications show that sources for sampling data were heterogeneous. Exceptionally in this context was also the study by Schairer et al.[46], who investigated if patients with inflammatory breast cancer, compared to those with other types of breast cancer, have a different help seeking behaviour. The authors used registered data and did not find any significant difference[46].

Different types of SD and the terminology of diagnosis delay

The different types of SD were analysed by the authors and summarized in Chart 1. In the

Chart 1. Time gap of system delay (SD) analysed by different authors. References of studies from developing countries were highlighted in *italic*.

Time interval of system delay	Reference
Time between first medical consultation and start of therapy	*17*,*23*,24,*48*
Time between first consultation and confirmed diagnosis	*44*,66
Time between first consultation and treatment	*48*
Time gap from first presentation (physician visit) to surgery	30
Time between abnormal mammogram and confirmed diagnosis	61,67,68
Time between report of abnormal mammogram to first follow-up	25
Time from abnormal mammogram to initiation of treatment	68
Time between diagnosis and first treatment	35,60
Time between diagnosis and definitive surgical treatment	28,58
Time gap from diagnosis to initiation of adjuvant chemotherapy	63
Time between diagnosis and start of adjuvant hormone therapy	57
Time to start adjuvant chemotherapy after surgery	22,29,64
Time gap specific for system delay was not defined	*16*,20,*27*,*36*,37,*39*,*40*,45,*53*,*56*,59

Abbreviations: E= English; Reg. Data= Registered data of a database; Tel. Inter.= Telephone interview; Med. Rec.= Medical records; P= Patient delay; Quest.= Questionnaire; S= System delay. * English, if not differently indicated.

case of 11 studies, a specific time gap of SD has not been defined (Chart 1). With the exception of one study[20], in 10 of these 11 studies focused on PD and SD, underlying causal factors were generally attributed either to PD or SD. A time gap of SD was defined in 16 studies carried out in developed countries and six studies carried out in developing countries (Chart 1). In contrast, four studies of developed and seven of developing countries, have not defined a time gap of SD (Chart 1; p = 0.0439). This indicates that studies carried out in developing countries had a more generalized approach to SD compared to studies carried out in developed countries, which more often defined a specific time gap of SD.

The most common form of SD analysed was the time gap between first medical consultation and start of any type of therapy (Chart 1)[17,23,24,48]. Other studies focused on more specific SD attributed it to different phases of breast cancer treatment, for example between diagnosis and chemotherapy, hormone therapy or surgical treatment (Chart 1)[28,57,58,63]. Yun et al.[28] defined in their study "surgical treatment delay" as the time gap between diagnosis and first surgical treatment.

Different definitions were applied for the term "diagnostic delay": Several authors defined diagnostic delay as the time gap from recognition of first symptoms to histological diagnosis[21,40,54]. In this case, there was no clear distinction between PD and SD by the time gap analysed, but underlying causal factors such as access barriers or patient attitudes have been attributed either to PD or SD. Other studies have defined diagnostic delay as the time gap between first presentation and final diagnosis[36,66], or suspected breast cancer and confirmed diagnosis[44]. Finally, "diagnostic delay" was also defined as the time gap from abnormal mammogram to diagnostic resolution[67,68]. Other terms also applied were "provider delay"[41,48], "doctor delay"[53,56] and "treatment delay"[28]. In general, there is no standardized nomenclature, as identical terms have distinct meanings and may refer to different time gaps.

Study objectives differ quantitatively and qualitatively between developing and developed countries

Of the 53 studies, 19 and 15 focused exclusively on PD or SD, respectively, whereas other 19 studies analysed both PD and SD (Table 1). All together, studies exclusively focused on SD were more frequently carried out in developed countries (N = 12) compared to developing countries (N = 3), whereas in the case of studies more focused on PD or both, PD *and* SD, the difference between developed (N = 17) and developing countries (N = 21) was smaller (p = 0.0313). Five out of six studies, that attributed poor knowledge or no information about breast cancer to affected women, were from developing countries[34,42,47,55,56] (Chart 2). The basic assumption that women are not well informed about breast cancer may lead authors from these countries to develop a strong-

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Chart 2. Factors identified to cause patient delay (PD) and their corresponding references. References of studies from developing countries were highlighted in *italic*.

Factor	Reference
Socioeconomic factors	
Lower educational level and literacy status	*16*,*17*,19,*23*,*33*,*40-42*,*49*,*62*
Financial costs too high or no health insurance	*16*,*27*,47,*49*,57,59,62
Older age	19,*27*,38,*40*,*49*,62
Younger age	*23*,31,*41*
Martial status: Single or divorced	19,22,26,*42*,*51*
No family history of breast cancer	*16*,*42*,66
Lower family income	24,*49*
Higher family income	*22*
Symptomatology experience	
Non-attribution of symptoms to cancer	*16*, 19, *23*, *34*, 36, *39*, 42, *47*, *49*, *51*, *53*, 59, 62, 66
Ignorance or negligence of symptoms	19,*39*,*45*,*47*,*53*,59
Other symptoms than breast lump or breast pain	*23*,38,40,*56*,65
Previous benign or harmless breast complaint	38,*40*,65
Painless breast lump vs. other symptoms	*42*,*56*
Attitudes of patients	
Fear of disease, treatment adverse effects, examination and chemotherapy	*18*,38,39,*42*,*47*,*53*,*56*,57,59,62
Family and career commitments and no support from family and friends	*18*,*23*,*39*,*42*,*53*,59,65
Reliance on traditional healers or preference for alternative treatment	*27*,*34*,*41*,*42*,*45*,*54*,*56*
No breast self examination	*16*,*19*,*40*,*51*
No participation on mammography screening program	21,31,32,36,38,*48*
No acceptance of hospital treatment or distrust in success of therapy and medical system	22,*23*,*41*,*54*
Poor knowledge of the disease and its outcomes	*42*,*47*,*55*
No information about breast cancer from affected women, family members or other sources	*34*,38,*56*
A comorbid condition	29,57,65
Previous negative health care experience	*18*,65
Fear of social isolation and sanctions by relatives	*42*,*53*
Strong religious beliefs or religious fatalism	22,*56*
Ethnic differences	
Afro Americans, Latin American and Asian versus Caucasian ethnicity or Chinese versus Malay and Indian ethnicity	19,49,*51*,57

er focus on PD or PD *and* SD compared to authors from developed countries.

Identified causal factors of PD and SD were summarized in Table 3 and Table 4, respectively. Overall, in 53 studies, 208 factors were identified two or more times (Chart 2 and Chart 3). Of these 208 identified causal factors, 124 contributed to PD and 84 to SD (Chart 2 and Chart 3). The number of identified factors that contributed to PD was higher for studies carried out in developing countries (N = 74) compared to developed countries (N = 50) and in the case of SD, the opposite was observed: More factors were identified in studies carried out in developed countries (N = 57), compared to developing countries (N = 27; p = 0.0001). This underlines the strong interest of authors from developing countries to better understand the reasons of PD.

Causal factors and PD terminology

Non-attribution of symptoms to cancer (N = 14), fear of disease, treatment adverse effects, examination and chemotherapy (N = 10), low educational level and literacy level (N = 10), and old or young age (N = 9) were the four most often identified causal factors of PD (Chart 2). The following factors were exclusively identified by studies carried out in developing countries: Reliance on traditional healers or preference for alternative treatment (N = 7), no breast self examination (N = 4), poor knowledge of the disease and its out-

Chart 3. Factors identified to cause system delay (SD) and corresponding references. References of studies from developing countries were highlighted in *italic*.

Factor	Reference
Socioeconomic factors	
Worse insurance status and insurance authorization delays	29, *43*, *48*, 58, 59, 61, 63
Older age	22, 28, 29, 63
Younger age	*23*,30,*43*
Lower family income	24,*43*,*48*,64
Lower educational level	22, 29, 48
Diagnostic factors	
False negative diagnostic test	*23*, 36, *48*, *54*, 59, 66
Delay in scheduling or getting diagnostic test results	*53*, 57, 59
Factors that affect decisions of physicians	
Having no mammogram or no participation in periodic mammography screening program	21, *23, 44*, 67
More comorbidities	22, 63
Fewer comorbidities	28
Access barriers	
Longer distance to health care centre	*16, 27, 41, 43, 45, 63*
Rural versus urbanized living place	*27, 41*
Urbanized versus rural living place	*35*
Communication between patient and physician	
Poor communication	56, 62
Good communication	62
Disease Management	
Other hospital versus teaching hospital or specialized cancer centre, respectively	*16*, 53, 56
High volume or public hospital versus smaller or private hospital, respectively	41, 49
Low volume versus larger hospital	50
Inappropriate surgery and biopsy management	*16, 29*
Preoperative components (imaging, biopsy, clinical visits)	51, 53
Comparison of different disease management programs or imaging and reporting data systems	34, 58
Limited knowledge about cancer by health care professionals	*33, 52*
Histopathological characteristics	
Higher staged tumor	18, *52*, 53
Lower staged tumor	50, 51
Positive lymph node state, lymphovascular invasion, overweight, smaller tumor and invasive versus *in situ* tumor	48, 62
Negative hormone receptor status	50, 62
Positive hormone receptor status	53
Ethnic differences	
Afro Americans, Latin American and/or Asian versus Caucasian ethnicity	18, 34, 50, 51, 53, 54, 56, 59, 61, 62, 65

comes (N = 3), fear of social isolation (N = 2) and painless breast lump vs. other symptoms (N = 2; Chart 2). Comorbid condition (N = 3) was the only factor identified exclusively in studies carried out in developed countries (Chart 2)[29,57,65].

The term PD was generally used for care delays that were dependent on patient behaviour. The authors who categorized data from patients defined PD as the time gap > 3 month from recognition of first symptoms to first medical visit [42,43,48,49,51,62]. Alternatively, no time gap was identified and patients were not categorized. In this case, PD was determined as a continuous variable or described by more detailed in-depth-interviews based on

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patients' perspective[23,24,26,27,34,39,46,52,53,55,59,65]. Attitudes can also cause PD *during* the process of breast cancer treatment[22,46]: Sheppard et al.[22] identified high religiosity and negative attitudes toward chemotherapy as independent causal factors of PD, between surgery and chemotherapeutic treatment (Chart 2).

Causal factors of SD

Poor insurance status and insurance authorization delays (N = 7), older or younger age (N = 7), false negative diagnostic tests (N = 6) and longer distance to health care centre (N = 6) were the four most common identified causal factors of SD (Chart 3). In the case of older patients increased time gap between diagnosis and adjuvant chemotherapeutic treatment was explained by postoperative complications and diagnostic or therapeutic interventions[29,63]. Vandergrift et al. additionally showed that missing supplemental insurance of Afro-American women also increased this time gap[63]. Authors of studies carried out in Colombia and Thailand argued that poor insurance status was associated with delayed diagnosis and referral for specialist treatment[43,48].

The factors comorbidity, communication, hospital volume, preoperative components, comparison of disease management program, several histopathological characteristics and ethnicity were exclusively identified to cause SD by authors of developed countries (Chart 3). Studies of developed countries had generally a stronger focus on the performance of the health care system and patient navigation during the treatment process.

Effects of several factors depend on the context, but are not decisive themselves and some factors can cause PD *and* SD

Long distances to health care centres and rural *vs*. urban areas were identified in several studies to cause SD as they are relevant access barriers (Chart 3)[16,23,27,41,45,63]. In a study carried out in Poland, the opposite was observed, as women living in urban areas suffered from SD[35]. In this case, the authors argued that physicians concentrate treatment procedures for patients from rural regions to reduce the number of visits. Similarly, comorbidities or clinical-histopathological characteristics like tumour stage and hormone receptor status influenced decisions of physicians in different context-dependent ways (Chart 2).

Lobb et al.[68], pointed out that improved communication between patient and physician can reduce health system barriers. Sheppard et al.[22] identified in their study an ambivalent nature of better communication that was dependent on the ethnic origin of patients (Chart 3):Better communication between patients and physicians led to decreased SD among Afro-American patients and to increased SD among patients of Caucasian origin[22]. According to their interpretation, Afro-American women may have relied on provider suggestion, whereas women of Caucasian origin with higher income and education rather seek information outside the patient-provider relationship to make their decisions[22].

Several studies have identified older age as an causal factor of PD (Chart 2)[19,27,38,40,49,62]. In their study, Inos et al.[38], pointed out that older women tend to underestimate the risk of breast cancer as breast cancer screening programs are mainly addressed to women aged 50-62 years. This is in agreement with findings of Brazilian studies that revealed decreased numbers of elderly women participating in mammography screening programs[69,70]. Similarly, in a study carried out in Lybia, PD was attributed to older aged women with poor knowledge about breast cancer[40]. In contrast, a study carried out in Turkey, the authors showed that young women aged 30-39 years more often ignored breast cancer symptoms compared with older patients[23]. Ozmen et al.[23], also identified in their study decreased SD among patients aged > 60 years. Their interpretation was that older patients are prioritized by physicians and receive a faster diagnostic process. Similarly, Bleicher et al.[30], identified increased preoperative delay in patients aged 65-79 years compared to patients > 80 years. Interestingly, authors of a study based on 21,818 breast cancer cases, argued that symptomatic presentation of disease was more common in younger women[31]. In this case young age ≤ 40 years, was a significant variable of PD in univariate analysis, but did not represent an independent variable of the final regression model.

In several cases, the authors did not explain why a determined factor had a unexpected effect: While in two studies, low family income was associated with PD, in a study carried out in Thailand, the opposite was verified and authors did not represent a causal argument of their result (Chart 2)[24,43,49].

As shown above in the case of age, some factors caused PD *and* SD. Lower educational level and lower family income were also associated with PD and SD (Chart 2 and 3). Lower educational level and literacy status were the most often

cited factor to cause PD (Chart 2). A Colombian study revealed that SD was not only associated with poor health insurance status, but also with low family income and educational level[48]. Fedewa et al.[29], used a large database to compare the time gap between surgical resection of the primary tumour and initiation of chemotherapy among patients from different regions of the USA. Their study revealed that SD > 90 days was not only more prominent among Afro-Americans, compared to patients of Caucasian origin, but that proportionally more often patients from regions with low education levels, measured by the frequency of school diploma, also suffered from SD[29]. The authors reported that lower socio-economic and educational status can also difficult navigation through the health care system[66,68].

These studies showed that several factors are not decisive, but depend on patient's social and cultural environment and on differences among health care systems and their personal decisions. Furthermore, several socio-economic factors have an influence on both PD *and* SD.

Final considerations

Studies carried out in developing countries more often focus on the general aspects of SD. In contrast, studies carried out in developed countries analysed more often a determined time gap of treatment. In general, authors from developing countries are more interested in PD or PD *and* SD combinations, and identified also more causal factors of PD compared to studies carried out in developed countries. In contrast, studies carried out in developed countries more often focus on specific aspects of SD. The stronger focus on PD in the case of studies carried out in developing countries is probably influenced by the author's assumption that patients in their country are not well informed about breast cancer. However, this does not necessarily mean that women from developed countries are really well informed. One should always keep in mind that questions of studies and their objectives are not only influenced by the social and cultural reality of researchers, but that there also can exist underlying "fashions of research" that differ timely and locally among countries.

The present review study showed that methodological approaches of studies were highly different. Interviews of few persons contrasted with the analysis of large databases, and while some studies were purely descriptive, others applied multivariate regression models to identify a reduced number of independent variables. Neither methodological approaches nor nomenclature about PD and SD are standardized.

Socio-economic factors, symptomatology experience and attitudes of patients contributed to PD. Socioeconomic and ethnic differences affected both PD *and* SD. Additionally, diagnostic factors, factors that affect decisions of physicians, access barriers, communication between patient and physician, disease management and histopathological characteristics of disease also affected SD. Some of these factors were not decisive, but mainly dependent on the social and cultural context.

Collaborations

AGQ Freitas contributed to the selection process of literature. M Weller contributed to the selection process of literature and was responsible for study design and manuscript draft.

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