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Exploring determinants of, and interventions for, delayed presentation of women with breast symptoms: a systematic review

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ABSTRACT

Purpose: Behaviour change interventions are more likely to be effective if they are sensitive to contextual determinants of behaviour. Delayed presentation of women with breast symptoms is a concern for both high-income and low- and medium-income countries. Our aim was to integrate evidence on determinants of time to presentation of women with breast symptoms with complementary evidence on interventions for promoting early presentation.

Methods: A systematic review was conducted according to PRISMA guidelines. Ten electronic databases were searched for relevant articles published between 1985 to May 2019. Pre-defined selection criteria were applied to retrieved records. Evidence on interventions, and on determinants were integrated through sequential explanatory synthesis design.

Results: Of the 4185 documents retrieved, 11 intervention studies and 10 determinants studies were included in the synthesis. Overall, evidence on interventions is of low quality, while that on determinants is of medium quality. Intervention studies were mostly individual-level with

almost exclusive focus on breast cancer awareness among postmenopausal women in high-income countries. Synthesis of evidence on determinants resulted in 10 domains. Juxtaposing the evidence on determinants of time to presentation of women with breast symptoms with one on the interventions to promote early presentation shows a mismatch between them.

Conclusions: Whilst there is strong evidence that women with breast symptoms face multi-level influences to presentation, current interventions have focused almost exclusively on breast cancer awareness in high-income countries. High quality multi-level interventions are required to promote early presentation of symptomatic women in different socio-cultural and economic settings.

Key words: *intervention, delayed presentation, breast symptoms, determinant, systematic review*

1. Introduction

Breast cancer kills more than 627,000 women globally, and the incidence and mortality continues to rise (Bray et al., 2018). Although it is the leading cancer in women in both high-income countries (HICs) and low- and medium-income countries (LMICs), there are disproportionately higher mortality and poorer survival rates in LMICs (Anderson et al., 2011; Bray et al., 2018). There are many determinants of breast cancer outcomes, however, the stage at diagnosis is generally recognized as the most important predictor of outcome (WHO, 2014). In HICs, 30-38% of women present at stages 3 or 4, while in LMICs, 50-90% present at these stages (Anderson et al., 2011). Evidence strongly suggests that delay of three months or more is associated with poorer outcomes (Neal et al., 2015; Richards et al., 1999a; Richards et al., 1999b). Population-based mammography screening for breast cancer is not cost-effective for LMICs, hence early symptomatic presentation is recommended for such settings (WHO, 2014). **Symptomatic presentation is a greater priority for LMICs where most women present with advanced disease, but HICs are also focusing on it through early diagnosis initiatives to further improve patient outcomes** (Richards et al., 1999b; Rubin et al., 2015).

Women experience two stages before treatment is initiated following self-discovery of breast symptoms: patient and provider intervals (Scott et al., 2013; Weller et al., 2012). Patient interval is the time between discovery and first contact with a healthcare professional (HCP) for the evaluation of symptoms, while provider interval is the time from first contact to the initiation of treatment (Scott et al., 2013). Patient interval has greater influence on the stage at diagnosis than provider interval because most cancer diagnoses come from symptomatic presentation of patients (Rubin et al., 2015). This systematic review is concerned with the patient interval.

Previous systematic reviews on delays by symptomatic women indicate that the focus has been on specific ethnic populations, age groups, and geographical regions; while others were conducted over five years ago (Bish et al., 2005; Jones et al., 2014; Ramirez et al., 1999;

Sharma et al., 2012). Moreover, other reviews have only synthesised evidence on interventions to promote early symptomatic presentation (Austoker et al., 2009; O'Mahony et al., 2017). It is not known if the current interventions match with multi-level determinants of symptomatic women's help-seeking behaviour in diverse socio-cultural and economic settings. Secondly, to our knowledge, this is the first review to integrate evidence on barriers to, and facilitators of, early presentation with evidence on interventions for promoting early presentation.

The aim of this systematic review was to integrate worldwide evidence on determinants of time to presentation of women with breast symptoms, with complementary evidence on interventions for promoting early presentation. The review was guided by the following questions: (a) **what are the patient-level determinants of help-seeking behaviour among women with breast symptoms?** (b) what are the healthcare system barriers to, and facilitators of, early presentation in this population, and (c) what interventions have been used to promote early presentation of women with breast symptoms?

2. Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009). A sequential explanatory synthesis design (**Figure 1: Sequential explanatory synthesis design**), developed by the Evidence for Policy and Practice Information (EPPI) centre was adopted (Oliver et al., 2005; Thomas et al., 2004).

2.1. Search strategy

Ten databases (Medline, CINAHL, SSCI, ASSIA, Cochrane register of controlled trials (CENTRAL), Cochrane Breast Cancer Group's Specialized Register (CBCG), World health organisation clinical trials registry platform (ICTRP), Clinicaltrials.gov, HINARI, and Google Scholar) were searched for the period between January, 1985 and May 2019. The search was initially undertaken between 1st May 2015 and 14th June 2015, and was re-run in May 2019. Aggregated results from both searches are reported in this review.

A search strategy was developed iteratively. First, a scoping review was conducted on two databases (MEDLINE, CINAHL) to identify index terms, 'free text' terms, and keywords contained in the titles and abstracts of relevant papers. Additionally, **the search strategy was piloted on five databases with the goal of identifying additional 'free-text' terms, controlled search terms and phrases.** A search strategy was developed and run in MEDLINE (**Table 1: Search strategy for MEDLINE**) and adapted for other databases. Hand-searching was undertaken on reference lists of included studies.

2.2. Eligibility criteria

All studies, irrespective of design, had to meet the following inclusion criteria: were conducted with women (≥ 18 years of age), reported in English, and published as primary research articles in peer-reviewed journals between 1985 and May 2019. Thereafter, specific criteria were applied to both the intervention and the barriers/facilitators studies.

Intervention studies were included in the review if they:

- reported on interventions that aimed at promoting early presentation of women with breast symptoms;
- had the primary outcomes of earlier stage at presentation or change in knowledge, skills, behaviour, beliefs, attitude that would potentially promote early presentation of women with breast symptoms;
- employed randomised controlled trials, non-randomised controlled trials and quasi-experimental designs. Observational and descriptive studies were also considered due to the limited evidence on this topic.

Barriers/facilitators studies were included in the review if they:

- reported barriers to, and/or facilitators of, early presentation of women with breast symptoms;
- collected data before women had their first contact with a healthcare professional;
- were quantitative, qualitative or mixed method studies.

We excluded full-text publications on barriers/facilitators that focused on women diagnosed with breast cancer (35); asymptomatic women (4); mixed cancers (4); used secondary data (3); and used a mixed sample, diagnosed with breast cancer and symptomatic (3) among other reasons as shown in figure 2. Additionally, one ongoing trial, and another that measured knowledge of breast cancer screening tools and early detection practices were also excluded.

2.3. Study selection and data extraction procedures

Following deduplication, one author (P.K) screened the articles for eligibility through a two-stage process (**Figure 2: PRISMA flowchart**).

Articles were selected based on titles and abstracts that met the eligibility criteria. Where the inclusion criteria were met, full documents were retrieved for second stage screening. In the second stage, full documents were reviewed on the same eligibility criteria. During both stages, a 10% random sample was chosen for review by an independent reviewer (E.L), and any disagreements were resolved by consensus. An inter-rater reliability of 97% was achieved at both stages.

Two data extraction forms (for intervention, and barriers/facilitators studies), specifically designed for this review, were developed and pilot tested. One reviewer (P.K) initially extracted the data and a second reviewer (E.L), independently counterchecked the data for accuracy and completeness. Extracted information for the barriers/facilitators studies included: citation details, country classification, and setting, type of study, methods, sampling, participants' characteristics, and findings. For the intervention studies, the information extracted included: citation details, country classification, setting, and type of study, methods, participant characteristics, content, aim and timing of intervention, theoretical underpinning of intervention, comparison/control group, outcome measures, and results.

2.4. Study methodological quality appraisal

The selected articles were initially appraised by one reviewer (P.K) and the second reviewer (E.L) independently counterchecked the accuracy of quality appraisal results. Any discrepancies identified were resolved by consensus. The included studies adopted diverse research designs. Barriers/facilitators studies either adopted qualitative or quantitative design, while intervention studies were either RCTs or non-RCTs.

The Critical Appraisal Skills Programme [CASP] (2013) was adopted for quality appraisal of included qualitative studies (Gough et al., 2017). The quantitative studies on barriers/facilitators were appraised using six generic criteria (Jones et al., 2014; Pluye et al., 2009). These six generic criteria were: clear aims of the research, appropriateness of research design, clarity of research methods, appropriateness of analytical methods, attempt to control confounding variables, and adequacy of data relative to conclusions and interpretations. All barriers/facilitators studies, regardless of their appraisal outcome were included in the synthesis, but studies of low quality were given less weight in the discussion of the findings. **(Supplementary file 1 and 2)**. Quality appraisal of the intervention studies was conducted using the Cochrane Collaboration Risk of Bias Tool for the RCTs (Higgins and Green, 2011), and the Effective Practice and Organisation of Care (EPOC) review group risk of bias criteria for the non-RCTs (Cochrane EPOC Group, 2013) (**Supplementary file 3 and 4**). **The adoption of different quality appraisal tools was informed by the diverse designs of included studies.**

2.5. Data synthesis

Three types of data synthesis were performed. First, owing to heterogeneity of intervention studies, meta-analysis was not feasible, and a narrative synthesis was performed. This involved textual description of the characteristics and findings of intervention studies in view of the review questions (Popay et al., 2006). Thematic synthesis of barriers/facilitators studies was performed in three phases: 'line-by-line coding', development of 'descriptive

themes’, and generation of ‘analytical themes’ (Thomas and Harden, 2008). Lastly, cross-study data synthesis was conducted according to Evidence for Policy and Practice Information (EPPI) Centre approach for combining **qualitative/quantitative and interventions evidence** (Thomas et al., 2004). A matrix (**Table 5: Comparison between “implications for intervention development” and current interventions to promote early presentation**) was used to compare the extent to which current interventions have addressed women’s views regarding determinants of early presentation.

3. Results

3.1. Results of the search

Twenty one studies were included in the review. Of these, **11** were intervention studies (**Table 2: Included Intervention studies: Setting, Type of study, Methods, Intervention content, Quality of evidence**), and 10 others investigated barriers/facilitators to women’s presentation with breast symptoms (**Table 3: Included Barriers/Facilitators Studies: Methodological Characteristics**).

3.2. Description of intervention studies

Sample size and setting: Sample sizes in five of the included studies ranged from 20 to 286 participants (Burgess et al., 2008; Burgess et al., 2009; Forbes et al., 2011; Forster et al., 2014; Mena et al., 2014). Five studies investigated larger samples of between 356 and 867 women (Campbell et al., 2016; Dodd et al., 2017; Forbes et al., 2012; Linsell et al., 2009; Zonouzy et al., 2019). One study did not report the number of women targeted by the intervention (Devi et al., 2007). Of the **11** studies, only three were conducted in LMICs (Devi et al., 2007; Mena et al., 2014; Zonouzy et al., 2019).

3.2.1. Risk of bias of included studies

Overall, the methodological quality of the studies was low, with nine having either unclear risk of bias or high risk of bias (Burgess et al., 2008; Campbell et al., 2016; Devi et al., 2007; Dodd et al., 2017; Forbes et al., 2012; Forbes et al., 2011; Forster et al., 2014; Mena et al., 2014; Zonouzy et al., 2019). The detailed results of risk of bias of studies is shown in **Table 2: (Included Intervention studies: Setting, Type of study, Methods, Intervention content, Quality of evidence)**.

3.2.2. Interventions

All but three studies targeted women who were invited for mammography screening, while the three targeted women in the general population (Devi et al., 2007; Mena et al., 2014;

Zonouzy et al., 2019). All the interventions were educational programmes using a range of teaching strategies.

The duration of most individual-level interventions ranged from one month to twelve months (Burgess et al., 2008; Burgess et al., 2009; Campbell et al., 2016; Dodd et al., 2017; Forbes et al., 2012; Forster et al., 2014; Linsell et al., 2009), with one being implemented for two years (Forbes et al., 2011). There were three community-level interventions, with one lasting five years from 1993 to 1998 (Devi et al., 2007), while another one lasted for three months (Zonouzy et al., 2019). The duration of implementation of the remaining intervention under this category was not specified (Mena et al., 2014).

3.2.3. Effects of interventions

Primary outcomes

Eight of the intervention studies had a primary outcome as breast awareness (Burgess et al., 2008; Burgess et al., 2009; Campbell et al., 2016; Dodd et al., 2017; Forbes et al., 2012; Forbes et al., 2011; Forster et al., 2014; Linsell et al., 2009). One intervention study (Mena et al., 2014) had knowledge, attitude and practice as the primary outcomes; while another (Devi et al., 2007) had down-staging of breast cancer from stage 3 or 4 to 1 or 2 at the point of presentation as its primary outcome. The remaining intervention had attitude, behavioural intention and behaviour as the study outcomes (Zonouzy et al., 2019).

Booklet plus 10-minute interaction or nudge stickers

Seven individual-level intervention studies (Burgess et al., 2008; Burgess et al., 2009; Campbell et al., 2016; Dodd et al., 2017; Forbes et al., 2012; Forbes et al., 2011; Linsell et al., 2009) used a booklet plus a 10-minute interaction; while one ((Forster et al., 2014) used a booklet plus three nudge stickers. All the intervention studies in this category had breast awareness as the primary outcome. For all intervention studies, at one month post intervention a higher proportion of women could correctly identify five or more non-lump breast symptoms, and were more confident in breast checking. However, after six or twelve months, some interventions reduced in their effectiveness, although the measures still remained higher than in the pre-intervention period (Burgess et al., 2009; Campbell et al., 2016; Linsell et al., 2009).

Public breast awareness campaigns

There were three interventions in this category. The down-staging programme reduced the proportion of women presenting for treatment at a late stage (stages 3 and 4) from 77% (69/90) in 1993 to 37% (42/115) in 1998 ($\chi^2=17.0$; $p<0.0001$) (Devi et al., 2007). The other community-based intervention focused on knowledge, attitude and practices and had mixed results (Mena et al., 2014). The study reported that women in the intervention community

gained more knowledge about: breast symptoms (82.3% vs 53.5%), genetical vulnerability to breast cancer (23.8% vs 9%), and importance of breast self-examination (90% vs 59.4) than referent community. However, both the intervention and the referent communities seemed to score similarly when it came to a belief that breast cancer is caused by evil spirits, or is an infectious disease. The third study reported significant differences between the two study groups post-intervention, indicating that the intervention group showed significant improvements in attitudes ($P=0.03$) and behavioural intention ($P=0.01$) but not for behaviour (Zonouzy et al., 2019).

3.3. Description of barriers /facilitators studies

Ten studies on barriers/facilitators met the inclusion criteria, and their methodological characteristics are summarised in **Table 3** :(**Included Barriers/Facilitators Studies: Methodological Characteristics**). All except one study were conducted in HICs (Khakbazan et al., 2014), which restricts generalizability of results to LMICs. Furthermore, most studies on barriers/facilitators is that most of them are atheoretical with only three using a theoretical/conceptual framework to underpin the study (Friedman et al., 2006; O'Mahony et al., 2011; O'Mahony et al., 2013). Only two studies were considered as being of low quality, while the rest were either of medium or high quality (Lam et al., 2009b; Li et al., 2012).

3.3.1 Determinants domains

A thematic synthesis of literature produced 33 free codes, which were organised into 10 descriptive themes. A higher level of abstraction organised the 10 themes in hierarchical order to produce five analytical themes as shown in **figure 3: (Multi-level conceptual model on determinants of presentation of women with breast symptoms)**. Determinants of delayed presentation of women with breast symptoms are described under the 10 descriptive themes.

Knowledge about breast symptoms

Women reported several aspects of knowledge about breast symptoms. Some thought that their painless breast lump was caused by either the Chinese medicine they had used, pathology of organs adjacent to breast, pre-existing chronic illness, or self-medication (Khakbazan et al., 2014; Lam et al., 2009a; Lam et al., 2009b; Li et al., 2012).

Furthermore, prior experiences or habits such as having had abortion/termination of pregnancy, traumatic bruising of the breast, wearing an underwire bra, smoking, and eating a poor diet were also reported by women as causes of breast cancer (Facione and Facione, 2006). Women who had no such experiences or habits delayed help-seeking, while those who had, thought they would reverse their breast symptoms by ceasing these habits. Moreover, some

women delayed if there was a mismatch between their pre-conceptions and how breast cancer actually presented (Facione and Facione, 2006; Lam et al., 2009a).

Another aspect of knowledge is how women interpreted their symptoms. Those who delayed often interpreted them as harmless, temporary, and judged that they did not require medical attention (Li et al., 2012; Nosarti et al., 2000; O'Mahony and Hegarty, 2009). Even for some who sought help, they did so for a primary health problem, with breast symptoms presented as secondary (Lam et al., 2009a; Lam et al., 2009b; Li et al., 2012).

Lump-symptoms were interpreted as being associated with breast cancer, and prompted more help-seeking behaviour than non-lump symptoms such as indrawn nipple, hot red area, persistent itching, and skin changes (Khakbazan et al., 2014; Lam et al., 2009a; Nosarti et al., 2000; O'Mahony et al., 2013). Moreover, the characteristic of the breast lump was an important influence on help-seeking behaviour. Those who had painful breast lumps were more likely to seek help promptly than those who had painless breast lumps (Khakbazan et al., 2014; Lam et al., 2009a; Nosarti et al., 2000; O'Mahony et al., 2013). This was partly because women attributed non-painful lumps to normal physiology such as breastfeeding or normal hormonal variations (Khakbazan et al., 2014; Lam et al., 2009a). Lastly, worsening of symptoms, development of new ones, and the interference with women's daily activities prompted help-seeking, while apparent fluctuation prompted delay (O'Mahony et al., 2011).

Emotional and psychological responses to breast symptoms

Overall, emotional and psychological reactions to breast symptoms inhibited help-seeking rather than promoted it. Those women who responded to their breast symptoms with fear, anxiety, worry, uncertainty and who perceived a threat of death, sought help as a means of controlling uncertainty, negative emotions and to avoid a possible poorer prognosis (Facione and Facione, 2006; Khakbazan et al., 2014; Lam et al., 2009a; Lam et al., 2009b). Whilst these are general emotional reactions, some women specifically delayed for fear of surgical treatment (Facione and Facione, 2006; Friedman et al., 2006; Nosarti et al., 2000). Significantly, women who reported contrary emotions such as reduced fear, indifference, and an optimistic perspective also delayed help-seeking (Khakbazan et al., 2014; Li et al., 2012).

Defence mechanisms of suppression and denial were used by some women to avoid confronting a potential cancer diagnosis, and its implications (Friedman et al., 2006; Khakbazan et al., 2014; Lam et al., 2009a; Lam et al., 2009b; Li et al., 2012; Nosarti et al., 2000; O'Mahony et al., 2011).

Beliefs and attitudes about breast cancer

Beliefs and attitudes about breast symptoms were largely shaped by past experiences with any cancer, religious beliefs, and myths. Fatalism, religious beliefs and negative past

cancer experiences made women view breast cancer as incurable and a ‘death sentence’ (Facione and Facione, 2006; Lam et al., 2009a; O'Mahony et al., 2011; O'Mahony et al., 2013). Some women resigned to their fate, resorting to prayers for God to cure them of their symptoms (Lam et al., 2009a; O'Mahony et al., 2011; O'Mahony et al., 2013).

Women who had in the past interacted with family members, relatives, friends and neighbours who had a breast cancer diagnosis tended to seek help more promptly than those who had no such experience (Facione and Facione, 2006; Friedman et al., 2006; Khakbazan et al., 2014; Li et al., 2012; O'Mahony et al., 2011). Women who had heard positive stories about early diagnosis and treatment from breast cancer survivors were more likely to seek help promptly (Facione and Facione, 2006; O'Mahony et al., 2011).

Competing obligations and self-care

Competing obligations such as child care, work-related, and professional commitments took precedence over help-seeking (Facione and Facione, 2006; Friedman et al., 2006; Khakbazan et al., 2014; Lam et al., 2009a; Lam et al., 2009b; Li et al., 2012; O'Mahony et al., 2011; O'Mahony et al., 2013). Women who had established self-care routines were more sensitive to bodily changes and promptly sought help on discovery of breast symptoms (Khakbazan et al., 2014).

Socio-demographic characteristics

Lower educational attainment and lower family incomes were associated with delayed help-seeking (Facione and Facione, 2006; Friedman et al., 2006; Khakbazan et al., 2014; Lam et al., 2009b; Li et al., 2012). Three studies reported that younger women were more likely to delay help-seeking than older women (Facione and Facione, 2006; Friedman et al., 2006; Li et al., 2012).

Social networks

Disclosure of breast symptoms to one's social networks had different impacts on help-seeking behaviour. To most women, disclosure to family members, relatives, friends and neighbours, helped them to interpret the symptoms more accurately, cope with psychological and emotional reactions, and help them in decision-making about help-seeking (Facione and Facione, 2006; Khakbazan et al., 2014; Lam et al., 2009a; Lam et al., 2009b; O'Mahony et al., 2011). At times the decision on seeking healthcare services was taken by a member of the social network rather than the woman herself (Lam et al., 2009b). However, in some instances, disclosure resulted in delayed presentation due to false reassurance and misinformation from social networks (Facione and Facione, 2006; Khakbazan et al., 2014).

Symptom impact on daily life and family

The occurrence of distressing symptoms and their interference with daily activities prompted women to seek help (Lam et al., 2009a; Lam et al., 2009b). In particular, the fear of their husbands leaving them as a consequence of them losing a breast made them delay seeking help. (Facione and Facione, 2006).

Relationship with healthcare professionals

Women reported that past experiences of discrimination, disrespect, frustration and prejudice with HCPs made them delay seeking help for the current health problem (Facione and Facione, 2006; O'Mahony et al., 2011; O'Mahony et al., 2013). Other negative past experiences with HCPs reported in these studies were dismissal of symptoms as frivolous, ridicule, and criticism when they sought to schedule an appointment. Lastly, women reported feelings of shame and embarrassment when they anticipated that their breast symptoms would only be evaluated by a male instead of a female HCP (Khakbazan et al., 2014; Li et al., 2012; O'Mahony et al., 2011).

Cost of healthcare services

The high cost of healthcare relative to the patient/family incomes made women delay help-seeking so that they would be able to meet their other basic needs (Friedman et al., 2006; Lam et al., 2009a; Lam et al., 2009b; O'Mahony et al., 2013).

Healthcare infrastructure

Some women attributed their delay to general unfamiliarity with healthcare services (Khakbazan et al., 2014; Lam et al., 2009a; Lam et al., 2009b; Li et al., 2012). This challenges were more common among older women and immigrants. Moreover, other help-seeking barriers reported include difficulty in making appointments, appointment delays, irregular presence of doctors, and short opening hours (Friedman et al., 2006; Khakbazan et al., 2014; Li et al., 2012; O'Mahony et al., 2013).

3.4. Cross-study results

The 10 determinants domains on barriers/facilitators helped identify 'implications for intervention development' as shown in **Table 4: (Barriers, Facilitators and “implications for intervention development” to promote early presentation among symptomatic women)**. In total, 15 implications were identified. A synthesis matrix was used to juxtapose implications alongside primary outcomes of intervention studies to examine the extent to which barriers/facilitators have informed the development of current interventions as shown in **Table 5 : (Comparison between “implications for intervention development” and current interventions to promote early presentation)**. Since some themes had more than one

implication, the numbers against each intervention indicates the specific implication being addressed by that particular intervention. Low breast cancer awareness has been addressed by two reliably evaluated interventions (Burgess et al., 2009; Linsell et al., 2009), and one other evaluated intervention (**Forbes et al., 2012**). **Moreover, negative social, cultural constructions of breast cancer, unhealthy beliefs and practices, and importance of early presentation** have been addressed by **three** other evaluated interventions (Devi et al., 2007; Mena et al., 2014; Zonouzy et al., 2019). Overall, only **five** out of 15 implications for intervention development have been addressed by any of the interventions, and only two interventions (Burgess et al., 2009; Linsell et al., 2009) have been reliably evaluated.

4. Discussion

Breast cancer in women remains a global health issue. Early detection and treatment has been linked to favourable outcomes. Most cancer diagnoses come from women presenting symptomatically rather than through screening, particularly in LMICs. This systematic review identified some of the barriers to, and facilitators of, early presentation of women with breast symptoms, and illustrated to what extent they have been addressed by current interventions.

4.1. Barriers/Facilitators studies

The quality of evidence on barriers/facilitators studies is adequate to inform the development of early presentation interventions, particularly for HICs because only one study was from LMICs (Khakbazan et al., 2014). Women reported **multi-level** contextual factors that may be broadly divided into patient-related determinants and healthcare system-related determinants. The major patient-related determinants reported by women related to knowledge about breast symptoms, social networks, reactions to symptom discovery, and beliefs and attitudes about breast cancer. The healthcare system determinants included cost of healthcare services, structure of healthcare system and women's past experience with healthcare professionals. Most determinants reported appear to influence appraisal interval rather than help-seeking interval. This agrees with previous studies which have reported that symptom appraisal phase account for more than two thirds of the patient delay (Andersen et al., 1995; Jones, 1990)

All but two determinants (Cost of healthcare services and Healthcare infrastructure) were simultaneously acting as barriers to, and facilitators of, early presentation. These competing forces resulted in a dynamic and non-linear help-seeking behavioural pattern that caused differences in lengths of time each woman took to appraise the symptoms and seek healthcare. Though the findings of this review agree with previous review findings, there are setting-specific determinants of women's delayed presentation (Jones et al., 2014; Ramirez et

al., 1999; Richards et al., 1999a), For instance, some women, particularly from China attributed the symptoms to Chinese medicine (Lam et al., 2009a; Lam et al., 2009b).

4.2. Intervention studies

There is a dearth of high quality evidence on interventions to promote early presentation of women with breast symptoms as suggested by current and previous reviews. A previous review which considered any intervention design identified only four interventions (Austoker et al., 2009), while in a more recent Cochrane review of interventions (RCTs) for raising breast cancer awareness in women, only two studies met the inclusion criteria (O'Mahony et al., 2017). Other than one interventions in this review, all the others were based on the assumption that increase in breast awareness would ultimately result in women presenting earlier, with one community-level intervention being able to demonstrate a down-staging effect of 25% fewer women presenting at stage 3 or 4 after 5 years post-intervention (Devi et al., 2007). This assumption may not be true as demonstrated by a recent study comparing cancer awareness among International Cancer Benchmarking Partner Countries (Forbes et al., 2013). This study demonstrated that whereas UK has the highest cancer awareness, it also has the highest perceived barriers to symptomatic presentation, which perhaps may have led to poor performance in 1-year cancer survival rates compared to countries with a similar healthcare system.

There is almost exclusive focus on single-level interventions despite the fact that this review, and previous literature has demonstrated that influences of health-seeking behaviour are multifactorial (DiClemente et al., 2013; Richards and Hallberg, 2015). The eight individual-level interventions were specifically developed to target postmenopausal women in HICs, which limits their generalization to LMICs, where majority of women diagnosed with breast cancer are pre-menopausal. Nonetheless, evidence from current interventions indicates that they have the potential to increase breast awareness in postmenopausal women, especially in the short term.

4.3. Integrating cross- study results

Juxtaposing barriers/facilitators alongside intervention studies allowed the examination of the extent to which the current interventions have addressed women's needs. There was incongruence between reported barriers/facilitators to early presentation on one hand, and interventions to address them. Of the 15 'implications to intervention development' arising from women's views, only **five** have been addressed by any of the interventions included in the review. Such mismatches indicate that determinants of time to presentation may not have been identified within the settings where the interventions have been developed and

evaluated. Similar studies have reported such incongruences (Rees et al., 2006; Shepherd et al., 2006).

This review has demonstrated that help-seeking behaviour of women with breast symptoms is influenced by multi-level determinants. These determinants may guide the identification of congruent behaviour change theories/models, and techniques, which would then inform the development of interventions to promote early presentation. Evidence suggests that behaviour change interventions that are underpinned by theory and rigorous empirical evidence are more likely to be effective (Michie et al., 2008; Richards and Hallberg, 2015).

4.4. Review strengths and limitations

A comprehensive search was conducted in ten databases to identify and select studies that met the inclusion criteria, assess their methodological quality, and synthesise evidence in accordance to PRISMA guidelines (Moher et al., 2009). Unlike previous reviews, this review used qualitative evidence to interrogate the evidence on current interventions in terms of their appropriateness for behavioural change among symptomatic women. A limitation of methods used in this review is that grey literature and non-English publications were excluded.

5. Conclusions

Early presentation of women with breast symptoms results in improvements of outcomes. Evidence strongly suggests that women's symptomatic presentation is influenced by multi-level contextual factors. Whilst evidence from current interventions suggests that they have the potential to increase breast awareness, their impact on the stage of breast cancer at presentation is uncertain because their exclusive focus on individual-level determinants leaves other influences of women's help-seeking behaviour unaddressed. Furthermore, results from intervention studies included in this review should be interpreted with caution as most of them are of low quality. Moreover, they are heterogeneous in terms of their design, content, outcomes measured, and the populations studied. Lastly, the interventions examined have exclusively focused on postmenopausal women in HICs, hence cannot be generalized to LMICs where the majority of women diagnosed with breast cancer are premenopausal.

6. Implications for practice and future research

The evidence identified in this review on determinants of help-seeking behaviour of symptomatic women may be considered by HCPs to inform development of multilevel **interventions** to shorten delays and promote early presentation. The predominantly individual-level nature of interventions reported in this review, as well as their overall low quality, prevents a strong recommendation on policy and practice. Future research should focus on

rigorous development of multi-level interventions based on local socio-cultural contextual evidence on determinants of time to presentation of symptomatic women. This is particularly important for LMICs where screening services are unavailable and majority of women with breast cancer present at late stages. Furthermore, future studies may adopt longitudinal approaches to evaluate the impact of interventions on the stage of breast cancer at presentation within a target population.

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