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Bioscience Research

Print ISSN: 1811-9506 Online ISSN: 2218-3973

Journal by Innovative Scientific Information & Services Network



RESEARCH ARTICLE

BIOSCIENCE RESEARCH, 202219(4):1864-1872.

OPEN ACCESS

Physicians' practices and attitudes toward screening mammography in average risk women, Madinah

Hadeel Ghunaim¹ and Samah Alfahl²

¹Department of Radiology, Faculty of Medicine, Taibah University, Madinah, Saudi Arabia

²Department of Family medicine, Faculty of Medicine, Taibah University, Madinah, Saudi Arabia

*Correspondence: hghunaim@taibahu.edu.sa Received 15-08-2022, Revised: 01-10-2022, Accepted: 10-10-2022 e-Published: 30-10-2022

Knowledge and familiarity of breast cancer screening protocols by primary health care (PHC) physicians can influence the counseling and education they give to women regarding breast examination and screening. This study aims to evaluate PHC physicians' attitude to and practices regarding breast cancer screening among women in Medina, Saudi Arabia. This was a descriptive cross-sectional study conducted using a multipart English questionnaire, focused on PHC physicians' awareness and their attitudes to recommending breast cancer screening and mammography to women 40 to 49 years old. The study sample was physicians in PHC centers in Medina. A total of 40 clinicians completed the survey. Overall, 36 (90.0%) of the respondents believed that clinical breast exam performed by a practitioner, and 31 (77.5%) believed that breast self-exam performed by the patient were effective in reducing breast cancer mortality in average risk women. Also, 35 (87.5%) of the respondents each believed that screening mammography for women over 40 years was effective in reducing breast cancer mortality in average risk women. Only, 14 (35.0%) of the respondents routinely recommended mammography to women who were 40 – 49 years old. A number of breast examination screening barriers were identified related to patient, provider and health system factors. Our survey showed that clinicians still believed in the effectiveness of clinical breast examination and breast self-examination, and continue to recommend it to women in Saudi Arabia. Some of the clinicians recommended mammography to at-risk women; however, effective utilization of this screening method is hampered by many barriers. Interventions to address these barriers will improve utilization.

Keywords: Breast cancer screening, Primary health care physician, Mammogram.

INTRODUCTION

Breast cancer is the most common cause of death among women globally. Worldwide, there were more than 2 million women newly diagnosed with breast cancer, and it accounts for about 11.6% of all cancers (Bray et al. 2018). In addition, it is the most common cancer associated with death among women in 2018 (Bray et al. 2018). Recently, the incidence of breast cancer in the Kingdom of Saudi Arabia (KSA) has increased, and have risen accounting for 30% of all newly diagnosed women with breast cancer (with a median age of 50 years) according to the Saudi Cancer Registry (SCR) (Alqahtani et al. 2020). More than 50% of breast cancer cases are diagnosed at a late stage in Saudi Arabia, compared to 20% in advanced countries which results in higher treatment cost, morbidity, and mortality rate (Alqahtani et al. 2020.)

Early detection of breast cancer, and knowledge and familiarity of primary health care (PHC) physicians about breast screening could play an essential role in early

detection, treatment and in achieving positive health outcomes for women. Therefore, the two fundamental strategies for early detection include early diagnosis and screening (Heena et al. 2019). A vital aspect of early detection of breast cancer is adequate knowledge of breast screening program and improved awareness of early breast cancer signs and symptoms by PHC physicians, healthcare workers and the general population. Breast screening is a test to detect breast cancer before the appearance of signs and symptoms. Breast self-examination (BSE), clinical breast examination (CBE), and mammography are well-known screening methods for breast cancer

According to the Saudi Ministry of Health breast cancer screening guidelines, mammography should be performed for women aged 40–49 years every 1 to 2 years; for women aged 50–69 years every 2 years, and mammography should not be performed for women aged 70–74 years (Al-Mulhim et al. 2018) It is in line with the American Cancer Society (ACS) guideline that strongly

recommend starting screening mammography annually for women aged 45-54 years, and women aged 40-44 years should have the opportunity to begin annual screening (Forefinger et al. 2015). The ACS guideline does not recommend CBE.

Even though screening mammography in KSA is free of cost and available in all regions country, and considering that yearly awareness is performed in the month of October about breast cancer and screening, the use of breast cancer screening methods are very limited in Saudi Arabia. One study in 2015 reported that out of 1135 women of 50 years age and older who visited a health facility, only 8% have had screening mammography (Bcheraoui et al. 2015). and another study in 2017 in Medina city reported that of 465 women with an average age of 34.9 ± 12.2 years, only 28% have had mammography (Al-Zalabani et al. 2018)

Breast cancer screening barriers can be addressed by physicians in the PHCs, especially the important factors reported by a study in 2017 (Abdel-Aziz et al. 2017), includes fear of physicians and the screening result, and lack of specialized clinics for BCS awareness. Others are the belief mammography is painful which may reduce the performance by 56% (Al-Zalabani et al. 2018).

The influence of PHC physician on female patient's decision to have regular screening mammogram is significant; we aim to further to explore physician's attitudes and their practices toward screening mammography among women at ages of 40 to 49 years in Madinah, Kingdom Saudi Arabia (KSA).

MATERIALS AND METHODS

Study design and study population

This study utilized a descriptive cross-sectional design to evaluate PHC physicians' awareness and practices of breast cancer screening among women 40 to 49 years of age in Madinah, (KSA). it was conducted in all PHC clinics in Minister of Health, National Guard Hospital, Military Hospital and the Medical Unit in Taibah University in Madinah city, KSA from February 1 to August 31, 2021.

All Saudi and non-Saudi physicians who worked in the PHC center including general and family medicine residents, specialists and consultants were invited to participate in the study. We excluded health care workers other than physicians, as well as physicians who had worked a year or less, and those working in outpatient clinics.

Data Collection

Data was collected using a multipart English electronic questionnaire. The questionnaire was validated before administration to the population. Face validity was ensured by two experts experienced in research methodology. Complete anonymity was provided to ensure confidentiality of the data.

After providing informed consent, participants completed the 3-part questionnaire. The first part assessed the demographic information of the participants including the physician age, gender, level of training, sub specialty and years of clinical practice. The second part was adapted and modified from a previously published tool—the National Survey of Primary Care Physicians' Cancer Screening Recommendations and Practices: Breast and Cervical Cancer Screening Questionnaire (Approval Form, National cancer institute 2009). it assessed PHC physician's awareness and attitudes with regards to offering screening mammography to at risk women based on a 5 points Likert-scale question (very effective, somewhat effective, not effective, not known and not sure) for 4 statements related to CBE, BSE, screening mammography for women 40-49 years old and those above 50 years. Also, multiple choice and closed questions were used. The third part is a self-administered questionnaire which elicited barriers facing PHC physicians regarding breast cancer screening. Also, 5 points Likert-scale (Never, rarely, sometimes, usually and not known/applicable) was used to assess the three main categories of barriers, i.e., physician-related barriers, women-related and facilities-related barriers.

Ethical considerations

Approval for this study was granted by the Research Ethics Committee, College of Medicine. Informed consent was obtained from the participants and their privacy and confidentiality was assured.

Statistical analysis

Statistical analysis was performed using IBM SPSS statistical software, version 24 (IBM Corp., Armonk, NY). Descriptive statistics including mean \pm standard deviation was used to report continuous variables, and frequency/proportions for categorical variables. Chi-square test was used to compare proportions according to age group of the physicians. Two-sided tests were used and a p-value <0.05 was considered significant.

RESULTS

Characteristics of the respondents

A total of 40 clinicians completed the survey. Table 1 summarizes the socio-demographic characteristics of the respondents. Overall, 30 (75.0%) of the respondents were less than 40 years old and 32 (80.0%) were females. The respondents were mainly consultants 12 (30.0%) and general practitioners 11 (27.5%) working mainly in the family medicine specialty 32 (80%). Majority of the respondent were working in a primary health care Centre 33 (82.5%), and 25 (62.5%) have worked for five years or more (Table 1).

Table 1: Socio demographic characteristics of the respondents

| Variables | N (%) |
|---------------------------------------|-----------|
| Age group (years) | |
| <40 | 30 (75.0) |
| ≥40 | 10 (25.0) |
| Sex | |
| Male | 8 (20.0) |
| Female | 32 (80.0) |
| Job | |
| Consultant | 12 (30.0) |
| Specialist | 9 (22.5) |
| Resident/Fellow | 8 (20.0) |
| General practitioner | 11 (27.5) |
| Specialty | |
| Family medicine | 32 (80.0) |
| Women's health | 3 (7.5) |
| GP | 2 (5.0) |
| Other | 3 (7.5) |
| Duration of clinical practice (years) | |
| <5 | 15 (37.5) |
| 5 – 10 | 6 (15.0) |
| 11 – 15 | 12 (30.0) |
| >15 | 7 (17.5) |
| Workplace | |
| Hospital | 3 (7.5) |
| PHC Centre | 33 (82.5) |
| Taibah University Medical Unit | 3 (7.5) |
| Other | 1 (2.5) |

Attitude and practices towards breast cancer screening procedures

Overall, 36 (90.0%) of the respondents believed that clinical breast exam performed by a practitioner was effective in reducing breast cancer mortality in average risk women. Most of the respondents 31 (77.5%), also believed that breast self-exam performed by the patient was effective in reducing breast cancer mortality in average risk women. Also, 35 (87.5%) of the respondents each believed that screening mammography for women 40 to 49 years and those 50 years old or more was effective in reducing breast cancer mortality in average risk women. Table 2 shows the attitude and practices of the respondents towards breast cancer screening procedures. The mean appropriate attitude score was 3.45 ± 1.04 . Overall, 29 (72.5%) of the respondents had appropriate attitude towards breast cancer screening procedures in lowering cancer mortality in average risk women (Table 2).

Only, 10 (25.0%) of the respondents routinely recommended clinical breast exam performed by a practitioner for women who were 40 – 49 years old. Among those who recommended this clinical breast exam 9 (90%) recommended that this should be done yearly, 1

(10%) recommended that it should be done six monthly (Table 2). Also, only 12 (30.0%) of the respondents routinely recommended breast self-exam performed by the patient for women who were 40 – 49 years old. Among those who recommended this self-breast exam performed by the patient 8 (67%) recommended that this should be done monthly, while 4 (33%) recommended it should be done yearly. Only, 14 (35.0%) of the respondents routinely recommended mammography for women who were 40 – 49 years old; and only 4 (28.6%) of them recommended that it should be done yearly, while others indicated it should be done more frequently (biannually).

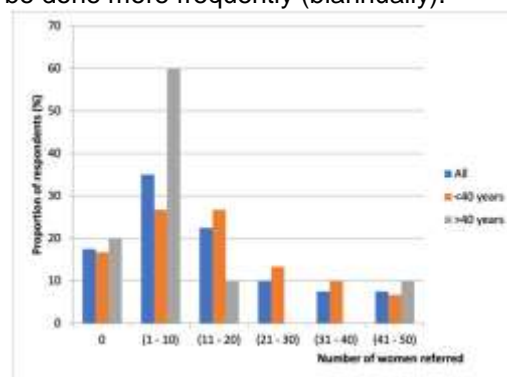


Figure1: Proportion of referral and number of at-risk women referred for screening mammography by the clinicians in a month

The respondents were asked to report how many average-risk women they referred for screening mammography during a typical month according to their age group (Figure 1).

Overall, 14 (35%) of all the respondents indicated that they referred 1 to 10 women. And another 9 (22.5%) indicated that they referred 11 to 20 women. There was no statistically significant difference in the proportion of women referrals according to the respondents age group ($P = 0.33$).

Also, the respondents were asked to indicate the person who usually provides breast cancer screening services to women in their setting (Table 2). Most of the respondents 21 (52.5%) indicated that breast cancer screening services was provided by a shared care team of multiple experts, while 11 (27.5%) indicated that they provided these services themselves. Furthermore, the respondents were asked to describe the breast cancer screening services they provide to patients (Table 2). Most of the respondents 34 (85.0%) indicated that they mainly refer women for mammography, while 30 (75.0%) indicated that they also took time to discuss the risks and benefits of breast cancer screening with the women. Only, 16 (40.0%) of the respondent indicated that they have taught women breast self-examination.

Table 2: Attitude and Practices towards breast cancer screening procedures in lowering cancer mortality in average risk women

| Appropriate attitude * | No | % |
|--|-----------|----------|
| Attitude towards clinical breast exam performed by a practitioner | 36 | 90.0 |
| Attitude towards breast self-exam performed by patient | 31 | 77.5 |
| Attitude towards screening mammography for women 40 to 49 years | 35 | 87.5 |
| Attitude towards screening mammography for women 50 years old or more | 35 | 87.5 |
| Attitude Score 0-4 (Mean \pm SD) \pm 0. | | |
| | | |
| Level of Attitude | | |
| Poor | 11 | 27.5 |
| Appropriate attitude | 29 | 72.5 |
| | | |
| Practices | | |
| Routinely recommended clinical breast exam for women 40 – 49 years old to be performed by a practitioner | | |
| No | 30 | 75.0 |
| Yes | 10 | 25.0 |
| Routinely recommended breast self-exam for women 40 – 49 years old to be performed by the patient | | |
| No | 28 | 70.0 |
| Yes | 12 | 30.0 |
| Routinely recommended mammography for women 40 – 49 years old | | |
| No | 26 | 65.0 |
| Yes | 14 | 35.0 |
| | | |
| Who usually provides breast cancer screening in your setting | | |
| My self | 11 | 27.5 |
| Physician assistant | 4 | 10.0 |
| Practice nurse | 1 | 2.5 |
| Radiologist | 1 | 2.5 |
| Shared care (team) | 21 | 52.5 |
| Other | 2 | 5.0 |
| | | |
| **Breast cancer screening services provided by the respondents to patients | | |
| Discuss risk and benefit of breast cancer screening | 30 | 75.0 |
| Refer for mammography | 34 | 85.0 |
| Perform clinical breast exam | 24 | 60.0 |
| Discuss mammography results with patients | 25 | 62.5 |
| Recommend follow up care for positive clinical breast exam cases | 22 | 55.0 |
| Recommend follow up care for positive clinical breast exam cases | 23 | 57.5 |
| Teach breast self-exam | 16 | 40.0 |

(*) = indicates those who indicated that they procedure is very effective or somewhat effective; SD = standard deviation; ** = overall percentage exceed 100% because respondents performed multiple services

Table 3: Breast cancer screening barriers toward average-risk women among the respondents

| Barriers | Never N (%) | Rarely N (%) | Some times N (%) | Usually N (%) |
|--|----------------|-----------------|------------------------|------------------|
| 1) Breast cancer screening barriers toward average-risk women among the respondents | | | | |
| a. I am not having enough time to discuss screening with my patients | 7 (17.5) | 7 (17.5) | 19 (47.5) | 7 (17.5) |
| b. I think it is early to expose the patient to radiation | 13 (32.5) | 8 (30.0) | 14 (35.0) | 5 (12.5) |
| c. I believe that the beginning of screening at the age of 40 years is not necessary | 15 (37.5) | 6 (15.0) | 13 (32.5) | 6 (15.0) |
| d. If there is no breast complain, breast examination by physician is not required | 9 (22.5) | 6 (15.0) | 20 (50.0) | 5 (12.5) |
| 2)When you talk to your asymptomatic, average -risk women about breast cancer screening, how often do you encounter the following? | | | | |
| a. Women who do not want to discuss breast cancer screening? | 6 (15.0) | 12 (30.0) | 16 (40.0) | 6 (15.0) |
| b. Women who have difficulty understanding the information I present about breast cancer screening | 3 (7.5) | 19 (47.5) | 14 (35.0) | 4 (10.0) |
| c. Women who refuse to do breast mammography | 2 (5.0) | 12 (30.0) | 22 (55.0) | 4 (10.0) |
| d. Women who are unaware of breast cancer screening | 3 (7.5) | 11 (27.5) | 22 (55.0) | 4 (10.0) |
| e. Women who do not perceive breast cancer as a serious health threat | 5 (12.5) | 13 (32.5) | 16 (40.0) | 6 (15.0) |
| Other | 17 (42.5) | 8 (20.0) | 13 (32.5) | 2 (5.0) |

Table 4: Breast cancer screening practice barriers toward average-risk women among the respondents

| Barriers | Never N (%) | Rarely N (%) | Some times N (%) | Usually N (%) | Don't know N (%) |
|---|----------------|-----------------|---------------------|------------------|---------------------|
| 3) How often do you encounter the following barriers to breast cancer screening for asymptomatic average risk women in practice | | | | | |
| a. My patients do not follow through complete screening mammography | 6 (15.0) | 7 (17.5) | 0 (0) | 4 (10.0) | 23 (57.5) |
| b. There is shortage of facilities/trained providers in my geographic area of practice to perform screening mammography | 9 (22.5) | 12 (30.0) | 0 (0) | 6 (15.0) | 13 (32.5) |
| c. Other | 17 (42.5) | 7 (17.5) | 0 (0) | 4 (10.0) | 12 (30.0) |
| a. Screening mammography? | 10 (25.0) | 6 (15.0) | 0 (0) | 0 (0) | 24 (60.0) |
| b. Follow-up for a lump found during clinical breast exam performed by a practitioner | 8 (20.0) | 8 (20.0) | 0 (0) | 0 (0) | 24 (60.0) |
| c. Follow-up for an abnormal mammogram | 6 (15.0) | 7 (17.5) | 0 (0) | 0 (0) | 27 (67.5) |

In addition, 28 (70.0%) of the respondents' indicated that they counsel average-risk women about breast self-awareness.

Breast cancer screening barriers encountered by the respondents

Tables 3 and 4 summarizes the barriers to breast cancer screening encountered by the respondents. Overall, 26 (65.0%) of the respondents have encountered clinicians who do not offer screening to women because they do not have enough time to discuss screening with

their patients, while other clinicians 19 (47.5%) indicate that they don't offer screening to average risk women because they think it is too early to expose their patients to radiation (Table 3).When considering breast cancer screening in asymptomatic average-risk women, 22 (65.0%) of the respondents have met women who do not want to discuss breast cancer screening, and 18 (45.0%) have encountered women who have difficulty understanding the information they gave about breast cancer screening. Furthermore, 26 (65.0%) of the respondents have met women who declined to do breast mammography they recommended, 26 (65.0%) of them

also have met women who are unaware of breast cancer screening.

The respondents were asked other practice barriers related to breast cancer screening toward average-risk women (Table 4). Most of the respondents 27 (67.5%) indicated that their patients do not complete screening mammography when recommended, while 19 (47.5%) of them indicated that there is shortage of facilities/trained providers in their area for doing screening mammography. However, when the respondents were asked to indicate how often their female patients wait more than 2 months after making an appointment to undergo screening mammography, follow-up for a lump found during breast examination by a practitioner, or follow-up for an abnormal mammography they indicated that they did not know in 24 (60.0%), 24 (60.0%) and 27 (67.5%), respectively (Table 4). Respondents were asked whether their primary care practice has a guideline for breast cancer screening, 37 (92.5%) of them indicated that there was a guideline for breast cancer screening.

DISCUSSION

This study found that the clinicians had appropriate attitude towards the effectiveness of breast cancer screening in lowering the risk of mortality for at-risk women. However, this appropriate attitude did not lead to correct practices as only one quarter of them recommended CBE for women 40 – 49 years old to be performed by a practitioner and only about one third of them recommended mammography for at-risk women. When asked their specific practices related to breast cancer screening, only 60% performed clinical breast examination and only 40% taught the women how to perform breast self-examination. A number of breast examination screening barriers were identified related to patient, provider and health system factors.

In this study, majority of the clinicians believed in the effectiveness of clinical breast examination by a practitioner and breast self-examination performed by patients in lowering cancer risk in at-risk women. Our findings are consistent with the results of similar studies conducted in the United States of America and elsewhere (Heena et al. 2019, Al-Mulhim et al. 2018, Bcheraoui 2015, Jones et al. 2012, Chong et al. 2002, Haji et al. 2002 and Loh et al. 2015). In Wisconsin, primary care providers were found to repeatedly overestimate the effectiveness of clinical and self-breast examinations and tending to over recommend them (Jones et al. 2012, Nachtigal et al. 2020). Similarly, about 70% of primary care physicians in Massachusetts surveyed were found to be teaching breast self-exams despite guideline recommendations against them (Loh et al. 2015). The key reasons for these differences are discrepancies in guideline recommendations (Oeffinger et al. 2015, Nachtigal et al. 2020, Siu 2016, NCCN 2018). For example, even though most primary care providers found the U.S. Preventive Services Task Force guidelines to be

the very useful in the USA, most clinicians surveyed continue to perform clinical breast exams and encourage self-breast exams which were not recommended by the guideline (Nachtigal et al. 2020, Siu 2016). Also, although some guideline recommends breast self-awareness by clients with the view to discussing any concerns with their primary care physicians (Siu 2016, NCCN 2018), this does not necessarily warrant the recommendation and promotion of breast self-examinations.

Despite the strong attitude towards the effectiveness of breast cancer screening methods, just about a quarter to one-third of the primary care providers in this study recommended either CBE by a provider, BSE by patients or mammography for women 40 – 49 years old covering different timelines. This reflect inadequate knowledge of current breast screening guidelines as was earlier documented (Heena et al.2019, Bcheraoui 2015). The practice of BSE in this study was consistent with those of Kumar et al in a survey of healthcare professionals in Pakistan (Kumar et al. 2009). Similarly, the findings of this study were better than thereport by Mahmoodi et al carried out in Tehran, but was lower compared to those found by a study in Singapore related to perceptions around breast cancer screening amongst public health nurses (Haji et al. 2002,Chong et al. 2002). Also, in the study by (Akhigbe AO and Omuemu, 2009), among health care workers (including 102 physicians (26.0%) in Nigeria and another study among health care professionals in Morocco, their findings regarding the recommendation of BSE and CBE as screening methods were higher compared to this study(Ghanem et al. 2011). The role and usefulness of either CBE by a provider or BSE in early breast cancer detection remains controversial as several studies have reported inconsistent findings regarding its importance. The American Cancer Society (ACS) and USPSTF no longer recommend monthly BSE as it increases anxiety, over recommendation of breast biopsies, biopsies for benign lesions and it has been shown not to have any survival benefit (Oeffinger et al. 2015, Siu 2016, Bulletins 2017). However, a number of studies assessing the potential benefits of BSE especially in developing countries argue that regular breast examination may be associated with a higher likelihood of early breast cancer detection (Mac Bride et al. 2012, McCready et al. , 2005, Wu and Lee J. 2019, Johnson. 2019, Bonsu et al. 2018). Therefore, BSE may be sustained as a screening method only in the context of making women to have higher 'breast awareness' and to contribute to early diagnosis (Roth et al. 2011).In this study, 70.0% of the respondents' indicated that they counsel average-risk women about breast self-awareness. There is a need to improve this among primary care providers in the region

The USPSTF guidelines found some evidence on the substantial benefit of mammography screening to lower breast cancer mortality in women who are aged 40 to 74 years (Siu. 2016). The number of breast cancer-related

deaths averted rises with age i.e., 40 to 49 years old women had the least benefit while women aged 60 to 69 years had the most benefit. Women aged 40 to 49 years who have a first-degree relative with breast cancer have a risk for breast cancer similar to that of women aged 50 to 59 years without a family history (Siu. 2016). Although USPSTF guidelines state with a grade C recommendation that the decision to screen before the age of 50 should be "an individual one," only 35% of the primary care clinicians in this study recommended mammograms to women aged 40–49 years. This is lower compared to previous studies in developed countries (Nachtigal et al. 2020, Loh et al. 2015) and this agrees with the finding of an earlier report from Saudi Arabia (Bcheraoui et al. 2015). This may probably be due to variations in the guidelines on when to recommend mammography. The ACS guidelines recommend screening with mammography annually for women 45 years old or over while the USPSTF recommends this for women over 50 years (Oeffinger et al. 2015, Siu. 2016). The consequences of this variations in screening practice include possible risk of false-positive tests, harm to patients as well as greater costs, without clear mortality benefits. There is a need for a harmonised guideline adopted at country level in order to influence the attitudes of providers and guide them in adopting appropriate breast cancer screening measures in particular using a shared-decision making process with clients (Schrager et al. 2020, Han et al. 2018). Further evaluation would be beneficial in evoking change and improving compliance with screening guideline by primary care providers.

In this study a number of barriers against breast screening for average risk women were observed which were related to patient factors like; lack of interest, difficulty in understanding information given by the providers or perception that breast cancer is not a serious illness. Also, some barriers were found operating at the provider level such as providers not having enough knowledge about breast cancer screening, not having enough time to counsel their clients and not wanting to expose their clients to radiation. Other barriers were found to be operating at the health system level such as shortage of facilities/trained providers for mammography and long waiting times for clients referred for mammography or follow-up after an abnormal mammogram to receive further care. Some of these barriers of breast cancer screening have been previously documented in KSA (Al-Zalabani et al. 2018, Abdel-Aziz et al. 2017). This calls for improvement in training of health care workers, sustained community education regarding the risk of breast cancer and importance of screening, and the provision of facilities and trained experts for mammography and follow-up assessments.

The study has some limitations. One key limitation is the small sample size. As this was a web-based survey we had hoped to elicit a high response rate which would have offered a higher diversity and study power to perform

additional analyses. The survey involved hospital staff working in one State of the KSA and therefore the findings may not be generalizable to the whole country. Another limitation was that the data related to the screening practices of the clinicians was collected via a self-reported survey rather than a review of patient's records. Thus, the data may be prone to self-report bias. Despite these limitations, the study provide evidence that will inform community education related to breast cancer screening and health systems strengthening.

CONCLUSION

Our survey showed that clinicians still believed in the effectiveness of CBE and BSE and continue to recommend it to women in Saudi Arabia. Some of the clinicians recommended mammography for at-risk women, effective utilization of these screening methods was hampered by many barriers operating at the patient-, provider- and health systems-level. Also, there is no clarity regarding the accepted screening guidelines, the adoption and promotion of one international guideline recommendation at the country level would ultimately improve evidence-based breast cancer screening for women by PHC physicians.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

ACKNOWLEDGEMENT

We thank our colleague dr. Rana Alrehaili for help in preparation of questionnaire form and follow up ethical approval form. We acknowledge dr. Abdullah Ghunaim for his help in collecting the data.

AUTHOR CONTRIBUTIONS

H.G. designed, wrote the manuscript and analyzed data. S.A. wrote and supervised the manuscript. All authors read and approved the final manuscript.

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