KNOWLEDGE ATTITUDE AND PRACTICES AMONG GENERAL FEMALE POPULATION OF KARACHI REGARDING BREAST CANCER RISK FACTORS, SCREENING AND BREAST SELF- EXAMINATION.

Gati Ara¹, Pooja Devi Manglani², Sareema Eman Akhtar³, Shahwar Kazimi⁴, Rimsha Tahir⁵

ABSTRACT

INTRODUCTION: Pakistan has high incidence of breast cancer in the region and breast cancer is more aggressive and is recognized to metastasize at an earlier age with presentation at late stage due to affordability, lack of awareness and poor attitude towards seeking medical care. This study targets general population of adult females to assess their knowledge, attitude and practices regarding breast cancer risk factors, screening modalities and Breast self- examination. **OBJECTIVES:** To assess the knowledge, attitude and practices among general female population of Karachi regarding breast cancer risk factors, screening and breast self- examination. **METHOD:** A Cross-Sectional Survey was conducted on a sample size of 400 females through convenience sampling. Data was collected in both Urdu and English languages via self- structured questionnaire in public places of Karachi. Both interview and self-administration was employed for data collection procedure. Data was analyzed using SPSS version 20. All qualitative variables were presented as frequency and percentage while all quantitative variables like age were presented as mean and standard deviation. Chi square was used as a test of association and p-value <0.05 was taken as significant. **RESULTS:** A total of n=400 females with mean age of 25.4 +/-1.7 years were included in the study. Majority of the respondents were Muslim females, and graduates. n=382 (95.5%) women had heard of breast cancer. The source of information regarding breast cancer was mostly newspapers and magazines etc. majority of women recognized lump in breast as a sign of cancer n=308 (77%) and n=187 (46.8%) recognized biopsy as a method of diagnosis. 31% women admitted they did not know how often clinical breast examination should be done once women turn forty years old. And 21% had gone through a clinical breast examination atleast once. Total n=252 (63%) females has heard of mammography. It was found that 75% of the participants never perform breast self- examination (BSE). Married women are more likely to Practice breast self-examination than single women. **CONCLUSION:** The knowledge regarding breast cancer still remains limited. Newspapers and other media are recognized as powerful tools to spread knowledge regarding the disease. Frequency of performing Breast self -examination is still very low and its importance must be emphasized. Also, an important reason for not performing BSE does not know how to perform it. Thus, better awareness of this procedure must be created among female.

KEY WORDS: knowledge, attitude, practice, breast cancer, risk factors, screening, breast self-examination

- 1. Assistant Professor, Department of Community Health Sciences, Ziauddin University.
- 2. MBBS, Private practitioner.
- 3. Student, Third year MBBS, Ziauddin University.
- 4. MBBS, Private practitioner.
- 5. MBBS, Private practitioner.

For correspondinance: Dr. Gati Ara, Assistant Professor, Department of Community Medicine, Dow Medical College, Dow University of Health Sciences. Postal address: House No. 188, Street 33, Khayaban-e- Qasim, Phase 8, DHA, Karachi, 75500,

Email: getiaral@gmail.com

How to cite this article: Ara G¹, Manglani PD², Akhtar SE³, Kazimi S⁴, Tahir R⁵ KNOWLEDGE ATTITUDE AND PRACTICES AMONG GENERAL FEMALE POPULATION OF KARACHI REGARDING BREAST CANCER RISK FACTORS, SCREENING AND BREAST SELF- EXAMINATION. JPUMHS; 2021:11:03, 15-21. http://doi.org/10.46536/jpumhs/2021/11.03.309

Received July 16th 2021, Accepted On 20th August 2021, Published On 30th September 2021.

INTRODUCTION

Breast Cancer is the most common cancer among women worldwide, comprising 23% of the female cancers. The worldwide incidence of breast cancer in 2012 was estimated to be 1.67 million. In the US one

person out of 8 suffers from breast cancer and it has become the second most common cause of death. The incidence of breast cancer in developed countries is high but the mortality rate has decreased due to increased efforts in promoting early detection, mammography

and advances in treatment techniques⁴As countries, compared to neighboring incidence of breast cancer in Pakistan is high. According to WHO the data shows that number of new cases in 2020 in both sexes and all ages include 25, 928 (14.5%) people out of 178 388 total. Every one in nine females is affected with this disease.6In Pakistan breast cancer is more aggressive and is known to metastasize at an earlier age with presentation at late stage due to affordability, lack of awareness and poor attitude towards seeking medical care. ⁷According to Vivek Kumar Pandey and et al. socioeconomic status plays a vital role in affecting an individual's health, family's health including their social security system etc.⁷A study from India with social and cultural background similar to Pakistan reported that the total awareness of women regarding breast cancer was 52% which was considered as moderate.9 Even in India breast cancer has become the most common and has overtaken cervical cancer in females¹⁰

According to Karachi Cancer Registry's report, Breast Cancer accounts for nearly 34.6% of all cancer cases in Karachi. 11 Most of the researches conducted in Pakistan regarding breast cancer knowledge, attitude and practices have mainly focused on medical professionals such as nurses, medical students and health care workers who already have some knowledge about Breast cancer. Keeping in account the increasing incidence and mortality rates of breast cancer in Pakistan prioritization of its awareness, early detection and treatment must be considered.

A similar study had been conducted in Karachi regarding knowledge, attitude and practices of breast cancer among urban women. According to this study, urban women of Karachi lacked appropriate awareness regarding breast cancer and there was widespread prevalence of fallacies and misconceptions. 12 But this study focused on females visiting tertiary care hospital and its outreach centers. The participants had positive attitude in seeking medical care which could have led them to gather information actively from available sources.¹³ Whereas our study counters this limitation by focusing on general female population.

Therefore, our study aimed to find the level of awareness and practices. It is hoped that the results would fill gaps in knowledge regarding this subject so that the results can be used to plan better awareness programs and also to prioritize breast cancer as a health issue while policy making.

METHODS AND MATERIALS

A Cross-Sectional Survey was conducted over a period of one year. A sample size of females was selected through convenience sampling. Data was collected in both Urdu and English languages via selfstructured questionnaire. Both interview and self-administration was employed for data collection procedure. Interview method was largely employed for women with no education. Data was collected in public place Educational Institutions, Shopping malls as well as private homes. All females above the age of 18 years were included in the study. Informed written consent was taken from all participants and confidentiality was maintained. Data was analyzed using SPSS version 20. All qualitative variables were presented as frequency and percentage while quantitative variables like age were presented as mean and standard deviation. Chi square was used as a test of association and p-value <0.05 was taken as significant.

RESULTS

A total of n=400 females with mean age of 25.4 +/- 1.7 years were included in the study. When the age was categorized it was found that almost 70% (of the females were in age group of 18- 25 years. When religion was reviewed 83% of the participants were Muslims, 10.2% were Hindus, 5. 5% followed Christianity and 0.9% belonged to other minority groups. Marital status revealed that majority n=285 (74.3%) females were never married and n=101 (25.3%) were married and n=13 (3.3%) were divorced or widowed. The educational level of respondents was estimated as n=5 (1.3%) had no education, females with primary level education were n=5(1.3%),Matriculation/Intermediate or equivalent were n=64 (16.1%), graduates were n=276 (were 41.5%) and post graduates were n=50(12.5%). The working status of study participants illustrated that n=34 (8.4%) were house wives, n=73 (18.3%) were working women and n=280 (70%) were students pursuing various fields.

When asked if they have heard about breast cancer n=382 (95.5%) women answered in the affirmative while n=18(4.5%) had not heard of a breast cancer ever. When enquired if they believe breast cancer is curable n=276 (69%) held yes, n=13 (13%) said no, n=75 (18.8%) supposed may be and n=35 (8.8%) sensed they didn't know.

The source of information regarding breast cancer was mostly newspapers, magazines, books and journals n=228 (57.1%), then family n=192 (48%), followed by internet

n=160 (40%), by TV and Radio n= 124 (31%) and lastly awareness programs and symposia n=92 (23%),

Most participants had no known co-morbid, n=342 (85.6%). Maximum participants n=349 (87.3%) had no family history of breast related tumor.

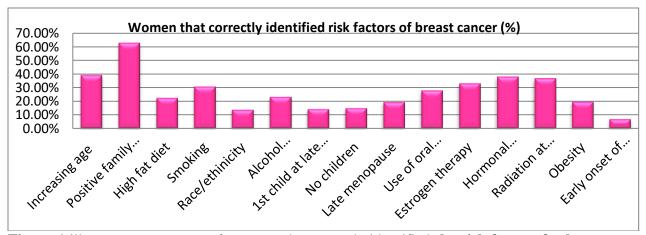


Figure 1 illustrates percentage of women who correctly identified the risk factors for breast cancer.

Most women recognized the preventive effect of increased physical activity n=169(42%) and healthy high fiber diet n=243 (61%) but only half n=203 (51%) believe that breastfeeding can prevent breast cancer.

The knowledge of **signs and symptoms of breast cancer** was varied. While most people recognized lump in breast as a sign of cancer n=308 (77%). Only n=207 (51.8%) recognized discharge from breast. Pain or soreness in breast was acknowledged by n=237 (59.3%), lump under armpit by n=230 (57.5%), swelling of breast by n=193 (48.3%), change in individual size of breast by n=187(46.8%). Discoloration of breast was known to even less individuals n=152 (38%), weight loss identified by n=117 (29.3%)

When inquired about the **methods of diagnosis** n=187 (46.8%) recognized biopsy while clinical breast examination by doctor was acknowledged by n=227 (56.8%), mammography/ sonography was identified by n=271 (67.8%) and blood test by n=63 (15.8%).

When asked how frequently Clinical Breast Examination (CBE) should be done once a woman turns 40 years of age, n=123 (30.8%)admitted they did not know and n=225 (56%) said once in a year. When inquired if they had Clinical gone through Examination n=82 (20.5%) responded in the affirmative while n=314 (78.5%) responded in negative. When asked about the reason for not going for CBE n=12 (3%) said they were reluctant because of monetary reasons, n=14 (3.5%) were reluctant because of extra time, n=28 (7%) had fear of outcome, n=111 (27.8%) thought they were too young for it, n=160 (40%) because they had no signs and symptoms, n=82 (20.5%) said that no one

recommended it to them while n=25 (6.3%) were unsure about the benefit of CBE.

When their knowledge of Mammography was assessed n=252 (63%) had heard of it and n=201 recognized it as an X ray exam that detects mass in breast. The recommended age for mammogram was recognized to be 45 years by n=17 (4.3%) and n = 194 (49%) simply did not know. Total n=55 (13.8%) of women believed that mammography is a painful procedure. Only n=128 (32%) of the women thought that mammography can detect a mass earlier than There clinically. was a significant relationship between educational status of women and the knowledge mammography. (P- Value= 0.009)

To assess the attitude of participants they were inquired how fast participants would seek medical advice if they developed a lump in breast, majority n=288 (72%) said within one week, n=56 (14%) said within one month, n=26 (14%) said in one to three months and n=29 (7.3%) said they won't bother at all.

When inquired about **Breast Self** - **Examination** (**BSE**) it was found that n=255 (64%) participants had heard of it. BSE was recognized as a method of diagnosis in n=199 (50%). The age to start BSE was held to be <25 years by n= 160 (40%). When asked if they knew how to perform BSE n=232 (58%) women admitted they did not know. They were inquired how frequently they should perform BSE to which varied responses were made where n=186 (46.5%) said monthly.

When asked if they perform BSE it was found that n=300 (75%) of participants (n=300) never do BSE. Only n=99(24.8%) women perform BSE, out of whom n=59 (14.8%) practice it monthly, and n=40 (10%) practice it less frequently. Out of the participants who perform BSE n=59 (14.8%)

started when they were younger than 25 years.

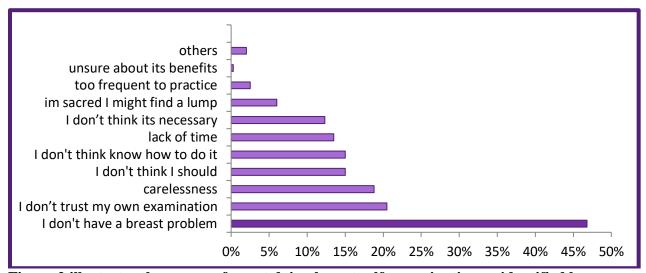


Figure 2 illustrates the reasons for not doing breast self- examination as identified by participants.

When the association was assessed between age and identification of risk factors a significant association was found between age and identifying risk of having no children

n=59, 15%(p- value: 0.008), having first child after 30 years n=56, 14%(p-value: 0.035) and taking oral contraceptive pills n=110,27.5% (p-value: 0.003).

Table 1: The association between Educational level and knowledge of risk factors

		None /		Matric/		Graduation		Post-		P
Risk Factors		elementary		intermediate				graduation		value
Trisk Tuctors		N	%	N	%	n	%	N	%	
Increasing age	yes	5	3.2	17	10.9	118	75	16	10	0.062
	No	5	2	47	19.3	158	64.8	34	13.9	
No children	Yes	0	0	10	16.9	35	59.3	14	23.7	0.021
	No	10	2.9	54	15.8	241	70.7	36	10.6	
Estrogen therapy	Yes	4	3.1	8	6.1	103	78.6	16	12.2	0.002
	No	6	2.2	56	20.8	173	64.3	34	12.6	
Radiation exposure at young age	Yes	6	4.1	16	10.9	111	75.5	14	9.5	0.027
	No	4	1.6	48	19	165	65.2	36	14.2	
Early menarche before 12 yrs	Yes	0	0	2	7.4	17	63.3	8	29.6	0.029
	No	10	2.7	62	16.6	259	69.4	42	11.3	
Smoking	Yes	3	2.5	10	8.2	92	75.4	17	13.9	0.046
	No	7	2.5	54	19.4	184	66.2	33	11.9	
Poor diet	yes	0	0	6	6.7	70	78.7	13	14.6	0.01
	No	10	3.2	58	18.6	206	66.2	37	11.9	

There was a significant association of age with identification of breast feeding as a protective factor n=202 (51%) (P-value: 0.0001). Women in older age groups (26 years and above) were more likely to recognize the protective effect of breast feeding.

There was a significant association of age with ever getting a clinical breast examination n=82, 20 %(p-value: 0.0001). There was a significant association of age with the practicing Breast Self-Examination n=99, 25% (p-value: 0.0001).

There was a significant difference among different educational groups in identifying

biopsy as a method of diagnosis n=187, 47% (p- value: 0.041).

There was a significant association between educational status of women and practice of Breast Self- Examination, n=99 (25%) (P value 0.04)

There was a significant association between education and frequency of performing BSE (p-value 0.006). There was a significant association between education and age at starting practicing BSE (p-value: 0.0001). There was a significant difference in knowledge of married and single women

with regard to some risk factors like the risk of having no children (p-value:0.004) and racial risk(p value:0.006). There was also a significant association of marital status with identifying the protective effect of breast feeding against breast cancer (p-value: 0.0001).

There was a significant association of marital status with the practice of BSE (p value: 0.0001). The age at which they started performing BSE (0.0001), and their frequency of performing BSE (0.0001)

TABLE 3: Association of marital status and the practice of Breast Self-Examination.

		Sir	ngle	Mai	rried	Divorced/ Widow		P Value
		n	%	N	%	n	%	
Practice BSE	Yes	52	52.2	42	42.4	5	5.1	0.0001
	No	233	77.7	59	19.7	7	2.3	
Don't practice BSE because don't have a breast problem	Yes	145	77.5	34	18.2	8	4.3	0.012
	No	141	66.2	67	31.5	5	2.3	
Don't practice BSE because don't think I should	Yes	52	86.7	5	8.3	3	5	0.001
	No	234	68.8	96	28.2	10	2.9	
Don't practice BSE because don't know how to	Yes	75	81.5	14	15.2	3	3.3	0.023
	No	211	68.5	87	28.2	10	3.2	

No significant difference was found in different religious groups with regard to their knowledge of risk factors, preventive factors, signs and symptoms or methods of diagnosis of breast cancer nor was there a significant difference in their practice of clinical or breast self- examination.

DISCUSSION

The study has yielded interesting results. According to WHO the burden of breast cancer is increasing globally and is influencing individuals emotional and physical well-being. In this study 95% of women had heard of the breast cancer while according to Sobani Z ul A, a study in Rawalpindi showed that 73% of illiterate and 87.8% of well-educated women have heard about breast cancer.

Cancer can be treated at an early stage by detection through organized screening programs and it has been found that most of the women who have been diagnosed with an early stage^{1, 2} cancer are treated with good prognosis with 80-90% chances of five-year survival rate. ¹⁵ Our results reflect that 276 women believed in the cure of this cancer which constitutes 69% of the statistics.

It was found that most of the information about breast cancer amongst the people were through newspaper, magazines and books. According to Sobani Z ul A, television had played a vital role in awareness through media in our country despite the religious barriers but it was found in his study that 27% of the targeted population received information through television which was quite contradictory to the thoughts. This was quite a number according to him since it was the highest source of spread of information regardless of the physicians, family members or even the internet.4

According to Centers for disease control and prevention there are combined factors for the risk of developing breast cancer, both the modifiable and non- modifiable play a role in development of breast cancer. The factors that amplify the risk of breast cancer in women are strong family history and genetic mutations. Our study illustrates that 60% of the women identify a positive family history to be the main risk factor in the development of breast cancer. On the assessment of the preventive measures of breast cancer 51%

believed that breast feeding reduces the probability of breast cancer.⁶

In a study conducted at The Agha Khan University Hospital it was found that 95% of the participants considered lump to be the cardinal sign, 85% believed change in size to be the sign, discharge was recognized by 87% of the people and similarly ulcer was recognized by 79% people. Amongst all of them there were still 71% of the people who believed pain to be one of the symptoms. unlike our study which showed that out of 400 women 77% believed lump in the breast as the cardinal sign, 46.8% recognized change in shape and 51.8% recognized discharge.

Different screening modalities of breast cancer have been recognized by our women but they need to be implemented for efficient results. The cure of this disease lies in the increasing awareness among the people especially in women aged above 35 years.⁹ Since breast cancer is becoming a major health concern in Pakistan, it has been reported that majority of the women present in later stages of the disease due to either critical financial expenses, undiagnosed symptoms or lack of awareness and the cancer itself becomes incurable. 18Our results showed that 67.8% of the women recognized mammography/sonography as the diagnostic method for screening, while 56.8% of the women acknowledge clinical breast examination.

Only 20.5% of the women had undergone CBE and 78.5% did not which compared to the study performed in tertiary care hospital of Lahore in which only 6.9% of the women have had their CBE done which is very poor as compared to our results.⁴ According to Asrat et al the sensitivity, specificity and accuracy of clinical breast examination was 54%, 78% and 57% respectively (19)In a cross sectional study conducted by Amaneul et el 30% of the nurses practiced CBE.¹¹

In developing countries where screening through mammography has been designated as standard for care, the rate of mortality of from breast cancer has declined.²⁰

BSE is recommended at the age of 20 every once in a month.²¹Our results showed that 64% of the women had heard about BSE which is comparatively on a higher side than only 42% of the women who had heard about BSE in surgical outpatient department of the K.J.Somaiya Medical College, Sion, Mumbai and 40% of the females recognized the age of onset for performing BSE less than 25 years.¹²

However, the knowledge on performing BSE was poor and was found that 58% of the

women did not know how to perform BSE. A descriptive study conducted in Tehran, Iran by Jarwandi S and co-workers at the Iranian Centre for Breast cancer found that out of 800 Iranian teachers only 6% of the females performed BSE once a month (9). In our study, statistics are a little higher and we found that 46.5% of the women from our targeted population performed BSE once a month while 20% of the participants did not trust their examination which is comparable to 33.1% of the women in a study conducted in Iraq.(1) According to Lovemore and et all majority of the people in the district of Bindura, Zimbabwe had not heard about the breast-self-examination and more than half of the people did not think that they could ever develop breast cancer.²²

CONCLUSION

The knowledge regarding breast cancer still remains limited. Newspapers and other media are recognized as powerful tools to spread knowledge regarding the disease. There is an association between educational status and knowledge of risk factors. Frequency of performing Breast self examination is still very low and it is found to be associated with marital status. There is a need for educating women its importance must be emphasized.

CONFLICT OF INTEREST: None to declare **ETHICS APPROVAL:** Institutional approval enclosed

AUTHORS CONTRIBUTIONS

GA designed methodology, questionnaire, analyzed and interpreted the data, wrote results and did final editing. PM wrote synopsis, designed questionnaire, did literature search, wrote introduction, and collected data. SEA wrote the discussion and references. SK and RT performed literature search, wrote synopsis and did data collection.

CONSENT TO PARTICIPATE: written and verbal consent was taken from subjects and next of kin

FUNDING: The work was not financially supported by any organization. The entire expense was taken by the authors

ACKNOWLEDGEMENTS: We would like to thank the all contributors and staff and other persons for providing useful information.

REFERENCES

- 1. Alwan NAS, Al-Attar WM, Eliessa RA, Madfaie ZA, Tawfeeq FN. Knowledge, attitude and practice regarding breast cancer and breast self-examination among a sample of the educated population in Iraq. East Mediterr Heal J. 2012;
- 2. Global Cancer Observatory [Internet]. [cited

- 2021 Feb 12]. Available from: https://gco.iarc.fr/
- 3. Sharifirad G, Reisi M, Javadzade S. Knowledge, attitudes, and practice of breast self-examination among female health workers in Isfahan, Iran. J Educ Health Promot [Internet]. 2013 [cited 2021 Feb 15];2(1):46. Available from: /pmc/articles/PMC3826030/
- 4. Sobani Z ul A, Saeed Z, Baloch HN ul A, Majeed A, Chaudry S, Sheikh A, et al. Knowledge attitude and practices among urban women of Karachi, Pakistan, regarding breast cancer. J Pak Med Assoc. 2012;
- 5. Country-specific I, Cancer P, Method R, Country-specific M, Both F, Lip B, et al. 220 892 332. 2020;928:1–2. Available from: https://gco.iarc.fr/today/data/factsheets/popul ations/586-pakistan-fact-sheets.pdf
- 6. Kumar S, Imam AM, Manzoor NF, Masood N. Knowledge, attitude and preventive practices for breast cancer among Health Care Professionals at Aga Khan Hospital Karachi. J Pak Med Assoc. 2009;
- 7. Ahmad S, Qureshi AN, Atta S, Gul M, Rizwan M, Ahmad S, et al. Knowledge, attitude and practice for breast cancer risk factors and screening modalities in staff nurses of Ayub Teaching Hospital Abbottabad. J Ayub Med Coll Abbottabad. 2011:
- 8. Pandey VK, Aggarwal P, Kakkar R. Modified BG prasad socio-economic classification, update 2019. Indian J Community Heal. 2019:
- 9. To Determine The Level Of Knowledge Regarding Breast Cancer And To Increase Awareness About Breast Cancer Screening Practices Among A Group Of Women In A Tertiary Care Hospital In Mumbai, India. Internet J Public Heal. 2012;
- Gupta S. Breast cancer: Indian experience, data, and evidence. South Asian J Cancer. 2016;
- 11. Akram M, Iqbal M, Daniyal M, Khan AU. Awareness and current knowledge of breast cancer. Biological Research. 2017.
- 12. Dyavarishetty P V., Kowli SS. Prevalence of risk factors for breast cancer in women aged 30 years and above in Mumbai. Int J Community Med Public Heal. 2018;
- 13. (No Title) [Internet]. [cited 2021 Feb 11]. Available from: https://gco.iarc.fr/today/data/factsheets/popul ations/586-pakistan-fact-sheets.pdf
- 14. CDC Page Not Found [Internet]. [cited

- 2021 Feb 11]. Available from: https://www.cdc.gov/cancer/breast/basic_inf o/risk factors.htm)
- 15. PAHO/WHO | Breast Cancer: Knowledge summaries for health professionals [Internet]. [cited 2021 Feb 11]. Available from: https://www.paho.org/hq/index.php?option=com_content&view=article&id=11242:breas t-cancer-summaries-health-professionals&Itemid=41581&lang=en
- 16. What Are the Risk Factors for Breast Cancer? | CDC [Internet]. [cited 2021 Feb 14]. Available from: https://www.cdc.gov/cancer/breast/basic_inf o/risk_factors.htm
- 17. Khalid A, Hassnain S, Gakhar H, Khalid B, Zulfiqar F, Wahaj A. Breast cancer among young girls: a KAP study conducted in Lahore. Int J Sci Reports. 2018;
- 18. Naqvi A, Zehra F, Ahmad R, Ahmad N. Developing a Research Instrument to Document Awareness, Knowledge, and Attitudes Regarding Breast Cancer and Early Detection Techniques for Pakistani Women: The Breast Cancer Inventory (BCI). Diseases. 2016:
- 19. Dagne AH, Ayele AD, Assefa EM. Assessment of breast self- examination practice and associated factors among female workers in Debre Tabor Town public health facilities, North West Ethiopia, 2018: Crosssectional study. PLoS One. 2019;
- 20. Dandash KF, Al-Mohaimeed A. Knowledge, attitudes, and practices surrounding breast cancer and screening in female teachers of buraidah, saudi arabia. Int J Health Sci (Qassim). 2007;
- 21. Ifediora CO, Azuike EC. Tackling breast cancer in developing countries: insights from the knowledge, attitudes and practices on breast cancer and its prevention among Nigerian teenagers in secondary schools. J Prev Med Hyg [Internet]. 2018 Dec 1 [cited 2021 Feb 15];59(4):E282–300. Available from:/pmc/articles/PMC6319123/
- 22. Makurirofa L, Mangwiro P, James V, Milanzi A, Mavu J, Nyamuranga M, et al. Women's knowledge, attitudes and practices (KAP) relating to breast and cervical cancers in rural Zimbabwe: A cross sectional study in Mudzi District, Mashonaland East Province. BMC Public Health [Internet]. 2019 Jan 24 [cited 2021 Feb 14];19(1). Available from: /pmc/articles/PMC6345058/