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Breast Self-Examination Practice and Its Determinants Among Reproductive Age Women in The Pastoral Community of Southern Ethiopia: A Community Based Cross-Sectional Study

Alo Edin^{1*}, Abdisa Haro², Mohammed Aliyi², Yimar Hotessa², Angefa Ayele¹

¹Department of Epidemiology, School of public Health, Institute of Health, Bule Hora University, Bule Hora, Ethiopia.

²Department of Nursing, Institute of Health, Bule Hora University, Bule Hora, Ethiopia.

*Corresponding Author: Alo Edin.

Abstract

Background: Breast self-examination is a simple and direct, non-invasive, and low-cost screening approach for breast cancer identification. Unlike in the Western world, women in Ethiopia frequently appear late for breast cancer screening and are expected to have a very short life expectancy. In Ethiopia, the majority of studies on breast self-examination practice were limited to university students and health care workers. As a result, there was a scarcity of evidence on the practice of breast self-examination, particularly at the community level. Thus, the current study was aimed to assess the magnitude of breast self-Examination practice and associated factors among reproductive age women in West Guji zone, Southern Ethiopia.

Methods: A Community based Cross-sectional study was conducted from March 1 to April 30, 2021 among 424 randomly selected Women of reproductive age in the West Guji zone. The study participants were selected using multi-stage sampling. Data were collected using pre-tested and structured Questionnaires through face-to-face interviews. A bivariable and multivariable logistic regression model was used to identify the association between dependent and independent variables. P-Value <0.25 was used to select candidate variables for Multivariable logistic regression. A p-value <0.05 and an adjusted odds ratio with 95% CI were used to identify the independent predictors of Breast Self-Examination practice.

Result: Overall breast self-examination practice was 14.6 % (95% CI, 11.4-18.4). Age [AOR=1.98; 95%CI (1.06-3.70)], monthly income [AOR=2.28; 95% CI (1.09-4.78)], and having a good knowledge of breast self-examination [AOR=2.15; 95%CI (1.14-4.05)] were statistically significant predictors and positively associated with Breast self-examination practice.

Conclusion: This study revealed a substantial proportion of breast self-examination practice. As a result, stakeholders in various positions should make much more effort to promote women's education, as well as encourage and advocate breast self-examination practice.

Keywords: breast; self-examination; women; pastoral; southern ethiopia

Introduction

Breast Cancer is one type of Cancer that is a malignant tumour that starts in the cells of the breast and it represents a range of diseases from non-invasive to metastatic carcinoma[1]. Breast self-examination is a simple, non-invasive, and cost-effective screening method used for early detection of breast cancer. The method involves the woman herself looking at and feeling each breast for possible

mass, discharge, and any change in size and shape of the breast as early as possible [2]. Routine BSE practice is the fundamental method used to detect early breast cancer and it can potentially save the lives of women [3]. Breast self-examination has been broadly recommended as a comparatively simple, non-invasive, cost-effective, convenient, painless, easy to apply, private, and non-harmful screening technique when comparing to other types of

screening approaches for breast cancer [4]. The rationale behind extending BSE practice as a screening test is the fact that more than 90% of cases of breast cancer can be detected by women themselves, for this reason, it is important that women should understand the importance of BSE as the key breast cancer detection mechanism [5]. The method involves the woman herself looking at and feeling each breast for possible development of lumps, discharge other than breast milk, swelling of the breast, skin irritation or dimpling, and nipple abnormalities and it will be the best approach for effective prevention of breast cancer and its complications [6].

Every year worldwide 1.15 million women are being diagnosed with breast cancer and more than half a million die from this disease [7]. Breast cancer is the major public health problem and remains the commonest form of cancer in women and the second leading cause of cancer-related morbidity and deaths next to lung cancer globally [8]. Any Delay in the screening of breast cancer and treatment can lead to the diagnosis of the disease at a more advanced stage, an increase in death rate, and a reduction in the chance of survival [9]. According to the Global Burden of Cancer (GLOBOCAN) 2018 estimate, among the 8.6 million new cancer cases globally, breast cancer accounted for 24.2% of cancer, of which 8.1% occurred in Sub-Saharan Africa [10]. The incidence of breast cancer has been increasing in most regions of the world, but there are huge inequalities between rich and poor countries. Incidence rates remain highest in more developed regions, but mortality is relatively much higher in less developed countries due to a lack of early detection and access to treatment facilities [11]. Breast selfexamination practice remains low in many African countries and it was only 8% on the study done in Khartoum, 16% in southwest Cameroon, 16.9% in eastern Uganda, and 12.8% in Nigeria [4,12-14]. Knowledge of BSE and breast cancer, income, level of education, ever heard about BSE, fear of detecting cancer, feeling that it deviates privacy, and feeling of embarrassment are Factors contributing to the low level of breast self-examination practices [15].

In Ethiopia, communicable and infectious diseases are still the major health issues in the country and many efforts and resources are engaged into it. Government, non-government organizations, and international partners all focused on these diseases [15]. Despite its high prevalence, reproductive organ

cancer is not managed as a major public health problem at any level of the health care delivery system. Cancer, particularly breast cancer, is on the bottom of the priority lists [16]. Even though BSE is least costly, less time consuming and non-invasive screening method, its practice has been poor among reproductive-age women [17]. A study Conducted in Arbaminch District, Ethiopia among women age 20-64 showed that the magnitudes of BSE practice were (21.3%) [17]. Another study conducted among women of reproductive age in southeast Ethiopia, the bale zone revealed that the magnitude of BSE practice was only 13.2 % [18]. The finding from the study done in Debre Berhan indicated that Lack of knowledge on how to perform BSE was the main reason for not practicing BSE and Knowing how to perform, when to perform, and position to perform BSE and having a perception that BSE is important and useful to detect breast cancer were significant predictors of Breast self-examination practice[19]. Breast self-examination is most likely be the only feasible approach to wide population coverage as it is

Breast self-examination is most likely be the only feasible approach to wide population coverage as it is a cheap and easy method. Moreover, most healthcare facilities in Ethiopia do not have advanced laboratory investigations for diagnostic breast cancer screening and timely detection of breast cancer is strongly recommended because of better treatment prognosis with more effective cost [20]. In Ethiopia, the majority of studies on breast self-examination practice were limited to university students and health care workers. As a result, there was a scarcity of evidence on the practice of breast self-examination, particularly at the community level. Thus, the current study was aimed to assess the magnitude of breast self-Examination practice and associated factors among reproductive age women in West Guji zone, Southern Ethiopia.

Methods

Study design and settings

A Community based cross -sectional study was conducted among women of reproductive age who were living in seven randomly selected kebeles of West Guji Zone, southern Ethiopia from March 1, 2021 to April 30, 2021. The area is located 462 Km from Addis Ababa, the capital city of Ethiopia, and 300Km from the Ethio- Kenya border. West Guji is Bordered on the south by Borena, on the west by southern nations, Nationalities, and Peoples Region, on the north by the Gedeo zone of Southern Nation,

Nationalities, and Peoples Region and Sidama Region, and on the west by the Guji Zones.

Population and sampling

Source population were all women of reproductive age who were living in West Guji zone while study population were all women in reproductive age group who were living in the study area for at least six months prior to the study period from seven randomly selected kebeles of West Guji Zone during data collection period.

Epi Info7 software Stat Cal was used to calculate the sample sizes. To determine the breast self-examination a single population proportion was used by considering the proportion of breast self-examination practice 21.3% [17]. and to identify predictors, a double population proportion was used. The final sample size was calculated with the assumptions of a confidence level of 95%, a margin of error (d) of 5%, design effect 1.5%, and adding 10% for non-response.

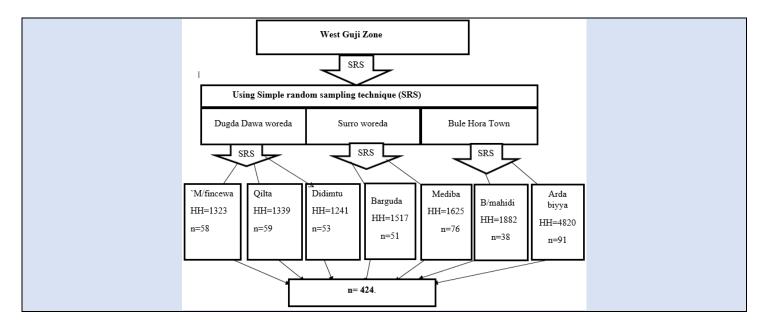
$$n = \frac{[(Z\alpha|2)^2p(1-p)]}{d^2}$$

Where: n=Sample.

p=proportion of breast self-examination practice among reproductive age women (21.3%) d=estimated margin of error for the study, 5% and $Z\alpha/2$ =the standard normal distribution z value of 1.96 (at 95% level of confidence).

Therefore, the final sample size for this study was 424.

First, using a simple random sample technique, two districts and one town administration were chosen from a total of nine districts and one town administration located in the West Guji zone (lottery method). In the following stage, seven study kebeles were randomly selected from each of the two districts and a town administration using the lottery technique. A List of households in each kebeles was utilized to prepare a sampling frame. Finally, households were chosen using a systematic random sampling technique. Women of reproductive age were interviewed from each selected household, with just one woman interviewed for families with two or more reproductive age women at random to avoid intra-household correlation (Fig.1).



Data collection tools and quality control

We used a pretested checklist containing three sections; socio-demographic factors, knowledge on breast self-examination, and breast self-examination practice. A pre-test was conducted on 5% of the sample population at Gerba Kebele. The reliability test for each of the knowledge questions of breast self-examination was calculated using Cronbach's alpha test. The result was 0.795 for knowledge questions about breast self-examination which indicates the

adequate reliability of the scale. Data was collected by female health extension workers and supervised by BSC nurses.

Operational definition

Breast self-examination (BSE): The self-examination of the breasts to identify any changes in the breasts [22].

BSE Practice: was assessed by using an item with the responses of "Yes or No" type like "did you perform

BSE in last six months?" Those who responded "Yes" were considered as if they were practicing BSE [23]. BSE Knowledge: Knowledge was measured by the total number of correct answers to eleven questions on knowledge related to BSE practice. Participants who scored mean and above the value of the provided eleven questions were categorized as knowledgeable while those who scored below the mean value were considered not knowledgeable [24].

Study variables

Dependent variable, Breast self-examination practice, Independent Variables were socio-demographic factors, knowledge on breast self-examination practice.

Data processing and analysis

The collected data was cleaned, coded, and entered using Epidata 3.1 and exported to SPSS 25 for further analysis. The result was presented using text, figures, and tables based on the types of data. Binary logistic regression has been fitted to identify associations between dependent and independent variables. Crude and adjusted odds ratios with 95% CI, and p-values were used to assess the strength of associations and statistical significance. The bivariable analysis was done to select the candidate variables for multivariable logistic regression. Variables with a p-value <0.25 in the bivariable

analysis were considered as a candidate for multivariable analysis. Adjusted OR and p value <0.05 on multivariable analysis were used to determine statistically significant association between the selected independent and the dependent variables.

Ethical considerations

The study protocol was reviewed and approved by the Institutional Health Research Ethics Review Committee of the Institute of Health, Bule Hora University, Ethiopia and informed consent was obtained from the medical director and each study participants. We guaranteed confidentiality by excluding name or any other personal identifiers from data collection sheets and reports.

Results

Socio-demographic characteristics

A total of 424 reproductive age women had been enrolled in this study. The median age of study participants was 27 years with IQR of (±8). About 372(87.7%) of respondents were married and near to one-third 137(32.3%) of study women had no formal education. More than half 236 (55.6%) of them were housewives. About 239 (56.4%) of the women were near to health centers or hospitals (5 Km or less) (Table 1).

Table 1: Socio demographic characteristics of study participants in West Guji Zone, Southern Ethiopia, 2021(n =424).

Characteristics	Frequency	Percentage	
Age Group			
15-24	134	31.6	
25-34	210	49.5	
35-49	80	18.9	
Marital status			
Single	11	2.6	
Married	372	87.7	
Divorced/separated	28	6.6	
Widowed	13	3.1	
Educational Level			
Uneducated	137	32.3	
Primary	121	28.5	
Secondary	95	22.4	
Tertiary and above	71	16.8	
Occupation			
House wife	236	55.6	
Government employee	93	21.9	
Merchant	76	17.9	
Others	19	4.48	
Monthly Income			
<500	61	14.4	
500-1200	116	27.4	
1201-2500	104	24.5	
2501-3500	47	11.1	
>3501	96	22.6	
Husband Educational Level			
No primary education	106	25	
Primary education (1-8)	130	30.6	
Secondary education (9-12)	100	23.6	

Tertiary education and above	88	20.8
Residence		
Urban	289	68.2
Rural	135	31.8
Distance from Health facility		
≤ 5 Km	239	56.4
>5 Km	185	43.6

Knowledge about Breast self-examination

Out of 424 participants, about one-third, 142 (33.49%) of them had good knowledge of breast self-examination and 54.5% of women know about breast cancer screening methods. The types of screening methods known by women were, BSE

81(48.8%), CBE 75 (45.2%), and mammography 10(6%) of respectively. Health professional 95(39.6%) was the predominant source of information for the respondents followed by television 88 (36.7%) (Table 2).

Table 2: Knowledge of breast self-examination among women of reproductive age in west Guji zone, Southern Ethiopia, 2021(n=424).

Characteristics	Frequency	Percentage
Know early detection of breast cancer can improve chance of Survival		
Yes	252	59.4
No	172	40.6
Know the types of breast cancer screening method		
Yes	166	39.2
No	258	60.8
Types of screening method known		
BSE	81	48.8
СВЕ	75	45.2
Mammography	10	6
Ever heard About BSE		
Yes	209	49.3
No	215	50.7
From where did you hear about BSE		

Television	88	36.7
Radio	18	7.5
Newspaper/magazines	13	5.4
Health professional	95	39.6
Breast cancer patients	26	10.8
When should women begin BSE		
At age less than 20 years	100	23.6
At age 20 years and above	324	76.4
How often should BSE is Performed		
Once in week	118	27.8
Once in month	101	23.8
Once in 3 months	124	29.2
Once in 6 months	81	19.1
What do we look during BSE		
Breast lamp	125	29.5
Change in size of the breast	81	19.1
Change in the nipple and unusual discharge	157	37
Change in the skin color of the breast	50	11.8
Others	11	2.6
Where will you go if any symptom of breast cancer		
Health facility	348	82.1
Traditional healer	60	14.2
Private clinic	14	3.3
Others	2	0.5

Breast self-examination Practice

This study showed that only 62 (14.6%) 95%CI (11.4, 18.4) of the study participants ever practiced breast self-Examination. Among the total of respondents who practiced BSE, only 9.2% were doing the breast self-examination regularly (monthly). The major reason for practicing BSE was

due to recommendation from health professional (37%). About 110(25.9%) of the participants reported that BSE is done with palm and three middle fingers. Nearly one fourth 92(21.7%) of respondents used to perform breast self-examination 2-3 days after a session of menstruation (Table 3).

Table 3: Breast self-examination practice among women of reproductive age in West Guji zone, Southern Ethiopia, 2021 (n=424).

Characteristics	Frequency	Percentage	
Did you perform BSE			
Yes	94	22.2	
No	330	77.8	
Why did you perform BSE			
Had previous breast problem	17	4	
Fear of breast cancer from family history	15	3.5	
Recommended by health Professional	157	37	
For early detection and treatment	129	30.4	
Fear of developing breast cancer	106	25	
How often you practice BSE			
Once in week	38	9	
Once in month	78	18.4	
Once in 3 months	20	4.7	
Once In 6 months	38	9	
When it comes to my mind	66	15.6	
I don't know	184	43.3	
How is BSE performed			
With palm and three middle finger	110	25.9	
Palpate with any of the fingers	109	25.7	
I don't know	205	48.3	
When do you perform BSE			
2 to 3 days after session of menstruation	92	21.6	
When it comes to my mind	80	18.9	
At a regular day of each month	39	9.2	
Few days before menses	111	26.2	
At any time in each month	102	24.1	
How many times in the last 12 months did you perform BSE			
10 to 12 times	39	9.2	
7 to 9 times	60	14.1	
4 to 5 times	61	14.4	

1 to 3 times	83	19.6
Did not perform BSE in the last 12 months	181	42.7
Reason for not practicing BSE		
Forgetfulness	25	5.9
Too busy/ not having enough time	3	0.7
Performing it causes discomfort	15	3.5
Fear of finding something or having breast cancer	55	12.97
Do not know how to do it	294	69.3
Not Convinced about its effectiveness	14	3.3
Others	18	4.3

Factors associated with Breast Self-Examination Practice

In bivariable analysis, marital status, age, income, residence, Knowledge of BSE were candidate variables for multiple logistic regressions at p-value <0.25. However, in multivariable analysis, age, monthly income, residence and knowledge about BSE were significantly associated with breast self-examination at p-value <0.05.

Women aged between 25-34 years old were 2 times more likely to practice breast self-examination than their counterparts [AOR= 1.98, 95%CI (1.07-3.70)], while the odds of breast self-examination were lower

by 66% among women belong to age between 35-49 years Compared to the women in the age of 15-24 years [AOR= 0.34, 95%CI (0.11-0.99)].

Women with monthly income between (2501-3500 Ethiopian Birr) were about 4 times higher odds of practicing breast self-examination compared to women having monthly income of less than 500 Ethiopian Birr [AOR=3.92, 95%CI (1.34-11.48). The women who have good knowledge

of breast self-examination were 2.15 times more likely to practice BSE than their counterparts [AOR=2.15;95%CI (1.14-4.05)] (Table 4).

Table 4: Bivariable and multivariable analysis of factors associated with breast self-examination among reproductive age women in West Guji zone, Southern Ethiopia, 2021.

Variables	Breast self-examination practice				P-value
	Yes	No	COR(95% CI)	AOR (95%CI)	
Maternal age					
15-24	18(13.4%)	116(86.6%)	1	1	
25-34	39(18.6%)	171(81.4%)	0.43(0.15-1.20)	1.98(1.068-3.70)	0.03*
35-49	5(6.2%)	75(93.8)	0.29(0.11-0.77)	0.34(0.11-0.99)	0.049*
Educational level					
No education	11(8%)	126(92%)	1	1	
Primary (1-8)	18(14.9%)	103(85.1%)	2.33(0.97-5.58)	1.44(0.62-3.35)	0.393
Secondary (9-12)	21(22.1%)	74(77.9%)	1.16(0.52-2.58)	1.84(0.77-4.37)	0.168
Tertiary and Above	12(16.9%)	59(83.1%)	0.71(0.32-1.57)	1.09(0.36-3.29)	0.867
Monthly income					
<500 ETB	6(9.8%)	55(90.2%)	1	1	
501-1200 ETB	11(9.5%)	105(90.5%)	0.95(0.32-2.81)	0.70(0.23-2.07)	0.521
1201-2500 ETB	19(18.3%)	85(81.7%)	0.98(0.391-2.49)	1.52(0.55-4.18)	0.418
2501-3500 ETB	17(36.2%)	30(63.8%)	0.46(0.19-1.08)	3.92(1.34-11.48)	0.013*

>3501 ETB	9(9.4%)	87(90.6%)	0.18(0.07-0.45)	0.51(0.16-1.64)	0.262
Residence					
Urban	51(17.6%)	238(82.4%)	2.41(1.21-4.8)	2.28(1.09-4.783)	0.029*
Rural	11(8.1%)	124(91.9%)	1	1	
Knowledge about BSE					
poor knowledge	34(12.1%)	248(87.9%)	1	1	
Good knowledge	28(19.7%)	114(80.3%)	0.55(0.32-0.96)	2.15(1.14-4.05)	0.018*

*Significant with P<0.05 and **Significant with P<0.001 CI=Confidence Interval, COR=Crude Odds Ratio, AOR=Adjusted Odds Ratio, ETB= Ethiopian Birr

Discussion

Regular breast self-examination is the most important means of identifying early breast cancer, and it has the potential to save women's lives. When compared to other forms of screening approaches for breast cancer, breast self-examination has been widely suggested as a relatively simple, non-invasive, cost-effective, convenient, painless, readily available, confidential, and non-harmful screening procedure. We examined the breast self-examination and the associated factors among reproductive age women in southern Ethiopia.

Our result showed that overall breast self-examination practice among reproductive age women in southern Ethiopia was 14.6%. This finding was consistent with the study conducted among women of childbearing age in Jimma, Southwest Ethiopia (15%), and in Bale zone, Southeast Ethiopia (13.2%) [18,21]. This similarity could be attributed to the characteristics of the study's population, as both studies included women of reproductive age.

The finding was lower than the study conducted in West Shoa Zone, Oromia Region, Ethiopia, Arba Minch Zuria District, Southern Region, Ethiopia, Tamil Nadu, India, and Ghana which reported respectively (32.6%,21.6%,18%, and 37.6%) [5,17,25,26]. The discrepancy in this study can be explained by the study members' differences. Participants in the previous research included university students and health care workers, who may have a better understanding of the value of breast selfexamination than those in this study. On the other hand, the finding of this study was higher than studies conducted in Adwa town, Ethiopia and Eritrea reporting 6.5% and 11.7% practice of BSE respectively [16,27]. This disparity could be attributed to differences in sample size, access to information or mass media, and the emphasis placed on breast self-examination. The odds of practicing breast self-examination among women aged (25-34)

years were 1.98 times higher compared to the women in the age group of (15-24) years and the women in the age of 35-49 years were 66 % less likely to perform breast self-Examination Compared to the women in the age of 15-24 years. This finding was supported by the Study Conducted in Bale zone, Ethiopia, Jimma, Addis Ababa, Bangladesh, and Southwest Cameroon [13,18,21,28,29]. This could be because at this age, women are more focused on their reproductive activity, which leads to a greater focus on and care for their breast health as a result of increased interaction with health facilities and health experts than at any other time in their lives. These chances may introduce mothers to knowledge that health experts can provide to assist them practice BSE.

In this study monthly income was one of the significant factors for the practice of breast selfexamination, the women who have earned income between (2501-3500) Ethiopian birr monthly were 3.92 times more likely to practice BSE as compared to women who have monthly income less than 500 Ethiopian Birr. This is consistent with a communitybased cross-sectional study conducted among women of childbearing age in Jima and Facility-based crosssectional study Conducted among women who Visit Primary health clinics in Gaza City, Palestine [21,30]. In contrary to this study, monthly income was not significantly associated with practice of BSE in study conducted among women aged 20-65 years in Woliata Sodo city and Arbaminch district [17,31]. This is because in the mentioned studies, around half of respondents had a monthly income below the poverty line.

In this study residence was also one of the significant factors for the practice of breast self-examination. The women who were urban Dwellers were 2.28 times more likely to Practice BSE compared to women who were rural dwellers. This finding is in line with the study conducted among female students in Jimma and among female clients in tertiary hospitals in Eastern Uganda [14,20]. The accessibility

and exposure to health-related activity may differ between urban and rural people, which could account for this. Women who live in urban areas have easy access to information via the media, and they also tend to be more knowledgeable about recent developments in disease prevention and exhibit positive health-seeking behaviors. However, there was no significant relationship between place of residence and practice of Breast Self-Examination in a study conducted among women of childbearing age in Jimma [21].

This study also showed that the odds of practicing breast self-examination were 2.15 times higher among women who have good knowledge of BSE compared to women who have poor knowledge of BSE. A similar result was found in a study conducted among female workers in Debra Tabor public health facilities, North West Ethiopia,2018, Secondary School Female Teachers in Gamo Gofa Zone, Southern Ethiopia,2018, Young Women in Tertiary Education in Addis Ababa, Ethiopia and female clients in a tertiary hospital in Eastern Uganda [14,15,28,32].

The possible explanation could be the knowledge of breast self-examination provided women the opportunity and experience to become aware and familiar with the normal shape and feel of their breast and this leads to improved breast health awareness which has a direct effect on the practice of breast self-examination.

Strengths and limitations of the study

The study's main strength is that the majority of prior studies in Ethiopia were limited to university students and health care workers, whereas our study was conducted at the community level, specifically the pastoral community. However, due to the fact that this was a cross-sectional study, causal conclusions cannot be inferred.

Conclusion

We found that the overall breast self-examination was substantial, requiring special attention. Women age, monthly income, residence, and knowledge about BSE was significantly associated with breast self-examination practice. As a result, all various parties, including non-governmental and government organizations, should collaborate to promote community awareness and improve women's knowledge of breast self-examination in

order to promote breast self-examination and early detection of breast cancer.

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Abbreviations

ACA: Cancer Association, American ACS: American Cancer Society, AOR: Adjusted Odd Ratio, BSE: Breast Self-Examination, CBE: Clinical Breast Examination, CI: Confidence Interval, COR: Crude Odd Ratio, CSA: Central Statistical Agency, ECA: Ethiopia Cancer Association, EDM: Early Detection Method, GLOBOCAN: Global Burden of Cancer, HC: Health Center, HBM: Health Belief Model, IARC: International Agency for Research of Cancer, LRCs: Low Resource Countries, MOH: Ministry of Health, RHB: Regional Health Bureau, ROC: Reproductive Organ Cancer, SPSS: Statistical Package for Social Science, WHO: World Health Organization.

Availability of data and materials

All necessary information was included in the manuscript.

Ethics approval and consent to participate

Ethical clearance was obtained from Bule Hora university research and publication directorate. After the purpose of the study was explained to participants, informed consent with a written signature was obtained. They were informed to withdraw at any time and or to refrain from responding questions. Study participants were also informed that all data obtained from them could be kept confidential using code instead of any personal identifiers. Furthermore, the research procedure was conducted in accordance with the principle expressed in the World Medical Association's Declaration of Helsinki.

Competing interest

The authors declare that they have no competing interests.

Consent for publication

Not applicable

Authors' contributions

MA, AH, YH, AE, AA conceived the idea and designed the study; led data analysis interpretation; developed the first draft of the manuscript and made all revisions based on coauthors comments and suggestions. AE, AA, AH critically revised the manuscript for important intellectual content; ensured the requirements of submission of the manuscript are met. MA, YH, AH, AE, AA, contributed towards analysis and data interpretation; revision and editing of manuscript. YH, AH, AE, AA, contributed towards review for expert opinion and revision of manuscript for important intellectual content. YH, AH supervised the study from design to writing of the manuscript. All authors read and agreed to final version of the manuscript for publication.

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