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Risk Factors associated with Breast Cancer among Patients Treated at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: Case control study

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Abstract:

Objectives: Many factors known to increase the risk of breast cancer, such as age, family history, early menarche, and late menopause are not modifiable. Modifiable factors include obesity, use of menopausal hormones, and breast feeding. This study aimed to assess risk factors associated with breast cancer among women at Tikur Anbessa Specialized Hospital.

Design: Facility based control study.

Methods: Case control study was conducted from May 2018 to June 2019. A total of 230 cases and 230 controls participated in the study. Data were analyzed using SPSS software. Multivariable logistic model based analysis was conducted to control the effect of potential confounding factors. Odds ratios and 95% confidence interval for the likelihood of developing breast cancer were calculated.

Results: The odds of breast cancer was higher among women between 40-49 years, (AOR: *3.29, 95%* CI: 1.39-7.77), being unemployed (AOR, 4.28 95% CI: 2.00-9.16), consumed solid oil (AOR, 6.77, 95% CI: 3.17-14.48) , using wood or animal dung as source of fuel (AOR, 5.30, 95% CI:1.59-17.64), post-menopausal status (AOR, 1.86, 95% CI: 1.12-3.11) ,who had previous benign surgery (AOR, 6.84 95% CI: 1.47-31.75) and early menarche, less than 12 years. On the other hand, the odd of breast cancer was lower among women who had moderate physical activities.

Conclusion: This study showed that occupational status, consumption of solid oil, and using wood or animal dung as source of fuel, early menarche, menopausal status and previous benign breast surgery were associated with breast cancer. On the other hand, physical activity was protective factors. Therefore, there is a need to design appropriate intervention to educate women about life style change or behavior modification to decrease their breast cancer risk.

Key words: *Breast cancer, Risk factors, reproductive risk factors, lifestyle.*

Strength and limitation of this Study

- To our knowledge this is the first study conducted among breast cancer patient in Ethiopia.
- During selection of control group, breast physical examination has been made by experienced oncology resident.
- Further analysis was not conducted by different ethnic group due to limited sample size and shortage of budget.
- Even though breast physical examination may be the only available breast cancer screening modality in resource limited countries like Ethiopia, and it has been made by experienced physician, which may not be highly sensitive to detect potential breast mass.

Background

There are several established risk factors for breast cancer. Many factors well known to increase the risk of breast cancer are not modifiable; these include age, family history, early menarche, and late menopause. Factors that are modifiable include post-menopausal obesity, use of menopausal hormones, and breast feeding. Mutations in BReast Cancer gen 1 (BRCA1) and BReast Cancer gen 2 (BRCA2) are also the most prominent cause of breast cancer [1, 2].

A case control study conducted in North India found that post‑menopausal women are 2.5 times at higher risk. The risk also increased by 2.68 times in women having a late menopause. Family history of breast cancer was reported in 21.3% of the cases and none of the controls [3] Another case control study from the same country revealed a significant association between breast cancer with positive family history in first degree relatives , number of abortions and past history of benign breast disease, age, menopausal status, use of oral contraceptives and

postmenopausal obesity [4]. Another case control study done in Malaysia showed that participants who had previous breast surgery were 2.3 times more likely to develop breast cancer [5]. On the other hand, use of oral contraceptives and Hormone Replacement Therapy were not significantly associated with breast cancer risk [6]. Case control study done in Central African Republic showed that women with breast cancer were more likely to be with little or no education, married, had abortion, and nulliparous [7]. On the other hand, decreased odds of breast cancer were associated with being employed, urban resident, late menarche, having term pregnancy and use of hormonal contraceptive [8]. Study conducted in Canada found an average increased breast cancer risk of 42% for women who worked for a ten year period in environments with high exposure to carcinogens [9].

Breast cancer poses a substantial public health threat in Ethiopia [10]. According to Addis Ababa City Cancer Registry, a total of 5,701 cancer cases were registered from September 2011 to August 2014. Based on this data breast cancer is, 33% of cancers among females [11].However, based on various studies conducted in the country there was poor community awareness towards the disease [12, 13]. Most patients and their families do not properly know about cancer and its treatment options. As a result, 80 to 90% of cancer patients already suffer from advanced and incurable cancers at the time of diagnosis [13, 14].Similar study also found that 71.2% of patients were at advanced stage at diagnosis [15]. Another study also showed that 88.9% of breast cancer patients had longer patient delay [16]. For such longer delay, the most important influential factors were rural residence, illiteracy, distance from health facility and having no lump in the armpit [15,16]. In addition inadequate screening, and treatment services, inadequate

diagnostic facilities and poorly structured referral, lack of money and sought traditional healer and alternative practices were also the main reason for patient late diagnosis. [15, 16, 17]

Even though many studies found different risk factors, the reasons of breast cancer are not fully understood, especially for most resource limited countries. For a country like Ethiopia with a huge population, different, ethnic geographical variations, life style and cultures habits, information on breast cancer associated risk factors are significantly limited. Targeting and supporting these populations to reduce their risk is an essential component of population health. Therefore, this study was aimed to assess risk factors for breast cancer among women at Tikur Anbessa Hospital. The study will help policy makers to raise community awareness, for reduction in morbidity and mortality by promoting interventions like, early detection and treatment of breast cancer. This study will also help to design and implement appropriate counseling, treatment, prevention and control strategies, including national breast cancer screening. In addition, this study will provide care givers with the necessary information regarding breast cancer in order to adopt modified life style.

Materials and Methods

Study design and period

Facility based case control study was conducted between May 2018 and June 2019 in Addis Ababa at Tikur Anbesa Specialized Hospital (TASH) Oncology Department, which is the largest hospital in Ethiopia with 700 beds [18]. This hospital is the country's sole cancer referral center which provides surgery, chemotherapy, radiotherapy and palliative care.

Eligibility criteria

During the study period, all consenting newly diagnosed breast cancer patients, with confirmed histology result, no observable mental disorders, no history of chronic disease and aged 18years and above were included in the study. Regarding controls, individuals free from breast mass after physical examination. Moreover, individuals who had no biological relationship with selected cases were included as controls.

Sampling and sample size determination

Since there was only one referral center for cancer treatment during the study period, the existing center (TASH) was used for the study. All voluntary and eligible cases and controls that came to Tikur Anbessa Specialized Hospital during the study period were recruited. Accordingly, a total of 460 participants (230 cases and 230 controls) participated in this study.

Data collection analysis and management

Informed consent was obtained from each study participant prior to data collection. Participants were interviewed by experienced and trained nurses in a convenient place to maintain privacy and confidentiality. Breast physical examination was conducted by oncology residents in order to select eligible controls. Data entry and analysis was done using SPSS Software, version 20. Logistic regression was conducted to see the association between breast cancer and risk factors. Then, stepwise multivariable analysis was done to adjust for potential confounding variables. P value less than 0.05 were considered as statistically significant while adjusted odds ratios with 95% CI were used to see the strength and direction of the association. Women who had sisters/mothers/daughters with breast cancer were categorized as having a first-degree family history of breast cancer. Women

were classified as menopausal if they had not menstruated during the 6 months before the date of data collection.

Data Quality Assurance and Ethical considerations

The data collection tools were prepared in English and translated to the local language in order to facilitate understanding by the study participants. The data collection tools were pretested in 5% of breast cancer patients not included in the study. Daily supervision was made on all questionnaires collected each day. This research was conducted based on research requirements, regulations and policies that safeguard the wellbeing of study participants and to ensure the reliability and integrity of this finding. Therefore, all methods were carried out in accordance with relevant guidelines and regulations.

This study was approved by Institutional Review Board of the College of Health Sciences of Addis Ababa University with protocol number 073/17/SPH. Written consent was obtained from each of the respondents after the purpose of the study was explained. During breast physical examination for screening of controls, participants who had breast mass were consulted by physicians and their results were given for free in order to get early diagnosis and treatment. Confidentiality and privacy were maintained throughout the study.

Patient and public involvement

Neither patients nor the public were involved in the design of this study.

Results

Bivariate analysis of Sociodemographic characteristics and anthropometric factors

In this study, a total of 230 breast cancer cases and 230 healthy controls were participated. The mean age (± SD) was 42.83 ± 12.06 for cases and 39.33 ± 11.14 years for controls. The odds of breast cancer was significantly higher among women aged 40-49 and >60 years. The odds of developing breast cancer among illiterate was 3.78 times higher (95% CI 1.47-9.72, P=0.006) compared with literate women. Similarly, the odds of breast cancer was also 2.82 times higher (95% CI: 1.52-5.22, P=0.001)) among unemployed women as compared with employed. It was also 2.43 times (95% CI: 1.43-4.14, P= 0.001) higher among women with lower socio economic status as compared with women with higher socioeconomic status (monthly income >2000 Ethiopian Birr) per month. However there was no significant association between breast cancer with place of resident and marital status. The odds of breast cancer was 2.13 times higher (95% CI. 1.06 - 4.28, P=0.034) among women with less than 59 KG as compared with women greater than 75 kg. Similarly, the odds of breast cancer was 2.48 times higher (95% CI: 1.07-5.75, P=0.035) among women with BMI 25-29.9 Kg/m2 (Table 1).

Table 1. Socio demographic characteristics and anthropometric risk factors associated with breast cases at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2020.

Variables	Case N (%)	Control N (%)	Bivariate analysis	
			COR (95% CI)	P-value
Residence				
Rural	67 (29.1)	56 (24.3)	1:00	
Urban	163 (70.9)	174 (75.7)	0.783(0.517-1.19)	0.247
Age group (years)				

<39	106 (46.1)	136 (59.1)	1:00	
40–49	58 (25.2)	45 (19.6)	*1.65(1.04-2.63)*	0.034
50-59	39(17.0)	36(15.7)	*1.39(0.827-2.34)*	0.214
>60	27 (11.7)	13 (5.7)	*2.67(1.31-5.41)*	0.007
Marital status				
Ever Married	207(90.0)	201(87.4)	1:00	
Never married	23(10.0)	29(12.6)	0.770(0.431-1.38)	0.378
Education level				
Literate	130(56.5)	196(85.2)	1:00	1:00
Illiterate	100(43.5)	34(14.8)	4.43(2.83-6.94)	0.0001
Occupation				
Employed	70(30.4)	131(57)	1:00	1:00
Unemployed	160(69.6)	99(43.0)	3.03(2.06-4.44)	0.0001
Income	(N=108)	(N=127)		
≥2000	52(48.1)	88(69.3)	1:00	1:00
<2000	56(51.9)	39(30.7)	2.43(1.43-4.14)	0.001
Height (mt)				
≥1.60	102(44.3)	91(39.6)	1:00	1:00
< 1.52	48 (20.9)	32(13.9)	1.34(0.788-2.27)	0.280
1.53 – 159	80(34.8)	107(46.5)	0.667(0.445-1.00)	0.050
Weight (KG)				
>75	14(6.1)	25(10.9)	1:00	
<59	143(62.2)	120(52.2)	2.13(1.064.28)	0.034
59.1 -65	37(16.1)	52(22.6)	1.27(0.583-2.77)	0.546
65.1 -74	36(15.7)	33(14.3)	1.95(0.869-4.36)	0.105
BMI(Kg/m2)				
> 30	10(4.3)	22(9.6)	1:00	
< 25	166(72.2)	160(69.6)	2.28(1.05 -4.97)	0.038
25-29.9	54(23.5)	48(20.9)	2.48(1.07-5.75)	0.035

Life style risk factors associated with breast cancer

In this study, neither cases nor controls had used HRT. On the other hand, 3 cases and none of the controls were smokers. However, 49, (21.3%) of cases and 66, (28.7%) of the controls had history of alcohol consumption. Regarding dietary habit, there was no significant association between vegetable and meat intake with breast cancer. However, there was nearly significant association between fruit and milk intake once a week or more with breast cancer, (COR1.95, 95% CI: 1.09-3.48), P=0.024 and COR 2.08, 95%CI: 1.19-3.67) respectively as compared with women who had intake Once a week or less. This study also indicated that the odd of breast cancer was 4.04 times higher among women who had used solid oil. Similarly, the odd of breast cancer was 6.46 times higher (95% CI: 3.78-11.03, P= 0.0001) among women who had used wood or animal dung as fuel source as with use electric as a source of fuel. Regarding physical activity, women who had strenuous physical activities like running, swimming less than 5 hour per week had 0.343 times lower risk of breast cancer (95% CI: 0.133-0.887, P=0.027). Similarly, women who had moderate physical activity such as walking, playing tennis less than 5 hour per week had 0.228 times less risk (95% CI: 0.133-0.392, P=0.0001) (Table 2).

Table. 2. Life style risk factors associated with breast cancer at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2020.

Variables	**Case N (%)**	**Controls N (%)**	**Bivariate analysis**	
No	227(98.7)	230(100%)	1:00	
Yes	3	0(0.0%)	1.01(0.998-1.03)	0.082
Alcohol intake				
Non drinker	181(78.7)	164(71.3)	1:00	
Drinker	49(21.3)	66(28.7)	0.673(0.439-1.03)	0.068
Vegetable intake				

Once a week or less	166(72.2)	158(68.7)	1:00	
More than Once a week	64(27.8)	72(31.3)	0.846(0.567-1.26)	0.414
Fruit intake				
Once a week or less	194(84.3)	210(91.3)	1:00	
More than Once a week	36(15.7)	20(8.7)	1.95(1.09-3.48)	0.024
Meat				
Once a week or less	207(90.0)	218(94.8)	1:00	
More than Once a week	23(10.0)	12(5.2)	2.02(979-1.4.16)	0.057
Milk take				
Once a week or less	189(82.5)	207(90.8)	1:00	
More than Once a week	40(15.7)	21(9.2)	2.086(1.19-3.67)	0.011
Solid oil				
No	45(19.6)	114(49.6)	1:00	
Yes	185(80.4)	116(50.4)	4.04(2.67-6.12)	0.0001
Source of fuel				
Electric	54(23.5)	111(48.3)	1:00	
Wood/Animal dung	88(38.3)	28(12.2)	6.46(3.78-11.03)	0.0001
Charcoal/Kerosene	3(1.3)	20(8.7)	0.308(0,088-1,08)	0.066
Combination	85((37.0)	71(30.9)	2.46(1.57-3.87)	0.0001
Strenuous exercise				
No exercise	209(90.9)	203(88.3)		
< 5 Hr per week	6(2.6)	17(7.4)	0.343(0.133-0..887)	0.027
5 Hr and above per week	15(6.5)	10(4.3)	1.46(0.640-3.32)	0.370
Moderate exercise				
No exercise	173(75.2)	126(54.8)		
< 5Hr per week	21(9.1)	67(29.1)	0.228(0.133-0.392)	0.0001
5 Hr and above per week	36(157)	37(16.1)	0.709(0.424-1.18)	0.188

Bivariate analysis of Reproductive risk factors associated with breast cancer

In this study the odds of breast cancer was higher among women who had age at menarche less than 12 years (COR: 4.50; 95%: 1.42-14.21, p= 0.010). On the other hand, there was no significant association between abortion, as well as age at first birth with breast cancer. The odd of breast cancer was 3.94 times higher among women who had family history of breast cancer. Similarly, the odds of breast cancer was 3.94 times higher among post-menopausal women (95% CI:1.28-12.06, P=0.016). In addition, women who had previous breast surgery were 5.09 times more likely to develop breast cancer (95% CI: 1.70 -15.19, P=0.04). However, there was no statistically significant association between breast cancer with age at menopause, use of oral contraceptive, duration of breast feeding and age at last birth (Table 3).

Table. 3. Reproductive risk factors associated with breast cancer at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2020.

Parameter	Case N (%)	Control N (%)	Bivariate analysis	
			COR (95% CI)	P Value
Age at menarche(years)				
>15	20(11.2)	60(28.6)	1:00	
12 -15	150(83.8)	144(68.6)	3.13(1.79-5.45)	0.0001
<12	9(5.0)	6(2.9)	*4.50*(1.42-14.21)	*0.010*
Family history of breast				
No	215 (93.5)	226(98.3)	1:00	
Yes	15(6.5)	4(1.7)	3.94(1.29-12.07)	0.016
Age at first birth (yrs)				
<20	57(33.3)	63(34.8)	1:00	
20–29	98(57.3)	108(59.7)	1.003(0.639-1.57)	0.990
30 and above	16(9.4)	10(5.5)	1.77(0.743-4.21)	0.198
Menopausal status				
Premenopausal (ref.)	117(50.9)	159(69.1)	1:00	

Post-menopausal	113(49.1)	71(30.9)	2.16(1.48-3.17)	0.000
Age at menopause (years)				
< 50	65(84.4)	50(79.4)	1:00	
50 and above	12(15.6)	13(20.6)	0.710(0.298-1.69)	0.439
Oral contraceptive use				
No	127(55.2)	112(48.7)	1:00	
Yes	103(44.8)	118(51.3)	0.770(0.534-1.11)	0.162
No abortion	163(70.9)	157(68.3)	1:00	
One	34(14.8)	48(20.9)	0.682(0.418-1.115	0.127
Two and above	33(14.3)	25(10.9)	1.27(0.723-2.24)	0.404
History of benign breast disease				
No	211(91.7)	226(98.3)	1:00	
Yes	19(8.3)	4(1.7)	5.09 (1.70-15.19)	0.004
Age at last birth (years)				
< 29	56(34.6)	67(39.6)	1:00	
30 -34	36(22.2)	27(16.0)	1.59(0.865-2.94)	0.135
35 -39	39(24.1)	37(21.9)	1.26(0.711-2.24)	0.427
40 years and above	31(19.1)	38(22.5)	0.976(0.540-1.77)	0.936

Multivariable analysis of Sociodemographic, anthropometric and lifestyle factors

Stepwise multivariable analysis was conducted by selecting variables which have P value ≤ 0.2 in bivariate analysis. The finding indicated that the odds of breast cancer was 3.29 times higher (95% CI: 1.39-7.77, P = 0.007) among women with 40- 49 age groups as compared with 39 year or less. It was also found that the odds of breast cancer was 4.28 times higher (95% CI: 2.00-9.16) among unemployed women. Regarding life style, milk intake and consumption of solid oil was significantly associated with breast cancer (AOR., 2.56 95% CI: 1.02 – 6.43, P= 0.045) and

(AOR, 6.77, 95% CI: 3.17-14.48) respectively. Similarly, the odd of breast cancer was 5.30 times higher (95% CI:1.59-17.64, P=0.007) among women had used wood or animal dung as source of fuel as compared with women who used electric. On the other hand, the odds of breast cancer was 0.276 times lower (95% CI: 0.114- 0.628, P= 0.002) among women who had moderate physical activities like swimming, table tennis, and basketball less than hour per week as compared with women who had no history of exercise (Table 4)

Table 4. Socio demographic, anthropometric and lifestyle factors associated with breast cancer at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2020.

Variables	Case N (%)	Control N (%)	Bivariate analysis		Multivariable analysis	
			COR (95% CI)	P-value	AOR (95% CI)	P-value
Age group (years)						
≤39	106 (46.1)	136 (59.1)	1:00		1:00	1:00
40–49	58 (25.2)	45 (19.6)	*1.65(1.04-2.63)*	0.034	*3.29(1.39-7.77)*	*0.007*
50-59	39(17.0)	36(15.7)	*1.39(0.827-2.34)*	0.214	*1.81(0.661-4.96)*	*0.248*
>60	27 (11.7)	13 (5.7)	*2.67(1.31-5.41)*	0.007	*2.44(0.515-11.55)*	*0.261*
Occupation						
Employed	70(30.4)	131(57)	1:00	1:00	1:00	
Unemployed	160(69.6)	99(43.0)	3.03(2.06-4.44)	0.0001	4.28 (2.00-9.16)	0.0001
Milk intake						
Once a week or less	189(82.5)	207(90.8)	1:00		1:00	
More than Once	40(15.7)	21(9.2)	2.086(1.19-3.67)	0.011	2.56(1.02-6.43)	0.045

a week						
Solid oil						
No	45(19.6)	114(49.6)	1:00		1:00	
Yes	185(80.4)	116(50.4)	4.04(2.67-6.12)	0.0001	6.77(3.17-14.48)	0.0001
Source of fuel						
Electric	54(23.5)	111(48.3)	1:00		1:00	
Wood /animal dung	88(38.3)	28(12.2)	6.46(3.78-11.03)	0.0001	5.30 (1.59-17.64)	0.007
Charcoal/Kerosene	3(1.3)	20(8.7)	0.308(0,088-1.08)	0.066	0.112(0.012-1.01)	0.051
Combination	85((37.0)	71(30.9)	2.46(1.57-3.87)	0.0001	2.45(1.16-5.15)	0.019
Moderate exercise						
No exercise	173(75.2)	126(54.8)	1:00		1:00	
< 5Hr per week	21(9.1)	67(29.1)	0.228(0.133-0.392)	0.0001	0.276(0.114-0.628)	0.002
5 Hr and above per week	36(157)	37(16.1)	0.709(0.424-1.18)	0.188	0.496(0.182-1.36)	0.172

Multivariable analysis of reproductive factors

As indicated above all reproductive health variables which have P value <0.2 were selected and included with in multi variable analysis model. The finding indicated that the odds of breast cancer was 10.83 times higher (95% CI: 2.49-46.97) among women who had age of menarche < 12 years as compared with women > 15 years. Similarly, the odds of breast cancer was also higher among post-menopausal women and women who had previous benign breast surgery (AOR, 1.86 95% CI: 1.12-3.11, P= 0.018) and 6.84(1.47-31.75, P= 0.014) respectively (Table 5)

Table 5. Reproductive factors associated with breast cancer at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2020.

Parameter	Case N(%)	Control N(%)	Bivariate analysis		Multivariable analysis	
			COR (95% CI)	P Value	AOR(95% CI)	P- Value
Age at menarche(years)						
>15	20(11.2)	60(28.6)	1:00		1:00	
12 -15	150(83.8)	144(68.6)	3.13(1.79-5.45)	0.0001	3.08(1.61-5.92)	0.001
<12	9(5.0)	6(2.9)	*4.50*(1.42-14.21)	*0.010*	10.83(2.49-46.97.04)	0.001
Menopausal status						
Premenopausal	117(50.9)	159(69.1)	1:00		1:00	
Post-menopausal	113(49.1)	71(30.9)	2.16(1.48-3.17)	0.000	1.86(1.12-3.11)	0.018
History of benign breast disease						
No	211(91.7)	226(98.3)	1:00		1:00	
Yes	19(8.3)	4(1.7)	5.09 (1.70-15.19)	0.004	6.84(1.47-31.75)	0.014

Discussion

In this study, potential risk factors associated with breast cancer were examined. This study revealed that various risk factors, including demographic, life style, reproductive, hormonal, factors, contributed to the incidence of breast cancer **[**19, 20].

There was no significant association between, place of residence and marital status in our finding. This is incomparable with study done in India that showed significant relationship between breast cancer and being married [4]. However, the odd of breast cancer was higher among women between 40 and 49 age groups. Similarly, the odd of breast cancer was 4.43 times higher among illiterate compared with literate women. This finding is supported by a similar

study done in Bangui, which indicated that the odd of breast cancer was higher among illiterate [7]. However this association was declined after stepwise multiple logistic regression models was applied. It was also found that the odd of breast cancer was 4.28 times higher among unemployed compared with employed women. This finding is also supported by the previous study done in Bangui [7]. However, the current study was incomparable with another study in India which reported a higher risk of breast cancer among women with higher educational status [20].

Even though, BMI was associated with increased risk of breast cancer [21], in this study, both weigh and BMI of cases were lower than controls, this lower weight and BMI among cases could be due to loss of weight among cases as a result of their disease. This finding is comparable with the study done in Malaysia [5]. However, there is also study which had found postmenopausal women with normal BMI, relatively high body fat levels were associated with an elevated risk of invasive breast cancer and the study explained that normal BMI categorization may be an inadequate proxy for the risk of breast cancer in postmenopausal women [22]. In this study, there was no significant association between alcohol consumption, vegetable and meat intake with breast cancer. However, this finding is not supported by similar studies conducted in different parts of US, which observed that a higher intake of fruits and vegetables was associated with a lower breast cancer risk [23, 24, 25]. This difference could be due to the difference in type and dosage pattern of such fruit and plant based dietary pattern. The other possible explanation could be consumption of such kinds of diet may be limited among study participants due to limited buying capacity.

However, the odd of breast cancer was 2.56 times higher among women who had consumed milk for more than once a week, compared with women who had consumed milk once a week or less. This finding is supported by study done in Western Mexico [26]. Similarly, the Mexico study also support our study regarding consumption of meat was not associated with breast cancer [26]. This association has been explained that high milk intake results in the consumption of cow estrogen metabolites as well as a high caloric intake, both of which increasing the risk of breast cancer [26]. However, this finding is not comparable with different studies, revealed that dairy consumption was inversely associated with the risk of developing breast cancer [27,28, 29]. This difference could be due to the dose, dairy-type, and time of consuming such products. In this study, there are two surprising results which had significant association with breast cancer, the first result was, and the odd of breast cancer was 6.77 times higher among women who used solid oil, this finding suggested that, since it is saturated fat, which may contain other factors which can increase the risk of breast cancer and the finding was supported by study done in China [30]. This finding also supported by study done in USA reviled that consumption of saturated fat is associated with increased breast cancer risk [31]. The second result was that the odds of breast cancer was 5.3 times higher among women who had used wood or animal dung as a source of fuel, which was supported by study done in USA revealed that indoor burning either wood or natural gas for long time was associated with higher risk of breast cancer [32].

In this study, the odds of breast cancer were lower among women who had average duration of strenuous exercise of less than 5 hours per week; however, the association was not significant. On the other hand, women who had moderate physical activity of less than 5 hours per week had reduced risk of breast cancer. This finding is comparable with the study done in UK which

indicated that physical activity was associated with a reduction in breast cancer risk [33]. And this study also supported by systematic review meta-analysis conducted in China stated that physical activity is significantly associated with a decrease in the risk of breast cancer [34].

In this study, only 5.0% of cases and 2.9% of controls had menarche less than 12 years of age. Late menarche (>15 years) was found to be significant protective factor for breast cancer, compared with earlier age at menarche (<12 years), this finding was supported by study done in Morocco [35]. This finding was also in agreement with study done in UK found that breast cancer risk increased by a factor of 1·050 (95% CI 1·044–1·057; p<0·0001) for every year younger at menarche, and independently by a smaller amount (1·029, 1·025–1·032; p<0·0001), for every year older at menopause. [36]. However, there was no association between age at first full-term pregnancy, which was not comparable with study done in Morocco [35].

The odd of breast cancer was 1.86 times higher among post-menopausal women. This finding was comparable with three different studies conducted in India [3, 4, 37]. It was also found that, 19(8.3%) of cases and 4(1.7%) of the controls had previous breast surgery. Women with previous benign breast surgery were 6.84 times more likely to have breast cancer. This finding was supported by studies conducted in India and Malaysia [4,5].

In this study, the odd of breast cancer was 1.86 times higher among post-menopausal women. This finding is comparable with a study done in Malaysia, indicated that post-menopausal women had 52% increased risk of breast cancer [5]. Similarly, in our study, oral contraceptive was not significantly associated with breast cancer, which was also supported by other study done in India [37]. However, this study is not supported by study done in Denmark found that

approximately 20% higher risk of breast cancer among women who currently use hormonal contraceptives. Similar studies conducted in India and United Kingdom also reported an increased risk of being diagnosed with breast cancer in women who have used hormonal contraception [4, 6, 38]. This difference could be due to length of contraceptive use and type of contraception. There was no significant association between breast cancer with parity and duration of breast feeding, which is comparable with two studies done in India [20, 37].

Study limitation

Some limitations should be considered to elucidate the findings of this study. Primarily the finding of our study was based on self-reporting and that could have introduced recall biases regarding their past exposure for different possible risk factors, this may result or under reporting of the outcome under study. Since this is a case control study, all the association may not be necessarily casual. The other most important limitation could be even though breast physical examination may be the only available breast cancer screening modality in resource limited countries like Ethiopia, and it has been made by experienced physician, which may not be highly sensitive and may miss the potential breast mass.

Conclusion and recommendation

Since this study was a case control study which serves as an indicative study usually used to provide early clues and inform further research using more rigorous scientific methods. In this study, socio demographic, lifestyle, anthropometric and reproductive risk factors were assessed. The finding indicated that the odds of breast cancer decreased among young age and employed women. Regarding lifestyle factors, the odds of breast cancer was higher among women who had

consumed milk more than once a week, who had consumed solid oil and women who used wood or animal dung as a source of fuel. However, the odds of breast cancer decreased among women who had physical exercise less than 5 hours per week. Finally, the odd of breast cancer was higher among women with early menarche, post-menopausal women and women with previous benign breast surgery. Since there was significant association between most of the modifiable risk factors and breast cancer, it is essential to design appropriate life style modification strategies which may contribute to prevent breast cancer. There is a need to design appropriate intervention to educate women about lifestyle change or behavior modification to decrease their breast cancer risk. In addition, since there are varieties of culture, food choice, feeding habit, physical activities and other risk factors, it is important to conduct future studies with a larger sample size including different regions or diverse population in order to come up with more representative evidence.

Declaration

Abbreviations

BC: Breast cancer; CI: Confidence Interval; Hr.: Hour; HRT: Hormone Replacement Therapy; SPSS: Statistical Package for Social Sciences; TASH: Tikur Anbessa Specialized Hospital.

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- **Conceptualization and design:** Fatuma Hassen, Fikre Enquselassie, Aster Tsegaye, Mathewos Assefa , Ahmed Ali, Adamu Addissie , Girma Taye.
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- **Supervision:** Fatuma Hassen, Fikre Enquselassie, Aster Tsegaye, Mathewos Assefa , Ahmed Ali, Adamu Addissie , Girma Taye.
- **Final approval:** Fatuma Hassen, Fikre Enquselassie, Aster Tsegaye, Mathewos Assefa , Ahmed Ali, Adamu Addissie , Girma Taye.

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Conflict of Interests:

- All authors declare that there is no conflict of interests regarding the publication of this paper manuscript.

Patient consent: Informed written consent form was signed by the participants.

Data sharing statement: Due to privacy and ethical concerns, supporting data cannot be made openly available.

Ethics approval: This study was approved by Institutional Review Board of College of Health Sciences of the Addis Ababa University with protocol or approval number, (073/17/SPH).

References

1. American Cancer Society. Breast Cancer Facts & Figures 2015-2016. Atlanta: American Cancer Society, Inc. 2015.
2. Ma C, Nepal M, Kim JH, et.al. A new look at molecular biology of breast cancer. Cancer Biology & Therapy. 2019; 20(1) doi.org/10.1080/15384047.2018.1507259.
3. Bhadoria AS, Kapil U, Sareen N, et.al. Reproductive factors and breast cancer: A case–control study in tertiary care hospital of North India. Indian J Cancer 2013:50(4) 316-321.
4. Takalkar U, Asegaonkar S, Kodlikeri P, et.al. Hormone Related Risk Factors and Breast Cancer: Hospital Based Case Control Study from India. Research in Endocrinology. 2014; (2014): 1-6.
5. Tan M-M, Ho W-K, Yoon S-Y, et al. A case- control study of breast cancer risk factors in 7,663 women in Malaysia. PLoS ONE. 2018; 13(9): 1-12.
6. Women s Health Concern. Breast Cancer risk factors. Medical advisory Council, British Menopause Society. Reviewed 2015, www. Women s health concern.

7. Balekouzou A, Yin P, Pamatika CM et.al. Reproductive risk factors associated with breast cancer in women in Bangui: a case–control study. BMC Women's Health. 2017; 17:(4): 1-9.

8. American Cancer Society, Breast Cancer Prevention and Early Detection, 2015.

9. Brophy JT, Keith MM, Watterson A et,al. "Breast cancer risk in relation to occupations with exposure to carcinogens and endocrine disruptors: A Canadian case control study." Environmental Health. 2012; 11(87):1-17.

10. Memirie ST, Habtemariam MK, Assefa M et.al. Estimates of Cancer Incidence in Ethiopia in 2015 Using Population-Based Registry Data. Journal of Global oncology. 2018; 4:1-11.

11. Addis Ababa City Cancer Registry, Tikur Anbessa Specialized Hospital School of Medicine, Addis Ababa University, Ethiopia, 2014. https://afcrn.org/membership/membership-list/100-addisababa.

12. Berhe S, Sinshaw W, Hailu M et.al. Assessment of Knowledge of Breast Cancer and Screening Methods among Nurses in University Hospitals in Addis Ababa, Ethiopia, 2011: ISRN. Oncology. 2013; 2013:1-8.

13. Workineh MU, Lake EA, Adella GA. Breast Self-Examination Practice and Associated Factors Among Women Attending Family Planning Service in Modjo Public Health Facilities Southwest Ethiopia. Breast Cancer: Targets and Therapy 2021;13: 459-469.

14. Ethiopian cancer Association, 2007.

15. Tesfaw A, Demis S, Munye T et.al. Patient Delay and Contributing Factors Among Breast Cancer Patients at Two Cancer Referral Centers in Ethiopia: A Cross-Sectional

Study. Journal of Multidisciplinary Healthcare 2020; 13: 1391–1401. DOI: 10.2147/JMDH.S275157.

16. Bedada T, Teshale HA, Hailu A et.al. Mulugeta T. Prevalence and Factors Contributing to Late Diagnosis of Breast Cancer among Women Attending Tikur Anbessa Specialized Hospital, Oncology Unit, Addis Ababa, Ethiopia, 2017. J Integr Oncol 2018; 7: (3): 1-8. doi:10.4172/2329-6771.1000214.
17. Federal Ministry of Health Ethiopia: Disease Prevention and Control Directorate National Cancer Control Plan 2016-2020. 2015.
18. Addis Ababa University, College of Health Science, Background of Tikur Anbessa Hospital, 2020.
19. Momenimovahed Z, Salehiniya H. Epidemiological characteristics of and risk factors for breast cancer in the world, Review, Breast Cancer - Targets and Therapy. 2019; 11:151-164.
20. Palachandra A., Ishawaraprasad G. D, Sreelatha C. Y. et.al. Risk factors associated with carcinoma breast in India: a case control study. Int Surg J. 2017;4 (9):3136-3140.
21. Liu K, Zhang W, Dai Z et.al. Association between body mass index and breast cancer risk: evidence based on a dose–response meta-analysis. Cancer Management and Research. 2018; 10 :143–151.
22. Iyengar NM, Arthur R, Manson JE et.al Association of Body Fat and Risk of Breast Cancer in Postmenopausal Women With Normal Body Mass Index: A Secondary Analysis of a Randomized Clinical Trial and Observational Study. *JAMA Oncology* ; 2019-02-01, *DOI:* 10.1001/jamaoncol.2018.5327.

23. Farvid MS, Chen WY, Michels KB et.al. Fruit and vegetable intake and risk of breast cancer. Proceedings of the American Association for Cancer Research Annual Meeting, Washington, DC. Philadelphia (PA): AACR; Cancer Res 2017; 77(13) .doi:10.1158/1538-7445.AM2017-5325A.

24. Farvid MS, Chen WY, Michels KB et.al. Fruit and vegetable consumption and breast cancer incidence: Repeated measures over 30 years of follow-up: BMJ. 2016; 353:i2343. doi: 10.1136/bmj.i2343.

25. Link LB, Canchola AJ, Bernstein L, et.al. Dietary patterns and breast cancer risk in the California Teachers Study cohort. AmJ Clin Nutr. 2013; 98: 1524–32.

26. Galván-Salazar HR, Arreola-Cruz A, Madrigal-Pérez D, et.al, Association of Milk and Meat Consumption with the Development of Breast Cancer in a Western Mexican Population. Breast Care. 2015;10: 393–396.

27. Yul L, Liu L, Wang F, et.al. Higher frequency of dairy intake is associated with a reduced risk of breast cancer: Results from a case-control study in Northern and Eastern China. Oncology letters. 2019; 17(3):2737-2744.

28. Shin WK, Lee HW, Shin A, et.al. Milk Consumption Decreases Risk for Breast Cancer in Korean Women under 50 Years of Age: Results from the Health Examinees Study. Nutrients. 2019; 12 (1). doi:10.3390/nu12010032

29. Zang J, Shen M, Du S et.al. The Association between Dairy Intake and Breast Cancer in Western and Asian Populations: A Systematic Review and Meta-Analysis. Journal of Breast Cancer. 2015; 18(4): 313-322.

30. Xia H, Ma S, Wang S.et.al. Meta-Analysis of Saturated Fatty Acid Intake and Breast Cancer Risk in China. Medicine. 2015; 94(52): 1-10.

31. Dandamudi A, Tommie J, Nommsen-Rivers L et.al. Dietary Patterns and Breast Cancer Risk: A Systematic Review . *Anticancer Res*; 2018; *38*(*6*):*3209-3222*. *doi*: *10.21873/anticanres.12586*.

32. White AJ, Sandler DP. Indoor Wood-Burning Stove and Fireplace Use and Breast Cancer in a Prospective Cohort Study in USA. Environ Health Prospect. 2017; 125(7): 1-7.

33. Guo W, Fensom GK, Reeves GK ,et.al Physical activity and breast cancer risk: results from the UK, Bio bank prospective cohort. British Journal of Cancer. 2020; 122:726–732.

34. Chen X , Wang O, Zhang Y, et.al. Tan X. Physical Activity and Risk of Breast Cancer: A Meta-Analysis of 38 Cohort Studies in 45 Study Reports. Value Health. 2019; 22 (1):104-128. doi: 10.1016/j.jval.2018.06.020.

35. Khalis M, Charbotel B, Chajès V, et al. Menstrual and reproductive factors and risk of breast cancer: A case-control study in the Fez region, Morocco. PLoS ONE 2018; 13(1): 1-12

36. V Beral, D Bull, K Pirie, et.al. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies THE LANCET Oncology. 2012; 13(11):1141-1151.

37. Mohite VR, Pratinidhi AK, Mohite RV. Reproductive risk factors and Breast cancer: a case control study from rural India Bangladesh. Journal of Medical Science. 2015; 14(3)258-264.

38. Hunter DJ Oral Contraceptives and the Small Increased Risk of Breast Cancer. N Engl J Med . 2017; 377(23):2276-2277 .doi: 10.1056/NEJMe1709636.

This study was more or less organized based on the following STROBE (Strengthening the Reporting of Observational studies in Epidemiology checklist:

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Association of Risk Factors and Breast Cancer Among Women Treated at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: Case-control study

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Abstract:

Objectives: Many factors known to increase the risk of breast cancer, such as age, family history, early menarche, and late menopause are not modifiable. Modifiable factors include obesity, use of menopausal hormones, and breast feeding. This study aimed to assess risk factors associated with breast cancer among women at Tikur Anbessa Specialized Hospital.

Design: Facility based case-control study.

Methods: Case-control study was conducted from May 2018 to June 2019. A total of 230 cases and 230 controls participated in the study. Data were analyzed using SPSS software. Multivariable logistic model based analysis was conducted to control the effect of potential confounding factors. Odds ratios and 95% confidence interval for the likelihood of developing breast cancer were calculated.

Results: The odds of breast cancer was higher among women between 40-49 years, (AOR: *3.29, 95%* CI: 1.39-7.77), and being unemployed (AOR, 4.28 95% CI: 2.00-9.16).Regarding life style risk factors, women consumed solid oil and using wood or animal dung as source of fuel had significantly higher odds of breast cancer. In addition, the odds of breast cancer was significantly higher among post-menopausal women, women who had previous benign surgery and women with early menarche (<12 years). On the other hand, the odd of breast cancer was significantly lower among women who had moderate physical activities.

Conclusion: This study showed that occupational status, consumption of solid oil, and using wood or animal dung as source of fuel, early menarche, menopausal status and previous benign breast surgery were associated with breast cancer. On the other hand, physical activity was protective factors. Therefore, there is a need to design appropriate intervention to educate women about life style change or behavior modification to decrease their breast cancer risk.

Key words: *Breast cancer, Risk factors, , lifestyle.*

Strength and limitation of this Study

- To our knowledge this is the first study conducted among breast cancer patient in Ethiopia.
- During selection of control group, breast physical examination has been made by experienced oncology resident.
- Further analysis was not conducted by different ethnic group due to limited sample size and shortage of budget.
- Even though breast physical examination may be the only available breast cancer screening modality in resource limited countries like Ethiopia, and it has been made by experienced physician, which may not be highly sensitive to detect potential breast mass.

Background

There are several established risk factors for breast cancer. Most factors which increase the risk of breast cancer are not modifiable; these include age, family history, early menarche, and late menopause. Factors that are modifiable include post-menopausal obesity, pot menopausal hormonal replacement therapy and breast feeding. Genetic risk factors like mutations in BReast Cancer gen 1 (BRCA1) and BReast Cancer gen 2 (BRCA2) are also the most prominent cause of breast cancer [1, 2]. This is established through studies conducted in various countries in Africa and elsewhere. [3].

Similarly study from Tanzania found that women who had their first full-term pregnancy at < 30 years were more likely to be of luminal-B and triple negative subtypes relative to luminal-A subtype. [4]. Another study done in Cairo also revealed that the most common risk factors for

breast cancer were previous family history of breast cancer and using hormonal contraceptives [5].

Breast cancer poses a substantial public health threat in Ethiopia [6]. According to Addis Ababa City Cancer Registry, breast cancer is, 33% of cancers among females [7]. However, based on various studies conducted in the country there was poor community awareness towards the disease [8,9]. Most patients and their families do not properly know about cancer and its treatment options. As a result, 80 to 90% of cancer patients already suffer from advanced and incurable cancers at the time of diagnosis [9,10].

Even though many studies found different risk factors, such risk factors are not studied well, , especially for most resource limited countries. For a country like Ethiopia with a huge population, different, ethnic geographical variations, life style and cultures habits, information on breast cancer associated risk factors are significantly limited. Targeting and supporting these populations to reduce their risk is an essential component of population health. Therefore, this study was aimed to assess risk factors for breast cancer among women at Tikur Anbessa Hospital. The result of this study will help to identify possible risk factors which can be used for for policy makers to raise community awareness, for reduction in morbidity and mortality

Materials and Methods

Study design and period

Facility based case-control study was conducted between May 2018 and June 2019 in Addis Ababa at Tikur Anbesa Specialized Hospital (TASH) Oncology Department, which is the largest

hospital in Ethiopia with 700 beds [11]. This hospital is the country's sole cancer referral center which provides surgery, chemotherapy, radiotherapy and palliative care.

Eligibility criteria

During the study period, all consenting newly diagnosed breast cancer patients, with confirmed histology result, no observable mental disorders, no history of chronic disease and aged 18 years and above were included in the study. The source of control groups was women accompanying breast cancer patients who had no biological relationship with selected cases were included as a control in the study. .Controls groups were breast mass free women by physical examination.

Sampling and sample size determination

Since there was only one referral center for cancer treatment during the study period, the existing center (TASH) was used for the study. All voluntary and eligible cases and controls that came to Tikur Anbessa Specialized Hospital during the study period were recruited by using convenient sampling techhnique. Sample size was calculated by taking age (≥65 years) as a risk factor for breast cancer, 80% power, 0.05 significance level at 95% CI, and 1:1 ratio of case to control. Percentage of exposed among control group was 11.9%, percentage of exposed among cases was 21.6% [12], and odds ratio of assumed to be 2.05. Accordingly, a total of 460 participants (230 cases and 230 controls) participated in this study.

Data collection analysis and management

Informed consent was obtained from each study participant prior to data collection. Participants were interviewed by experienced and trained nurses in a convenient place to maintain privacy and

confidentiality. Breast physical examination was conducted by oncology residents in order to select eligible controls. Data entry and analysis was done using SPSS Software, version 20. Binary logistic regression was conducted to see the association between breast cancer and risk factors. Finally, stepwise multivariable analysis was done to adjust for potential confounding variables by selecting variables which have P value ≤ 0.05 in bivariate analysis. P value less than 0.05 were considered as statistically significant while adjusted odds ratios with 95% CI were used to see the strength and direction of the association.

Study variables

Based on American Cancer Society fact and figure for breast cancer, Age at diagnosis was categorized as less than 40 ,40-49,50-59, and 60 years and above. BMI was calculated and categorized as follows <25 normal, 25-29.9 overweight, and >30 obese. Menarche was defined as the age at which the first menses was occurred. Age at first live birth was defined as the age when the first full term birth occurred. Abortion was defined as the termination of pregnancy before 28 weeks of pregnancy. Parity was defined as the number of pregnancies that a participant had. Women who had sisters/mothers/daughters with breast cancer were categorized as having a first-degree family history of breast cancer. Women were classified as menopausal if they had not menstruated during the past one year before the date of data collection. Breast surgery was defined as weather study participant had surgery for non-cancer lump.

Data Quality Assurance and Ethical considerations

The data collection tools were prepared in English and translated to the local language in order to facilitate understanding by the study participants. The data collection tools were pretested in 5%

of breast cancer patients not included in the study. Daily supervision was made on all questionnaires collected each day. This research was conducted based on research requirements, regulations and policies that safeguard the wellbeing of study participants and to ensure the reliability and integrity of this finding. Therefore, all methods were carried out in accordance with relevant guidelines and regulations.

This study was approved by Institutional Review Board of the College of Health Sciences of Addis Ababa University with protocol number 073/17/SPH. Written consent was obtained from each of the respondents after the purpose of the study was explained. During breast physical examination for screening of controls, participants who had breast mass were consulted by physicians and their results were given for free in order to get early diagnosis and treatment. Confidentiality and privacy were maintained throughout the study.

Patient and public involvement

Neither patients nor the public were involved in the design of this study.

Results

Bivariate analysis of Socio demographic characteristics and anthropometric factors

In this study, a total of 230 breast cancer cases and 230 healthy controls were participated. The mean age (± SD) was 42.83 ± 12.06 for cases and 39.33 ± 11.14 years for controls. The odds of breast cancer was significantly higher among women aged 40-49 and >60 years. The odds of developing breast cancer among illiterate was 3.78 times higher (95% CI 1.47-9.72, P=0.006) compared to literate women. Similarly, the odds of breast cancer was also 2.82 times higher

(95% CI: 1.52-5.22, P=0.001)) among unemployed women as compared to employed. It was also 2.43 times (95% CI: 1.43-4.14, P= 0.001) higher among women with lower socio economic status as compared to women with higher socioeconomic status (monthly income >2000 Ethiopian Birr) per month. However there was no significant association between breast cancer with place of resident and marital status. The odds of breast cancer was 2.13 times higher (95% CI. 1.06 - 4.28, P=0.034) among women with less than 59Kg as compared to women greater than 75 Kg. Similarly, the odds of breast cancer was 2.48 times higher (95% CI: 1.07-5.75, P=0.035) among women with BMI 25-29.9 Kg/m2 (Table 1).

Table 1. Socio demographic characteristics and anthropometric risk factors associated with breast cancer .

Variables	**Case**	**Control**	**Bivariate analysis**	
	N (%)	**N (%)**	**COR (95% CI)**	**P-value**
Residence				
Rural	67 (29.1)	56 (24.3)	1:00	
Urban	163 (70.9)	174 (75.7)	0.783(0.517-1.19)	0.247
Age group (years)				
<39	106 (46.1)	136 (59.1)	1:00	
40–49	58 (25.2)	45 (19.6)	*1.65(1.04-2.63)*	0.034
50-59	39(17.0)	36(15.7)	*1.39(0.827-2.34)*	0.214
>60	27 (11.7)	13 (5.7)	*2.67(1.31-5.41)*	0.007
Marital status				
Ever Married	207(90.0)	201(87.4)	1:00	
Never married	23(10.0)	29(12.6)	0.770(0.431-1.38)	0.378
Education level				
Literate	130(56.5)	196(85.2)	1:00	1:00

Illiterate	100(43.5)	34(14.8)	4.43(2.83-6.94)	0.0001
Occupation				
Employed	70(30.4)	131(57)	1:00	1:00
Unemployed	160(69.6)	99(43.0)	3.03(2.06-4.44)	0.0001
Income	(N=108)	(N=127)		
≥2000	52(48.1)	88(69.3)	1:00	1:00
<2000	56(51.9)	39(30.7)	2.43(1.43-4.14)	0.001
Height (m)				
≥1.60	102(44.3)	91(39.6)	1:00	1:00
< 1.52	48 (20.9)	32(13.9)	1.34(0.788-2.27)	0.280
1.53 – 159	80(34.8)	107(46.5)	0.667(0.445-1.00)	0.050
Weight (kg)				
>75	14(6.1)	25(10.9)	1:00	
<59	143(62.2)	120(52.2)	2.13(1.064.28)	0.034
59.1 -65	37(16.1)	52(22.6)	1.27(0.583-2.77)	0.546
65.1 -74	36(15.7)	33(14.3)	1.95(0.869-4.36)	0.105
BMI(kg/m2)				
Obese (> 30)	10(4.3)	22(9.6)	1:00	
25-29.9(Overweight)	54(23.5)	48(20.9)	2.48(1.07-5.75)	0.035
Normal (< 25)	166(72.2)	160(69.6)	2.28(1.05 -4.97)	0.038

Bivariate analysis using binary logistic regression. 1:00 is Oddis Ratio (OR) for reference/comparison group.

***CI: Confidence interval, COR: Crude Odds Ratio*.**

Life style risk factors associated with breast cancer

In this study, neither cases nor controls had used HRT. On the other hand, 3 cases and none of the controls were smokers. However, 49, (21.3%) of cases and 66, (28.7%) of the controls had history of alcohol consumption. Regarding dietary habit, there was no significant association between vegetable and meat intake with breast cancer. This study also indicated that the odd of breast cancer was 4.04 times higher among women who had used solid oil. Similarly, the odd of

breast cancer was 6.46 times higher among women who had used wood or animal dung as fuel source as with use electric as a source of fuel. Regarding physical activity, women who had strenuous physical activities like running, swimming less than 5 hour per week had 0.343 times lower risk of breast cancer . Similarly, women who had moderate physical activity such as walking, playing tennis less than 5 hour per week had 0.228 times less risk (Table 2).

Table. 2. Association of life style risk factors with breast cancer

Variables	Case N (%)	Controls N (%)	Bivariate analysis	
			COR (95% CI)	P Value
Smoking				
No	227(98.7)	230(100%)	1:00	
Yes	3	0(0.0%)	1.01(0.998-1.03)	0.082
Alcohol intake				
Non drinker	181(78.7)	164(71.3)	1:00	
Drinker	49(21.3)	66(28.7)	0.673(0.439-1.03)	0.068
Vegetable intake				
Once a week or less	166(72.2)	158(68.7)	1:00	
More than Once a week	64(27.8)	72(31.3)	0.846(0.567-1.26)	0.414
Fruit intake				
Once a week or less	194(84.3)	210(91.3)	1:00	
More than Once a week	36(15.7)	20(8.7)	1.95(1.09-3.48)	0.024
Meat				
Once a week or less	207(90.0)	218(94.8)	1:00	
More than Once a week	23(10.0)	12(5.2)	2.02(979-1.4.16)	0.057
Milk take				
Once a week or less	189(82.5)	207(90.8)	1:00	
More than Once a week	40(15.7)	21(9.2)	2.086(1.19-3.67)	0.011

Solid oil				
No	45(19.6)	114(49.6)	1:00	
Yes	185(80.4)	116(50.4)	4.04(2.67-6.12)	0.0001
Source of fuel				
Electric	54(23.5)	111(48.3)	1:00	
Wood/Animal dung	88(38.3)	28(12.2)	6.46(3.78-11.03)	0.0001
Charcoal/Kerosene	3(1.3)	20(8.7)	0.308(0,088-1,08)	0.066
Combination	85((37.0)	71(30.9)	2.46(1.57-3.87)	0.0001
Strenuous exercise				
No exercise	209(90.9)	203(88.3)	1:00	
< 5 Hr per week	6(2.6)	17(7.4)	0.343(0.133-0..887)	0.027
5 Hr and above per week	15(6.5)	10(4.3)	1.46(0.640-3.32)	0.370
Moderate exercise				
No exercise	173(75.2)	126(54.8)	1:00	
< 5Hr per week	21(9.1)	67(29.1)	0.228(0.133-0.392)	0.0001
5 Hr and above per week	36(157)	37(16.1)	0.709(0.424-1.18)	0.188

Bivariate analysis using binary logistic regression. 1:00 is Oddis Ratio (OR) for reference/comparison group.

Hr: Hour, ***CI: Confidence Interval, COR: Crude Odds Ratio***

Reproductive risk factors associated with breast cancer

In this study the odds of breast cancer was 3.16 times higher among women who had age at menarche less than 12 years . On the other hand, there was no significant association between abortion, as well as age at first birth with breast cancer. Similarly, the odds of breast cancer was 2.34 times higher among post-menopausal women . In addition, women who had previous breast surgery were 8.82 times more likely to develop breast cancer . However, there was no statistically significant association between breast cancer with age at menopause, use of oral contraceptive, duration of breast feeding and age at last birth (Table 3). Based on multivariable

logistic regression analysis, the association between family history and breast cancer was declined.

Table. 3. Association of reproductive risk factors with breast cancer

Parameter	Case N (%)	Control N (%)	Bivariate analysis COR (95% CI)	P Value	Multivariable analysis AOR (95% CI)	P Value
Age at menarche(years)						
>15	20(11.2)	60(28.6)	1:00		1:00	1:00
12 -15	150(83.8)	144(68.6)	3.13(1.79-5.45)	0.0001	5.94(1.84-19.15)	0.003
<12	9(5.0)	6(2.9)	*4.50*(1.42-14.21)	*0.010*	*3.16(1.78-5.56)*	*0.001*
Family history of breast						
No	215 (93.5)	226(98.3)	1:00		1:00	1:00
Yes	15(6.5)	4(1.7)	3.94(1.29-12.07)	0.016	2.60(0.765-8.81)	0.126
Menopausal status						
Premenopausal (ref.)	122(53.0)	161(70.0)	1:00		1:00	1:00
Post-menopausal	108(47.0)	69(30.0)	2.06(1.41-3.03)	0.001	2.34(1.50- 3.64)	0.001
History of benign breast disease						
No	211(91.7)	226(98.3)	1:00		1:00	1:00
Yes	19(8.3)	4(1.7)	5.09 (1.70-15.19)	0.004	8.82(1.96-39.60)	0.005

Stepwise multiple logistic regression . 1:00 is Oddis Ratio (OR) for reference/comparison group.

Adjusted for: age at menarch, , menoposal status, history off surgery, and family history with first degree relatives.

CI: Confidence interval, COR, Cruude odds ratio, AOR: Adjusted Odds Ratio

Multivariable analysis of Sociodemographic, anthropometric and lifestyle factors

. The finding indicated that the odds of breast cancer were 3.29 times higher among women with 40- 49 age groups as compared to women 39 year or less. It was also found that the odds of breast cancer were 4.28 times higher among unemployed women. Regarding life style, milk intake and consumption of solid oil was significantly associated with breast cancer. Similarly, the odd of breast cancer was 5.30 times higher among women had used wood or animal dung as source of fuel as compared to women who used electric. On the other hand, the odds of breast cancer was 0.276 times lower among women who had moderate physical activities like swimming, table tennis, and basketball less than hour per week as compared with women who had no history of exercise (Table 4)

Table 4. Association of Socio demographic, anthropometric and lifestyle factors with breast cancer

Variables	Case	Control	Bivariate analysis		Multivariable analysis	
	N (%)	N (%)	COR (95% CI)	P-value	AOR (95% CI)	P-value
Age group (years)						
≤39	106 (46.1)	136 (59.1)	1:00		1:00	1:00
40–49	58 (25.2)	45 (19.6)	*1.65(1.04-2.63)*	0.034	*3.29(1.39-7.77)*	*0.007*
50-59	39(17.0)	36(15.7)	*1.39(0.827-2.34)*	0.214	*1.81(0.661-4.96)*	*0.248*
>60	27 (11.7)	13 (5.7)	*2.67(1.31-5.41)*	0.007	*2.44(0.515-11.55)*	*0.261*
Occupation						
Employed	70(30.4)	131(57)	1:00	1:00	1:00	1;00
Unemployed	160(69.6)	99(43.0)	3.03(2.06-4.44)	0.0001	4.28 (2.00-9.16)	0.0001
Milk intake						
Once a week or less	189(82.5)	207(90.8)	1:00		1:00	1:00
More than Once a week	40(15.7)	21(9.2)	2.086(1.19-3.67)	0.011	2.56(1.02-6.43)	0.045
Solid oil						
No	45(19.6)	114(49.6)	1:00		1:00	1;00
Yes	185(80.4)	116(50.4)	4.04(2.67-6.12)	0.0001	6.77(3.17-14.48)	0.0001
Source of fuel						
Electric	54(23.5)	111(48.3)	1:00		1:00	1;00
Wood /animal dung	88(38.3)	28(12.2)	6.46(3.78-11.03)	0.0001	5.30 (1.59-17.64)	0.007
Charcoal/Kerose	3(1.3)	20(8.7)	0.308(0,088-1.08)	0.066	0.112(0.012-1.01)	0.051

ne						
Combination	85((37.0)	71(30.9)	2.46(1.57-3.87)	0.0001	2.45(1.16-5.15)	0.019
Moderate exercise						
No exercise	173(75.2)	126(54.8)	1:00		1:00	1;00
< 5Hr per week	21(9.1)	67(29.1)	0.228(0.133-0.392)	0.0001	0.276(0.114-0.628)	0.002
5 Hr and above per week	36(157)	37(16.1)	0.709(0.424-1.18)	0.188	0.496(0.182-1.36)	0.172

Stepwise multiple logistic regression. ***Adjusted for age, income, education, occupation, height, weight, BMI, fruit intake, milk intake, solid oil intake, sources of fuel, frequency of moderate exercise, frequency of streanus exercise***, ***1:00 is Oddis Ratio (OR) for reference/comparison group.***

Discussion

In this study, potential risk factors associated with breast cancer were examined. This study revealed that various risk factors, including demographic, life style, reproductive, hormonal, factors, are associated with incidence of breast cancer [13,14].

There was no significant association between, place of residence and marital status and risk of breast cancer in our study. This finding was supported by study from Uganda [15]. However, which is different with study done in India that showed significant relationship between breast cancer and being married [16. The odd of breast cancer was higher among women between 40 and 49 age groups. Similarly, the odd of breast cancer was 4.43 times higher among illiterate compared to literate women. This finding is supported by a similar study done in Bangui, which indicated that the odd of breast cancer was higher among illiterate [17]. However this association was declined after stepwise multiple logistic regression models was applied. It was also found that the odd of breast cancer was 4.28 times higher among unemployed compared to employed

women, this might be due to Employed women may have more family income and they may spend money for screening and medical care. Early screening (early screening identify cancer at early stage) and as a result of their better economic level and awareness. This finding is also supported by the previous study done in Bangui [17]. However, the current study was incomparable with another study in India which reported a higher risk of breast cancer among women with higher educational status [18].

Even though, BMI was associated with increased risk of breast cancer [19], in this study, both weigh and BMI of cases were lower than controls, this lower weight and BMI among cases could be due to loss of weight among cases as a result of advanced stage of their disease at time of diagnosis. This finding is comparable with the study done in Malaysia [20]. However, there is also study which had found postmenopausal women with normal BMI, relatively high body fat levels were associated with an elevated risk of invasive breast cancer and the study explained that normal BMI categorization may be an inadequate proxy for the risk of breast cancer in postmenopausal women [19]. In this study, there was no significant association between alcohol consumption, vegetable and meat intake with breast cancer. However, this finding is not supported by similar studies conducted in different parts of US, which observed that a higher intake of fruits and vegetables was associated with a lower breast cancer risk [21-23]. This difference could be due to the difference in type, frequency, and amount of such fruit and plant based dietary pattern. The other possible explanation could be consumption of such kinds of diet may be limited among study participants due to limited purchasing power.

However, the odd of breast cancer was 2.56 times higher among women who had consumed milk for more than once a week, compared to women who had consumed milk once a week or

less. This finding is supported by study done in Western Mexico [24]. Similarly, the Mexico study also support our study regarding consumption of meat was not associated with breast cancer [24]. This association has been explained that high milk intake results in the consumption of cow estrogen metabolites as well as a high caloric intake, both of which increasing the risk of breast cancer [24]. However, this finding is not comparable with different studies, revealed that dairy consumption was inversely associated with the risk of developing breast cancer [25-27]. This difference could be due to the amount, dairy-type, and time of consuming such products. In this study, there are two unexpected results which had significant association with breast cancer, the first result was, and the odd of breast cancer was 6.77 times higher among women who used solid oil, this finding suggested that, since it is saturated fat, which may contain other factors which can increase the risk of breast cancer and the finding was supported by study done in China [28]. This finding also supported by study done in USA reviled that consumption of saturated fat is associated with increased breast cancer risk [29]. The second result was that the odds of breast cancer was 5.3 times higher among women who had used wood or animal dung as a source of fuel, which was supported by study done in USA revealed that indoor burning either wood or natural gas for long time was associated with higher risk of breast cancer [30].

Based on the result of bivariate analysis, the odds of breast cancer were lower among women who had average duration of strenuous exercise of less than 5 hours per week; however, the association was not significant after adjusted for confounding variable. On the other hand, women who had moderate physical activity of less than 5 hours per week had reduced risk of breast cancer. This finding is comparable with the study done in UK and Sudan which indicated that physical activity was associated with a reduction in breast cancer risk [31, 32]. And this

study also supported by systematic review meta-analysis conducted in China stated that physical activity is significantly associated with a decrease in the risk of breast cancer [33].

In this study, only 5.0% of cases and 2.9% of controls had menarche less than 12 years of age. Late menarche (>15 years) was found to be significant protective factor for breast cancer, compared to earlier age at menarche (<12 years), this finding was supported by study done in Morocco [34]. This finding was also in agreement with study done in UK found that breast cancer risk increased by a factor of 1·050 (95% CI 1·044–1·057; p<0·0001) for every year younger at menarche, and independently by a smaller amount (1·029, 1·025–1·032; p<0·0001), for every year older at menopause. [35]. Our study didn't find association between age at first full-term pregnancy, which was different with study done in Morocco [34]. On the on other hand, this finding was comparable with study done in Uganda revealed that there was no association btween breast cancer and early age at at first pregnancy [15].

The odd of breast cancer was 2.34 times higher among post-menopausal women. This finding was comparable with different studies conducted in India [3, 16,]. It was also found that, 19(8.3%) of cases and 4(1.7%) of the controls had previous breast surgery. Women with previous benign breast surgery were 8.82 times more likely to have breast cancer. This finding was supported by studies conducted in India Malaysia and Sudan [17,20, 32].

In this study, the odd of breast cancer was 2.34 times higher among post-menopausal women. This finding is comparable with a study done in Malaysia, indicated that post-menopausal women had 52% increased risk of breast cancer [20]. Similarly, in our study, oral contraceptive was not significantly associated with breast cancer, which was also supported by other study

done in India [36]. However, this study is not supported by study done in Cameroon [37]. and it was also contradict with study in Denmark found that approximately 20% higher risk of breast cancer among women who currently use hormonal contraceptives. Similar studies conducted in India and United Kingdom also reported an increased risk of being diagnosed with breast cancer in women who have used hormonal contraception [16, 38, 39]. This difference could be due to length of contraceptive use and type of contraception. There was no significant association between breast cancer with parity and duration of breast feeding, which is comparable with two studies done in India [14,36].

Study limitation

Some limitations should be considered to elucidate the findings of this study. Primarily the finding of our study was based on self-reporting and that could have introduced recall biases regarding their past exposure for different possible risk factors, this may result or under reporting of the outcome under study. Since this is a case control study, all the association may not be necessarily casual. The other most important limitation could be even though breast physical examination may be the only available breast cancer screening modality in resource limited countries like Ethiopia, and it has been made by experienced physician, which may not be highly sensitive and may miss the potential breast mass.

Conclusion and recommendation

Since this study was a case control study which serves as an indicative study usually used to provide early clues and inform further research using more rigorous scientific methods. In this study, socio demographic, lifestyle, anthropometric and reproductive risk factors were assessed.

The finding indicated that the odds of breast cancer decreased among young age and employed women. Regarding lifestyle factors, the odds of breast cancer was 6.8 times higher among women consumed solid oil. In addition, women who used wood or animal dung as a source of fuel had 5.3 times higher odds of breast cancer. However, the odds of breast cancer decreased among women who had moderate physical exercise less than 5 hours per week. Finally, the odd of breast cancer was higher among women with early menarche (< 12 years), post-menopausal women and women with previous benign breast surgery. Since there was significant association between most of the modifiable risk factors and breast cancer, it is essential to design appropriate life style modification strategies which may contribute to prevent breast cancer. There is a need to design appropriate intervention to educate women about lifestyle change or behavior modification to decrease their breast cancer risk. In addition, since there are varieties of culture, food choice, feeding habit, physical activities and other risk factors, it is important to conduct future studies with a larger sample size including different regions or diverse population in order to come up with more representative evidence.

Declaration

Abbreviations

CI: Confidence Interval; Hr.: Hour; HRT: Hormone Replacement Therapy; SPSS: Statistical Package for Social Sciences; TASH: Tikur Anbessa Specialized Hospital.

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- All authors declare that there is no conflict of interests regarding the publication of this paper manuscript.

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References

1. American Cancer Society. Breast Cancer Facts & Figures 2015-2016. Atlanta: American Cancer Society, Inc. 2015.
2. Ma C, Nepal M, Kim JH, et.al. A new look at molecular biology of breast cancer. Cancer Biology & Therapy. 2019; 20(1) . doi.org/10.1080/15384047.2018.1507259.
3. Bhadoria AS, Kapil U, Sareen N, et.al. Reproductive factors and breast cancer: A case–control study in tertiary care hospital of North India. Indian J Cancer 2013;50 (4) 316-321.
4. Rweyemamu LP, Akan G, Ismael C. etal .The distribution of reproductive risk factors disclosed the heterogeneity of receptor-defned breast cancer subtypes among Tanzanian women. BMC Women's Health (2021) 21:423 doi.org/10.1186/s12905-021-01536-6.
5. Eman M. Seif El-Nasr. Breast Cancer risk factors and screening practices Among Women Attending Family Health Centers in Cairo Governorate**.** IOSR-JNHS 2017; 6(3): 12-23. DOI: 10.9790/1959-0603011223.

6. Memirie ST, Habtemariam MK, Assefa M et.al. Estimates of Cancer Incidence in Ethiopia in 2015 Using Population-Based Registry Data. Journal of Global oncology. 2018; 4:1-11.

7. Addis Ababa City Cancer Registry, Tikur Anbessa Specialized Hospital School of Medicine, Addis Ababa University, Ethiopia, 2014. https://afcrn.org/membership/membership-list/100-addisababa.

8. Berhe S, Sinshaw W, Hailu M et.al. Assessment of Knowledge of Breast Cancer and Screening Methods among Nurses in University Hospitals in Addis Ababa, Ethiopia, 2011: ISRN. Oncology. 2013; 2013:1-8.

9. Workineh MU, Lake EA, Adella GA. Breast Self-Examination Practice and Associated Factors Among Women Attending Family Planning Service in Modjo Public Health Facilities Southwest Ethiopia. Breast Cancer: Targets and Therapy 2021;13: 459-469.

10. Ethiopian cancer Association, 2007.

11. Addis Ababa University, College of Health Science, Background of Tikur Anbessa Hospital, 2020.

12. Hadjisavvas A, Loizidou MA, Middleton N, etal. An investigation of breast cancer risk factors in Cyprus: a case control study. BMC Cancer. 2010; 10(447). doi.biomedcentral.com/1471-2407/10/447.

13. Momenimovahed Z, Salehiniya H. Epidemiological characteristics of and risk factors for breast cancer in the world, Review, Breast Cancer - Targets and Therapy. 2019; 11:151-164.

14. Palachandra A., Ishawaraprasad G. D, Sreelatha C. Y. et.al. Risk factors associated with carcinoma breast in India: a case control study. Int Surg J. 2017;4 (9):3136-3140.

15. Galukandea M, Wabingab H, Mirembec F,et al. Breast Cancer Risk Factors among Ugandan Women at a Tertiary Hospital: A Case-Control Study.Oncology. 2016; 90(6): 356–362. doi:10.1159/000445379.

16. Takalkar U, Asegaonkar S, Kodlikeri P, et.al. Hormone Related Risk Factors and Breast Cancer: Hospital Based Case Control Study from India. Research in Endocrinology. 2014; (2014): 1-6.

17. Balekouzou A, Yin P, Pamatika CM et.al. Reproductive risk factors associated with breast cancer in women in Bangui: a case–control study. BMC Women's Health. 2017; 17:(4): 1-9.

18. Liu K, Zhang W, Dai Z et.al. Association between body mass Association of Body Fat and Risk of Breast Cancer in Postmenopausal Women with Normal Body Mass Index: Cancer Management and Research. 2018; 10:143–151.

19. Iyengar NM, Arthur R, Manson JE et.al. Association of Body Fat and Risk of Breast Cancer in Postmenopausal Women With Normal Body Mass Index: A Secondary Analysis of a Randomized Clinical Trial and Observational Study. *JAMA Oncology*. 2019 ; 5(2): 155–163. doi: 10.1001/jamaoncol.2018.5327.

20. Tan M-M, Ho W-K, Yoon S-Y, et al. A case- control study of breast cancer risk factors in 7,663 women in Malaysia. PLoS ONE. 2018; 13(9): 1-12.

21. Farvid MS, Chen WY, Michels KB et.al. Fruit and vegetable intake and risk of breast cancer. Proceedings of the American Association for Cancer Research Annual Meeting, Washington, DC. Philadelphia (PA):AACR; Cancer Res 2017; 77(13) .doi:10.1158/1538-7445.AM2017-5325A.

22. Farvid MS, Chen WY, Michels KB et.al. Fruit and vegetable consumption and breast cancer incidence: Repeated measures over 30 years of follow-up: BMJ. 2016; 353:i2343. doi: 10.1136/bmj.i2343.

23. Link LB, Canchola AJ, Bernstein L, et.al. Dietary patterns and breast cancer risk in the California Teachers Study cohort. AmJ Clin Nutr. 2013; 98: 1524–32.

24. Galván-Salazar HR, Arreola-Cruz A, Madrigal-Pérez D, et.al, Association of Milk and Meat Consumption with the Development of Breast Cancer in a Western Mexican Population. Breast Care. 2015;10: 393–396.

25. Yul L, Liu L, Wang F, et.al. Higher frequency of dairy intake is associated with a reduced risk of breast cancer: Results from a case-control study in Northern and Eastern China. Oncology letters. 2019; 17(3):2737-2744.

26. Shin WK, Lee HW, Shin A, et.al. Milk Consumption Decreases Risk for Breast Cancer in Korean Women under 50 Years of Age: Results from the Health Examinees Study. Nutrients. 2019; 12 (1). doi:10.3390/nu12010032

27. Zang J, Shen M, Du S et.al. The Association between Dairy Intake and Breast Cancer in Western and Asian Populations: A Systematic Review and Meta-Analysis. Journal of Breast Cancer. 2015; 18(4): 313-322.

28. Xia H, Ma S, Wang S.et.al. Meta-Analysis of Saturated Fatty Acid Intake and Breast Cancer Risk in China. Medicine. 2015; 94(52): 1-10.

29. Dandamudi A, Tommie J, Nommsen-Rivers L et.al. Dietary Patterns and Breast Cancer Risk: A Systematic Review . *Anticancer Res*; 2018; *38*(*6*):*3209-3222*. *doi*: *10.21873/anticanres.12586*.

30. White AJ, Sandler DP. Indoor Wood-Burning Stove and Fireplace Use and Breast Cancer in a Prospective Cohort Study in USA. Environ Health Prospect. 2017; 125(7): 1-7.

31. Guo W, Fensom GK, Reeves GK ,et.al Physical activity and breast cancer risk: results from the UK, Bio bank prospective cohort. British Journal of Cancer. 2020; 122:726–732.

32. Ahmed HG ,Musa RM, Eltybe MM et al. Role of Some Risk Factors in the Etiology of Breast Cancer in the Sudan. The Open Breast Cancer Journal, 2010; 2: 71-78 DOI: 10.2174/1876817201002010071.

33. Chen X , Wang O, Zhang Y, et.al. Tan X. Physical Activity and Risk of Breast Cancer: A Meta-Analysis of 38 Cohort Studies in 45 Study Reports. Value Health. 2019; 22 (1):104-128. doi: 10.1016/j.jval.2018.06.020.

34. Khalis M, Charbotel B, Chajès V, et al. Menstrual and reproductive factors and risk of breast cancer: A case-control study in the Fez region, Morocco. PLoS ONE 2018; 13(1): 1-12.

35. V Beral, D Bull, K Pirie, et.al. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies THE LANCET Oncology. 2012; 13(11):1141-1151.

36. *Mohite VR, Pratinidhi AK, Mohite RV. Reproductive risk factors and Breast cancer: a case control study from rural India* Bangladesh. Journal of Medical Science. 2015; 14(3)258-264.

37. Paul, E. , Henri, E. , Valère, M.et al. Risk Factors for Breast Cancer in the City of Douala: A Case Control Study. *Advances in Breast Cancer Research*. 2020; 9: 66-77. doi: 10.4236/abcr.2020.93006.

38. Women s Health Concern. Breast Cancer risk factors. Medical advisory Council, British Menopause Society. Reviewed 2015, www. Women s health concern.

39. Hunter DJ Oral Contraceptives and the Small Increased Risk of Breast Cancer. N Engl J Med . 2017; 377(23):2276-2277 .doi: 10.1056/NEJMe1709636

This study was more or less organized based on the following STROBE (Strengthening the Reporting of Observational studies in Epidemiology checklist:

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Association of Risk Factors and Breast Cancer Among Women Treated at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: Case-control study

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Abstract:

Objectives: Many factors known to increase the risk of breast cancer, such as age, family history, early menarche, and late menopause are not modifiable. Modifiable factors include obesity, use of menopausal hormones, and breast feeding. This study aimed to assess risk factors associated with breast cancer among women at Tikur Anbessa Specialized Hospital.

Design: Facility based case-control study.

Methods: Case-control study was conducted from May 2018 to June 2019. A total of 230 cases and 230 controls participated in the study. Data were analyzed using SPSS software. Multivariable logistic model based analysis was conducted to control the effect of potential confounding factors. Odds ratios and 95% confidence interval for the likelihood of developing breast cancer were calculated.

Results: The odds of breast cancer was higher among women between 40-49 years, (AOR: *3.29, 95%* CI: 1.39-7.77), and being unemployed (AOR, 4.28 95% CI: 2.00-9.16).Regarding life style risk factors, women consumed solid oil and using wood or animal dung as source of fuel had significantly higher odds of breast cancer. In addition, the odds of breast cancer was significantly higher among post-menopausal women, women who had previous benign surgery and women with early menarche (<12 years). On the other hand, the odd of breast cancer was significantly lower among women who had moderate physical activities.

Conclusion: This study showed that occupational status, consumption of solid oil, and using wood or animal dung as source of fuel, early menarche, menopausal status and previous benign breast surgery were associated with breast cancer. On the other hand, physical activity was protective factors. Therefore, there is a need to design appropriate intervention to educate women about life style change or behavior modification to decrease their breast cancer risk.

Key words: *Breast cancer, Risk factors, , lifestyle.*

Strength and limitation of this Study

- To our knowledge this is the first study conducted among breast cancer patient in Ethiopia.
- During selection of control group, breast physical examination has been made by experienced oncology resident.
- Further analysis was not conducted by different ethnic group due to limited sample size and shortage of budget.
- Even though breast physical examination may be the only available breast cancer screening modality in resource limited countries like Ethiopia, and it has been made by experienced physician, which may not be highly sensitive to detect potential breast mass.

Background

There are several established risk factors for breast cancer. Most factors which increase the risk of breast cancer are not modifiable; these include age, family history, early menarche, and late menopause. Factors that are modifiable include post-menopausal obesity, post menopausal hormonal replacement therapy and breast feeding. Genetic risk factors like mutations in BReast Cancer gen 1 (BRCA1) and BReast Cancer gen 2 (BRCA2) are also the most prominent cause of breast cancer [1, 2]. This is established through studies conducted in various countries in Africa and elsewhere. [3].

Similarly study from Tanzania found that women who had their first full-term pregnancy at < 30 years were more likely to be of luminal-B and triple negative subtypes relative to luminal-A subtype. [4]. Another study done in Cairo also revealed that the most common risk factors for

breast cancer were previous family history of breast cancer and using hormonal contraceptives [5].

Breast cancer poses a substantial public health threat in Ethiopia [6]. According to Addis Ababa City Cancer Registry, breast cancer is, 33% of cancers among females [7]. However, based on various studies conducted in the country there was poor community awareness towards the disease [8,9]. Most patients and their families do not properly know about cancer and its treatment options. As a result, 80 to 90% of cancer patients already suffer from advanced and incurable cancers at the time of diagnosis [9,10].

Even though many studies found different risk factors, such risk factors are not studied well, , especially for most resource limited countries. For a country like Ethiopia with a huge population, different, ethnic geographical variations, life style and cultures habits, information on breast cancer associated risk factors are significantly limited. Targeting and supporting these populations to reduce their risk is an essential component of population health. Therefore, this study was aimed to assess risk factors for breast cancer among women at Tikur Anbessa Hospital. The result of this study will help to identify possible risk factors which can be used for for policy makers to raise community awareness, for reduction in morbidity and mortality

Materials and Methods

Study design and period

Facility based case-control study was conducted between May 2018 and June 2019 in Addis Ababa at Tikur Anbesa Specialized Hospital (TASH) Oncology Department, which is the largest

hospital in Ethiopia with 700 beds [11]. This hospital is the country's sole cancer referral center which provides surgery, chemotherapy, radiotherapy and palliative care.

Eligibility criteria

During the study period, all consenting newly diagnosed breast cancer patients, with confirmed histology result, no observable mental disorders, no history of chronic disease and aged 18 years and above were included in the study. The source of control groups was women accompanying breast cancer patients who had no biological relationship with selected cases were included as a control in the study. .Controls groups were breast mass free women by physical examination.

Sampling and sample size determination

Since there was only one referral center for cancer treatment during the study period, the existing center (TASH) was used for the study. All voluntary and eligible cases and controls that came to Tikur Anbessa Specialized Hospital during the study period were recruited by using convenient sampling techhnique. Sample size was calculated by taking age (≥65 years) as a risk factor for breast cancer, 80% power, 0.05 significance level at 95% CI, and 1:1 ratio of case to control. Percentage of exposed among control group was 11.9%, percentage of exposed among cases was 21.6% [12], and odds ratio of assumed to be 2.05. Accordingly, a total of 460 participants (230 cases and 230 controls) participated in this study.

Data collection analysis and management

Informed consent was obtained from each study participant prior to data collection. Participants were interviewed by experienced and trained nurses in a convenient place to maintain privacy and confidentiality. Breast physical examination was conducted by oncology residents in order to

select eligible controls. Data entry and analysis was done using SPSS Software, version 20. Binary logistic regression was conducted to see the association between breast cancer and risk factors. Finally, stepwise multivariable analysis was done to adjust for potential confounding variables by selecting variables which have P value ≤ 0.05 in bivariate analysis. The association between breast cancer and different variables was assessed. These variables include socio demographic variables including age, educational status, occupational status, and income. Anthropometric and life style variables included in the model were, weight, BMI, fruit intake, milk intake, consumption of solid/saturated oil, source of fuel, frequency of strenuous exercise and frequency of moderate exercise. In addition, age at menarche, menopausal status family history with first degree relatives, and previous benign disease were also included. P- Value less than 0.05 were considered as statistically significant while adjusted odds ratios with 95% CI were used to see the strength and direction of the association.

In our analysis, potential confounding variables associated with breast cancer were included in the stepwise multiple logistic regression model. After these analysis, income, educational states, height, weight, BMI, fruit intake and frequency of strenuous exercise was considered as potential confounding variables.

When conducting logistic regression analysis, for most of the study variables, reference group was selected by considering the most normative group or if the group is considered as preventive factor for negative outcomes. However, for some variables like, weight and Body mass index (BMI), the highest category was considered as a reference category, since there was inverse relationship between higher BMI and higher weight in our study. For some variables including consumption of vegetable, fruit, meat and milk, the lowest category was considered as references based on similar studies.

Study variables

Based on American Cancer Society fact and figure for breast cancer, Age at diagnosis was categorized as less than 40 ,40-49,50-59, and 60 years and above. BMI was calculated and categorized as follows <25 normal, 25-29.9 overweight, and >30 obese. Menarche was defined

as the age at which the first menses was occurred. Age at first live birth was defined as the age when the first full term birth occurred. Abortion was defined as the termination of pregnancy before 28 weeks of pregnancy. Parity was defined as the number of pregnancies that a participant had. Women who had sisters/mothers/daughters with breast cancer were categorized as having a first-degree family history of breast cancer. Women were classified as menopausal if they had not menstruated during the past one year before the date of data collection. Breast surgery was defined as weather study participant had surgery for non-cancer lump.

Data Quality Assurance and Ethical considerations

The data collection tools were prepared in English and translated to the local language in order to facilitate understanding by the study participants. The data collection tools were pretested in 5% of breast cancer patients not included in the study. Daily supervision was made on all questionnaires collected each day. This research was conducted based on research requirements, regulations and policies that safeguard the wellbeing of study participants and to ensure the reliability and integrity of this finding. Therefore, all methods were carried out in accordance with relevant guidelines and regulations.

This study was approved by Institutional Review Board of the College of Health Sciences of Addis Ababa University with protocol number 073/17/SPH. Written consent was obtained from each of the respondents after the purpose of the study was explained. During breast physical examination for screening of controls, participants who had breast mass were consulted by physicians and their results were given for free in order to get early diagnosis and treatment. Confidentiality and privacy were maintained throughout the study.

Patient and public involvement

Neither patients nor the public were involved in the design of this study.

Results

Bivariate analysis of Socio demographic characteristics and anthropometric factors

In this study, a total of 230 breast cancer cases and 230 healthy controls were participated. The mean age (± SD) was 42.83 ± 12.06 for cases and 39.33 ± 11.14 years for controls. The odds of breast cancer was significantly higher among women aged 40-49 and >60 years. The odds of developing breast cancer among illiterate was 3.78 times higher (95% CI 1.47-9.72, P=0.006) compared to literate women. Similarly, the odds of breast cancer was also 2.82 times higher (95% CI: 1.52-5.22, P=0.001)) among unemployed women as compared to employed. It was also 2.43 times (95% CI: 1.43-4.14, P= 0.001) higher among women with lower socio economic status as compared to women with higher socioeconomic status (monthly income >2000 Ethiopian Birr) per month. However there was no significant association between breast cancer with place of resident and marital status. The odds of breast cancer was 2.13 times higher (95% CI. 1.06 - 4.28, P=0.034) among women with less than 59Kg as compared to women greater than 75 Kg. Similarly, the odds of breast cancer was 2.48 times higher (95% CI: 1.07-5.75, P=0.035) among women with BMI 25-29.9 Kg/m2 (Table 1).

Table 1. Socio demographic characteristics and anthropometric risk factors associated with breast cancer .

Variables	Case	Control	Bivariate analysis	
	N (%)	N (%)	COR (95% CI)	P-value

Residence				
Rural	67 (29.1)	56 (24.3)	1:00	
Urban	163 (70.9)	174 (75.7)	0.783(0.517-1.19)	0.247
Age group (years)				
<39	106 (46.1)	136 (59.1)	1:00	
40–49	58 (25.2)	45 (19.6)	*1.65(1.04-2.63)*	0.034
50-59	39(17.0)	36(15.7)	*1.39(0.827-2.34)*	0.214
>60	27 (11.7)	13 (5.7)	*2.67(1.31-5.41)*	0.007
Marital status				
Ever Married	207(90.0)	201(87.4)	1:00	
Never married	23(10.0)	29(12.6)	0.770(0.431-1.38)	0.378
Education level				
Literate	130(56.5)	196(85.2)	1:00	1:00
Illiterate	100(43.5)	34(14.8)	4.43(2.83-6.94)	0.0001
Occupation				
Employed	70(30.4)	131(57)	1:00	1:00
Unemployed	160(69.6)	99(43.0)	3.03(2.06-4.44)	0.0001
Income	(N=108)	(N=127)		
≥2000	52(48.1)	88(69.3)	1:00	1:00
<2000	56(51.9)	39(30.7)	2.43(1.43-4.14)	0.001
Height (m)				
≥1.60	102(44.3)	91(39.6)	1:00	1:00
< 1.52	48 (20.9)	32(13.9)	1.34(0.788-2.27)	0.280
1.53 – 159	80(34.8)	107(46.5)	0.667(0.445-1.00)	0.050
Weight (kg)				
>75	14(6.1)	25(10.9)	1:00	
<59	143(62.2)	120(52.2)	2.13(1.064.28)	0.034
59.1 -65	37(16.1)	52(22.6)	1.27(0.583-2.77)	0.546
65.1 -74	36(15.7)	33(14.3)	1.95(0.869-4.36)	0.105
BMI(kg/m2)				

Obese (> 30)	10(4.3)	22(9.6)	1:00	
25-29.9(Overweight)	54(23.5)	48(20.9)	2.48(1.07-5.75)	0.035
Normal (< 25)	166(72.2)	160(69.6)	2.28(1.05 -4.97)	0.038

Bivariate analysis using binary logistic regression. 1:00 is Oddis Ratio (OR) for reference/comparison group.

***CI: Confidence interval, COR: Crude Odds Ratio*.**

Life style risk factors associated with breast cancer

In this study, neither cases nor controls had used HRT. On the other hand, 3 cases and none of the controls were smokers. However, 49, (21.3%) of cases and 66, (28.7%) of the controls had history of alcohol consumption. Regarding dietary habit, there was no significant association between vegetable and meat intake with breast cancer. This study also indicated that the odd of breast cancer was 4.04 times higher among women who had used solid oil. Similarly, the odd of breast cancer was 6.46 times higher among women who had used wood or animal dung as fuel source as with use electric as a source of fuel. Regarding physical activity, women who had strenuous physical activities like running, swimming less than 5 hour per week had 0.343 times lower risk of breast cancer . Similarly, women who had moderate physical activity such as walking, playing tennis less than 5 hour per week had 0.228 times less risk (Table 2).

Table. 2. Association of life style risk factors with breast cancer

Variables	**Case N (%)**	**Controls N (%)**	**Bivariate analysis**	
			COR (95% CI)	**P Value**
Smoking				
No	227(98.7)	230(100%)	1:00	
Yes	3	0(0.0%)	1.01(0.998-1.03)	0.082
Alcohol intake				

Non drinker	181(78.7)	164(71.3)	1:00	
Drinker	49(21.3)	66(28.7)	0.673(0.439-1.03)	0.068
Vegetable intake				
Once a week or less	166(72.2)	158(68.7)	1:00	
More than Once a week	64(27.8)	72(31.3)	0.846(0.567-1.26)	0.414
Fruit intake				
Once a week or less	194(84.3)	210(91.3)	1:00	
More than Once a week	36(15.7)	20(8.7)	1.95(1.09-3.48)	0.024
Meat				
Once a week or less	207(90.0)	218(94.8)	1:00	
More than Once a week	23(10.0)	12(5.2)	2.02(979-1.4.16)	0.057
Milk take				
Once a week or less	189(82.5)	207(90.8)	1:00	
More than Once a week	40(15.7)	21(9.2)	2.086(1.19-3.67)	0.011
Solid oil				
No	45(19.6)	114(49.6)	1:00	
Yes	185(80.4)	116(50.4)	4.04(2.67-6.12)	0.0001
Source of fuel				
Electric	54(23.5)	111(48.3)	1:00	
Wood/Animal dung	88(38.3)	28(12.2)	6.46(3.78-11.03)	0.0001
Charcoal/Kerosene	3(1.3)	20(8.7)	0.308(0,088-1,08)	0.066
Combination	85((37.0)	71(30.9)	2.46(1.57-3.87)	0.0001
Strenuous exercise				
No exercise	209(90.9)	203(88.3)	1:00	
< 5 Hr per week	6(2.6)	17(7.4)	0.343(0.133-0..887)	0.027
5 Hr and above per week	15(6.5)	10(4.3)	1.46(0.640-3.32)	0.370
Moderate exercise				
No exercise	173(75.2)	126(54.8)	1:00	
< 5Hr per week	21(9.1)	67(29.1)	0.228(0.133-0.392)	0.0001

5 Hr and above per week	36(157)	37(16.1)	0.709(0.424-1.18)	0.188

Bivariate analysis using binary logistic regression. 1:00 is Oddis Ratio (OR) for reference/comparison group.

Hr: Hour, ***CI: Confidence Interval, COR: Crude Odds Ratio***

Reproductive risk factors associated with breast cancer

In this study the odds of breast cancer was 3.16 times higher among women who had age at menarche less than 12 years . On the other hand, there was no significant association between abortion, as well as age at first birth with breast cancer. Similarly, the odds of breast cancer was 2.34 times higher among post-menopausal women. In addition, women who had previous breast surgery were 8.82 times more likely to develop breast cancer. However, there was no statistically significant association between breast cancer with age at menopause, use of oral contraceptive, duration of breast feeding and age at last birth However the association between breast cancer with family history of first degree relatives was declined after stepwise multiple logistic regression models was applied (Table 3).

Table. 3. Association of reproductive risk factors with breast cancer

Parameter	**Case N (%)**	**Control N (%)**	**Bivariate analysis**		**Multivariable analysis**	
			COR (95% CI)	**P Value**	**AOR (95% CI)**	**P Value**
Age at menarche(years)						
>15	20(11.2)	60(28.6)	1:00		1:00	1:00
12 -15	150(83.8)	144(68.6)	3.13(1.79-5.45)	0.0001	5.94(1.84-19.15)	0.003
<12	9(5.0)	6(2.9)	*4.50*(1.42-14.21)	*0.010*	*3.16(1.78-5.56)*	*0.001*
Family history						

of breast						
No	215 (93.5)	226(98.3)	1:00		1:00	1:00
Yes	15(6.5)	4(1.7)	3.94(1.29-12.07)	0.016	2.60(0.765-8.81)	0.126
Menopausal status						
Premenopausal (ref.)	122(53.0)	161(70.0)	1:00		1:00	1:00
Post-menopausal	108(47.0)	69(30.0)	2.06(1.41-3.03)	0.001	2.34(1.50- 3.64)	0.001
History of benign breast disease						
No	211(91.7)	226(98.3)	1:00		1:00	1:00
Yes	19(8.3)	4(1.7)	5.09 (1.70-15.19)	0.004	8.82(1.96-39.60)	0.005

Stepwise multiple logistic regression . 1:00 is Oddis Ratio (OR) for reference/comparison group.

Adjusted for: age at menarch, , menoposal status, history off surgery, and family history with first degree relatives.

CI: Confidence interval, COR, Cruude odds ratio, AOR: Adjusted Odds Ratio

Multivariable analysis of Sociodemographic, anthropometric and lifestyle factors

. The finding indicated that the odds of breast cancer were 3.29 times higher among women with 40- 49 age groups as compared to women 39 year or less. It was also found that the odds of breast cancer were 4.28 times higher among unemployed women. Regarding life style, milk intake and consumption of solid oil was significantly associated with breast cancer. Similarly, the odd of breast cancer was 5.30 times higher among women had used wood or animal dung as source of fuel as compared to women who used electric. On the other hand, the odds of breast cancer was 0.276 times lower among women who had moderate physical activities like swimming, table tennis, and basketball less than hour per week as compared with women who

had no history of exercise. However the association between breast cancer with educational status, income, height, weight, BMI and frequency of strenuous exercise was declined after stepwise multiple logistic regression models was applied (Table 4)

Table 4. Association of Socio demographic, anthropometric and lifestyle factors with breast cancer

Variables	Case	Control	Bivariate analysis		Multivariable analysis	
	N (%)	N (%)	COR (95% CI)	P-value	AOR (95% CI)	P-value
Age group (years)						
≤39	106 (46.1)	136 (59.1)	1:00		1:00	1:00
40–49	58 (25.2)	45 (19.6)	*1.65(1.04-2.63)*	0.034	*3.29(1.39-7.77)*	*0.007*
50-59	39(17.0)	36(15.7)	*1.39(0.827-2.34)*	0.214	*1.81(0.661-4.96)*	*0.248*
>60	27 (11.7)	13 (5.7)	*2.67(1.31-5.41)*	0.007	*2.44(0.515-11.55)*	*0.261*
Occupation						
Employed	70(30.4)	131(57)	1:00	1:00	1:00	1;00
Unemployed	160(69.6)	99(43.0)	3.03(2.06-4.44)	0.0001	4.28 (2.00-9.16)	0.0001
Milk intake						
Once a week or less	189(82.5)	207(90.8)	1:00		1:00	1:00
More than Once a week	40(15.7)	21(9.2)	2.086(1.19-3.67)	0.011	2.56(1.02-6.43)	0.045
Solid oil						
No	45(19.6)	114(49.6)	1:00		1:00	1;00
Yes	185(80.4)	116(50.4)	4.04(2.67-6.12)	0.0001	6.77(3.17-14.48)	0.0001
Source of fuel						

Electric	54(23.5)	111(48.3)	1:00		1:00	1;00
Wood /animal dung	88(38.3)	28(12.2)	6.46(3.78-11.03)	0.0001	5.30 (1.59-17.64)	0.007
Charcoal/Kerosene	3(1.3)	20(8.7)	0.308(0,088-1.08)	0.066	0.112(0.012-1.01)	0.051
Combination	85((37.0)	71(30.9)	2.46(1.57-3.87)	0.0001	2.45(1.16-5.15)	0.019
Moderate exercise						
No exercise	173(75.2)	126(54.8)	1:00		1:00	1;00
< 5Hr per week	21(9.1)	67(29.1)	0.228(0.133-0.392)	0.0001	0.276(0.114-0.628)	0.002
5 Hr and above per week	36(157)	37(16.1)	0.709(0.424-1.18)	0.188	0.496(0.182-1.36)	0.172

Stepwise multiple logistic regression. ***Adjusted for age, income, education, occupation, height, weight, BMI, fruit intake, milk intake, solid oil intake, sources of fuel, frequency of moderate exercise, frequency of strenuous exercise***, ***1:00 is Oddis Ratio (OR) for reference/comparison group.***

Discussion

In this study, potential risk factors associated with breast cancer were examined. This study revealed that various risk factors, including demographic, life style, reproductive, hormonal, factors, are associated with incidence of breast cancer **[**13,14].

There was no significant association between, place of residence and marital status and risk of breast cancer in our study. This finding was supported by study from Uganda [15]. However, which is different with study done in India that showed significant relationship between breast cancer and being married [16. The odd of breast cancer was higher among women between 40 and 49 age groups. Similarly, the odd of breast cancer was 4.43 times higher among illiterate compared to literate women. This finding is supported by a similar study done in Bangui, which

indicated that the odd of breast cancer was higher among illiterate [17]. However this association was declined after stepwise multiple logistic regression models was applied. It was also found that the odd of breast cancer was 4.28 times higher among unemployed compared to employed women, this might be due to Employed women may have more family income and they may spend money for screening and medical care. Early screening (early screening identify cancer at early stage) and as a result of their better economic level and awareness. This finding is also supported by the previous study done in Bangui [17]. However, the current study was incomparable with another study in India which reported a higher risk of breast cancer among women with higher educational status [18].

Even though, BMI was associated with increased risk of breast cancer [19], in this study, both weigh and BMI of cases were lower than controls, this lower weight and BMI among cases could be due to loss of weight among cases as a result of advanced stage of their disease at time of diagnosis. This finding is comparable with the study done in Malaysia [20]. However, there is also study which had found postmenopausal women with normal BMI, relatively high body fat levels were associated with an elevated risk of invasive breast cancer and the study explained that normal BMI categorization may be an inadequate proxy for the risk of breast cancer in postmenopausal women [19]. In this study, there was no significant association between alcohol consumption, vegetable and meat intake with breast cancer. However, this finding is not supported by similar studies conducted in different parts of US, which observed that a higher intake of fruits and vegetables was associated with a lower breast cancer risk [21-23]. This difference could be due to the difference in type, frequency, and amount of such fruit and plant

based dietary pattern. The other possible explanation could be consumption of such kinds of diet may be limited among study participants due to limited purchasing power.

However, the odd of breast cancer was 2.56 times higher among women who had consumed milk for more than once a week, compared to women who had consumed milk once a week or less. This finding is supported by study done in Western Mexico [24]. Similarly, the Mexico study also support our study regarding consumption of meat was not associated with breast cancer [24]. This association has been explained that high milk intake results in the consumption of cow estrogen metabolites as well as a high caloric intake, both of which increasing the risk of breast cancer [24]. However, this finding is not comparable with different studies, revealed that dairy consumption was inversely associated with the risk of developing breast cancer [25-27]. This difference could be due to the amount, dairy-type, and time of consuming such products. In this study, there are two unexpected results which had significant association with breast cancer, the first result was, and the odd of breast cancer was 6.77 times higher among women who used solid oil, this finding suggested that, since it is saturated fat, which may contain other factors which can increase the risk of breast cancer and the finding was supported by study done in China [28]. This finding also supported by study done in USA reviled that consumption of saturated fat is associated with increased breast cancer risk [29]. The second result was that the odds of breast cancer was 5.3 times higher among women who had used wood or animal dung as a source of fuel, which was supported by study done in USA revealed that indoor burning either wood or natural gas for long time was associated with higher risk of breast cancer [30].

Based on the result of bivariate analysis, the odds of breast cancer were lower among women who had average duration of strenuous exercise of less than 5 hours per week; however, the

association was not significant after adjusted for confounding variable. On the other hand, women who had moderate physical activity of less than 5 hours per week had reduced risk of breast cancer. This finding is comparable with the study done in UK and Sudan which indicated that physical activity was associated with a reduction in breast cancer risk [31, 32]. And this study also supported by systematic review meta-analysis conducted in China stated that physical activity is significantly associated with a decrease in the risk of breast cancer [33].

In this study, only 5.0% of cases and 2.9% of controls had menarche less than 12 years of age. Late menarche (>15 years) was found to be significant protective factor for breast cancer, compared to earlier age at menarche (<12 years), this finding was supported by study done in Morocco [34]. This finding was also in agreement with study done in UK found that breast cancer risk increased by a factor of 1·050 (95% CI 1·044–1·057; p<0·0001) for every year younger at menarche, and independently by a smaller amount (1·029, 1·025–1·032; p<0·0001), for every year older at menopause. [35]. Our study didn't find association between age at first full-term pregnancy, which was different with study done in Morocco [34]. On the on other hand, this finding was comparable with study done in Uganda revealed that there was no association btween breast cancer and early age at at first pregnancy [15].

The odd of breast cancer was 2.34 times higher among post-menopausal women. This finding was comparable with different studies conducted in India [3, 16,]. It was also found that, 19(8.3%) of cases and 4(1.7%) of the controls had previous breast surgery. Women with previous benign breast surgery were 8.82 times more likely to have breast cancer. This finding was supported by studies conducted in India Malaysia and Sudan [17,20, 32].

In this study, the odd of breast cancer was 2.34 times higher among post-menopausal women. This finding is comparable with a study done in Malaysia, indicated that post-menopausal women had 52% increased risk of breast cancer [20]. Similarly, in our study, oral contraceptive was not significantly associated with breast cancer, which was also supported by other study done in India [36]. However, this study is not supported by study done in Cameroon [37]. and it was also contradict with study in Denmark found that approximately 20% higher risk of breast cancer among women who currently use hormonal contraceptives. Similar studies conducted in India and United Kingdom also reported an increased risk of being diagnosed with breast cancer in women who have used hormonal contraception [16, 38, 39]. This difference could be due to length of contraceptive use and type of contraception. There was no significant association between breast cancer with parity and duration of breast feeding, which is comparable with two studies done in India [14,36].

Study limitation

Some limitations should be considered to elucidate the findings of this study. Primarily the finding of our study was based on self-reporting and that could have introduced recall biases regarding their past exposure for different possible risk factors, this may result or under reporting of the outcome under study. Since this is a case control study, all the association may not be necessarily casual. The other most important limitation could be even though breast physical examination may be the only available breast cancer screening modality in resource limited countries like Ethiopia, and it has been made by experienced physician, which may not be highly sensitive and may miss the potential breast mass.

Conclusion and recommendation

Since this study was a case control study which serves as an indicative study usually used to provide early clues and inform further research using more rigorous scientific methods. In this study, socio demographic, lifestyle, anthropometric and reproductive risk factors were assessed. The finding indicated that the odds of breast cancer decreased among young age and employed women. Regarding lifestyle factors, the odds of breast cancer was 6.8 times higher among women consumed solid oil. In addition, women who used wood or animal dung as a source of fuel had 5.3 times higher odds of breast cancer. However, the odds of breast cancer decreased among women who had moderate physical exercise less than 5 hours per week. Finally, the odd of breast cancer was higher among women with early menarche (< 12 years), post-menopausal women and women with previous benign breast surgery. Since there was significant association between most of the modifiable risk factors and breast cancer, it is essential to design appropriate life style modification strategies which may contribute to prevent breast cancer. There is a need to design appropriate intervention to educate women about lifestyle change or behavior modification to decrease their breast cancer risk. In addition, since there are varieties of culture, food choice, feeding habit, physical activities and other risk factors, it is important to conduct future studies with a larger sample size including different regions or diverse population in order to come up with more representative evidence.

Declaration

Abbreviations

CI: Confidence Interval; Hr.: Hour; HRT: Hormone Replacement Therapy; SPSS: Statistical Package for Social Sciences; TASH: Tikur Anbessa Specialized Hospital.

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Conflict of Interests:

- All authors declare that there is no conflict of interests regarding the publication of this paper manuscript.

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Ethics approval: This study was approved by Institutional Review Board of College of Health Sciences of the Addis Ababa University with protocol or approval number, (073/17/SPH).

References

1. American Cancer Society. Breast Cancer Facts & Figures 2015-2016. Atlanta: American Cancer Society, Inc. 2015.
2. Ma C, Nepal M, Kim JH, et.al. A new look at molecular biology of breast cancer. Cancer Biology & Therapy. 2019; 20(1) _ doi.org/10.1080/15384047.2018.1507259.
3. Bhadoria AS, Kapil U, Sareen N, et.al. Reproductive factors and breast cancer: A case–control study in tertiary care hospital of North India. Indian J Cancer 2013;50 (4) 316-321.

4. Rweyemamu LP, Akan G, Ismael C. etal .The distribution of reproductive risk factors disclosed the heterogeneity of receptor-defned breast cancer subtypes among Tanzanian women. BMC Women's Health (2021) 21:423 doi.org/10.1186/s12905-021-01536-6.
5. Eman M. Seif El-Nasr. Breast Cancer risk factors and screening practices Among Women Attending Family Health Centers in Cairo Governorate**.** IOSR-JNHS 2017; 6(3): 12-23. DOI: 10.9790/1959-0603011223.
6. Memirie ST, Habtemariam MK, Assefa M et.al. Estimates of Cancer Incidence in Ethiopia in 2015 Using Population-Based Registry Data. Journal of Global oncology. 2018; 4:1-11.
7. Addis Ababa City Cancer Registry, Tikur Anbessa Specialized Hospital School of Medicine, Addis Ababa University, Ethiopia, 2014. https://afcrn.org/membership/membership-list/100-addisababa.
8. Berhe S, Sinshaw W, Hailu M et.al. Assessment of Knowledge of Breast Cancer and Screening Methods among Nurses in University Hospitals in Addis Ababa, Ethiopia, 2011: ISRN. Oncology. 2013; 2013:1-8.
9. Workineh MU, Lake EA, Adella GA. Breast Self-Examination Practice and Associated Factors Among Women Attending Family Planning Service in Modjo Public Health Facilities Southwest Ethiopia. Breast Cancer: Targets and Therapy 2021;13: 459-469.
10. Ethiopian cancer Association, 2007.
11. Addis Ababa University, College of Health Science, Background of Tikur Anbessa Hospital, 2020.

12. Hadjisavvas A, Loizidou MA, Middleton N, etal. An investigation of breast cancer risk factors in Cyprus: a case control study. BMC Cancer. 2010; 10(447). doi.biomedcentral.com/1471-2407/10/447.

13. Momenimovahed Z, Salehiniya H. Epidemiological characteristics of and risk factors for breast cancer in the world, Review, Breast Cancer - Targets and Therapy. 2019; 11:151-164.

14. Palachandra A., Ishawaraprasad G. D, Sreelatha C. Y. et.al. Risk factors associated with carcinoma breast in India: a case control study. Int Surg J. 2017;4 (9):3136-3140.

15. Galukandea M, Wabingab H, Mirembec F,et al. Breast Cancer Risk Factors among Ugandan Women at a Tertiary Hospital: A Case-Control Study.Oncology. 2016; 90(6): 356–362. doi:10.1159/000445379.

16. Takalkar U, Asegaonkar S, Kodlikeri P, et.al. Hormone Related Risk Factors and Breast Cancer: Hospital Based Case Control Study from India. Research in Endocrinology. 2014; (2014): 1-6.

17. Balekouzou A, Yin P, Pamatika CM et.al. Reproductive risk factors associated with breast cancer in women in Bangui: a case–control study. BMC Women's Health. 2017; 17:(4): 1-9.

18. Liu K, Zhang W, Dai Z et.al. Association between body mass Association of Body Fat and Risk of Breast Cancer in Postmenopausal Women with Normal Body Mass Index: Cancer Management and Research. 2018; 10:143–151.

19. Iyengar NM, Arthur R, Manson JE et.al. Association of Body Fat and Risk of Breast Cancer in Postmenopausal Women With Normal Body Mass Index: A Secondary Analysis of a Randomized Clinical Trial and Observational Study. *JAMA Oncology*. 2019 ; 5(2): 155–163. doi: 10.1001/jamaoncol.2018.5327.

20. Tan M-M, Ho W-K, Yoon S-Y, et al. A case- control study of breast cancer risk factors in 7,663 women in Malaysia. PLoS ONE. 2018; 13(9): 1-12.

21. Farvid MS, Chen WY, Michels KB et.al. Fruit and vegetable intake and risk of breast cancer. Proceedings of the American Association for Cancer Research Annual Meeting, Washington, DC. Philadelphia (PA):AACR; Cancer Res 2017; 77(13) .doi:10.1158/1538-7445.AM2017-5325A.

22. Farvid MS, Chen WY, Michels KB et.al. Fruit and vegetable consumption and breast cancer incidence: Repeated measures over 30 years of follow-up: BMJ. 2016; 353:i2343. doi: 10.1136/bmj.i2343.

23. Link LB, Canchola AJ, Bernstein L, et.al. Dietary patterns and breast cancer risk in the California Teachers Study cohort. AmJ Clin Nutr. 2013; 98: 1524–32.

24. Galván-Salazar HR, Arreola-Cruz A, Madrigal-Pérez D, et.al, Association of Milk and Meat Consumption with the Development of Breast Cancer in a Western Mexican Population. Breast Care. 2015;10: 393–396.

25. Yul L, Liu L, Wang F, et.al. Higher frequency of dairy intake is associated with a reduced risk of breast cancer: Results from a case-control study in Northern and Eastern China. Oncology letters. 2019; 17(3):2737-2744.

26. Shin WK, Lee HW, Shin A, et.al. Milk Consumption Decreases Risk for Breast Cancer in Korean Women under 50 Years of Age: Results from the Health Examinees Study. Nutrients. 2019; 12 (1). doi:10.3390/nu12010032

27. Zang J, Shen M, Du S et.al. The Association between Dairy Intake and Breast Cancer in Western and Asian Populations: A Systematic Review and Meta-Analysis. Journal of Breast Cancer. 2015; 18(4): 313-322.

28. Xia H, Ma S, Wang S.et.al. Meta-Analysis of Saturated Fatty Acid Intake and Breast Cancer Risk in China. Medicine. 2015; 94(52): 1-10.

29. Dandamudi A, Tommie J, Nommsen-Rivers L et.al. Dietary Patterns and Breast Cancer Risk: A Systematic Review . *Anticancer Res*; 2018; *38*(*6*):*3209-3222*. *doi*: *10.21873/anticanres.12586*.

30. White AJ, Sandler DP. Indoor Wood-Burning Stove and Fireplace Use and Breast Cancer in a Prospective Cohort Study in USA. Environ Health Prospect. 2017; 125(7): 1-7.

31. Guo W, Fensom GK, Reeves GK ,et.al Physical activity and breast cancer risk: results from the UK, Bio bank prospective cohort. British Journal of Cancer. 2020; 122:726–732.

32. Ahmed HG ,Musa RM, Eltybe MM et al. Role of Some Risk Factors in the Etiology of Breast Cancer in the Sudan. The Open Breast Cancer Journal, 2010; 2: 71-78 DOI: 10.2174/1876817201002010071.

33. Chen X , Wang O, Zhang Y, et.al. Tan X. Physical Activity and Risk of Breast Cancer: A Meta-Analysis of 38 Cohort Studies in 45 Study Reports. Value Health. 2019; 22 (1):104-128. doi: 10.1016/j.jval.2018.06.020.

34. Khalis M, Charbotel B, Chajès V, et al. Menstrual and reproductive factors and risk of breast cancer: A case-control study in the Fez region, Morocco. PLoS ONE 2018; 13(1): 1-12.

35. V Beral, D Bull, K Pirie, et.al. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies THE LANCET Oncology. 2012; 13(11):1141-1151.

36. *Mohite VR, Pratinidhi AK, Mohite RV. Reproductive risk factors and Breast cancer: a case control study from rural India* Bangladesh. Journal of Medical Science. 2015; 14(3)258-264.

37. Paul, E. , Henri, E. , Valère, M.et al. Risk Factors for Breast Cancer in the City of Douala: A Case Control Study. *Advances in Breast Cancer Research*. 2020; 9: 66-77. doi: 10.4236/abcr.2020.93006.

38. Women s Health Concern. Breast Cancer risk factors. Medical advisory Council, British Menopause Society. Reviewed 2015, www. Women s health concern.

39. Hunter DJ Oral Contraceptives and the Small Increased Risk of Breast Cancer. N Engl J Med . 2017; 377(23):2276-2277 .doi: 10.1056/NEJMe1709636

This study was more or less organized based on the following STROBE (Strengthening the Reporting of Observational studies in Epidemiology checklist: