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Breast Cancer and Its Determinants in Ethiopia: A Systematic Review and Meta-Analysis

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Breast Cancer and Its Determinants in Ethiopia: A Systematic Review and

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23 Abstract

Objectives: Breast cancer is the leading cause of cancer morbidity and mortality among women.
There is no representative data regarding the magnitude and risk factors of breast cancer in
Ethiopia. Hence, this review was intended to identify the determinants of breast cancer in
Ethiopia.

Design: A systematic review and meta-analysis was conducted. Databases like PubMed/MEDLINE, HINARI, Science Direct, and Google Scholar were searched to find articles. Low-quality articles were excluded. Heterogeneity was assessed using the I² statistics at the value >20% and the p-values <0.01 from the Cochrane Q-test. The effect estimates for pooled proportion and pooled odds ratio along with a 95% confidence interval were determined using the random effect model as a remedial for the heterogeneity problem. Setting: The studies conducted in Ethiopian were screened and included in this extended analysis. Participants: All people male and females, all age groups were included in this analysis. **Outcomes:** The pooled proportion of breast cancer was the primary outcome of this study whereas the determinants that affect the occurrence of breast cancer were the secondary outcome identified in this study.

Results: The pooled proportion of breast cancer is 22. 98% (95%CI: 19.48, 26.48) in Ethiopia. Consuming packed foods (POR=2.12, 95%CI:1.41, 3.17), presence of high cholesterol (POR=4.08; 95%CI: 2.75, 6.07), physical inactivity (POR=3.27; 95%CI: 1.80, 5.94), high body mass index (POR=2.27; 95%CI: 0.85, 6.03), post-menopause (POR=2.25; 95%CI: 1.63, 3.10), family history of cancer (POR=3.65; 95%CI: 0.85, 15.71), and lack of breastfeeding (POR=2.76; 95%CI: 0.90, 7.92) were the determinants of breast cancer.

44 Conclusions: The magnitude of breast cancer is high according to this review. Processed food
45 consumption, high cholesterol in the body, lack of physical activity, high body mass index, post46 menopause, family history of cancer, and lack of breastfeeding were the risk factors for breast
47 cancer.

48 Keywords: breast cancer, cancer, determinants of breast cancer, risk factors, Ethiopia

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50 Article Summary

- 51 Strengths and limitations of this study
 - ✤ This study is the first systematic review and meta-analysis on breast cancer in Ethiopia.
 - The evidence generated from this systematic review and meta-analysis might be more representative of the country's situation than pocket studies.
 - Only a few studies were found to pool the odds ratio for some factors.
 - Only four out of 11 regions had studies regarding breast cancer with the dominance of Addis Ababa city.

58 Background

Breast cancer (BC) is a diverse disease with numerous morphological and molecular subgroups ¹.
It is found to be the most common cause of cancer deaths in 11 regions of the world ². It is one of
the most frequently diagnosed cancers and the leading cause of cancer deaths in females
worldwide ³. The recent global burden of cancer statistics (GLOBOCAN) showed that BC has
surpassed lung cancer and accounted for 2.3 million (11.7%) of all new cancer cases globally. It
affects one in four women and contributes to one in six deaths of women ⁴.

According to GLOBOCAN 2002, breast cancer incidence rates were increasing faster in most low- and middle-income countries (LMICs) than in places previously known for their high incidence rates ⁵. In this regard, the global cancer burden by 2040 will be 28.4 million cases, a 47% increase over the cancer burden in 2020 ⁴. Most of these expected new occurrences of cancer will be in the developing world ⁶. Even if the incidence rate is higher in developed countries than in developing countries ⁴, ⁷, the reverse is true regarding the death rate (15 BC deaths in developing countries versus 12.8 in developed countries per 100,000) ⁴. In 2019, there Page 5 of 45

BMJ Open

were estimated 5900 incident cases of breast cancer in Ethiopia with the highest agestandardized incidence rate of 12.5 per 100,000 and a death rate of 9.7 per 100,000 ⁸.

Previous studies identified that the incidence of BC varies widely across the world due to differences in the level of education, economic status, environmental conditions, eating habits, lifestyle variables, and other cultural traditions. Westernized lifestyles (namely delayed pregnancies/childbirth, reduced breastfeeding, early age at menarche, sedentary lifestyles, and poor diet) and improving cancer registration and cancer detection are among the factors for the projected rise of breast cancer count in LMICs ⁹⁻¹¹. Lack of knowledge about the disease, improper screening programs, delayed diagnosis, and insufficient medical facilities are also there for the increasing breast cancer burden in underdeveloped countries 9, 12, 13. Widespread urbanization, shifting patterns of reproductive and environmental risk factors, obesity, decreased physical activity, and rising life expectancy are among the major factors contributing to the steady rise in breast cancer incidence in low-income nations. Low socio-economic level, on the other hand, is related to an increased incidence of aggressive premenopausal breast cancers, as well as late-stage diagnosis and lower survival. Late menopause and early menarche are also among the risk factors that could increase the exposure of breast tissue to estrogen hormone. In contrast to this, pregnancy and appropriate breastfeeding help to reduce the risk of breast cancer 9, 12-15

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90 Comprehensive identification of the magnitude and determinants of breast cancer is critical for 91 developing nations like Ethiopia, as this will aid in the development and implementation of 92 effective breast cancer prevention initiatives. Breast cancer is not well studied in Ethiopia. 93 Different pocket studies done so far may not represent the entire picture of the determinants of 94 breast cancer in Ethiopia because most of them were limited to small sample sizes, limited

populations, and limited research regions. It is critical to disclose information about breast cancer to reduce risk factors. As a result, the purpose of this study was to determine the magnitude of breast cancer and its determinants in Ethiopia.

Study design

A systematic review and meta-analysis was conducted. The protocol was registered on Prospero with registration number (CRD42023417733). To conduct this review, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist ¹⁶ was used.

Searching strategy

A comprehensive search of databases like PubMed/MEDLINE, HINARI, Science Direct, and Google Scholar was used to find the relevant articles. The searches were limited to articles written using the English language. In addition to the electronic database search, grey literature was searched using Google search, and the Digital Libraries of Universities. Finally, the reference lists of the included articles for related studies were searched. To facilitate the article searching process, the keywords: ["breast" OR "mammary gland" AND "cancer" OR "tumor" OR "malignancy" OR "breast cancer" OR "breast malignancy" OR "breast tumor" AND "Risk factors" OR "Associated factors" OR "Determinants" OR "predictors" AND "Ethiopia" OR "Addis Ababa" OR "Northern Ethiopia" OR "North west Ethiopia" OR "Southern Ethiopia" OR "South Western Ethiopia" OR "Western Ethiopia" OR "East Ethiopia"] were used. The final date of searching was March 6, 2023.

- **Eligibility criteria**
- **Inclusion criteria**

Page 7 of 45

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1 2		
2 3 4	117	To be included in this review, the study should report either the determinants of breast cancer
5 6	118	and/or the magnitude (incidence, prevalence, number) of breast cancer.
7 8 0	119	Study setting: Studies conducted in Ethiopia (both institution-based and population-based) were
9 10 11	120	part of this systematic review.
12 13	121	Study population: The study involved all human population (male, female, children, and adults)
14 15	122	in Ethiopia.
16 17 18	123	Study design: All observational studies (cross-sectional, case-control, and cohort) that reported
19 20	124	the magnitude of breast cancer and its determinants were evaluated to be included.
21 22	125	Publication status: Both published and unpublished studies were considered for inclusion.
23 24 25	126	Exclusion criteria
26 27	127	Articles with unclear methodologies, studies whose full-text papers were not available after at
28 29	128	least two personal email contacts with the corresponding authors, and articles that didn't indicate
30 31 22	129	the outcome of interest were excluded.
32 33 34	130	Outcome variables assessment
35 36	131	There were two outcomes in this study: the first outcome was the magnitude of confirmed breast
37 38	132	cancer based on the operational definition of those studies. The total number of people who had
39 40 41	133	breast cancer was divided by the total number of people participating in the study and multiplied
42 43	134	by 100 which was used to determine the magnitude of breast cancer. The second outcome of this
44 45	135	review was the determinants of breast cancer.
46 47 48	136	Study selection and data extraction
49 50	137	All the articles searched from Databases were imported into EndNote version X7, and duplicates
51 52	138	were removed. Based on the predefined inclusion criteria, two authors (ATS and AED)
53 54 55	139	independently assessed and identified papers by their titles, abstracts, and full texts. The screened
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items were then compiled, and any disagreement was handled by inviting and discussing with the
third author (DRT). Data extraction was performed using the Joanna Briggs Institute (JBI) data
extraction format ¹⁷⁻¹⁹. The data extraction format included the primary author, publication year,
study period, region, study area, study setting, study design, study population, publication status,
sample size, response rate, and the number of cases/breast cancer. For the second outcome, data
were extracted into a two-by-two table.

146 Quality assessment

JBI meta-analysis of statistics assessment and review instrument (MAStARI) quality appraisal tool was used to assess the quality of the articles ¹⁹. The JBI parameters included an appropriate sampling frame, proper sampling technique, study subject and setting description, sufficient time to exposure measurement, use of valid methods for the identified conditions, a valid measurement for variables and conditions, using appropriate statistical analysis including control of confounding. Accordingly, quality was categorized as low (total score of ≤ 2), moderate (total score of 3–4), or high (total score of >5) in terms of their likelihood ¹⁹. The quality of the included studies was assessed by two independent authors (ATS and DRT). The discrepancy during the quality appraisal of the studies was resolved by the agreement of the two reviewers. Finally, papers with an overall quality score of <37.5% and/or those not reporting the outcome of interest were excluded from the systematic review and meta-analysis (Additional file 1).

158 Data synthesis strategy

The data were extracted into Microsoft Excel. Then it was exported to the STATA software, version 14, for further analysis. The standard errors of the included studies were calculated using the formula $SE = \sqrt{p(1-p)}/n$. The I² statistics and the p-values of the Cochrane Q-test were used to identify the heterogeneity problem. The p-values of the Cochrane Q test < 0.1 were used Page 9 of 45

BMJ Open

to indicate the presence of heterogeneity among the studies. The Higgins I² test statistics was used to calculate the percentage of total variance due to heterogeneity across the studies. Heterogeneity was declared for the I^2 value > 20%. As a remedial for the heterogeneity among the studies by the test statistic, the DerSimonian-Laird's impact was evaluated using a random-effects model. Moreover, the subgroup analysis by region, study design, study setting, and study population was done to identify the possible source of heterogeneity. The effect sizes were expressed as proportion and odds ratio along with a 95% confidence interval (CI). The forest plots were used to display the meta-analysis results. Publication bias was investigated graphically using a funnel plot and statistically using Egger's weighted regression and/or Begg's rank correlation tests and decided as significant at p-value < 0.05. A leave-one-out sensitivity meta-analysis was used to assess the robustness of the findings.

Patient and public involvement: No patient was involved in this study.

Result

About 1644 articles were identified through database searching while 19 of them were included

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in this systematic review and meta-analysis (Figure 1).

Description of included studies in the systematic review and meta-analysis

Of the total 19 articles included with 96044 participants, the majority of them were from Addis Ababa (AA), followed by southern nations, nationalities and peoples (SNNP) and Amhara regions (Table 1).

Table 1: Descriptive summary of 19 studies included in the meta-analysis to estimate breast cancer magnitude and its determinants in Ethiopia

Studi	Author	Reg	Population	Study	Sampl	Respon	Proport
es ID	(Year)	ions		design	e size	se rate	ion (%)
2	Abebe et al (2017) ²⁰	AA	Cancer patients	Cross- section al	112	93.0%	25
3	Ayele et al	SN	General women	Cross-	7,580	99%	0.09

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	(2021) ²¹	NP		section al			
4	Ayele et al (2022) ²²	Oro mia	Deceased women	Cross- section al	800	98.0%	2.63
5	Duche et al. (2021) ²³	AA	Women with breast cancer	Case- control	226	97.0%	48.67
6	Endalamaw et al (2021) ²⁴	Am har a	Children attended the OPD	Cross- section al	1270	98.97%	0.08
7	Gebretsadik et al (2021) ²⁵	SN NP	Cancer patients	Cross- section al	3002	100%	18.62
8	Hailu et al. (2020) ²⁶	AA	Patients seen for suspicion of cancer	Cross- section al	9,261	100.0%	6.34
9	Hassen et al (2021) ²⁷	AA	Women with breast cancer	Case- control	460	100%	50
10	Hassen et al (2022) ²⁷	AA	Women with breast cancer	Case- control	460	100%	50
11	Kibret et al (2022) ²⁸	SN NP	Cancer patients	Cross- section al	1,810	100%	4.97
12	Kumie et al (2020) ²⁹	Am har a	Women with breast cancer	Cross- section al	182	100%	50
13	Mekonen et al (2021) ³⁰	AA	Cancer patients	Case- control	100	100.0%	50
14	Memirie et al. (2018) ³¹	AA	Cancer patients	Cross- section al	64,28 5	100%	21.76
17	Shalamo (2022) ³²	SN NP	Women with breast cancer	Case- control	408	95%	32.11
18	Solomon et al (2019) ³³	AA	Cancer patients	Cross- section al	919	100%	14.8
19	Tefera B et al. (2016) ³⁴	Am har a	Cancer patients	Cross- section al	540	100.0%	14.07
22	Timotewos et al (2018) ³⁵	AA	Cancer patients	Cross- section al	4139	100%	22.54
23	Tolessa et al (2021) ³⁶	AA	Women with breast cancer	Case- control	348	100.0%	33.33
24	Woldu et al	AA	Cancer patients	Cross-	142	100%	14.79

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3 4		(2017) ³⁷ section al							
5 6	184								
7 8 9	185	Prevalence of breast cancer in Ethiopia							
10 11	186	Nineteen (19) articles were included to pool the magnitude of breast cancer ²⁰⁻³⁸ . Accordingly,							
12 13	187	the pooled proportion of breast cancer in Ethiopia was found to be 22. 98% (95%CI: 19.48,							
14 15	188	26.48; I ² =99.9%, p=0.000) (Figure 2).							
16 17 18	189	Subgroup analysis							
19 20	190	Since significant heterogeneity was found when pooling the magnitude of breast cancer,							
21 22	191	subgroup analysis was done to further check for the source of heterogeneity. As of the subgroup							
23 24 25	192	analysis by region, the proportion of breast cancer was found to be 30.19%; 95%CI: 23.65, 36.74							
25 26 27	193	in AA, 20.91%;95%CI: 2.59, 39.24 in Amhara, 13.66%;95%CI:4.81, 22.51 in SNNP, and							
28 29	194	2.63%;95%CI:1.52,3.73 in Oromia (Additional file 2). The result of subgroup analysis by study							
30 31	195	setting showed that the pooled magnitude of breast cancer was high for institution-based studies							
32 33 34	196	(24.86%;95%CI:20.69, 29.02) while 14.79%; 95%CI: -2.56, 32.15) for population-based studies							
35 36	197	(Additional file 3). When analyzed by study design, the pooled proportion of breast cancer is							
37 38	198	highest for studies by case-control study design (43.79%;95%CI: 36.21, 51.38) than studies by							
39 40 41	199	cross-sectional design (14.27%; 95%CI: 10.24, 18.3) (Additional file 4). Furthermore, the							
42 43	200	subgroup analysis was done by the study population. Accordingly, the pooled magnitude of							
44 45	201	breast cancer is found to be (43.9%; 95%CI: 36.45,51.34), (19.77%; 95%CI: 14.33, 25.21), (
46 47	202	6.34%; 95%CI: 5.84, 6.83), (2.63%; 95%CI: 1.52, 3.73), (0.09%; 95%CI: 0.02, 0.16), and							
48 49 50	203	(0.08%; 95%CI: -0.08, 0.23) among women participated in case-control studies of breast cancer,							
51 52	204	among cancer patients, among patients seen for the suspicion of cancer at the oncology unit,							
53 54 55	205	among deceased women, among general women and among children attended pediatric							

Page 12 of 45

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outpatient department (OPD), respectively (Additional file 5). A significant source of heterogeneity was observed across all the sub-group analyses done by region, study design, study

setting and study population (Table 2).

209	Table 2: Subgroup analysis for the pooled proportion of breast cancer in Ethiopia						
	Variables	subgroup	No of included studies	Sample size	Proportion of Breast cancer	Heterog across studies	jeneity the
						l ^{2 (} %)	p-value
	Region	Addis Ababa	11	80452	30.19%	99.7%	0.000
		Amhara	3	1992	20.91%	99.3%	0.000
		SNNP	4	12800	13.66%	99.7%	0.000
		Oromia	1	800	2.63%	0.0%	-
	Study	Cros-sectional	13	94042	14.27%	99.9%	0.000
	design	Case-control	6	2002	43.79%	91.6%	0.000
	setting	Population-based	3	76004	14.79%	100%	0.000
		Institution-based	16	20040	24.86%	99.5%	0.000
	Population	Women in case- control study of breast cancer	6	2084	43.9%	91.8%	0.000
		Cancer patients	9	75049	19.77%	99.3%	0.000
		suspected patients evaluated at oncology unit	1	9261	6.34%	0.0%	-
		Deceased women	1	800	2.63%	0.0%	-
		General women	1	7580	0.09%	0.0%	-
		Children attended paediatric OPD	1	1270	0.08%	0.0%	-
210							

Publication bias

212	The funnel plot appeared asymmetric indicating the presence of publication bias (Additional file
213	6), Egger's test ($P = 0.017$). Hence, further analysis was done using trim and fill analysis since
214	publication bias was observed (Additional file 7).

Sensitivity Analysis

Page 13 of 45

BMJ Open

A leave-one-out sensitivity analysis was done to test the reliability of the findings. According to
the sensitivity analyses output, using the random-effects model was robust, and no single study
affected the pooled proportion of breast cancer (Additional file 8).

10 219 Determinants of breast cancer
 11

In individual studies, factors like young age, age at menarche, residence, occupation, exposure to smoking dried meat, use of processed foods, lack of intake of milk, fruits, and eating sea foods, high cholesterol, fuel source (wood, charcoal, kerosene, animal dung), lack of physical activity, menopause, contraceptive use, family history of cancer, history of abortion, benign breast disease and breast injury, radiation exposure, absence of breastfeeding, high body mass index (BMI), anemia and thrombocytosis were found to be the determinants of breast cancer. From these, age, age at menarche, use of processed foods, high cholesterol, lack of physical activity, menopause status, family history of cancer, absence of breastfeeding, and BMI were reported to be significant in more than one study and pooled together. However, only seven (7) factors showed statistical significance in the meta-analysis. Accordingly, those people who consume processed foods/drinks have 2.12 (POR=2.12, 95%CI:1.41, 3.17, I²=0.0%, p=0.826) times more odds of breast cancer than their counterparts (Additional file 9). This meta-analysis also revealed that the risk of breast cancer is increased by 4 (POR=4.08; 95%CI: 2.75, 6.07, I²=0.0%, p=0.888) in the presence of high cholesterol including solid oil as compared to low cholesterol (Additional file 10). Those individuals who are physically inactive had 3.27 (POR=3.27; 95%CI: 1.80, 5.94, $I^2=65.2\%$, p=0.090) times more odds of breast cancer than their counterparts (Additional file 11). The pooled odds of breast cancer is 2.25 (POR=2.25; 95%CI: 1.63, 3.10, $I^2=0.0\%$, p=0.433) times more likely in post-menopausal women than premenopausal women (Figure 3). In another way, the pooled odds of breast cancer is 3.65 (POR=3.65; 95%CI: 0.85, 15.71) times more likely

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for those people who have a family history of cancer as compared to those without a family history of cancer (Additional file 12). Regarding the BMI, when compared to those people having normal BMI, high BMI was associated with 2.27 (POR=2.27; 95%CI: 0.85, 6.03) times increased odds of breast cancer (Additional file 13). Those women who had no history of breastfeeding have 2.76 (POR=2.76; 95%CI: 0.90, 7.92) times more odds of breast cancer compared to their counterparts (Additional file 14).

DISCUSSION

According to this study, the pooled proportion of breast cancer in Ethiopia is 22. 98 (95%CI: 19.48, 26.48). This finding is high when compared to the age-standardized incidence rate of breast cancer in Ethiopia (12.1 per 100,000 populations)⁸ The observed variation could be due to a difference in the denominator. As it is shown in the subgroup analysis, the proportion of breast cancer varies in different situations. For example, the proportion of pooled breast cancer is higher-19.77% in confirmed cancer patients, 6.34% among patients seen for the suspicion of cancer at the oncology unit, 2.63% among deceased women, 0.09% among general women, and 0.08% among children attended pediatric OPD. This shows that breast cancer varies depending on the study population (male vs female, child versus adult, deceased versus alive, patient versus healthy population). In another way, this finding is low as compared to the breast cancer cases (25%) among women newly diagnosed with cancers in the GLOBOCAN 2012 and 2018 study ³⁹, ⁴⁰ and the study in the United states of America (USA) (29%) ⁴¹. The possible reason might be that the proportion in the current analysis is inclusive of all populations even though dominated by cancer populations. Furthermore, the difference in socio-economic and demographic conditions might be another reason for this variation. Developed countries have improved cancer

Page 15 of 45

BMJ Open

detection, registration, and reporting than Ethiopia which could make a difference between countries regarding breast cancer proportions.

In this systematic review and meta-analysis, factors such as the use of processed foods/drinks, high cholesterol, lack of physical activity, post-menopausal status, family history of cancer, absence of breastfeeding, and high BMI including obesity were reported as risk factors for breast cancer. Accordingly, a family history of cancer including breast cancer was reported as a risk factor for breast cancer (pooled OR=3.65;95%CI:0.85, 15.71). This finding is consistent with the studies conducted in Iran ^{42, 43}, the United kingdom ⁴⁴, China ⁴⁵, and Malaysia ⁴⁶. This might be due to the presence of some inherited defect that will facilitate the development of the disease.

This study also revealed non-breastfeeding as a risk factor for breast cancer which is in line with the finding of previous systematic review ⁴⁷, studies done in China ⁴⁵, Iran ⁴², USA (^{48, 49} where studies conducted in stated that breastfeeding minimizes the risk of breast cancer. The possible reason could be because of the hormonal effect of breastfeeding for the protection or reduction of breast cancer. Both the current study and previous studies revealed the protective effect of breastfeeding for breast cancer. The possible mechanism for the observed protective probability of breast cancer in this study might be attributed to the differentiation induced to the breast lobe by lactation that might transform cancer-prone stem cell 1 to refractive stem cell 2⁵⁰. There might also be less exposure of breast tissues to hormones as breastfeeding inhibits ovulation and the hormones from the ovulation cycles ⁵¹.

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This current finding also showed that high BMI is the risk factor for breast cancer in which people with high BMI were about 2.27 times more likely to develop breast cancer than their counterparts. This finding is similar to the previous study ^{46, 49, 52-55}, and studies in Iran ^{42, 43} but contrasts with the finding of the study conducted in Northern California ⁵⁶. High BMI including

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obesity is found to be a risk factor for breast cancer in postmenopausal women ⁵⁷⁻⁵⁹. Increased body fat might increase the level of circulating estrogens and decrease levels of sex hormonebinding globulin ⁶⁰. Besides, the inflammation that accompanies obesity might also contribute to breast cancer development ⁶¹.

In this study, it was also found that lack of physical activity is a risk factor for breast cancer and it was reported by previous studies ^{42, 62, 63}. The possible explanation for the association between breast cancer and lack of physical activity might be that physical inactivity could increase the probability of fat accumulation in the body as some studies ^{42, 43} found that obesity is a risk factor for breast cancer.

This study revealed that the use of processed food and/or drink was found as a risk factor for breast cancer. This is consistent with the finding of the individual studies conducted in Latin America ⁶⁴, Iran ⁶⁵ and other reviews ^{53, 66}. According to this study, consumption of packed food/drinks was found to be the risk factor for breast cancer. This result is in line with the study findings of other countries which implies that a decrease in the intake of packed or ultra-processed food or drink should be encouraged to reduce the incidence of breast cancer among women. The possible reason for this association might be due to the presence of different additives to processed foods during the processes that could initiate cancer development. Other reasons might be that packed foods are rich in energy/added sugar, saturated and trans-fatty acids, and salt and have low content in fibers and vitamins that would increase the risk of breast cancer 67.

In this review, a positive association between high cholesterol level and breast cancer was found.
However, studies are contradicting in this regard. Some studies found high cholesterol as a risk
factor ⁶⁸ while some found it as a protective factor ^{69, 70}. Those studies that found the protective

Page 17 of 45

BMJ Open

effect of high cholesterol explained it as "statin-the cholesterol-lowering medication might reduce the breast cancer risk too" ^{71, 72}. In this study, the total cholesterol including the use of hard oil was used as high cholesterol and was found to be associated with increased breast cancer risk. The possible reason for the positive association between high cholesterol and breast cancer is that cholesterol is the precursor for estrogen which is the cause of breast cancer ^{73, 74}. Women with high body fat might have an increased risk of breast cancer though their BMI is normal.

Moreover, the current study revealed that post-menopausal status is one of the risk factors for breast cancer which is consistent with the previous studies ⁷⁵ where it was indicated as a breast cancer risk is higher in postmenopausal than premenopausal women. However, this result seems to contradict the finding in another meta-analysis in which premenopausal women had about 43% higher risk of breast cancer than postmenopausal women of the same age. In another way, that study added that postmenopausal women with high body fat had an increased risk of breast cancer than premenopausal women ⁵⁹. Hence, the association between the increased possibility of breast cancer and postmenopausal status in this study might be justified as those postmenopausal women could have high body fat as well. Another possible explanation is that post-menopausal women in this study might have reached menopause at late age commonly after 50 years as late menopause is found to be a risk factor in another study ⁴⁵. Because extended menstruation could expose the breast tissue to increased exposure to hormones like estrogen ⁵³. Besides, the use of postmenopausal hormone replacement therapy couldn't be ruled out from the possible reasons as this might increase the breast cancer risk in postmenopausal women⁴⁷. This implies that the hormonal change in pre-and post-menopausal contributes to a risk or solution for breast cancer among women.

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This finding implies that breast cancer is increasing in the country and deserves attention. Although the disease is partly due to non-modifiable risk factors, the presence of modifiable factors calls for all concerned bodies to focus on the disease to prevent the disease, diagnose and treat it timely, and minimize the risk of death and economic impact of the disease. Breast cancer screening should be initiated and strengthened in the country. Decentralization of the cancer registry is required.

The strengths of this study are that it is the first systematic review and meta-analysis on breast cancer in Ethiopia. Next, it shares the strengths of systematic review and meta-analysis over a single study as the evidence generated from this systematic review and meta-analysis might be more representative of the country's situation than pocket studies. The limitation of this study is that only a few studies were found to pool the odds ratio for some factors. In addition, only four out of 11 regions had studies regarding breast cancer with the dominance of Addis Ababa city and were directly included in this systematic review and meta-analysis. However, the big regions of the country were covered.

343 Conclusion

The magnitude of breast cancer in this study is high compared to the finding from the 2019 cancer burden in Ethiopia ⁸. Furthermore, the use of processed foods, high BMI, high cholesterol, physical inactivity, post-menopausal status, family history of cancer, and lack of breastfeeding were the facilitators of breast cancer development.

Post-menopausal women, in particular, late menopause women should stick to the lifestyle modifications that help to control body fat. It would be better if the people of Ethiopia use food sources such as fruits and vegetables, homegrown varieties of crops, and the like rather than seeking to adopt the Westernized food culture (processed foods). It is highly recommended to Page 19 of 45

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3 4	352	practice regular physical exercise to regulate body weight, and body fat and then to protect
5 6	353	against the risk of breast cancer. Appropriate breastfeeding should be practiced for at least 2
/ 8 9	354	years after delivery as this contributes to the minimization of breast cancer risk. Regular breast
10 11	355	examination should be practiced to detect and control the problem timely.
12 13 14 15	356	List of abbreviations
16	357	AA-Addis Ababa, BC-breast cancer, BMI- Body mass index, GLOBOCAN-Global burden of
17 18	358	cancer, JBI-Joanna Briggs Institute, LMICs- low- and middle-income countries, OPD- outpatient
19 20	359	department, POR-pooled odds ratio, SNNP- Southern nations, nationalities and peoples, USA-
21 22 23	360	United states of America
24 25	361	Ethics approval and consent to participate
26 27 28	362	N/A
29 30 21	363	Consent for publication
32 33	364	N/A
34 35 36	365	Availability of data and materials
37 38	366	The data extracted from included studies and analyzed in this review are available from the
39 40 41	367	corresponding author based on the reasonable request.
42 43	368	Competing interests
44 45 46	369	The authors declare that they have no competing interests.
47 48 49	370	Funding
50 51	371	No funding was obtained to conduct this systematic review and meta-analysis
52 53 54	372	Authors Contributions
55 56		
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ATS conceptualized the study, designed the methods, wrote the protocol, searched, screened critically evaluated the studies, extracted the data, analyzed the data, and wrote the manuscript. DRT was involved in the critical appraisal of the studies, and data extraction and wrote the first draft of the result. AED searched, screened, and critically appraised the studies, extracted the data, and interpreted the result. ML searched and screened the studies, drafted the methods and wrote the introduction for the study. MCC and ETG extracted the data and prepared the manuscript. JWF, BRF, and BB designed the methods, searched the studies, and extracted and analyzed the data.

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- ³⁵ 580 **List of figures**

37

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52 53

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1 2

- Figure 1: Flow chart of studies selection for the systematic review and meta-analysis of breast
- $_{40}$ 582 cancer and its determinants in Ethiopia
- Figure 2: Forest plot of the pooled proportion of breast cancer in Ethiopia
- Figure 3: The pooled odds ratio showing the association between menopausal status and breast
 cancer in Ethiopia
- 49 586 Additional files

587 Additional file 1: Critical appraisal of full texts downloaded for the systematic review and meta588 analysis of breast cancer and its determinants in Ethiopia

Page 25 of 45

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2 3	589	Additional file 2: subgroup analysis of the pooled proportion of breast cancer by regions in
4 5 6	590	Ethiopia
7 8	591	Additional file 3: subgroup analysis of the pooled proportion of breast cancer by study setting in
9 10	592	Ethiopia
12	593	Additional file 4: subgroup analysis of the pooled proportion of breast cancer by study design in
13 14 15	594	Ethiopia
16 17	595	Additional file 5: subgroup analysis of the pooled proportion of breast cancer by study
17 18 19	596	population in Ethiopia
20 21	597	Additional file 6: Funnel plot with 95% confidence limits of the pooled proportion of breast
22 23 24	598	cancer in Ethiopia
24 25	599	Additional file 7: Filled funnel plot with pseudo 95% confidence limits from the trim and fill
26 27 28	600	analysis of the pooled proportion of breast cancer in Ethiopia
29	601	Additional file 8: Sensitivity analysis of the level of breast cancer: Prevalence and 95%
30 31 32	602	confidence interval of breast cancer in Ethiopia
33 34	603	Additional file 9: The pooled odds ratio showing the association between processed food and
35 36	604	breast cancer in Ethiopia
37 38	605	Additional file 10: The pooled odds ratio of the association between cholesterol level and breast
39 40 41	606	cancer in Ethiopia
42	607	Additional file 11: The pooled odds ratio showing the association between physical activity and
43 44 45	608	breast cancer in Ethiopia
46 47	609	Additional file 12: The pooled odds ratio showing the association between family history of
48 49	610	cancer and breast cancer in Ethiopia
50 51	611	Additional file 13: The pooled odds ratio of the association between BMI and breast cancer in
52 53 54 55 56	612	Ethiopia
57 58 59		24

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Additional file 14: The pooled odds ratio of the association between breast feeding/lack of livebirth and breast cancer in Ethiopia

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Figure 1: Flow chart of studies selection for the systematic review and meta-analysis of breast cancer and its determinants in Ethiopia

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	Year of			%
Author	publication		ES (95% CI)	Weight
Abebe et al	2017		25.00 (16.98, 33.02)	4.40
Ayele et al	2021		0.09 (0.02, 0.16)	5.71
Ayele et al	2022	•	2.63 (1.52, 3.73)	5.68
Duch e et al.	2021		48.67 (42.16, 55.19)	4.77
Endalamaw et al	2021		0.08 (-0.08, 0.23)	5.71
Gebretsadik et al	2021	•	18.62 (17.23, 20.01)	5.66
Hailu et al.	2020		6.34 (5.84, 6.83)	5.71
Hassen et al	2021		 50.00 (45.43, 54.57) 	5.21
Hassen et al	2022		50.00 (45.43, 54.57)	5.21
Kibret et al	2022		4.97 (3.97, 5.97)	5.69
Kumie et al	2020		• 50.00 (42.74, 57.26)	4.59
Mekonen et al	2021		50.00 (40.20, 59.80)	3.95
Memirie et al.	2018		21.76 (21.44, 22.08)	5.71
Shalamo	2022		32.11 (27.58, 36.64)	5.21
Solomon et al	2019	+	14.80 (12.50, 17.09)	5.58
lefera Betal.	2016	-	14.07 (11.14, 17.01)	5.49
limotewos et al	2018		22.54 (21.27, 23.81)	5.67
Folessa et al	2021		33.33 (28.38, 38.29)	5.13
Wolduetal	2017		14.79 (8.95, 20.63)	4.93
Dverall (I-squared	= 99.9%, p = 0.000)	\diamond	22.98 (19.48, 26.48)	100.00
NOTE: Weights an	e from random effects analysis			



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7.	Gebretsadik (2021)	2	2	1	1	2	2	1	1	4	50	Include	ed froi aur (AE
8.	Hailu (2020)	2	1	1	1	2	2	1	1	5	62.5	Include	nini h
11.	Kibret (2022)	1	1	3	3	2	2	1	3	3	37.5	Include	ng, tp
12.	Kumie (2020)	1	1	1	1	2	2	1	1	6	75	Include	, Al tra
14.	Memirie (2018)	2	1	1	3	2	2	1	1	4	50	Include	
15.	Schwartz (2020)	2	2	3	1	2	2	1	3	2	25	Exclude	Outcome of interest not reported
16.	Schwartz (2021)	2	2	3	1	2	2	1	3	2	25	Exclude	Outcome of interest not reported
18.	Solomon (2019)	1	1	3	3	2	1	1	1	5	62.5	Include	on Ju
19	Tefera B (2016)	2	1	3	1	2	2	1	3	3	37.5	Include	hnola
21	Tesfaw (2018)	1	1	1	2	2	2	1	1	5	62.5	Exclude	No outcome of interest reported
24.	Woldu (2017)	1	2	1	3	2	2	3	1	3	37.5	Include	⊅
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	he exposure mea	sured	l in a v	alid a	and re	eliable	e way	?					Bib
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17.	(2022)	1	2	2	1	1	2	1	1	3	1	6	60	
23.	Tolessa (2021)	1	2	1	1	1	1	1	1	3	1	8	80	include G
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3.	Were the s	ame o	criteria	a used	for id	entific	ation	of cas	es and	d contro	ols?			ilar on
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5.	Was expos	ure m	easur	ed in t	the sai	me wa	ly for c	cases a	and co	ontrols?				hnc 1
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1	Abate	3	3	3	1	1	3	1	3	3	3	33	exclude	The outcome of interest is not shown in this
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22	Timotewos	3	3	3	1	1	1	1	1	3	5	77	Include	1. ge
	(2018)													nce
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	 4. Were the study subjects and the setting described in detail? 5. Was the data analysis conducted with sufficient coverage of the identified sample? 6. Were valid methods used for the identification of the condition? 7. Was the condition measured in a standard, reliable way for all participants? 8. Was there appropriate statistical analysis? 9. Was the response rate adequate, and if not, was the low response rate managed appropriately?
	1-Yes 2-No 3-Unclear 4-Not applicable
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Page 34 of 45

Author	Year of publication			ES (95% CI)	9 V
ΔΔ					
Abebe et al	2017			25 00 (16 98 33 02)	Δ
Duche et al	2021			A8 67 (A2 16 55 10)	7
Duche et al.	2020			40.07 (42.10, 33.19)	
	2020		_	0.34(3.04, 0.03)	
	2021	i		50.00 (45.43, 54.57)	
Hassen et al	2022			50.00 (45.43, 54.57)	0
Mekonen et al	2021			- 50.00 (40.20, 59.80)	3
Memirie et al.	2018			21.76 (21.44, 22.08)	5
Solomon et al	2019	●		14.80 (12.50, 17.09)	5
Timotewos et al	2018	•		22.54 (21.27, 23.81)	Ę
Tolessa et al	2021			33.33 (28.38, 38.29)	Ę
Woldu et al	2017			14.79 (8.95, 20.63)	4
Subtotal (I-square	d = 99.7%, p = 0.000)	<	>	30.19 (23.65, 36.74)	Ę
SNNP					
Ayele et al	2021	•		0.09 (0.02, 0.16)	Ę
Gebretsadik et al	2021	•		18.62 (17.23, 20.01)	ļ
Kibret et al	2022			4.97 (3.97, 5.97)	ļ
Shalamo	2022	i i		32.11 (27.58, 36.64)	1
Subtotal (I-square	d = 99.7%, p = 0.000)			13.66 (4.81, 22.51)	2
Oromia					
Ayele et al	2022			2.63 (1.52, 3.73)	ł
Subtotal (I-square	ed = .%, p = .)	>		2.63 (1.52, 3.73)	Ę
Amhara					
Endalamaw et al	2021			0.08 (-0.08, 0.23)	Ę
Kumie et al	2020	i i		50.00 (42.74, 57.26)	4
Tefera B et al.	2016	-		14.07 (11.14, 17.01)	Ę
Subtotal (I-square	d = 99.3%, p = 0.000)		>	20.91 (2.59, 39.24)	
Overall (I-squared	l = 99.9%, p = 0.000)			22.98 (19.48, 26.48)	1
NOTE: Weights ar	e from random effects analysis		-		
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Author	Year of			ES (95% CI)	% Wei
stitution-based					
Abebe et al	2017		_	25.00 (16.98, 33.02)	4.4(
Ayele et al	2022			2.63 (1.52, 3.73)	5.68
Duche et al.	2021			48.67 (42.16, 55.19)	4.77
Endalamaw et al	2021	• i		0.08 (-0.08, 0.23)	5.7
Gebretsadik et al	2021	•		18.62 (17.23, 20.01)	5.6
Hailu et al.	2020			6.34 (5.84, 6.83)	5.7
Hassen et al	2021			50.00 (45.43, 54.57)	5.2
lassen et al	2022			50.00 (45.43, 54.57)	5.2
Kibret et al	2022			4.97 (3.97, 5.97)	5.6
Kumie et al	2020			50.00 (42.74, 57.26)	4.5
Mekonen et al	2021			- 50.00 (40.20, 59.80)	3.9
Shalamo	2022		•	32.11 (27.58, 36.64)	5.2
Solomon et al	2019	+		14.80 (12.50, 17.09)	5.5
Tefera B et al.	2016	+		14.07 (11.14, 17.01)	5.4
Tolessa et al	2021	-	•	33.33 (28.38, 38.29)	5.1
Woldu et al	2017			14.79 (8.95, 20.63)	4.9
Subtotal (I-square	d = 99.5%, p = 0.000)			24.86 (20.69, 29.02)	82.
population-based					
Ayele et al	2021	•		0.09 (0.02, 0.16)	5.7
Memirie et al.	2018			21.76 (21.44, 22.08)	5.7
Timotewos et al	2018	•		22.54 (21.27, 23.81)	5.6
Subtotal (I-square	d = 100.0%, p = 0.000)		-	14.79 (-2.56, 32.15)	17.
Overall (I-squared	l = 99.9%, p = 0.000)	\diamond		22.98 (19.48, 26.48)	100
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Page 36 of 45

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Author	Year of publication	ES (95% CI)	% Weigh
Cross-sectional			
Abebe et al	2017) 4.40
Avele et al	2021	• 0.09 (0.02, 0.16)	5.71
Avele et al	2022	• 2.63 (1.52, 3.73)	5.68
Endalamaw et al	2021	• 0.08 (-0.08, 0.23)	5.71
Gebretsadik et al	2021	• 18.62 (17.23, 20.01) 5.66
Hailu et al.	2020	• 6.34 (5.84, 6.83)	5.71
Kibret et al	2022	• 4.97 (3.97, 5.97)	5.69
Kumie et al	2020	50.00 (42.74, 57.26) 4.59
Memirie et al.	2018	21.76 (21.44, 22.08	,) 5.71
Solomon et al	2019	• 14.80 (12.50, 17.09) 5.58
Tefera B et al.	2016	14.07 (11.14, 17.01) 5.49
Timotewos et al	2018	22.54 (21.27, 23.81) 5.67
Woldu et al	2017	14.79 (8.95, 20.63)	4.93
Subtotal (I-square	d = 99.9%, p = 0.000)	14.27 (10.24, 18.30) 70.53
Case-control			
Duche et al.	2021	48.67 (42.16, 55.19) 4.77
Hassen et al	2021	50.00 (45.43, 54.57) 5.21
Hassen et al	2022	50.00 (45.43, 54.57) 5.21
Mekonen et al	2021	50.00 (40.20, 59.80) 3.95
Shalamo	2022	32.11 (27.58, 36.64) 5.21
Tolessa et al	2021	33.33 (28.38, 38.29) 5.13
Subtotal (I-square	d = 91.6%, p = 0.000)	43.79 (36.21, 51.38) 29.47
Overall (I-squared	= 99.9%, p = 0.000)	22.98 (19.48, 26.48) 100.0
OTE: Weights ar	a from random effects analysis		

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Author	Year of publication			ES (95% CI)	% Weigh
cancer patients			l l		
Abebe et al	2017	-		25.00 (16.98, 33.02)	4.40
Gebretsadik et al	2021			18.62 (17.23, 20.01)	5.66
Kibret et al	2022	۲		4.97 (3.97, 5.97)	5.69
Mekonen et al	2021		I	- 50.00 (40.20, 59.80)	3.95
Memirie et al.	2018			21.76 (21.44, 22.08)	5.71
Solomon et al	2019	+		14.80 (12.50, 17.09)	5.58
Tefera B et al.	2016	-	1	14.07 (11.14, 17.01)	5.49
Timotewos et al	2018			22.54 (21.27, 23.81)	5.67
Woldu et al	2017		- ;	14.79 (8.95, 20.63)	4.93
Subtotal (I-squared	d = 99.3%, p = 0.000)	<	\geq	19.77 (14.33, 25.21)	47.07
general women					
Ayele et al	2021	•		0.09 (0.02, 0.16)	5.71
Subtotal (I-squared	d = .%, p = .)			0.09 (0.02, 0.16)	5.71
deceased women			1		
Ayele et al	2022	۲		2.63 (1.52, 3.73)	5.68
Subtotal (I-squared	d = .%, p = .)	0		2.63 (1.52, 3.73)	5.68
breast cancer wom	en				
Duche et al.	2021		I	48.67 (42.16, 55.19)	4.77
Hassen et al	2021			50.00 (45.43, 54.57)	5.21
Hassen et al	2022			50.00 (45.43, 54.57)	5.21
Kumie et al	2020		· •	50.00 (42.74, 57.26)	4.59
Shalamo	2022			32.11 (27.58, 36.64)	5.21
Tolessa et al	2021			33.33 (28.38, 38.29)	5.13
Subtotal (I-squared	d = 91.8%, p = 0.000)			43.90 (36.45, 51.34)	30.11
children attended th	ne OPD				
Endalamaw et al	2021	•		0.08 (-0.08, 0.23)	5.71
Subtotal (I-squared	d = .%, p = .)			0.08 (-0.08, 0.23)	5.71
patients seen for su	uspicion of cancer	-			/
Hailu et al.	2020		1	6.34 (5.84, 6.83)	5.71
Subtotal (I-squared	d = .%, p = .)	¥.	1	6.34 (5.84, 6.83)	5.71
	= 99.9%, p = 0.000)		\diamond	22.98 (19.48, 26.48)	100.00
Overall (I-squared			1		
Overall (I-squared NOTE: Weights are	e from random effects analysis				
Overall (I-squared NOTE: Weights are	e from random effects analysis				















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Breast Cancer and Its Determinants in Ethiopia: A Systematic Review and Meta-Analysis

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Breast Cancer and Its Determinants in Ethiopia: A Systematic Review and

Meta-Analysis Adisu Tafari Shama^{1*}, Dufera Rikitu Terefa¹, Adisu Ewunetu Desisa¹, Matiyos Lema¹, Melese Chego Cheme¹, Edosa Tesfaye Geta¹, Jira Wakoya Feyisa¹, Bikila Regassa Feyisa^{1, 2}, Bayise Biru^{1,3} Affiliations 1Department of Public Health, Institute of Health Sciences, Wollega University, Nekemte, Ethiopia 2Department of Epidemiology, Faculty of Public Health, Jimma University, Jimma, Ethiopia 3Department of Human Nutrition and Dietetics, Faculty of Public Health, Jimma University, Jimma, Ethiopia *Corresponding author: Adisu Tafari Shama e-mail address: adisuteferi1906@gmail.com Word count=4737

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1 2		
2 3 4	23	Abstract
5 6	24	Objectives: Breast cancer is the leading cause of cancer morbidity and mortality among women.
7 8 9 10	25	Still, there is a paucity of studies to know the magnitude of the problem in the country Ethiopia.
	26	Hence, this review was intended to pool the prevalence and identify the determinants of breast
11 12	27	cancer in Ethiopia.
13 14 15	28	Design: A systematic review and meta-analysis was conducted.
16 17	29	Data sources: Databases like PubMed/MEDLINE, HINARI, Science Direct, Google and Google
18 19	30	Scholar as well as websites of organizations were searched between 25 February to 6 March
20 21 22	31	2023.
22 23 24	32	Eligibility criteria: All observational studies in Ethiopia that reported either the magnitude
25 26	33	and/or determinants of breast cancer regardless of publication status were included
27 28	34	Data extraction and synthesis: Two authors independently assessed and extracted the data.
29 30	35	Joanna Briggs Institute (JBI) meta-analysis of statistics assessment and review instrument
31	36	(MAStARI) quality appraisal tool was used to assess the quality of the articles. Effect estimates
33	37	were done by using the random effect model. The meta-analysis results were displayed by using
34 35 36	38	forest plots.
37	39	Results: Nineteen 19 articles were reviewed with 24,435 total participants. The pooled
38 39	40	proportion of breast cancer was 17.94(95%CI: 12.03, 23.85) in Ethiopia. Consuming packed
40 41	41	foods (POR=2.12, 95%CI:1.41, 3.17), presence of high cholesterol (POR=4.08; 95%CI: 2.75,
42 43	42	6.07), physical inactivity (POR=3.27; 95%CI: 1.80, 5.94), high body mass index (POR=2.27;
44	43	95%CI: 0.85, 6.03), post-menopause (POR=2.25; 95%CI: 1.63, 3.10), family history of cancer
45 46	44	(POR=3.65; 95%CI: 0.85, 15.71), and lack of breastfeeding (POR=2.76; 95%CI: 0.90, 7.92)
47 48 49	45	were the determinants of breast cancer.
50 51	46	Conclusions: The magnitude of breast cancer is high according to this review. Processed food
52	47	consumption, high cholesterol in the body, lack of physical activity, high body mass index, post-
53 54 55 56 57	48	menopause, family history of cancer, and lack of breastfeeding were the risk factors for breast

cancer. The use of healthy food sources such as fruits and vegetables, and homegrown varieties of crops rather than seeking processed foods would help. PROSPERO Registration Number: CRD42023417733 Keywords: breast cancer, cancer, determinants of breast cancer, risk factors, Ethiopia **Article Summary** Strengths and limitations of this study The inclusion of prediction interval is a strong aspect of this study, as it is uncommon in many meta-analyses The review included only observational studies. The narrow scope of the review (only one country) ◆ A limited number of studies were found to pool the odds ratio for some factors. Background Breast cancer (BC) is a diverse disease with numerous morphological and molecular subgroups ¹. It is found to be the most common cause of cancer deaths in 11 regions of the world². It is one of the most frequently diagnosed cancers and the leading cause of cancer deaths in females worldwide ³. The recent global burden of cancer statistics (GLOBOCAN 2020) showed that BC has surpassed lung cancer and accounted for 2.3 million (11.7%) of all new cancer cases globally. It affects one in four new cancer cases of women and contributes to one in six deaths of women from cancer ⁴. The cancer burden is increasing worldwide and is estimated to be 28.4 million cases by 2040, which is a 47% increase over the cancer burden in 2020. A Higher death rate occurs in developing countries than in developed (15 BC deaths in developing countries versus 12.8 in developed countries per 100,000)⁴. In Ethiopia too there were an estimated 5900 incident cases

of breast cancer with the highest age-standardized incidence rate of 12.5 per 100,000 and a death
rate of 9.7 per 100,000 in 2019 ⁵.

Previous studies identified that the incidence of BC varies widely across the world due to differences in the level of education, economic status, environmental conditions, eating habits, lifestyle variables, and other cultural traditions. Westernized lifestyles (namely delayed pregnancies/childbirth, reduced breastfeeding, early age at menarche, sedentary lifestyles, and poor diet) and improving cancer registration and cancer detection are among the factors contributing to the projected rise of breast cancer in LMICs ⁶⁻⁹. Lack of knowledge about the disease, improper screening programs, delayed diagnosis, and insufficient medical facilities are also contributing factors to the increasing breast cancer burden in underdeveloped countries ^{6, 10,} ¹¹. Widespread urbanization, shifting patterns of reproductive and environmental risk factors, obesity, decreased physical activity, and rising life expectancy are among the major factors contributing to the steady rise in breast cancer incidence in low-income nations. Low socio-economic level, on the other hand, is related to an increased incidence of aggressive premenopausal breast cancers, as well as late-stage diagnosis and lower survival. Late menopause and early menarche are also among the risk factors that could increase the exposure of breast tissue to estrogen hormone. In contrast to this, pregnancy and appropriate breastfeeding help to reduce the risk of breast cancer ^{6, 10-13}.

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90 Comprehensive identification of the magnitude and determinants of breast cancer is critical for 91 developing nations like Ethiopia, as this will aid in the development and implementation of 92 effective breast cancer prevention initiatives. Breast cancer is not well studied in Ethiopia. 93 Although there is one recently published review, the focus of that study was more on 94 determinants of the problem ¹⁴. Different pocket studies done so far may not represent the entire

Page 6 of 48

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> 95 picture of the determinants of breast cancer in Ethiopia. Most of them were limited to small 96 sample sizes, limited portions of populations covered, and limited research regions. In this 97 regard, many of the regions were not addressed in the previous studies and our study also helps 98 to show this gap for further study, let alone intervention. It is critical to shed light on the risk 99 factors for breast cancer. As a result, this study aimed to determine the magnitude of breast 100 cancer and its determinants in Ethiopia.

101 Methods

102 Study design

103 A systematic review and meta-analysis was conducted. The protocol was registered on 104 Prospective Registry of Systematic Reviews (PROSPERO) with registration number 105 (CRD42023417733) and no change made to the protocol. To conduct this review, the Preferred 106 Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist ¹⁵ was used.

107 Searching strategy

A comprehensive search of databases like PubMed/MEDLINE, HINARI, Science Direct, and Google Scholar was used to find the relevant articles. The searches were limited to articles written using the English language. In addition to the electronic database search, grey literature was searched using Google search, and the Digital Libraries of Universities. Finally, the reference lists of the included articles for related studies were searched. To facilitate the article searching process, the keywords: ["breast" OR "mammary gland" AND "cancer" OR "tumor" OR "malignancy" OR "breast cancer" OR "breast malignancy" OR "breast tumor" AND "Risk factors" OR "Associated factors" OR "Determinants" OR "predictors" AND "Ethiopia" OR "Addis Ababa" OR "Northern Ethiopia" OR "North west Ethiopia" OR "Southern Ethiopia" OR "South Western Ethiopia" OR "Western Ethiopia" OR "East Ethiopia"] were used (Additional

1 2									
2 3 4	118	file 1). Searching started on February 25, 2023, and the final date of searching was March 6,							
5 6 7	119	2023.							
7 8 9	120	Eligibility criteria							
10 11	121	Inclusion criteria							
12 13	122	To be included in this review, the study should report either the determinants of breast cancer							
14 15 16	123	and/or the magnitude (incidence, prevalence, number) of breast cancer.							
17 18	124	Study setting: Studies conducted in Ethiopia (both institution-based and population-based) were							
19 20	125	part of this systematic review.							
21 22 23	126	Study population: The study involved all human population (male, female, children, and adults)							
23 24 25	127	in Ethiopia who has been evaluated for cancer.							
26 27	128	Exposure: those with modifiable or non-modifiable risk factors							
28 29	129	Study design: All observational studies (cross-sectional and case-control) that reported the							
30 31 32	130	magnitude of breast cancer and its determinants were evaluated to be included.							
33 34	131	Publication status: Both published and unpublished studies were considered for inclusion.							
35 36	132	Exclusion criteria							
37 38 39	133	Articles with low quality, unclear methodologies and articles that didn't indicate the outcome of							
40 41	134	interest were excluded (Additional file 2). Excluding the studies whose full-text papers were not							
42 43	135	available after at least two personal email contacts with the corresponding authors was an							
44 45 46	136	exclusion criterion but all full texts were available.							
40 47 48	137	Outcome variables assessment							
49 50	138	There were two outcomes in this study: the first outcome was the magnitude of confirmed breast							
51 52	139	cancer. This outcome can occur in any population group. Therefore, the population for this							
55 55	140	outcome was a human population of any age who was evaluated for cancer.							
56 57									
58 50		6							
60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml							

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Breast cancer: When the diagnosis was confirmed by pathological tests in addition to the history and physical examination ¹⁶. Hence, the data were sought if the diagnosis of breast cancer was confirmed by pathological tests. The total number of people who had breast cancer was divided by the total number of people participating in the study and multiplied by 100 which was used to determine the proportion of breast cancer. The second outcome/variables of this review were the determinants of breast cancer. Modifiable and non-modifiable factors were searched from the literature to pool their value together. For the variables whose categorization didn't overlap (e.g. age category), the category repeatedly reported in the studies or the established categorization was assumed to get the privilege. Early age at menarche: this is the starting of menstruation early and mostly before the age of 12 years ^{17, 18}. Late menopause: it is delayed age at menopause which is after the age of 55 years in most cases 17. Benign breast disease and breast injury: those breast diseases such as atypical ductal hyperplasia or lobular carcinoma¹⁷. Menopause status: this is categorized as postmenopausal if the woman has already stopped menstruation (either absence of menstruation for at least 1 year (any age) or due to bilateral oophorectomy or estrogen deprivation therapy) and premenopausal otherwise ^{16, 19, 20}. Body mass index (BMI): is an index which is determined based on the weight and height measurement and it is classified as high if the value is >25kg/M² ¹⁶. Age (<30, 30-49, >50)^{17, 20}, residence (rural vs urban), occupation (unemployed vs employed), exposure to smoking dried meat, use of industry processed foods, lack of intake of milk, fruits, and sea foods, high cholesterol (total cholesterol >200 mg/dl)²¹, energy source; fuel source

Page 9 of 48

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(wood/charcoal/kerosene/animal dung vs electricity), lack of physical activity, contraceptive use, family history of cancer, history of abortion, absence of breastfeeding, benign breast disease, and breast injury, radiation exposure, anemia and thrombocytosis were also the variables for which data were sought in the literature.

Study selection and data extraction

All the articles searched from Databases were imported into EndNote version X7, and duplicates were removed. Based on the predefined inclusion criteria, two authors (ATS and AED) independently assessed and identified papers by their titles, abstracts, and full texts. The screened items were then compiled, and any disagreement was handled by inviting and discussing with the third author (DRT). Data extraction was performed using the Joanna Briggs Institute (JBI) data extraction format ²²⁻²⁴. The data extraction format included the primary author, publication year, study period, region, study area, study setting, study design, study population, publication status, sample size, response rate, and the number of cases/breast cancer. For the second outcome, data were extracted into a two-by-two table.

Quality assessment

JBI meta-analysis of statistics assessment and review instrument (MAStARI) quality appraisal tool was used to assess the quality of the articles ²⁴. The JBI parameters included an appropriate sampling frame, proper sampling technique, study subject and setting description, sufficient time to exposure measurement, use of valid methods for the identified conditions, a valid measurement for variables and conditions, using appropriate statistical analysis including control of confounding. Accordingly, quality was categorized as low (total score of ≤ 2), moderate (total score of 3–4), or high (total score of >5) in terms of their likelihood ²⁴. The quality of the included studies was assessed by two independent authors (ATS and DRT). The discrepancy

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during the quality appraisal of the studies was resolved by the agreement of the two reviewers.
Finally, papers with an overall quality score of <37.5% and/or those not reporting the outcome of
interest were excluded from the systematic review and meta-analysis (Additional file 2).

190 Data synthesis strategy

The data were extracted into Microsoft Excel. Then it was exported to the STATA software, version 14, for further analysis. The standard errors of the included studies were calculated using the formula $SE = \sqrt{p(1-p)}/n$. The I² statistics and the p-values of the Cochrane Q-test were used to identify the heterogeneity problem. The p-values of the Cochrane Q test < 0.1 were used to indicate the presence of heterogeneity among the studies. The Higgins I² test statistics was used to calculate the percentage of total variance due to heterogeneity across the studies. Heterogeneity was declared for the I² value > 20% 25 . As a remedial for the heterogeneity among the studies by the test statistic, the DerSimonian-Laird's impact was evaluated using a random-effects model ²⁶. Moreover, the subgroup analysis by region, study design, study setting, and study population was done to identify the possible source of heterogeneity. The effect sizes were expressed as proportion and odds ratio along with a 95% confidence interval (CI). Moreover, the 95% prediction interval was computed by using the comprehensive meta-analysis to indicate the location of true proportion in comparable population 27 . The forest plots were used to display the meta-analysis results. Publication bias was investigated graphically using a funnel plot and statistically using Egger's weighted regression and/or Begg's rank correlation tests and decided as significant at p-value $< 0.05^{28, 29}$. A leave-one-out sensitivity meta-analysis was used to assess the robustness of the findings.

- **Patient and public involvement:** No patient was involved in this study.
- **Result**

1 2 3								
4	210	Description	of inclu	ded studies in	the systematic re	eview a	nd me	ta-analysis
5 6 7	211	About 1644	articles v	were identified	through database	search	ing wl	nile 19 of them were included
7 8 9	212	in this system	matic re	view and meta	a-analysis (Figure	1). Tl	ne tota	l number of participants was
10 11	213	24,435.						
12 13	214	Studies cove	red the p	period between	a 2011 to 2021 ^{16,}	18-21, 3	⁰⁻⁴³ , 13	were cross-sectional ^{21, 30-41} ,
14 15 16	215	six were case	e-control	16, 18-20, 42, 43	18 were published] 16, 18,	19, 21, 3	⁰⁻⁴³ , 1 was unpublished ²⁰ , the
17 18	216	majority-16	were ins	titution-based	16, 18-21, 30, 32-36, 3	8, 39, 41	⁻⁴³ , an	d 3 of them were population-
19 20	217	based studies	31, 37, 40	⁰ . The majority	v of them-10 were	done i	n Ado	lis Ababa (AA) ^{16, 18, 19, 30, 35,}
21 22 23	218	^{37, 38, 40-43} , fo	llowed b	by southern nat	tions, nationalities	and p	eoples	(SNNP)- four studies ^{20, 31, 34,}
24 25	219	³⁶ and Amha	ra region	ns (3 studies) ²¹	^{1, 33, 39} (Table 1).			
26	220	Table 1: De	scriptive	e summary of	19 studies inclu	ded in	the m	eta-analysis to estimate
27 28	221	breast canc	er magr	nitude and its	determinants in	Ethiop	oia	-
29 30 31 32 33		Author (Year)	Age	Study design	Period	Sa mpl e siz e	Pro port ion (%)	Factors
35 36 37		Abebe et al (2017) ³⁰	>=18 years	Cross- sectional	June 1-31, 2015	112	26. 5	
38 39		Ayele et al	>=15	Cross-	Mar- Apr	7,5	10.	6
40		(2021) 31	years	sectional	2018	80	2	
41		Ayele et al $(2022)^{32}$	>=15	Cross-	2011-2012	800	2.1	
42 43 44 45 46		Duche et al. (2021) ¹⁶	>15 years	Case- control	April to September 2017	226		Physical inactivity, postmenopausal, breast feeding, BMI>25,
47 48 49 50 51		Endalama w et al (2021) ³³	<15y ears	Cross- sectional	January 1, 2019 to March 30, 2019	100	10	
52 53 54 55		Gebretsad ik et al (2021) ³⁴	No age limit	Cross- sectional	January 2013 and Jan. 2019	300 2	18. 6	
56		Hailu et al.	No	Cross-	January 2014	200	29.	
57 58					10			

(2020) ³⁵	age limit	sectional	and December 2018	2	3	
Hassen et al (2021) ⁴²	>18 years	Case- control	May 2018 to June 2019	460		Anemia, thrombocytosis
Hassen et al (2022)	>18 years	Case- control	May 2018 to June 2019	460		Age between 40- 49, Early menarche, unemployment, milk intake, solid oil, use of unclean energy, Physical inactivity, breast disease
Kibret et al (2022) ³⁶	No age limit	Cross- sectional	Jan to Jun 2021	1,8 10	25. 4	
Kumie et al (2020) ²¹	>18 years	Cross- sectional	January 22 to May 26, 2020	182		High cholesterol
Mekonen et al (2021) ⁴³	>=18 years	Case- control	February to April 2020	100		
Memirie et al. (2018) ³⁷	>=15 years	Cross- sectional	2012 to 2015	110 5	22. 9	
Shalamo (2022) ²⁰	>15 years	Case- control	March 1 – April 30, 2022	408	0,	Age, use of packed food, eating fruits and fish, contraceptive use, History of abortion, Radiation exposure, Breast injury, history of Cancer
Solomon et al (2019) ³⁸	No age limit	Cross- sectional	Jan 1, 2010 and Dece. 15, 2014	919	14. 8	5
Tefera B et al. (2016) ³⁹	N age limit	Cross- sectional	Sept 2014 to Aug 2015	540	14. 1	
Timotewo s et al (2018) ⁴⁰	No age limit	Cross- sectional	2012–2013	413 9	22. 5	
Tolessa et al (2021) ¹⁸	>20 years	Case- control	Feb 1 to March 30, 2020	348		Early menarche, residence, dried meat, use of packed foods, Family history of

59

							Cancer, lack of breast feeding, overweight
	Woldu et al (2017) ⁴¹	No age limit	Cross- sectional	November 2015 to June 2016	142	14. 8	
222	Prevalence	of breas	t cancer in Et	hiopia			
223	Of the total	19 inclu	ided studies, t	welve (12) article	s were	inclu	ded to pool the prevalence o
224	breast cance	er ^{16, 18-21}	^{, 30-43} . Accordi	ngly, the pooled p	proporti	ion of	breast cancer in Ethiopia was
225	found to be	17. 94%	(95%CI: 12.0	3, 23.85; I ² =98.7%	‰, <i>p</i> <0.	<i>000).</i> '	The 95% prediction interval is
226	located betw	veen 8%	and 34%. Thi	s indicates that the	e true r	nagnit	ude in 95% of all comparable
227	populations	falls in th	he interval betw	ween 8% and 34%	²⁷ (Fig	ure 2).	
228	Subgroup a	nalysis					
229	Since signi	ficant he	eterogeneity w	vas found when	pooling	g the	magnitude of breast cancer
230	subgroup an	alysis wa	as done to furt	her check for the s	source	of hete	erogeneity. As of the subgroup
231	analysis by	region, th	ne proportion of	of breast cancer wa	s found	to be	21.51%; 95%CI: 15.91, 27.11
232	in AA, 18.9	97%; 959	%CI: 12.82, 2	25.13 in SNNP, 1	4%;959	%CI:	11.10, 16.90 in Amhara, and
233	2.7%;95%C	I:1.57,3.8	83 in Oromia	(Additional file 3)). The 1	result	of subgroup analysis by study
234	setting show	ved that	the pooled ma	agnitude of breast	cancer	r was	high; 21.18%; 95%CI: 18.83,
235	24.54) for p	opulation	n-based studie	s while (17.57%;	95%CI	: 10.0	8, 25.06) for institution-based
236	studies (Add	ditional fi	ile 4). Furthern	nore, the subgroup	analys	sis was	done by the study population.
237	Accordingly	v, the po	oled magnitud	de of breast cance	er is fo	ound t	o be 26.14%; 95%CI: 19.87,
238	32.42), (19.	05%; 959	%CI: 15.91,22	2.18), (10.10%; 95	%CI: 1	1.73, 1	8.67), (2.70%; 95%CI: 1.57,
239	3.83), and (10.0%; 9	95%CI: -8.59,	28.59), among w	omen	with c	ancer, among cancer patients,
240	among eligi	ble wom	en evaluated	with Ultrasound-g	uided	FNAC	, among deceased women for
241	whom cause	es of deat	th were done t	hrough verbal auto	opsy, a	nd am	ong children who had cancer),
242	respectively	(Additio	onal file 5).				

Publication bias The funnel plot appeared symmetric indicating the absence of publication bias (Additional file 6). Egger's test (P = 0.707) and Begg's test (p=0.311) also confirmed this because they both are non-significant being above p > 0.5. **Sensitivity Analysis** A leave-one-out sensitivity analysis was done to test the reliability of the findings. According to the sensitivity analyses output, using the random-effects model was robust, and no single study affected the pooled proportion of breast cancer (Additional file 7). **Determinants of breast cancer** In individual studies, factors like young age, age at menarche, residence, occupation, exposure to smoking dried meat, use of processed foods, lack of intake of milk, fruits, and eating sea foods, high cholesterol, fuel source (wood, charcoal, kerosene, animal dung), lack of physical activity, menopause, contraceptive use, family history of cancer, history of abortion, benign breast disease and breast injury, radiation exposure, absence of breastfeeding, high body mass index (BMI), anemia and thrombocytosis were found to be the determinants of breast cancer. From these, age, age at menarche, use of processed foods, high cholesterol, lack of physical activity, menopause status, family history of cancer, absence of breastfeeding, and BMI were reported to be significant in more than one study and pooled together. However, only seven (7) factors showed statistical significance in the meta-analysis. Accordingly, those people who consume processed foods/drinks have 2.12 (POR=2.12, 95%CI:1.41, 3.17, $I^2=0.0\%$, p=0.826) times more odds of breast cancer than their counterparts (Additional file 8). This meta-analysis also revealed that the risk of breast cancer is increased by 4 (POR=4.08; 95%CI: 2.75, 6.07, I²=0.0%, p=0.888) in the presence of high cholesterol including solid oil as compared to low cholesterol (Additional file

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9). Those individuals who are physically inactive had 3.27 (POR=3.27; 95%CI: 1.80, 5.94, $I^2=65.2\%$, p=0.090) times more odds of breast cancer than their counterparts (Additional file 10). The pooled odds of breast cancer is 2.25 (POR=2.25; 95%CI: 1.63, 3.10, $I^2=0.0\%$, p=0.433) times more likely in post-menopausal women than premenopausal women (Figure 3). In another way, the pooled odds of breast cancer is 3.65 (POR=3.65; 95%CI: 0.85, 15.71) times more likely for those people who have a family history of cancer as compared to those without a family history of cancer (Additional file 11). Regarding the BMI, when compared to those people having normal BMI, high BMI was associated with 2.27 (POR=2.27; 95%CI: 0.85, 6.03) times increased odds of breast cancer (Additional file 12). Those women who had no history of breastfeeding have 2.76 (POR=2.76; 95%CI: 0.90, 7.92) times more odds of breast cancer compared to their counterparts (Additional file 13).

277 DISCUSSION

In total, 24 articles were assessed for inclusion and five (5) were excluded from this review. The reason for exclusion was mainly due to the lack of an intended outcome report. Here are the citations of excluded studies ⁴⁴⁻⁴⁸. Data of 19 articles were extracted 12 for prevalence and 6 for determinants study. Accordingly, the pooled proportion of breast cancer in Ethiopia is found to be 17. 94 (95%CI: 12.03, 23.85). Although the result seems low when compared with the one in Iranian women (23.6%)⁴⁹, it is still high when compared to the age-standardized incidence rate of breast cancer in Ethiopia (12.1 per 100,000 populations) ⁵. The observed variation could be due to a difference in the denominator. As shown in the subgroup analysis, the proportion of breast cancer varies in different situations. For example, the proportion of pooled breast cancer is higher-26.14% in cancer-diagnosed women which is even higher than the one in Iranian women ⁴⁹, 19.05% among general cancer patients, 10.1% in eligible women evaluated by ultrasound-

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guided FNAC, and 2.7% among post-death verbal autopsy for deceased women. This shows that breast cancer varies depending on the study population). In another way, this finding is low as compared to the breast cancer cases (25%) among women newly diagnosed with cancers in the GLOBOCAN 2012 and 2018 study ^{50, 51} and the study in the United States of America (USA) (29%) ⁵². The difference in socio-economic and demographic conditions might be the possible reason for this variation. Developed countries have improved cancer detection, registration, and reporting than Ethiopia which could make a difference between countries regarding breast cancer proportions. Although the prevalence seems low when compared to the developed settings, this result is still high in comparison with the previous estimation. This alerts us that breast cancer deserves attention, especially in women. Because the subgroup analysis indicated a high prevalence of breast cancer among women who suffered from cancer.

In this systematic review and meta-analysis, factors such as the use of processed foods/drinks, high cholesterol, lack of physical activity, post-menopausal status, family history of cancer, absence of breastfeeding, and high BMI including obesity were reported as risk factors for breast cancer. Accordingly, a family history of cancer including breast cancer was reported as a risk factor for breast cancer (pooled OR=3.65; 95%CI: 0.85, 15.71). This finding is consistent with previous studies conducted in Ethiopia¹⁴, Iran^{53, 54}, the United kingdom⁵⁵, China⁵⁶, and Malaysia ⁵⁷. This might be due to the presence of some inherited defect that will facilitate the development of the disease. Given that biological exposure is non-modifiable, screening and follow-up of the breast condition would help to get timely treatment that can halt the bad consequences of the disease ¹⁴.

This study also revealed non-breastfeeding as a risk factor for breast cancer which is in-line with the finding of previous systematic review ^{14, 58}, studies done in China ⁵⁶, Iran ⁵³, USA ^{59, 60} where

Page 17 of 48

BMJ Open

studies conducted stated that breastfeeding minimizes the risk of breast cancer. The possible reason could be because of the hormonal effect of breastfeeding for the protection or reduction of breast cancer. Both the current study and previous studies revealed the protective effect of breastfeeding for breast cancer. The possible mechanism for the observed protective probability of breast cancer in this study might be attributed to the differentiation induced to the breast lobe by lactation that might transform cancer-prone stem cell 1 to refractive stem cell 2⁶¹. There might also be less exposure of breast tissues to hormones as breastfeeding inhibits ovulation and the hormones from the ovulation cycles ⁶². The result is a good indication to promote breastfeeding which has dual benefits for both the mother and child.

This current finding also showed that high BMI is the risk factor for breast cancer in which people with high BMI were about 2.27 times more likely to develop breast cancer than their counterparts. This finding is similar to the previous study ^{57, 60, 63-66}, and studies in Iran ^{53, 54} but contrasts with the finding of the study conducted in Northern California ⁶⁷. High BMI including obesity is found to be a risk factor for breast cancer in postmenopausal women 68-70. Increased body fat might increase the level of circulating estrogens and decrease the levels of sex hormone-binding globulin ⁷¹. Besides, the inflammation that accompanies obesity might also contribute to breast cancer development ⁷².

In this study, it was also found that lack of physical activity is a risk factor for breast cancer and it was reported by previous studies ^{53, 73, 74}. The possible explanation for the association between breast cancer and lack of physical activity might be that physical inactivity could increase the probability of fat accumulation in the body as some studies ^{53, 54} found that obesity is a risk factor for breast cancer. Therefore, adherence to regular physical exercise and healthy foods would help

Page 18 of 48

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to control weight and reduce body fat given that both overweight and physical inactivity are thetwo modifiable and related risk factors for breast cancer.

This study revealed that the use of processed food and/or drink was a risk factor for breast cancer. This is consistent with the finding of the individual studies conducted in Latin America ⁷⁵, Iran ⁷⁶ and other reviews ^{64, 77}. According to this study, consumption of packed food/drinks was found to be the risk factor for breast cancer. This result is in line with the study findings of other countries which imply that a decrease in the intake of packed or ultra-processed food or drink should be encouraged to reduce the incidence of breast cancer among women 75 64, 76, 77. The possible reason for this association might be due to the presence of different additives to processed foods during the processes that could initiate cancer development ⁷⁸. Other reasons might be that packed foods are rich in energy/added sugar, saturated and trans-fatty acids, and salt and have low content in fibers and vitamins that would increase the risk of breast cancer ⁷⁹.

In this review, a positive association between high cholesterol level and breast cancer was found. However, studies are contradicting in this regard. Some studies found high cholesterol as a risk factor ⁸⁰ while some found it as a protective factor ^{81, 82}. Those studies that found the protective effect of high cholesterol explained it as "statin-the cholesterol-lowering medication might reduce the breast cancer risk too" ^{83, 84}. In this study, the total cholesterol including the use of hard oil was used as high cholesterol and was found to be associated with increased breast cancer risk. The possible reason for the positive association between high cholesterol and breast cancer is that cholesterol is the precursor for estrogen which is the cause of breast cancer^{85, 86}. Women with high body fat might have an increased risk of breast cancer though their BMI is normal.

Moreover, the current study revealed that post-menopausal status is one of the risk factors for breast cancer which is consistent with the previous studies ^{14, 87} where it was indicated as a breast Page 19 of 48

BMJ Open

cancer risk is higher in postmenopausal than premenopausal women. However, this result seems to contradict the finding in another meta-analysis in which premenopausal women had about 43% higher risk of breast cancer than postmenopausal women of the same age. In another way, that study added that postmenopausal women with high body fat had an increased risk of breast cancer than premenopausal women ⁷⁰. Hence, the association between the increased possibility of breast cancer and postmenopausal status in this study might be justified as those postmenopausal women could have high body fat as well. Another possible explanation is that post-menopausal women in this study might have reached menopause at late age commonly after 50 years as late menopause is found to be a risk factor in another study 56 . Because extended menstruation could expose the breast tissue to increased exposure to hormones like estrogen ⁶⁴. Besides, the use of postmenopausal hormone replacement therapy couldn't be ruled out from the possible reasons as this might increase the breast cancer risk in postmenopausal women ⁵⁸. This implies that the hormonal change in pre-and post-menopausal contributes to a risk or solution for breast cancer among women. Although there are differences in explanation models regarding the postmenopausal stage, it is imperative to care for oneself because age extremes are mostly known to have a high risk for disease including chronic conditions like breast cancer ¹⁷.

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This study has its own implications for research, practice, and policy. The practical implication is that a program on non-communicable diseases like breast cancer in the country should be strengthened to combat the problem given the prevalence in this study is high. On top of that, a protective effect of breastfeeding found in this study implies that programs that address breastfeeding promotion should incorporate the protective role of breastfeeding in their promotion activities. This research also alerts future research to investigate factors like residence, occupation, smoke-dried meat consumption, unclean energy sources, and the protective effects of

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foods like milk, seafood, and fruits including their risk and protective mechanisms. The issue of postmenopausal status is still non-conclusive in the literature. It deserves further analysis to put under its appropriate classification (risk or protective factor for breast cancer). Moreover, researchers and policy-makers should work together on how to intervene and prevent the consumption of globalized and commercially processed foods as they are contributing to the breast cancer burden. The infection prevention-dominated policy of the country should be revisited to incorporate the prevention of non-communicable diseases. Although the disease is partly due to non-modifiable risk factors, the presence of modifiable factors calls for all concerned bodies to focus on the disease to prevent the disease, diagnose and treat timely, and minimize the risk of death and economic impact. This may include the initiation and strengthening of breast cancer screening in the country. Decentralization of the cancer registry is also required.

The strengths of this study are that it is the first systematic review and meta-analysis on breast cancer in Ethiopia which pooled the prevalence of breast cancer. Next, it shares the strengths of systematic review and meta-analysis as the evidence generated from this systematic review and meta-analysis might be more representative of the country's situation than pocket studies. Thirdly, the study estimated the prediction interval for the result obtained which is uncommon in many previous meta-analyses. However, the review was not free of limitations. The first limitation could be the narrow scope of the review in which a single country is covered. Nonetheless, it can still serve the studied country to consider in their policy decisions. The other drawback was that some of the regions had no primary studies regarding breast cancer and were not included in this review. Although the big regions of the country were covered, the majority of the studies were done in Addis Ababa city which is the country's capital. The other is that the

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403 evidence pooled together was merely from observational studies (cross-sectional and case-404 control studies).

Conclusion

The magnitude of breast cancer in this study is high compared to the finding from the 2019 cancer burden in Ethiopia ⁵. On top of that, the subgroup analysis by population in our study showed that the magnitude of breast cancer in cancer affected women (26.14%) is higher than that of women's data analyzed in Iranian study (23.6) ⁴⁹. In another way, the use of processed foods, high BMI, high cholesterol, physical inactivity, post-menopausal status, family history of cancer, and lack of breastfeeding were the facilitators of breast cancer development.

Post-menopausal women, in particular, late menopause women should stick to the lifestyle modifications that help to control body fat. It would be better if the people of Ethiopia use food sources such as fruits and vegetables, homegrown varieties of crops, and the like rather than seeking to adopt the Westernized food culture (processed foods). It is highly recommended to practice regular physical exercise to regulate body weight, and body fat and then to protect against the risk of breast cancer. Appropriate breastfeeding should be practiced for at least 2 years after delivery as this contributes to the minimization of breast cancer risk. Regular breast examination should be practiced to detect and control the problem timely.

420 List of abbreviations

421 AA-Addis Ababa, BC-breast cancer, BMI- Body mass index, GLOBOCAN-Global burden of
422 cancer, JBI-Joanna Briggs Institute, LMICs- low- and middle-income countries, OPD- outpatient
423 department, POR-pooled odds ratio, SNNP- Southern nations, nationalities and peoples, USA424 United states of America

425 Ethics approval and consent to participate

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2 3 4	426	Ethical approval was not applicable because the review of previous studies was done.							
5 6 7	427	Consent for publication							
8 9 10	428	N/A							
10 11 12 13 14 15 16	429	Availability of data and materials							
	430	The data extracted from included studies and analyzed in this review are available from the							
	431	corresponding author based on the reasonable request							
17		control pontaning warned carbon and reasonance requeen							
18 19 20	432	Competing interests							
21 22	433	The authors declare that they have no competing interests.							
23 24 25	434	Funding							
26 27 28	435	No funding was obtained to conduct this systematic review and meta-analysis							
29 30	436	Authors Contributions							
32 33	437	ATS conceptualized the study, designed the methods, wrote the protocol, searched, screened							
34 25	438	critically evaluated the studies, extracted the data, analyzed the data, and wrote the manuscript.							
35 36	439	DRT was involved in the critical appraisal of the studies, and data extraction and wrote the first							
37 38	440	draft of the result. AED searched, screened, and critically appraised the studies, extracted the							
39	441	data, and interpreted the result. ML searched and screened the studies, drafted the methods and							
40 41	442	wrote the introduction for the study. MCC and ETG extracted the data and prepared the							
42 43	443	manuscript. JWF, BRF, and BB designed the methods, searched the studies, and extracted and							
44 45	444	analyzed the data. ATS is the guarantor.							
46 47 48	445	Acknowledgements							
49 50	446	Not applicable							
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3 ⊿	678	Additional file 2: Critical appraisal of full texts downloaded for the systematic review and meta-
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20 21	686	Additional file 6: Funnel plot with 95% confidence limits of the pooled proportion of breast
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28 29	690	Additional file 8: The pooled odds ratio showing the association between processed food and
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Page 30 of 48 BMJ Open: first published as 10.1136/bmjopen-2023-080080 on 2 November 2024. Downloaded from http://bmjopen.bmj.com/ on June 10, 2025 at Agence Bibliographique de I Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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Flow chart of studies selection for the systematic review and meta-analysis of breast cancer and its determinants in Ethiopia

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Abebe et al	2017	26.50 (18.06, 34.94)	7.67
Ayelele et al	2021	10.20 (1.73, 18.67)	7.66
Ayelele et al	2022	2.70 (1.57, 3.83)	9.05
Endalamaw et al	2021	10.00 (-8.59, 28.59)	4.79
Gebretsadik et al	2021	18.60 (17.21, 19.99)	9.04
Hailu et al.	2020	2 9.30 (27.31, 31.29)	8.99
Kibret et al	2022	25.40 (20.87, 29.93)	8.62
Memirie et al.	2018	22.90 (20.42, 25.38)	8.94
Solomon et al	2019	14.80 (12.50, 17.10)	8.96
Tefera B et al.	2016	1 4.10 (11.16, 17.04)	8.89
Timotewos et al	2018	± 22.50 (21.23, 23.77)	9.05
Woldu et al	2017	14.80 (8.96, 20.64)	8.35
Overall, DL (I ² = 98. ²	7%, p < 0.000)	17.94 (12.03, 23.85)	100.00

Forest plot of the pooled proportion of breast cancer in Ethiopia

532x345mm (57 x 57 DPI)

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Figure 3: The pooled odds ratio showing the association between menopausal status and breast cancer in Ethiopia

157x138mm (96 x 96 DPI)

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Search strategy

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Page 34 of 48

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19 Abebe et al 2017	26.50 (18.06, 34.94)	7.67 g
20 Hailu et al. 2020	29.30 (27.31, 31.29)	8.99 te bi
21 Solomon et al 2019	14.80 (12.50, 17.10)	8.965
²² Timotewos et al 2018	22.50 (21.23, 23.77)	9.05 <u>6</u>
²³ Woldu et al 2017 ²⁴ Subgroup DL $(l^2 = 0.5 8)(l = 1.0 000)$		8.35¥r. 023
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28 Ayelele et al 2021	10.20 (1.73, 18.67)	7.66 g
29 Gebretsadik et al 2021	18.60 (17.21, 19.99)	9.04 ⁰
30 Kibret et al 2022	25.40 (20.87, 29.93)	8.62 g
³¹ Subgroup, DL (l ² = 83.5%, p = 0.002)	18.97 (12.82, 25.13)	25.32 ses in b
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$_{26}^{35}$ Subgroup, DL (l ² = 100.0%, p < 0.000)	 ▲ /ul>	9.05
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42 Subgroup, DL ($1 = 0.0\%$, $\beta = 0.069$)	14.00 (11.10, 16.90)	
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44 45 Memirie et al. 2018	22.90 (20.42, 25.38)	8.94 =
46 Subgroup, DL ($l^2 = 0.0\%$, p < 0.000)	22.90 (20.42, 25.38)	8.94
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48 Heterogeneity between groups: $p = 0.000$ 49 Overall DL ($t^2 = 98.7\%$ $p < 0.000$)	17 94 (12 03 23 85)	100.00 ··· · · · ·
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Breast Cancer and Its Determinants in Ethiopia: A Systematic Review and Meta-Analysis

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Secondary Subject Heading:	Health policy, Health services research, Oncology, Public health, Nutrition and metabolism
Keywords:	Risk Factors, Primary Health Care, PUBLIC HEALTH, Chronic Disease

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Breast Cancer and Its Determinants in Ethiopia: A Systematic Review and

Meta-Analysis Adisu Tafari Shama^{1*}, Dufera Rikitu Terefa¹, Adisu Ewunetu Desisa¹, Matiyos Lema¹, Melese Chego Cheme¹, Edosa Tesfaye Geta¹, Jira Wakoya Feyisa¹, Bikila Regassa Feyisa^{1, 2}, Bayise Biru^{1,3} Affiliations 1Department of Public Health, Institute of Health Sciences, Wollega University, Nekemte, Ethiopia 2Department of Epidemiology, Faculty of Public Health, Jimma University, Jimma, Ethiopia 3Department of Human Nutrition and Dietetics, Faculty of Public Health, Jimma University, Jimma, Ethiopia *Corresponding author: Adisu Tafari Shama e-mail address: adisuteferi1906@gmail.com Word count=4648

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Abstract **Objectives:** Breast cancer is the leading cause of cancer morbidity and mortality among women. Still, there is a paucity of studies to know the magnitude of the problem in Ethiopia. Hence, this review was intended to pool the prevalence and identify the determinants of breast cancer in Ethiopia. **Design:** A systematic review and meta-analysis was conducted. Data sources: Databases like PubMed/MEDLINE, HINARI, Science Direct, and Google Scholar as well as websites of organizations were searched between 25 February to 6 March 2023. Eligibility criteria: All observational studies in Ethiopia that reported either the magnitude and/or determinants of breast cancer regardless of publication status were included

Data extraction and synthesis: Two authors independently assessed and extracted the data. Joanna Briggs Institute (JBI) meta-analysis of statistics assessment and review instrument (MAStARI) quality appraisal tool was used to assess the quality of the articles. Effect estimates were done by using the random effect model. The meta-analysis results were displayed by using forest plots.

Results: Seventeen 17 articles were reviewed with 24,435 total participants. The pooled proportion of breast cancer morbidity among cancer patients was 20. 58% (95%CI: 17.25, 23.90) in Ethiopia. Consuming packed foods (POR=2.12, 95%CI:1.41, 3.17), presence of high cholesterol (POR=4.08; 95%CI: 2.75, 6.07), physical inactivity (POR=3.27; 95%CI: 1.80, 5.94), high body mass index (POR=2.27; 95%CI: 0.85, 6.03), post-menopause (POR=2.25; 95%CI: 1.63, 3.10), family history of cancer (POR=3.65; 95%CI: 0.85, 15.71), and lack of breastfeeding (POR=2.76; 95%CI: 0.90, 7.92) were the determinants of breast cancer.

45 Conclusions: One of five cancer patients is diagnosed with breast cancer in Ethiopia.
46 Furthermore, more than one quarter of women with cancer suffer from breast cancer. Processed
47 food consumption, high cholesterol in the body, lack of physical activity, high body mass index,
48 post-menopause, family history of cancer, and lack of breastfeeding were the risk factors for

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breast cancer. The use of healthy food sources such as fruits and vegetables, and homegrown varieties of crops rather than seeking processed foods would help. PROSPERO Registration Number: CRD42023417733 Keywords: breast cancer, cancer, determinants of breast cancer, risk factors, Ethiopia **Article Summary** Strengths and limitations of this study The inclusion of prediction interval is a strong aspect of this study, as it is uncommon in many meta-analyses The review included only observational studies. The narrow scope of the review (only one country) ◆ A limited number of studies were found to pool the odds ratio for some factors. Background Breast cancer (BC) is a diverse disease with numerous morphological and molecular subgroups ¹. It is found to be the most common cause of cancer deaths in 11 regions of the world². It is one of the most frequently diagnosed cancers and the leading cause of cancer deaths in females worldwide ³. The recent global burden of cancer statistics (GLOBOCAN 2020) showed that BC has surpassed lung cancer and accounted for 2.3 million (11.7%) of all new cancer cases globally. It affects one in four new cancer cases of women and contributes to one in six deaths of women from cancer ⁴. The cancer burden is increasing worldwide and is estimated to be 28.4 million cases by 2040, which is a 47% increase over the cancer burden in 2020. A Higher death rate occurs in developing countries than in developed (15 BC deaths in developing countries versus 12.8 in developed countries per 100,000)⁴. In Ethiopia too there were an estimated 5900 incident cases

of breast cancer with the highest age-standardized incidence rate of 12.5 per 100,000 and a death
rate of 9.7 per 100,000 in 2019 ⁵.

Previous studies identified that the incidence of BC varies widely across the world due to differences in the level of education, economic status, environmental conditions, eating habits, lifestyle variables, and other cultural traditions. Early age at menarche, westernized lifestyles (namely delayed pregnancies/childbirth, reduced breastfeeding, sedentary lifestyles, and poor diet), and improving cancer registration and cancer detection are among the factors associated with the breast cancer in LMICs ⁶⁻⁹. Lack of knowledge about the disease, improper screening programs, delayed diagnosis, and insufficient medical facilities are also contributing factors to the increasing breast cancer burden in underdeveloped countries ^{6, 10, 11}. Widespread urbanization, shifting patterns of reproductive and environmental risk factors, obesity, decreased physical activity, and rising life expectancy are among the major factors contributing to the steady rise in breast cancer incidence in low-income nations. Low socio-economic level, on the other hand, is related to an increased incidence of aggressive premenopausal breast cancers, as well as late-stage diagnosis and lower survival. Late menopause and early menarche are also among the risk factors that could increase the exposure of breast tissue to estrogen hormone. In contrast to this, pregnancy and appropriate breastfeeding help to reduce the risk of breast cancer 6, 10-13

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90 Comprehensive identification of the magnitude and determinants of breast cancer is critical for 91 developing nations like Ethiopia, as this will aid in the development and implementation of 92 effective breast cancer prevention initiatives. Breast cancer is not well studied in Ethiopia. 93 Although there is one recently published review, the focus of that study was more on 94 determinants of the problem ¹⁴. Different pocket studies done so far may not represent the entire

Page 6 of 48

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> 95 picture of the determinants of breast cancer in Ethiopia. Most of them were limited to small 96 sample sizes, limited portions of populations covered, and limited research regions. In this 97 regard, many of the regions were not addressed in the previous studies and our study also helps 98 to show this gap for further study, let alone intervention. It is critical to shed light on the risk 99 factors for breast cancer. As a result, this study aimed to determine the magnitude of breast 100 cancer and its determinants in Ethiopia.

101 Methods

102 Study design

103 A systematic review and meta-analysis was conducted. The protocol was registered on 104 Prospective Registry of Systematic Reviews (PROSPERO) with registration number 105 (CRD42023417733) and no change made to the protocol. To conduct this review, the Preferred 106 Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist ¹⁵ was used.

107 Searching strategy

A comprehensive search of databases like PubMed/MEDLINE, HINARI, Science Direct, and Google Scholar was used to find the relevant articles. The searches were limited to articles written using the English language. In addition to the electronic database search, grey literature was searched using Google search, and the Digital Libraries of Universities. Finally, the reference lists of the included articles for related studies were searched. To facilitate the article searching process, the keywords: ["breast" OR "mammary gland" AND "cancer" OR "tumor" OR "malignancy" OR "breast cancer" OR "breast malignancy" OR "breast tumor" AND "Risk factors" OR "Associated factors" OR "Determinants" OR "predictors" AND "Ethiopia" OR "Addis Ababa" OR "Northern Ethiopia" OR "North west Ethiopia" OR "Southern Ethiopia" OR "South Western Ethiopia" OR "Western Ethiopia" OR "East Ethiopia"] were used (Additional

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2 3 4	118	file 1). Searching started on February 25, 2023, and the final date of searching was March 6,
5 6 7	119	2023.
7 8 9	120	Eligibility criteria
10 11	121	Inclusion criteria
12 13 14	122	To be included in this review, the study should report either the determinants of breast cancer
14 15 16	123	and/or the magnitude (incidence, prevalence, number) of breast cancer morbidity.
17 18	124	Study setting: Studies conducted in Ethiopia (both institution-based and population-based) were
19 20 21	125	part of this systematic review.
22 23	126	Study population: The study involved all human population (male, female, children, and adults)
24 25	127	in Ethiopia who has been evaluated for cancer and confirmed to be cancer patients.
26 27 28	128	Exposure: those with modifiable or non-modifiable risk factors.
29 30	129	Study design: All observational studies (cross-sectional and case-control) that reported the
31 32	130	magnitude of breast cancer morbidity and its determinants were evaluated to be included.
33 34 35	131	Publication status : Both published and unpublished studies were considered for inclusion.
36	132	Exclusion criteria
37 38 39	133	Articles with low quality, unclear methodologies and articles that didn't indicate the outcome of
40 41	134	interest were excluded (Additional file 2). Excluding the studies whose full-text papers were not
42 43 44	135	available after at least two personal email contacts with the corresponding authors was an
45 46	136	exclusion criterion but all full texts were available.
47 48	137	Outcome variables assessment
49 50 51	138	There were two outcomes in this study: the first outcome was the magnitude of confirmed breast
52 53 54 55 56	139	cancer disease/morbidity among patients with cancer diagnosis. This outcome can occur in any
57 58 59		6
60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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population group. Therefore, the population for this outcome was a human population of any agewho was evaluated for cancer disease.

Breast cancer: When the diagnosis was confirmed by pathological tests in addition to the history and physical examination ¹⁶. Hence, the data were sought if the diagnosis of breast cancer was confirmed by pathological tests. The total number of people who had breast cancer was divided by the total number of people participating in the study and multiplied by 100 which was used to determine the proportion of breast cancer morbidity.

147 The second outcome/variables of this review were the determinants of breast cancer. Modifiable 148 and non-modifiable factors were searched from the literature to pool their value together. For the 149 variables whose categorization didn't overlap (e.g. age category), the category repeatedly 150 reported in the studies or the established categorization was assumed to get the privilege.

Early age at menarche: this is the starting of menstruation early and mostly before the age of
 152 12 years ^{17, 18}.

Late menopause: it is delayed age at menopause which is after the age of 55 years in most cases
 154 ¹⁷.

155 Benign breast disease and breast injury: those breast diseases such as atypical ductal
 156 hyperplasia or lobular carcinoma ¹⁷.

Menopause status: this is categorized as postmenopausal if the woman has already stopped
menstruation (either absence of menstruation for at least 1 year (any age) or due to bilateral
oophorectomy or estrogen deprivation therapy) and premenopausal otherwise ^{16, 19, 20}.

Body mass index (BMI): is an index which is determined based on the weight and height 161 measurement and it is classified as high if the value is $>=25 \text{kg/M}^2$ ¹⁶.

Age (<30, 30-49, >50) ^{17, 20}, residence (rural vs urban), occupation (unemployed vs employed), exposure to smoking dried meat, use of industry processed foods, lack of intake of milk, fruits, and sea foods, high cholesterol (total cholesterol >200 mg/dl) ²¹, energy source; fuel source (wood/charcoal/kerosene/animal dung vs electricity), lack of physical activity, contraceptive use, family history of cancer, history of abortion, absence of breastfeeding, benign breast disease, and breast injury, radiation exposure, anemia and thrombocytosis were also the variables for which data were sought in the literature.

169 Study selection and data extraction

All the articles searched from Databases were imported into EndNote version X7, and duplicates were removed. Based on the predefined inclusion criteria, two authors (ATS and AED) independently assessed and identified papers by their titles, abstracts, and full texts. The screened items were then compiled, and any disagreement was handled by inviting and discussing with the third author (DRT). Data extraction was performed using the Joanna Briggs Institute (JBI) data extraction format ²²⁻²⁴. The data extraction format included the primary author, publication year, study period, region, study area, study setting, study design, study population, publication status, sample size, response rate, and the number of cases/breast cancer. For the second outcome, data were extracted into a two-by-two table.

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179 Quality assessment

JBI meta-analysis of statistics assessment and review instrument (MAStARI) quality appraisal tool was used to assess the quality of the articles ²⁴. The JBI parameters included an appropriate sampling frame, proper sampling technique, study subject and setting description, sufficient time to exposure measurement, use of valid methods for the identified conditions, a valid measurement for variables and conditions, using appropriate statistical analysis including control
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of confounding. Accordingly, quality was categorized as low (total score of ≤ 2), moderate (total score of 3–4), or high (total score of >5) in terms of their likelihood ²⁴. The quality of the included studies was assessed by two independent authors (ATS and DRT). The discrepancy during the quality appraisal of the studies was resolved by the agreement of the two reviewers. Finally, papers with an overall quality score of <37.5% and/or those not reporting the outcome of interest were excluded from the systematic review and meta-analysis (Additional file 2).

191 Data synthesis strategy

The data were extracted into Microsoft Excel. Then it was exported to the STATA software, version 14, for further analysis. The standard errors of the included studies were calculated using the formula $SE = \sqrt{p(1-p)}/n$. The I² statistics and the p-values of the Cochrane Q-test were used to identify the heterogeneity problem. The p-values of the Cochrane Q test < 0.1 were used to indicate the presence of heterogeneity among the studies. The Higgins I^2 test statistics was used to calculate the percentage of total variance due to heterogeneity across the studies. Heterogeneity was declared for the I² value > 20% ²⁵. As a remedial for the heterogeneity among the studies by the test statistic, the DerSimonian-Laird's impact was evaluated using a random-effects model ²⁶. Moreover, the subgroup analysis by region, study design, study setting, and study population was done to identify the possible source of heterogeneity. The effect sizes were expressed as proportion and odds ratio along with a 95% confidence interval (CI). Moreover, the 95% prediction interval was computed by using the comprehensive meta-analysis to indicate the location of true proportion in comparable population ²⁷. The forest plots were used to display the meta-analysis results. Publication bias was investigated graphically using a funnel plot and statistically using Egger's weighted regression and/or Begg's rank correlation tests and decided

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207	as significant	t at p-val	ue < $0.05^{28,29}$.	A leave-one-out	sensitiv	ity me	eta-analysis was used to assess	
208	the robustness of the findings.							
209	Patient and	public ii	nvolvement: N	o patient was invo	olved ir	n this s	tudy.	
210	Result							
211	Description	of inclu	led studies in	the systematic re	view a	nd me	ta-analysis	
212	About 1644	articles v	were identified	through database	search	ing wł	nile 17 of them were included	
213	in this system	matic rev	view and meta	-analysis (Figure	1). Th	e tota	l number of participants was	
214	16055.							
215	Studies cove	red the p	period between	2011 to 2021 ^{16,}	18-21, 30	-41, 11	were cross-sectional ^{21, 30-39} ,	
216	six were case	e-control	16, 18-20, 40, 41	16 were published	1 6, 18, 1	19, 21, 3	0-41, 1 was unpublished ²⁰ , the	
217	majority-15	were inst	itution-based ¹	6, 18-21, 30-34, 36, 37,	³⁹⁻⁴¹ , a	nd 2 o	f them were population-based	
218	studies ^{35, 38} . The majority of them-10 were done in Addis Ababa (AA) ^{16, 18, 19, 30, 33, 35, 36, 38-41} ,							
219	followed by	souther	n nations, nati	onalities and peo	ples (S	SNNP)	- three studies ^{20, 32, 34} and	
220	Amhara regio	ons (3 stu	udies) ^{21, 31, 37} (Table 1).				
221	Table 1 [.] De	scriptive	summary of	17 studies inclu	ded in	the m	eta-analysis to estimate	
222	breast canc	er magr	nitude and its	determinants in	Ethion	ia		
	Author		Study	Period	Sa	Pro	Factors	
	(Year)	Age	design		mnl	nort		
	(Tear)		ucsign		e line	ion		
					siz	(%)		
					6	(70)		
	Abehe et	>=18	Cross-	June 1-31	112	26		
	al	vears	sectional	2015		5		
	(2017) 30	Juli				0		
	Duche et	>15	Case-	April to	226		Physical inactivity	
	al.	vears	control	September			postmenopausal	
	207 208 209 210 211 212 213 214 215 216 217 218 219 220 221 222	 207 as significant 208 the robustness 209 Patient and 210 Result 211 Description 212 About 1644 213 in this system 214 16055. 215 Studies cove 216 six were case 217 majority-15 where case 218 studies ^{35, 38}. 219 followed by 220 Amhara region 221 Table 1: Description 222 Description Abebe et al (2017) ³⁰ Duche et al. 	207as significant at p-val208the robustness of the significant and public in209Patient and public in210Result211Description of inclue212About 1644 articles with213in this systematic rest21416055.215Studies covered the p216six were case-control217majority-15 were inst218studies $^{35, 38}$. The maj219followed by souther220Amhara regions (3 str221Table 1: Descriptive breast cancer magnAuthor (Year)AgeAbebe et al (2017) 30 >=18 yearsDuche et al.>15 years	207as significant at p-value < $0.05^{-28,29}$.208the robustness of the findings.209Patient and public involvement: N210Result211Description of included studies in r212About 1644 articles were identified213in this systematic review and meta21416055.215Studies covered the period between216six were case-control $^{16, 18-20, 40, 41}$,217majority-15 were institution-based 1 218studies $^{35, 38}$. The majority of them-1219followed by southern nations, nati220Amhara regions (3 studies) $^{21, 31, 37}$ (regions) (3 studies) $^{21, 31, 37}$ (regions) (3 studies) $^{21, 31, 37}$ (regions) (3 studies) (7 and 18 are regions) (3 studies) (2 are regions) (3 studies) (3 are regions) (3 are regions) (3 studies) (3 are regions) (3 are re	207as significant at p-value < $0.05^{28,29}$. A leave-one-out s208the robustness of the findings.209Patient and public involvement: No patient was invol210Result211Description of included studies in the systematic re212About 1644 articles were identified through database213in this systematic review and meta-analysis (Figure21416055.215Studies covered the period between 2011 to 2021 ^{16,} 216six were case-control ^{16, 18-20, 40, 41} , 16 were published217majority-15 were institution-based ^{16, 18-21, 30-34, 36, 37,218studies ^{35, 38}. The majority of them-10 were done in A219followed by southern nations, nationalities and pec220Amhara regions (3 studies) ^{21, 31, 37} (Table 1).221Table 1: Descriptive summary of 17 studies inclue breast cancer magnitude and its determinants in Muthor (Year)221Abebe et al222Study design223Period Closs- al.}	207as significant at p-value < $0.05^{28,29}$. A leave-one-out sensitive208the robustness of the findings.209Patient and public involvement: No patient was involved in210Result211Description of included studies in the systematic review and212About 1644 articles were identified through database search213in this systematic review and meta-analysis (Figure 1). The21416055.215Studies covered the period between 2011 to 2021 ^{16, 18-21, 30} 216six were case-control ^{16, 18-20, 40, 41} , 16 were published ^{16, 18, 21} 217majority-15 were institution-based ^{16, 18-21, 30-34, 36, 37, 39-41, a218studies ^{35, 38}. The majority of them-10 were done in Addis A219followed by southern nations, nationalities and peoples (S220Amhara regions (3 studies) ^{21, 31, 37} (Table 1).221Table 1: Descriptive summary of 17 studies included in breast cancer magnitude and its determinants in Ethiop221Abebe et e al (Year)Study years sectional sectional 2015Period 2015Sa mpl e e siz e al.</br>}	207as significant at p-value < 0.05 $^{28, 29}$. A leave-one-out sensitivity me208the robustness of the findings.209Patient and public involvement: No patient was involved in this s210Result211Description of included studies in the systematic review and me212About 1644 articles were identified through database searching wh213in this systematic review and meta-analysis (Figure 1). The total21416055.215Studies covered the period between 2011 to 2021 $^{16, 18-21, 30-41}$, 11216six were case-control $^{16, 18-20, 40, 41}$, 16 were published $^{16, 18, 19, 21, 30}$ 217majority-15 were institution-based $^{16, 18-21, 30-41}$, and 2 o218studies $^{35, 38}$. The majority of them-10 were done in Addis Ababa of219followed by southern nations, nationalities and peoples (SNNP)220Amhara regions (3 studies) $^{21, 31, 37}$ (Table 1).221Table 1: Descriptive summary of 17 studies included in the m222Mahara regions (3 studies) $^{21, 31, 37}$ (Table 1).221Table 4: Descriptive summary of 17 studies included in the m222Mahara regions (3 studies) $^{21, 31, 37}$ (Table 1).231AuthorAgeStudyPeriodSaProMote 4>=18Cross- alJune 1-31, 11226. al212Case- April to al.226Sa	

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breast feeding,

BMI>=25,

January 1,

March 30,

2019 to

Gebretsad ik et al (2021) ³²	No age limit	Cross- sectional	January 2013 and Jan. 2019	300 2	18. 6	
Hailu et al. (2020) ³³	No age limit	Cross- sectional	January 2014 and December 2018	200 2	29. 3	
Hassen et al (2021) ⁴⁰	>18 years	Case- control	May 2018 to June 2019	460		Anemia, thrombocytosis
Hassen et al (2022)	>18 years	Case- control	May 2018 to June 2019	460		Age between 40- 49, Early menarche, unemployment, milk intake, solid oil, use of unclean energy, Physical inactivity, breast disease
Kibret et al (2022) ³⁴	No age limit	Cross- sectional	Jan to Jun 2021	1,8 10	25. 4	
Kumie et al (2020) ²¹	>18 years	Cross- sectional	January 22 to May 26, 2020	182		High cholesterol
Mekonen et al (2021) ⁴¹	>=18 years	Case- control	February to April 2020	100		
Memirie et al. (2018) ³⁵	>=15 years	Cross- sectional	2012 to 2015	110 5	22. 9	
Shalamo (2022) ²⁰	>15 years	Case- control	March 1 – April 30, 2022	408	0	Age, use of packed food, eating fruits and fish, contraceptive use, History of abortion, Radiation exposure, Breast injury, history of Cancer
Solomon et al (2019) ³⁶	No age limit	Cross- sectional	Jan 1, 2010 and Dece. 15, 2014	919	14. 8	
Tefera B et al. (2016) ³⁷	N age limit	Cross- sectional	Sept 2014 to Aug 2015	540	14. 1	
Timotewo s et al (2018) ³⁸	No age limit	Cross- sectional	2012–2013	413 9	22. 5	

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Tolessa et al (2021) ¹⁸	>20 years	Case- control	Feb 1 to March 30, 2020	348		Early menarche, residence, dried meat, use of packed foods, Family history of Cancer, lack of breast faeding, overweight
Woldu et	No	Cross	November	142	14	leeding, overweight
vvoluu et		01035-	INOVEITIDEI	142	14.	
al	age	sectional	2015 to June		8	
(2017) ³⁹	limit		2016			

Prevalence of breast cancer in Ethiopia

Of the total 17 included studies, twelve (10) articles were included to pool the prevalence of breast cancer ^{16, 18-21, 30-41}. Accordingly, the pooled proportion of breast cancer morbidity among those patients evaluated for cancer in Ethiopia was found to be 20. 58% (95%CI: 17.25, 23.90; $I^2=93.8\%$, *p*<0.000). The 95% prediction interval is located between 8% and 34%. This indicates that the true magnitude in 95% of all comparable populations falls in the interval between 8% and 34% ²⁷ (Figure 2).

30 230 Subgroup analysis 31

Since significant heterogeneity was found when pooling the magnitude of breast cancer morbidity, subgroup analysis was done to further check for the source of heterogeneity. As of the subgroup analysis by region, the proportion of breast cancer was found to be 21.76%; 95%CI: 17.27, 26.2 in AA, 21.64%; 95%CI: 15.02, 28.27 in SNNP, and 14%; 95%CI: 11.10, 16.90 in Amhara (Additional file 3). The result of subgroup analysis by study setting showed that the pooled magnitude of breast cancer morbidity was high; 22.58%; 95%CI: 21.45, 23.72 for population-based studies while 19.84%; 95%CI: 15.03, 24.65 for institution-based studies (Additional file 4). Furthermore, the subgroup analysis was done by the study population. Accordingly, the pooled magnitude of breast cancer is found to be 26.14%; 95%CI: 19.87, 32.42, 19.05%; 95%CI: 15.91, 22.18, and 10.0%; 95%CI: -8.59, 28.59 among women with cancer,

among general cancer patients, and among children who had cancer, respectively (Additional file5).

Publication bias

The funnel plot appeared symmetric indicating the absence of publication bias (Additional file 6). Egger's test (P = 0.533) and Begg's test (p=0.727) also confirmed this because they both are non-significant being above p>0.5.

247 Sensitivity Analysis

A leave-one-out sensitivity analysis was done to test the reliability of the findings. According to
the sensitivity analyses output, using the random-effects model was robust, and no single study
affected the pooled proportion of breast cancer morbidity (Additional file 7).

Determinants of breast cancer

In individual studies, factors like young age, age at menarche, residence, occupation, exposure to smoking dried meat, use of processed foods, lack of intake of milk, fruits, and eating sea foods, high cholesterol, fuel source (wood, charcoal, kerosene, animal dung), lack of physical activity, menopause, contraceptive use, family history of cancer, history of abortion, benign breast disease and breast injury, radiation exposure, absence of breastfeeding, high body mass index (BMI), anemia and thrombocytosis were found to be the determinants of breast cancer. From these, age, age at menarche, use of processed foods, high cholesterol, lack of physical activity, menopause status, family history of cancer, absence of breastfeeding, and BMI were reported to be significant in more than one study and pooled together. However, only seven (7) factors showed statistical significance in the meta-analysis. Accordingly, those people who consume processed foods/drinks have 2.12 (POR=2.12, 95%CI: 1.41, 3.17, I²=0.0%, p=0.826) times more odds of breast cancer than their counterparts (Additional file 8). This meta-analysis also revealed that the

Page 15 of 48

BMJ Open

risk of breast cancer is increased by 4 (POR=4.08; 95%CI: 2.75, 6.07, $I^2=0.0\%$, p=0.888) in the presence of high cholesterol including solid oil as compared to low cholesterol (Additional file 9). Those individuals who are physically inactive had 3.27 (POR=3.27; 95%CI: 1.80, 5.94, . $I^2=65.2\%$, p=0.090) times more odds of breast cancer than their counterparts (Additional file 10). The pooled odds of breast cancer is 2.25 (POR=2.25; 95%CI: 1.63, 3.10, $I^2=0.0\%$, p=0.433) times more likely in post-menopausal women than premenopausal women (Figure 3). In another way, the pooled odds of breast cancer is 3.65 (POR=3.65; 95%CI: 0.85, 15.71) times more likely for those people who have a family history of cancer as compared to those without a family history of cancer (Additional file 11). Regarding the BMI, when compared to those people having normal BMI, high BMI was associated with 2.27 (POR=2.27; 95%CI: 0.85, 6.03) times increased odds of breast cancer (Additional file 12). Those women who had no history of breastfeeding have 2.76 (POR=2.76; 95%CI: 0.90, 7.92) times more odds of breast cancer compared to their counterparts (Additional file 13).

277 DISCUSSION

In total, 24 articles were assessed for inclusion and seven (7) were excluded from this review. The reason for exclusion was mainly due to the lack of an intended outcome report and non-similarity of study population. Here are the citations of excluded studies ⁴²⁻⁴⁸. Data of 17 articles were extracted 10 for prevalence and 7 for determinants study. Accordingly, the pooled proportion of breast cancer morbidity in Ethiopia is found to be 20. 58% (95%CI: 17.25, 23.90). Although the result seems low when compared with the one in Iranian women $(23.6\%)^{49}$, it is still high when compared to the age-standardized incidence rate of breast cancer in Ethiopia (12.1 per 100,000 populations)⁵. The observed variation could be due to a difference in the denominator. As shown in the subgroup analysis, the proportion of breast cancer morbidity

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varies in different situations. For example, the proportion of pooled breast cancer morbidity is higher-26.14% in cancer-diagnosed women which is even higher than the one in Iranian women ⁴⁹ and 19.05% among general cancer patients. This shows that breast cancer varies depending on the study population. In another way, this finding is low as compared to the breast cancer cases (25%) among women newly diagnosed with cancers in the GLOBOCAN 2012 and 2018 study ⁵⁰, ⁵¹ and the study in the United States of America (USA) (29%) ⁵². The difference in socio-economic and demographic conditions might be the possible reason for this variation. Developed countries have improved cancer detection, registration, and reporting than Ethiopia which could make a difference between countries regarding breast cancer proportions. Although the prevalence of breast cancer morbidity seems low when compared to the developed settings, this result is still high in comparison with the previous estimation. This alerts us that breast cancer deserves attention, especially in women. Because the subgroup analysis indicated a high prevalence of breast cancer disease among women who suffered from different forms of cancer. In this systematic review and meta-analysis, factors such as the use of processed foods/drinks, high cholesterol, lack of physical activity, post-menopausal status, family history of cancer, absence of breastfeeding, and high BMI including obesity were reported as risk factors for breast cancer. Accordingly, a family history of cancer including breast cancer was reported as a risk factor for breast cancer (pooled OR=3.65; 95%CI: 0.85, 15.71). This finding is consistent with previous studies conducted in Ethiopia¹⁴, Iran^{53, 54}, the United kingdom⁵⁵, China⁵⁶, and Malaysia ⁵⁷. This might be due to the presence of some inherited defect that will facilitate the development of the disease. Given that biological exposure is non-modifiable, screening and follow-up of the breast condition would help to get timely treatment that can halt the bad consequences of the disease ¹⁴.

Page 17 of 48

BMJ Open

This study also revealed non-breastfeeding as a risk factor for breast cancer which is in-line with the finding of previous systematic review ^{14, 58}, studies done in China ⁵⁶, Iran ⁵³, USA ^{59, 60} where studies conducted stated that breastfeeding minimizes the risk of breast cancer. The possible reason could be because of the hormonal effect of breastfeeding for the protection or reduction of breast cancer. Both the current study and previous studies revealed the protective effect of breastfeeding for breast cancer. The possible mechanism for the observed protective probability of breast cancer in this study might be attributed to the differentiation induced to the breast lobe by lactation that might transform cancer-prone stem cell 1 to refractive stem cell 2⁶¹. There might also be less exposure of breast tissues to hormones as breastfeeding inhibits ovulation and the hormones from the ovulation cycles ⁶². The result is a good indication to promote breastfeeding which has dual benefits for both the mother and child.

This current finding also showed that high BMI is the risk factor for breast cancer in which people with high BMI were about 2.27 times more likely to develop breast cancer than their counterparts. This finding is similar to the previous study ^{57, 60, 63-66}, and studies in Iran ^{53, 54} but contrasts with the finding of the study conducted in Northern California ⁶⁷. High BMI including obesity is found to be a risk factor for breast cancer in postmenopausal women ⁶⁸⁻⁷⁰. Increased body fat might increase the level of circulating estrogens and decrease the levels of sex hormonebinding globulin ⁷¹. Besides, the inflammation that accompanies obesity might also contribute to breast cancer development ⁷².

In this study, it was also found that lack of physical activity is a risk factor for breast cancer and it was reported by previous studies ^{53, 73, 74}. The possible explanation for the association between breast cancer and lack of physical activity might be that physical inactivity could increase the probability of fat accumulation in the body as some studies ^{53, 54} found that obesity is a risk factor

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> for breast cancer. Therefore, adherence to regular physical exercise and healthy foods would help to control weight and reduce body fat given that both overweight and physical inactivity are the two modifiable and related risk factors for breast cancer.

This study revealed that the use of processed food and/or drink was a risk factor for breast cancer. This is consistent with the finding of the individual studies conducted in Latin America ⁷⁵, Iran ⁷⁶ and other reviews ^{64, 77}. According to this study, consumption of packed food/drinks was found to be the risk factor for breast cancer. This result is in line with the study findings of other countries which imply that a decrease in the intake of packed or ultra-processed food or drink should be encouraged to reduce the incidence of breast cancer among women 75 64, 76, 77. The possible reason for this association might be due to the presence of different additives to processed foods during the processes that could initiate cancer development ⁷⁸. Other reasons might be that packed foods are rich in energy/added sugar, saturated and trans-fatty acids, and salt and have low content in fibers and vitamins that would increase the risk of breast cancer ⁷⁹.

In this review, a positive association between high cholesterol level and breast cancer was found. However, studies are contradicting in this regard. Some studies found high cholesterol as a risk factor ⁸⁰ while some found it as a protective factor ^{81, 82}. Those studies that found the protective effect of high cholesterol explained it as "statin-the cholesterol-lowering medication might reduce the breast cancer risk too" ^{83, 84}. In this study, the total cholesterol including the use of hard oil was used as high cholesterol and was found to be associated with increased breast cancer risk. The possible reason for the positive association between high cholesterol and breast cancer is that cholesterol is the precursor for estrogen which is the cause of breast cancer ^{85, 86}. Women with high body fat might have an increased risk of breast cancer though their BMI is normal.

Page 19 of 48

BMJ Open

Moreover, the current study revealed that post-menopausal status is one of the risk factors for breast cancer which is consistent with the previous studies ^{14, 87} where it was indicated as a breast cancer risk is higher in postmenopausal than premenopausal women. However, this result seems to contradict the finding in another meta-analysis in which premenopausal women had about 43% higher risk of breast cancer than postmenopausal women of the same age. In another way, that study added that postmenopausal women with high body fat had an increased risk of breast cancer than premenopausal women⁷⁰. Hence, the association between the increased possibility of breast cancer and postmenopausal status in this study might be justified as those postmenopausal women could have high body fat as well. Another possible explanation is that post-menopausal women in this study might have reached menopause at late age commonly after 50 years as late menopause is found to be a risk factor in another study ⁵⁶. Because extended menstruation could expose the breast tissue to increased exposure to hormones like estrogen ⁶⁴. Besides, the use of postmenopausal hormone replacement therapy couldn't be ruled out from the possible reasons as this might increase the breast cancer risk in postmenopausal women ⁵⁸. This implies that the hormonal change in pre-and post-menopausal contributes to a risk or solution for breast cancer among women. Although there are differences in explanatory models regarding the postmenopausal stage, it is imperative to care for oneself because age extremes are mostly known to have a high risk for disease including chronic conditions like breast cancer ¹⁷.

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This study has its own implications for research, practice, and policy. The practical implication is that a program on non-communicable diseases like breast cancer in the country should be strengthened to combat the problem given the prevalence in this study is high. On top of that, a protective effect of breastfeeding found in this study implies that programs that address breastfeeding promotion should incorporate the protective role of breastfeeding in their

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promotion activities. This research also alerts future research to investigate factors like residence, occupation, smoke-dried meat consumption, unclean energy sources, and the protective effects of foods like milk, seafood, and fruits including their risk and protective mechanisms. The issue of postmenopausal status is still non-conclusive in the literature. It deserves further analysis to put under its appropriate classification (risk or protective factor for breast cancer). Moreover, researchers and policy-makers should work together on how to intervene and prevent the consumption of globalized and commercially processed foods as they are contributing to the breast cancer burden. The infection prevention-dominated policy of the country should be revisited to incorporate the prevention of non-communicable diseases. Although the disease is partly due to non-modifiable risk factors, the presence of modifiable factors calls for all concerned bodies to focus on the disease to prevent the disease, diagnose and treat timely, and minimize the risk of death and economic impact. This may include the initiation and strengthening of breast cancer screening in the country.

The strengths of this study are that it is the first systematic review and meta-analysis on breast cancer in Ethiopia which pooled the prevalence of breast cancer. Next, it shares the strengths of systematic review and meta-analysis as the evidence generated from this systematic review and meta-analysis might be more representative of the country's situation than pocket studies. Thirdly, the study estimated the prediction interval for the result obtained which is uncommon in many previous meta-analyses. However, the review was not free of limitations. The first limitation could be the narrow scope of the review in which a single country is covered. Nonetheless, it can still serve the studied country to consider in their policy decisions. The other drawback was that some of the regions had no primary studies regarding breast cancer and were not included in this review. The majority of the studies were done in Addis Ababa city which is

401 the country's capital. The other is that the evidence pooled together was merely from402 observational studies (cross-sectional and case-control studies).

Conclusion

In Ethiopia, out of five patients evaluated for cancer disease, one received a diagnosis of breast
cancer. Additionally, more than a quarter of cancer disease in women is breast cancer, according
to this study. In another way, the use of processed foods, high BMI, high cholesterol, physical
inactivity, post-menopausal status, family history of cancer, and lack of breastfeeding were the
facilitators of breast cancer development.

Post-menopausal women, in particular, late menopause women should stick to the lifestyle modifications that help to control body fat. It would be better if the people of Ethiopia use food sources such as fruits and vegetables, homegrown varieties of crops, and the like rather than seeking to adopt the Westernized food culture (processed foods). It is highly recommended to practice regular physical exercise to regulate body weight, and body fat and then to protect against the risk of breast cancer. Appropriate breastfeeding should be practiced for at least 2 years after delivery as this contributes to the minimization of breast cancer risk. Regular breast examination should be practiced to detect and control the problem timely.

417 List of abbreviations

AA-Addis Ababa, BC-breast cancer, BMI- Body mass index, GLOBOCAN-Global burden of
cancer, JBI-Joanna Briggs Institute, LMICs- low- and middle-income countries, OPD- outpatient
department, POR-pooled odds ratio, SNNP- Southern nations, nationalities and peoples, USAUnited states of America

422 Ethics approval and consent to participate

423 Ethical approval was not applicable because the review of previous studies was done.

Consent for publication N/A Availability of data and materials The data extracted from included studies and analyzed in this review are available from the corresponding author based on the reasonable request. **Competing interests** The authors declare that they have no competing interests. Funding No funding was obtained to conduct this systematic review and meta-analysis **Authors Contributions** ATS conceptualized the study, designed the methods, wrote the protocol, searched, screened critically evaluated the studies, extracted the data, analyzed the data, and wrote the manuscript. DRT was involved in the critical appraisal of the studies, and data extraction and wrote the first draft of the result. AED searched, screened, and critically appraised the studies, extracted the data, and interpreted the result. ML searched and screened the studies, drafted the methods and wrote the introduction for the study. MCC and ETG extracted the data and prepared the manuscript. JWF, BRF, and BB designed the methods, searched the studies, and extracted and analyzed the data. ATS is the guarantor. Acknowledgements Not applicable References 1. 2. 2019;144(8):1941-53.

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38	668	Figure	e 1: Flow chart of studies selection for the systematic review and meta-analysis of breast
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7 8	677	Additional file 3: subgroup analysis of the pooled proportion of breast cancer by regions in
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15 16	681	Additional file 5: subgroup analysis of the pooled proportion of breast cancer by study
17 18 10	682	population in Ethiopia
19 20 21	683	Additional file 6: Funnel plot with 95% confidence limits of the pooled proportion of breast
22 23	684	cancer in Ethiopia
24 25	685	Additional file 7: Sensitivity analysis of the level of breast cancer: Prevalence and 95%
26 27	686	confidence interval of breast cancer in Ethiopia
28 29	687	Additional file 8: The pooled odds ratio showing the association between processed food and
30 31	688	breast cancer in Ethiopia
32 33	689	Additional file 9: The pooled odds ratio of the association between cholesterol level and breast
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37 38	691	Additional file 10: The pooled odds ratio showing the association between physical activity and
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45 46 47	695	Additional file 12: The pooled odds ratio of the association between BMI and breast cancer in
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Figure 1: Flow chart of studies selection for the systematic review and meta-analysis of breast cancer and its determinants in Ethiopia

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Figure 2: Forest plot of the pooled proportion of breast cancer in Ethiopia

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Page 32 of 48

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Figure 3: The pooled odds ratio showing the association between menopausal status and breast cancer in Ethiopia

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Search strategy

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Page 34 of 48

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	8.	Hailu (2020)	2	1	1	1	2	2	1	1	5	62.5	Include	
	11.	Kibret (2022)	1	1	3	3	2	2	1	3	3	37.5	Include	
	12.	Kumie (2020)	1	1	1	1	2	2	1	1	6	75	Include	://bmjc
-	14.	Memirie (2018)	2	1	1	3	2	2	1	1	4	50	Include	aini.
	15.	Schwartz (2020)	2	2	3	1	2	2	1	3	2	25	Exclude	Outconfe of interest not repo
	16.	Schwartz (2021)	2	2	3	1	2	2	1	3	2	25	Exclude	Outcome ognterest not repo
	18.	Solomon (2019)	1	1	3	3	2	1	1	1	5	62.5	Include	on Ju
	19	Tefera B (2016)	2	1	3	1	2	2	1	3	3	37.5	Include	ne 10,
	21	Tesfaw (2018)	1	1	1	2	2	2	1	1	5	62.5	Exclude	No out ame of interest repor
	24.	Woldu (2017)	1	2	1	3	2	2	3	1	3	37.5	Include	A A
	Q1. Were	the criteria for in	clusic	on in t	he sa	mple	clearl	y defi	ned?					ger
	Q2. Were	the study subject	s and	l the s	etting	g desc	ribed	in de	tail?					ICe
	Q3. Was t	he exposure mea	sured	l in a v	/alid a	and re	liable	e wav	?					Bit
	-		rd;	toria	icod f	for m	easur	, emen	t of t	he co	ndition?			Slio

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05	Were conf	Jundi	ng fact	ors id	ontific	42								3-08	
06.	Were strat	egies	to dea	l with	confo	undin	g facto	ors sta	ated?					inc	
Q7.	Were the c	utcor	nes m	easure	ed in a	valid	and re	eliable	wav?					ludi	
Q8.	Was appro	priate	statis	tical a	nalysis	s used	?		,					ng f	
														emt Ises	
		l ah a		C			h al ! a a							seig	
Becord								07	08	00	010	Total	%		son for exclusion
no.	(vear)	QI	QZ	Q3	Q4	CD .	QU	Q/	Qð	QS	QIU	score	70		
5.	Duche	1	2	1	1	1	2	3	1	3	1	6	60		
	(2021)					•	6							peri tan	
9.	Hassen	1	1	1	1	1	2	2	1	2	1	7	70	include of the	
10	(2021) Hassen	1	2	2	2	1	1	1	1	2	1	6	60		
10.	(2022)	-	5	5	5	1	1			2	-	0	00	ninii ht	
13.	Mekonen (2021)	1	3	1	1	1	2	1	1	3	1	7	70	include <u>e</u> · tp	
17.	Shalamo (2022)	1	2	2	1	1	2	1	1	3	1	6	60	include	
23.	Tolessa	1	2	1	1	1	1	1	1	3	1	8	80	include	
4	(2021)									1					
1. 2	Were the g	roups	s comp	arabi	e otne	r than annro	nthe p	resen	ceord	lisease	in cases	s or the abs	sence of a		
2.	Were the s	ame o	riteria	ns ma nused	for ide	appio	ation	of cas	es and	1 contro	ls?			nil:	
4.	Was expos	ure m	easure	ed in a	stand	lard, v	valid a	nd reli	iable v	vav?				n Ju arte	
5.	Was expos	ure m	easure	ed in t	he san	ne wa	y for c	cases a	and co	, ntrols?				ine schr	
6.	Were confe	oundi	ng fact	tors id	entifie	ed?								10, 10,	
7.	Were strat	egies	to dea	l with	confo	undin	g facto	ors sta	ated?					202 Digie	
8.	Were outco	omes	assess	ed in	a stan	dard,	valid a	nd re	liable	way for	cases a	and control	s?	ະ. ເ	
9.	Was the ex	posur	e peri	od of	intere	st long	g enou	igh to	be me	eaningfu	ul?			IT A	
10.	Was appro	priate	statis	tical a	nalysis	s used	?							gen	
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Recorc no.	l Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total score	%	ıt, includiı	Byverall Byppraisal	Reason for exclusio
20	Tekle (2019)	4	4	3	2	2	3	1	2	2	1	1	3	27	Enseigne ng for uses relate	22Xclude VerNovember 202	Outcome of intere not reported
1.	Were the tw	o grou	ups sin	nilar a	nd reci	ruited	from t	the sar	me po	pulatic	n?			•	d to	- -	
2.	Were the ex	posur	es mea	asured	simila	rly to	assign	peopl	e to b	oth ex	posed a	nd une	kposed group	s?	tex		
3.	Was the exp	osure	measu	ured ir	a vali	d and	reliabl	le way	?						t ar	าไอะ	
4	Were conto	unding	g facto	rs ider	itified	, 			10						ng c	ide	
-			N 00 11 1	with co	ontour	iaing t	actors	stated	יג							-	
5.	Were strate	gies to		nonte	froo of	the e	uteem	a at th	o ctor	+ of +b	- ctudu	lar at th	a mamant a	found	ata (A		
5. 6. 7	Were strate, Were the gr	oups/j	partici	pants f	free of	the o	utcom d rolia	e at th	e star	t of the	e study	(or at tł	ne moment o	fexpos	ata) Sure Mi	d from	
5. 6. 7.	Were strate Were the gr Were the ou	oups/j itcome	partici es mea	pants f asured	free of in a va	the or alid an	utcom d relia	e at th ble wa	ne star ay?	t of the	e study	(or at th	ne moment o	f expos	atauminin	d from http	
5. 6. 7. 8.	Were strate Were the gr Were the ou Was the foll	oups/j itcome ow up	partici partici es mea time r	pants f asured report	free of in a va ed and	the or alid an suffic	utcom d relia ient to	e at th ble wa b be lo	ie star ay? ng eno	t of the ough fo	e study or outco	(or at th omes to	ne moment o occur?	f expos	r (ABES) . ataumining, ۸ sur	d from http://	
5. 6. 7. 8. 9.	Were strate Were the gr Were the ou Was the foll Was follow	gies to oups/j itcome ow up up con gies to	partici partici es mea time r nplete	pants f asured report , and i	free of in a va ed and f not, v	the or alid an suffic were t	utcom d relia ient to he rea	e at th ble wa b be lo sons t	ne star ay? ng end o loss d?	t of the ough fo to follo	e study or outco ow up d	(or at th omes to escribe	ne moment o occur? d and explore	f expos ed?	r (ABES) . ataomining, Al tr	d from http://bmj	

Record	Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total	%	Overall	Reason for exclusion
no.	(year)										score		appraisal	ech
1	Abate	3	3	3	1	1	3	1	3	3	3	33	exclude	The outcome of antegest is not shown in this
	(2016)													study. Besides, 🍰 mge size, sampling
														techniques and ana sis methods were not
														clearly described.
22	Timotewos	3	3	3	1	1	1	1	1	3	5	77	Include	٨ge
	(2018)													nce
1.	1. Was the sample frame appropriate to address the target population?												B	
2.	2. Were study participants sampled in an appropriate way?												blic	
3.	Was the samp	ole siz	e ade	quate	e?									nge
				-										a ph
														iqu
								ala la	++ //l					

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4. 5. 6. 7. 8. 9.	Were the study subject Was the data analysi Were valid methods Was the condition m Was there appropria Was the response ra	ects and the setting described in detail? is conducted with sufficient coverage of the identified sample? used for the identification of the condition? neasured in a standard, reliable way for all participants? ite statistical analysis? te adequate, and if not, was the low response rate managed appropriately?	23-080080 on 2 Novembe Ensei ight, including for uses r
1-Yes	2- No 3-Unclear	4-Not applicable	2024. Downloaded from http://bmjopen.bmj.com/ on June 10, 2025 at Agence Bibliographi gnement Superieur (ABES) . plated to text and data mining, Al training, and similar technologies.
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Page 42 of 48



Abebe et al (2017)

Woldu et al (2017)





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