SYSTEMATIC REVIEW AND META-ANALYSIS ON RISK FACTORS OF BREAST CANCER AMONG WOMEN IN SUB-SAHARAN AFRICA

MSC THESIS

BY

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HAWASSA UNIVERSITY DEPARTMENT OF STATISTICS

NOVEMBER, 2023

HAWASSA, ETHIOPIA

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Approval sheet I

This is to certify that the thesis prepared by Musefa Kedir, entitled: "Systematic Review and Meta-Analysis in Risk Factors of Breast Cancer Among Women in Sub-Saharan African" and submitted in partial fulfillment of the requirements for the Degree of Master of Science in Biostatistics complies with the regulations of the University and meets the accepted standards with respect to originality and quality. The assistance and the help received during the course of this investigation have been duly acknowledged.

_______________________ _______________ ___________

Name of Advisor Signature Date

Approval Sheet II

We, the undersigned, members of the Board examiners of the final open defense by **Musefa Kedir** have read and evaluated her thesis entitled and examined the candidate. This is therefore to certify that the thesis has been "Systematic Review and Meta-Analysis in Risk Factors of Breast Cancer Among Sub-Saharan African Women" accepted in partial fulfillment of the requirement of the degree of Master of Science in Applied Statistics.

Name of Department Head	Signature	Date
Name of Main Advisor	Signature	Date
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Name of Internal Examiner-1	Signature	Date
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Final approval and acceptance of this thesis is contingent upon the submission of the final copy of the thesis to the school of graduate studies (SGS) through the department/ School graduate committee (DGC/SGC) of the candidate's department.

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Declaration

I honestly declare that the thesis is my original work, has not been presented for degrees in any other university and all sources of material used for the thesis have been duly acknowledged. Name: **Musefa Kedir**

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Date: _________________________

This thesis has been submitted for examination with my approval as a University Advisor **Dereje Danbe (**PhD)

Signature: ______________________

Date: _________________________

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Abbreviations

ACS	American Cancer Society
WHO	world health organization
SSA	Sub-Saharan Africa
DNA	Deoxynucleic Acid
BC	Breast cancer
BCS	breast-conserving surgery
PERSIMA	preferred reporting items for systematic review and meta-analysis
SSA	Sub-Saharan African countries
RCTs	Randomized controlled trials
IARC	International Agency for Research on Cancer
JBI	Joanna Briggs Institute
CAR	Central African Republic
PFHBC	positive family history of breast cancer
NFHBC	negative family history of breast cancer
OCP	oral contraceptive method
NOCP	non user of contraceptive method
OLS	ordinary least squares
UW	underweight
OW	over weight
NCDs	Noncommunicable diseases
WPE	Patient active in physical exercise
WOPH	Patient are not active in physical exercise

Abstract

In the 21st century, cancer, specifically breast cancer is expected to be a leading cause of mortality, affecting people under 70 in many countries. Among the commonly reported cancer types, female breast cancer is the most frequently occurring cancer globally. It is the second most common cause of death for women in Africa and stands as the most common form of cancer affecting women in Sub-Saharan Africa (SSA). The aim of this finding is to identify breast cancer risk factors in Sub-Saharan Africa by using systematic review and meta-analysis. We conducted a systematic search of international databases including PubMed/Medline, Scopus, Google Scholar, and Google engi ne to collect relevant studies from 2000 to March 2023. The random-effects model in R software was employed to estimate pooled odds ratios at a 5% significance level. Publication bias was assessed using Egger and Funnel plot methods, with adjustments made using the Trim and Fill method. A sensitivity analysis was performed to ensure the model's robustness and stability in data analysis. This study analyzed a total of 24 articles, including 22 case–control, 1 cross-sectional, and 1 cohort study, with a combined participant count of 17,321. The findings revealed several variables associated with an increased risk of breast cancer: like positive family history of breast cancer (OR=1.87, 95% CI 1.58 to 2.21), alcohol consumption (OR=1.47, 95% CI 1.11 to 1.96), postmenopausal status of the patients, (OR=1.36, 95% CI 1.02 to 1.81), lower educational level (vs. university level) (OR=1.36, 95% CI 1.10 to 1.70), and residing in an urban area (OR=0.54, 95% CI 0.31 to 0.95) reduced the risk of breast cancer. variables like ever breastfeeding, early age at menarche, physical exercise, BMI, oral contraceptive use and smoking status had no statistically significant association with breast cancer. Theis systematic review and meta-analysis enhance our understanding of breast cancer risk factors in sub-Saharan Africa. The study identified significant association between educational level, residence, alcohol consumption, family history of breast cancer, and menopausal status, while other variables did not link to breast cancer significantly. Smoking also did not display a statistically significant association. This underscores the importa nce of rising awareness about major risk factors, such as education, residence, alcohol intake, fa mily history, and menopausal status, to inform decision making and encourage preventive action like reducing alcohol consumption and adhering to regular screenig.

Keywords: Breast cancer, Risk factors, systematic review, Meta-analysis, sub-Sahara Africa

1. INTRODUCTION

1.1 Background of Study

According to Diabate et al., (2018), cancer refers to a collection of illnesses that arise from the unchecked proliferation and dispersion of abnormal cells throughout the body. One of these types of cancer is breast cancer, which is characterized by the development of malignant tumors in the cells of the breast tissue. These cells are composed of glands called lobules, which produce milk, and ducts that link the lobules to the nipple.

The global burden of cancer has increased significantly, with an estimated 19.3 million new cases and 10 million deaths recorded in 2020 according to (IARC, 2020) report. This means that one in every five people around the world will experience cancer at some point in their lives, and the disease claims the lives of one in eight men and one in eleven women. More than 60% of newly diagnosed cancer cases and over 70% of cancer-related deaths are attributed to the ten most common types of cancers. Among the commonly reported cancer types, female breast cancer is the most frequently occurring cancer globally, accounting for 11.7% of all new cases followed by lung cancer (11.4%), colorectal cancer (10.0%), prostate cancer (7.3%), and stomach cancer (5.6%) (IARC, 2020).

In 2020, breast cancer affected 2.3 million women worldwide and led to 685,000 deaths. As of the end of 2020, there existed 7.8 million women who had received a breast cancer diagnosis within the previous five years and were still living, making breast cancer the most common cancer globally. This disease ranks as the most prevalent cancer among women in 86% of countries and is the leading cause of female cancer-related deaths in 58% of nations. It is the second leading cause of female cancer-related fatalities in 95% of countries, emphasizing the urgent need to address it as a major public health concern on a global scale (WHO, 2023). It accounted for 684,996 fatalities, with an age-adjusted rate of 13.6 per 100,000 (Ferlay et al., 2021) On a global scale. While the highest incidence rates were observed in more developed regions, Asia and Africa collectively bore the burden of 63% of all breast cancer deaths in 2020 (Ferlay et al., 2021). The prognosis for women diagnosed with breast cancer varies significantly between high-income countries, where most survive, and many low and middle-income nations, where survival rates are notably lower (Ginsburg et al., 2017).

Despite the higher prevalence of breast cancer in Western Europe and North America (Xu et al., 2023), developing countries are witnessing a rise in cases due to extended lifespans, urbanization, and the adoption of Western lifestyles. For this reason, it is a problem affecting women worldwide and is considered a significant public health issue specifically in sub-Saharan Africa (SSA) (Black & Richmond, 2019). It is commonly detected in women, with an adjusted incidence rate of 28 per 100,000 women. It is also the second most common cause of death for women in Africa and stands as the most common form of cancer affecting women in Sub-Saharan Africa (SSA), accounting for 94,378 cases in 2012. This surpasses the number of cases of cervical cancer, which is the second most prevalent female cancer, with 93,225 cases (Edward et al., 2017; Ferlay et al., 2014). On a global scale, SSA experiences the highest mortality rates from breast cancer, with a five-year survival rate of less than 40%, a stark contrast to the 86% survival rate in the United States (Cumber et al., 2017).

The average age of diagnosis of breast cancers among African women tends to be young, with estimates that a majority of cancers develop among women 50 years or younger; a considerably younger age than seen in Caucasian populations (Sighoko et al., 2013). The combined occurrence and fatality rates of breast cancer among African women stand at 34.5 cases and 17.2 deaths per 100,000 females (Zeru et al., 2019). Within Africa, there is noticeable regional variation in breast cancer incidence, as reported by Togo, with rates of 16% in Senegal, 10% in the Republic of South Africa, and 4% in Kenya, Additionally in North Africa, it takes the lead as the most prevalent cancer among women, accounting for 14% to 42% of all female cancer cases (Togo el.al., 2010).

Sub-Sahara exhibits the highest age-standardized incidence rate worldwide, with a figure of 17.3 cases per 100,000 women annually. Within this region, the Southern Africa and West African regions display notably elevated age-standardized incidence rates, recording 38.9 and 38.6 cases per 100,000 women annually respectively, furthermore, in all of Africa, the Northern Africa region records the highest incidence rate, with a rate of 43.2 cases per 100,000 (Azubuike et al., 2018). Looking at specific countries, the prevalence of breast cancer varies, with the Central African Republic, Rwanda, and Sierra Leone reporting prevalence rates of 15.3%, 4.6%, and 3.3%, respectively (Balekouzou et al., 2016; Ntirenganya et al., 2014). Mauritius and Nigeria emerge as the nations with the highest incidence rates in the entire African continent, reporting 64.2 and 50.4 cases per 100,000 women, respectively (Azubuike et al., 2018).

According to (Gebremariam et al., 2019), in Ethiopia, cancer is becoming a significant public health issue, and more than 50% of newly detected cancer cases in women are due to breast and cervical cancer.

Based on the studies conducted in Sub-Saharan Africa, various risk factors associated with breast cancer among women have been identified. Research conducted by Augustin et al. (2017) highlighted a positive family history of breast cancer as a significant risk factor. D Huo et al. (2008) emphasized the role of alcohol consumption. Fatuma et al. (2022) pointed to the importance of educational level, while Inarie et al. (2019) underscored the impact of menopausal status. Additionally, Mohammed et al. (2013) discussed the relationship between residence (urban vs rural) and breast cancer incidence. Moreover, Larry et al. (2022) and Lidia et al. (2021) found evidence of early age at menarche, breastfeeding history, physical exercise, BMI, and oral contraception use as factors deserving consideration. Interestingly, Michael et al. (2006) and Henock et al. (2021) explored the role of smoking status, although a consistent statistical significance was not observed across all studies. Therefore, recognizing elements that contribute to the risk of breast cancer plays a crucial role in developing preventive measures against this ailment.

1.2 Statement of Problem

Various studies in sub-Saharan Africa have provided important information about the risk factors associated with breast cancer among women. However, research conducted in this region highlights significant disparities in findings concerning these risk factors and frequently, they display discrepancies and contradictions in their reported results, which makes it challenging to draw clear and unified conclusions about the impact of specific risk factors. This inconsistency underscores the pressing need for a systematic review and meta-analysis in this region. Employing such an approach is essential to unify the divergent findings, provide a comprehensive and evidence-based overview, and address the existing knowledge gaps in breast cancer epidemiology. Therefore, this research aims to fill this gap by offering a comprehensive and Coordinated assessment of risk factors, and it attempts to answer the following inquiries.

- What are the most significant risk factors of breast cancer among women in SSA countries?

- Are breast cancer risk factors in Sub-Saharan African women consistent across studies in the meta-analysis?

1.3 Objectives of study

1.3.1 General Objective:

- The primary objective of this study is to comprehensively identify and analyze the various risk factors contributing to breast cancer incidence among women in Sub-Saharan Africa.

1.3.2 Specific objectives:

- To determine the most significant risk factors for breast cancer among women in SSA.
- To analyze variations in identified breast cancer risk factors among Sub-Saharan African women across studies.

1.4 Significant of study

The study's findings could potentially contribute to a better understanding of the burden of breast cancer in Sub-Saharan African countries and inform future research and public health interventions aimed at reducing the incidence and impact of the disease.

systematic review and meta-analysis on the associated factors of breast cancer among women in SSA countries is a significant study that provides important information on the burden of breast cancer in the country and can inform efforts to prevent, diagnose, and treat the disease.

1.5 Organization of the Study

This research work is presented in five chapters. The first chapter provides the background of the study, statement of the problem, the objective of the study, and the significance of the study were presented. Chapter two contains an overview of breast cancer and literature reviews of previous studies related to this study. Chapter three contains the description of the data set, the statistical methodology used to analyze breast cancer patient data with studies selection criteria, method of checking quality of studies, and other important concepts could be included in this chapter. Chapter four contains descriptive statistics result, result quality checked, result of meta-analysis, interpretation, and discussion of the result. Finally, conclusions and recommendations based on the findings of the study were included.

1.6 Operational Definitions

Breast cancer: is a disease where cells divide abnormally without control and invade other tissues damaging the genetic material called Deoxyribonucleic Acid.

Lifestyle factors (Behavioral factors): are behaviors such as smoking or way of living that determines how the body organ's function.

Reproductive factors: are reproduction related factors that influence hormone related cancers such as breast cancer in this case.

Risk factor: is any attribute, characteristic or exposure of an individual that affect the likelihood of developing a disease or injury.

Systematic review: is a research method that involves systematically collecting, evaluating, and synthesizing all available evidence related to a specific research question or topic. It is a rigorous and structured approach to summarizing the results of multiple studies, often used in healthcare and other fields to inform decision-making, policy development, or further research (Higgins et al., 2003).

Forest plot: A forest plot is a graphical representation commonly used in meta-analyses and systematic reviews to display the results of individual studies along with summary statistics. It provides a visual summary of the effect sizes and their confidence intervals from multiple studies on the same topic. The forest plot gets its name from its appearance, where individual study results are shown as vertical line segments that resemble a forest of trees.

2. LITERATURE REVIEW

2.1 Overview of Breast cancer

Noncommunicable diseases (NCDs) are currently the leading cause of global deaths, as stated by the World Health Organization in 2021. Among NCDs, cancer is anticipated to emerge as the primary contributor to mortality and a significant obstacle to increasing life expectancy worldwide in the 21st century. According to 2015 data from the World Health Organization (WHO), cancer ranks as either the primary or secondary cause of death in individuals under 70 years of age in 91 out of 172 countries and holds the third or fourth position in an additional 22 countries. Among this breast cancer is one type of cancer, globally female breast cancer is the most frequently diagnosed cancer, accounting for 11.6% of total cases, following lung cancer (STEVENS et al., 2018).

Breast cancer is characterized by uncontrolled cell division and the invasion of surrounding tissues, leading to damage to the genetic material known as Deoxyribonucleic Acid (DNA) (Sudip & Banerjee, 2015). It predominantly originates from the glandular tissue within the breast, specifically the lobules and ducts connecting them to the nipple, according to the American Cancer Society (ACS, 2016).

Breast cancer stands as the predominant form of cancer found among women residing in sub-Saharan Africa. In the year 2020, approximately 129,000 women in this geographical region received a fresh diagnosis of this ailment. Regrettably, the prospects for survival among these women are typically dim, with an average of 50% succumbing to the disease within three years of being diagnosed (WHO, 2021).

The management and control of breast cancer in sub-Saharan Africa (SSA) have become pressing public health issues. In SSA, breast cancer is the most common cancer among women and exhibits some of the highest mortality rates globally for this disease. Historically, breast cancer has been considered a health concern primarily affecting affluent nations with established early detection initiatives. However, breast cancer screening efforts in SSA have shown less success compared to high-income countries (Black & Richmond, 2019).

Several factors contribute to the risk of breast cancer. These encompass personal and family history, including genetic predisposition, personal breast cancer history, ductal or lobular carcinoma in situ, benign breast disease, hormone levels, menstrual cycles, and bone density. Reproductive factors, such as pregnancy, fertility treatments, breastfeeding, hormonal contraceptives, and postmenopausal hormone therapy, also play a role. Additionally, environmental elements, such as radiation exposure, diethylstilbestrol exposure, environmental pollutants, and occupational hazards, contribute to risk. Other risk factors include tobacco use, obesity, physical activity, dietary choices, and alcohol consumption (Farhadihosseinabadi et al., 2018).

Breast cancer is typically diagnosed either through screening examinations before symptoms manifest or after a woman detects a lump. Most masses are discovered via mammograms, and the majority of breast lumps turn out to be non-cancerous. In cases where cancer is suspected, microscopic analysis of breast tissue is necessary for a definitive diagnosis. This analysis helps determine the extent of cancer spread (in situ or invasive) and characterizes the type of the disease (Neal et al., 2010).

Treatment decisions hinge on factors such as cancer stage, biological characteristics, patient age, and a thorough evaluation of potential risks and benefits. Early-stage breast cancer typically involves surgery, often complemented by radiation therapy, chemotherapy, hormonal therapy, or targeted therapy. Metastatic cancer is primarily treated with systemic therapies like chemotherapy, targeted therapy, or hormonal therapy.

Breast cancer surgery serves the dual purpose of removing cancer from the breast and providing critical staging information. Surgical options include mastectomy, which removes the entire breast, and breast-conserving surgery (BCS), which removes only the cancerous tissue and a margin of surrounding healthy tissue. BCS carries a slightly higher risk of cancer recurrence in the breast compared to mastectomy. Younger women under 40 and patients with larger or more aggressive tumors are more likely to undergo mastectomy. Both BCS and mastectomy often involve removing one or more regional lymph nodes from the armpit (axilla) to determine whether the disease has spread beyond the breast. The presence of cancer cells in these lymph nodes guides decisions regarding subsequent surgeries, radiation therapy, and medical treatments (Mcguire et al., 2009).

2.2 Literatures related to risk factors of breast cancer among women

Researchers conducted examinations of a range of outcomes in both the global and sub-Saharan contexts to determine the risk of breast cancer and various cardiovascular diseases.

2.2.1 Socio-demographic factors breast cancer

2.2.1.1 Residence

A case-control investigation carried out in Bangui has suggested that women residing in urban areas exhibit a reduced likelihood of developing breast cancer by a factor of 0.16 in comparison to those dwelling in rural locales (Augustin et al., 2017). Conversely, a separate case-control study conducted at a Tertiary Hospital in Uganda did not yield significant evidence to support the notion that a woman's place of residence significantly influences her risk of breast cancer (Galukande et al., 2016). In contrast, a study conducted by (Fei et al., 2015), utilizing Pearson correlation and ordinary least squares (OLS) models, investigated the interplay between socioeconomic factors and cancer incidence. Their analysis revealed that breast cancer incidence rates were notably higher in urban settings when compared to rural regions.

2.2.1.2 Educational level

In accordance with the findings of (Augustin et al., 2017) in their case-control study, it was determined that women with limited or no educational background faced significantly higher odds of developing breast cancer, with respective odds ratios of 11.23 and 2.40 when compared to those with a university education. Similarly, a separate Case-Control Study conducted in Northern Algeria suggested an inverse relationship between the number of years of education and the risk of breast cancer, specifically noting an odds ratio of 0.63 for individuals with 11 or more years of education compared to those with no schooling (Mokhtar et al., 2020).

On the contrary, a comprehensive matched case-control systematic review and meta-analysis conducted among Iranian women, encompassing findings from seven different studies, did not establish any significant association between illiteracy and the likelihood of developing breast cancer (Khoramdad et al., 2022).

2.2.1.3 Marital status

According to the case-control study conducted by (Augustin et al., 2017), they observed that the likelihood of developing breast cancer was 2.09 times higher among married women compared to their single counterparts.

In another study led by (Hinyard et al., 2017), which focused on breast cancer-related outcomes in women under 65, it was established that unmarried women faced a 1.18 times higher likelihood of receiving a later-stage diagnosis compared to their married counterparts. Additionally, in adjusted analyses, unmarried women were found to have a greater risk of mortality resulting from breast cancer. Furthermore, (Martinez et al., 2017) also reported higher overall mortality rates among unmarried breast cancer patients when compared to their married counterparts.

Similarly, in a case-control study investigating risk factors for breast cancer in Nigerian women, (Michael et al., 2006) found evidence suggesting that having ever been married was associated with a reduced risk of developing breast cancer, with an odds ratio (OR) of 0.43.

2.2.2 Behavioral Risk factors

2.2.2.1 Body mass Index

In a dose-response meta-analysis examining the relationship between body mass index (BMI) and breast cancer risk, (Liu et al., 2018) presented compelling evidence. Their analysis, which encompassed various studies and employed a random-effects model, revealed a potential linear association between BMI and the risk of breast cancer. Specifically, for every 5 kg/m2 increase in BMI, there was a 2% increase in the risk of breast cancer.

Likewise, a systematic review and meta-analysis conducted in the Eastern Mediterranean Region (EMR) by (Namiranian et al., 2014) suggested that obesity (BMI greater than 30) and overweight status (BMI between 25 and 30) were significant risk factors for breast cancer among women residing in the EMR.

However, it is important to note that some studies have yielded inconsistent findings. For instance, a hospital-based case-control study carried out in Malaysia found a different perspective. According to (Min-min et al., 2018), a higher BMI was associated with a lower risk of breast cancer in their study population. Specifically, individuals classified as overweight (with a BMI range of 23.0–27.4 kg/m2) exhibited a 33% reduced risk, while those classified as obese (BMI of 27.5 kg/m2 or higher) had a 53% reduced risk of developing breast cancer.

2.2.2.2 Physical activity

In a systematic review and meta-analysis focusing on Chinese women, the results put forth by (Gao et al., 2013) indicated a noteworthy protective effect associated with physical activity when it comes to reducing the risk of breast cancer.

Similarly, a case-control study conducted in Bangui, Central African Republic, as reported by (Augustin et al., 2017), offered supporting evidence for the benefits of physical activity. Their findings suggested that women who engaged in regular physical activities exhibited a lower odds ratio for breast cancer compared to those who did not incorporate physical activity into their lifestyle.

Likewise, in a case-control study examining risk factors for breast cancer among Moroccan women under the age of 40, (Laamiri et al., 2016) arrived at a similar conclusion. Their research indicated a negative association between physical activity and the likelihood of developing breast cancer in this specific population.

2.2.2.3 Alcohol intake

A systematic review and meta-analysis involving Chinese women, as conducted by (Gao et al., 2013), failed to identify any significant link between alcohol consumption and the risk of breast cancer. Similarly, a Case-Control Study carried out among Ugandan women, as reported by (Galukande et al., 2016), found no substantial association between the use of alcohol and the likelihood of being diagnosed with cancer. Similarly, in a study involving Iranian women (Khoramdad et al., 2022), two of the studies under evaluation revealed no discernible connection between alcohol consumption and the risk of breast cancer.

Contrastingly, a study conducted across three Sub-Saharan African countries, as presented by (Frank et al., 2014), yielded different results. Their findings suggested that the risk of breast cancer remained relatively consistent regardless of when women-initiated alcohol consumption. Compared to non-drinkers, those who had been drinking for less than 10 years had a 41% higher odds of breast cancer, while those with 10 to 19 years of drinking experience had 71% higher odds, and those with 20 or more years had 82% higher odds. Additionally, for every 10-year increase in the duration of alcohol consumption, there was a 54% increase in the risk of breast cancer.

Moreover, systematic reviews conducted in the Eastern Mediterranean Region, covering both developed and developing countries, have consistently found a positive association between alcohol consumption and breast cancer, as highlighted by (Namiranian et al., 2014). Furthermore, research conducted in the United States of America (USA) suggested that even moderate alcohol use, defined as two drinks per day, increased the risk of both premenopausal and postmenopausal breast cancer, as reported by the (Cancer Prevention Research Program et al., 2003).

2.2.2.4 Smoking

In a comprehensive matched case-control systematic review and meta-analysis conducted by (Khoramdad et al., 2022), the collective findings of nine studies pointed to a significant association between smoking and an increased risk of breast cancer, with the risk being elevated by up to 83%.

Additionally, a study carried out by (Michael et al.,2017) suggested a modest yet discernible rise in the likelihood of breast cancer among women who were cigarette smokers, particularly those who initiated smoking during their teenage years or around the time of their first menstruation.

Conversely, while not achieving statistical significance, research undertaken by (Larry et al., 2022) argued that cigarette smoking tended to increase the odds of developing breast cancer when compared to individuals who did not smoke.

2.2.3 Reproductive risk factors

2.2.3.1 Age at menarche

A study conducted by (Romieu et al., 2021) focusing on black South African women with breast cancer revealed that reproductive factors, such as the age at which they experienced their first menstrual period (menarche), were statistically significant in their association with breast cancer risk. This relationship held true for women of all ages, including both premenopausal and postmenopausal individuals.

In a similar vein, a case-control study conducted among black Tanzanian women, as reported by (Larry et al., 2022), supported the notion that early menarche, which has long been known to increase breast cancer risk in high-income and transitioning countries, played a role in this population as well.

Furthermore, another case-control study conducted in Tunisia, examining the impact of menstrual and reproductive factors on breast cancer risk, as conducted by (Msolly et al., 2013), revealed a significantly reduced risk of breast cancer among women who experienced menarche at a later age, specifically at or above 12 years.

Similarly, a case-control study conducted among Moroccan women under the age of 40, with a focus on risk factors associated with breast cancer, as presented by (Laamiri et al., 2016), demonstrated a noteworthy pattern. They found that women who had an early onset of menstruation (below 12 years) were more prevalent among breast cancer patients compared to the control group. This early onset of menstruation was associated with a significant increase in breast cancer risk, with an odds ratio (OR) of 2.474.

2.2.3.2 Family History Breast cancer

A systematic review and meta-analysis conducted in Iran by (Shamshirian et al., 2020) revealed a consistent trend. Their analysis, comparing two groups, indicated that individuals with a family history of breast cancer had 1.80 times higher odds of developing breast cancer.

Similarly, findings from a Case-Control study conducted in Northern Algeria, as reported by (Mokhtar et al., 2020), supported this association, highlighting a statistically significant link between a family history of breast cancer and the emergence of breast cancer.

Likewise, a study conducted in the Central African Republic, as presented by (Augustin et al., 2017), affirmed this trend. Their research indicated that women with a family history of cancer faced a 2.31 times higher risk of developing breast cancer compared to those without such a family history.

Furthermore, a case-control study investigating the impact of menstrual and reproductive factors on breast cancer risk in Tunisia, carried out by (Msolly et al., 2013), underscored the importance of family history. Their study demonstrated that a positive family history of breast cancer was associated with a significantly increased risk of developing breast cancer.

2.2.3.3 Breastfeeding

A meta-analysis conducted by (Zhou et al., 2015) presented a comprehensive view. Their pooled results indicated that breastfeeding had a protective effect against breast cancer. Specifically, the summary relative risk (RR) for breast cancer in individuals who ever breastfed compared to those who never breastfed was 0.613. Similarly, research conducted by (D Huo et al., 2008) in Nigerian women supported this notion. They found that for every additional 12 months of breastfeeding, the risk of breast cancer decreased by 7%.

Furthermore, a multicenter case-control study carried out in India, as suggested by (Gajalakshmi et al., 2009), demonstrated an inverse relationship between the lifetime duration of breastfeeding and the risk of breast cancer among premenopausal women.

Moreover, a dose-response meta-analysis conducted by (Unar-munguía et al., 2017) focused on the mode of breastfeeding and its impact on breast cancer risk. Their findings indicated that exclusive breastfeeding among parous women was associated with a reduced risk of breast cancer when compared to parous women who did not exclusively breastfeed.

2.2.3.3 Menopausal status

An Unmatched Case-Control Study conducted in Ethiopia by (Henok et al., 2021) presented findings indicating that the risk of breast cancer was notably higher in postmenopausal women compared to their premenopausal counterparts. Specifically, the adjusted odds ratio (AOR) was 6.8, with a 95% confidence interval (CI) ranging from 1.92 to 24.16.

Similarly, a study conducted at Tikur Anbessa Specialized Hospital in Addis Ababa, Ethiopia, as reported by (Fatuma et al., 2022), supported this observation.

Conversely, a meta-analysis conducted by the (Collaborative Group on Hormonal Factors in Breast Cancer, 2012) offered a contrasting perspective. Their analysis suggested that women who had not yet reached menopause faced a higher risk of developing breast cancer compared to women who were already postmenopausal but within the same age group. This elevated risk was particularly evident among women aged 45 to 54 years, with a relative risk of 1.43 (95% CI: 1.33–1.52, p<0.001).

2.2.3.4 Oral Contraception methods (OCP)

A systematic review and meta-analysis conducted by (Kanadys et al., 2021) yielded interesting findings. Their analysis suggested that the combined crude odds ratio for breast cancer among individuals who had ever used oral contraceptives (OCP) was 1.01, with a 95% confidence interval ranging from 0.95 to 1.07, when compared to those who had never used them. Importantly, this study found no significant increase in risk among different subgroups, including premenopausal women (1.06, 0.92–1.22), postmenopausal women (0.99, 0.89–1.10), or nulliparous women (1.02, 0.82–1.26). In contrast, (Bardaweel et al., 2019) suggested a different perspective. Their research indicated that regular use of oral contraceptives (OCP) was associated with an increased risk of breast cancer, with an odds ratio (OR) of 2.25 and a 95% confidence interval of 1.34-2.79. Interestingly, the duration of OCP use did not appear to influence the risk of breast cancer.

Similarly, in a meta-analysis of prospective cohort studies conducted by (Hang et.al. 2012), the collective relative risk (RR) for breast cancer among individuals who had ever used oral contraceptives (OC) in comparison to those who had never used them was 1.08, with a 95% confidence interval of 0.99-1.17. This indicated that the risk of breast cancer among women who had ever used OCP might be slightly higher than that of those who had never used.

Systematic review and Meta-analysis

A systematic review is a structured and comprehensive approach to analyzing and summarizing existing literature on a specific topic, utilizing rigorous methods to identify, evaluate, and synthesize relevant studies. It aims to provide a comprehensive overview of existing evidence, minimizing bias and subjectivity.

Conversely, a meta-analysis is a statistical technique used to quantitatively combine data from multiple studies on the same topic. It employs a statistical model, often a random-effects or fixed-effects model, to pool results from individual studies. This process derives a more precise estimate of the effect size or outcome of interest by accounting for variability between studies, offering increased statistical power and a more robust conclusion compared to individual studies (Higgins et al., 2003).

2.4 Conceptual framework

In essence, a conceptual framework is a researcher's way of organizing and summarizing existing literature related to a particular phenomenon. By considering the perspectives of other researchers and their own observations, the researcher outlines the necessary steps to be taken throughout the study (Regoniel, 2015).

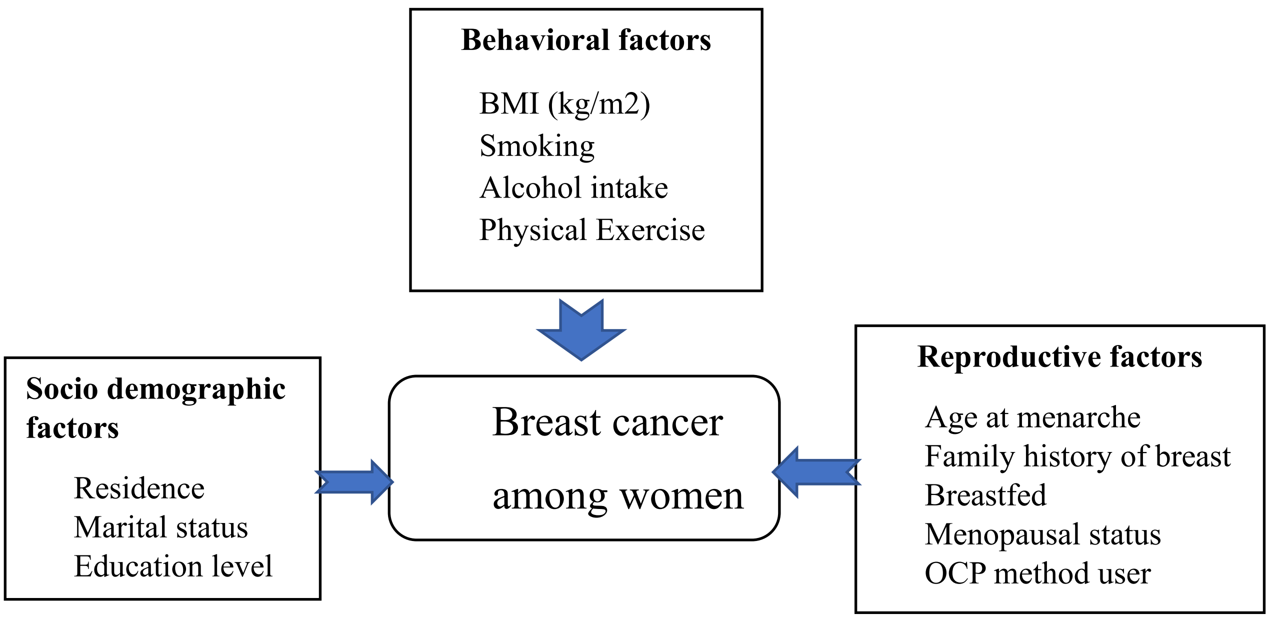

Figure 2.1: Conceptual framework

3. METHODOLOGY

3.1 Study Area and Target population

The settings for this systematic review and meta-analysis on Sub-Saharan African. It is a place with many different countries that have unique cultures and landscapes. There are more than 1 billion people living in this region, according to the latest information from the (Sub-Saharan Africa - World Atlas). The countries here have various types of governments, like republics and monarchies, and they are split into different parts for better organization.

The study target population of interest in this review was women in the reproductive age group and above who were living in SSA.

3.2 Variables of study

The phenomena of interest of this study were to review patient characteristics that may act as risk factors or predictors for breast cancer among women in reproductive age and above. According to (American Cancer Society, Breast Cancer Risk and Prevention) fact and figure for breast cancer there are several risk factors and predictors for breast cancer, including demographic characteristics, reproductive risk factors, and behavioral risk factors. Here are some of the main ones:

Table 3.1 Descriptions of Risk factors of breast cancer

Socio-demographic characteristics risk factors		
No	Variables	Categories
1	Residence	Rural, urban
2	Marital status	Married, Single, Divorced/Widowed
3	Education level	illiterate, below diploma, university level
Behavioral risk factors		
No	**Variables**	**Categories**
1	Smoking	Yes, no
2	Alcohol intake	Yes, no
3	Physical Activity	yes, no

4	BMI (kg/m^2)	Underweight (<18.5), Normal (18.5-25), Overweight (25.5-29.5), Obese (≥30)
Reproductive risk factors		
No	**Variables**	**Categories**
1	Age at menarche (years)	Early age (≤ 12), late age (>12)
2	Family history of breast cancer	Yes, no
3	Breast feeding	Ever breastfed, never breastfed
4	Menopausal status	Postmenopausal, premenopausal
5	Oral contraception method uses	Yes, no

3.3 Types of study design

Since the objective of this study was to explore the various factors that may contribute to risk of developing breast cancer among women in sub-Saharan Africa, the observational study designs (cohort, case–control and cross-sectional studies) that assessed predictors or determinants of breast cancer were included in the review. The research that was conducted by using randomized controlled trials (RCTs) study design was not included in this study, the reason why we excluded the randomized controlled trials (RCTs) from this systematic review and meta-analysis is the distinction between studying risk factors or exposures versus interventions. RCTs are primarily designed to evaluate the efficacy or effectiveness of interventions, such as treatments, therapies, or preventive measures. They involve random assignment of participants to different groups, including control and experimental groups, to assess the impact of the intervention on the outcome of interest. However, the focus of this study lies specifically on identifying and analyzing the risk factors or exposures associated with breast cancer among Sub-Saharan African countries women. As such, RCTs may not be directly applicable to this research question, as they do not inherently address the relationship between risk factors and breast cancer incidence.

3.4 Information sources and search strategy

A systematic review and Meta-analysis were made using the articles published online and stored in Scopus, PubMed, Google Scholar and Google engine. The search was done by using the following

Medical Subject Headings (MeSH) search terms; “Risk factor*”, “Associated factor*”, “predicto r*", determinant*, "Breast Neoplasms", "Breast cancer", "Women", "female", "Africa", "sub-Sahara", and by names of all sub-Saharan African countries through using string term "AND" and "OR". A combination of MeSH terms and free terms were used for the searching strategy to conduct this systematic review and meta-analysis. The search was covering the period from 2000 to march 2023 to keep the review current. Only studies published in English language were considered. The reference lists of the included studies were manually searched to identify any articles that have not been identified by the electronic search.

3.5 Study selection

The process of identifying relevant studies was done by first creating a list of citations in EndNote20, eliminating any duplicates. Afterward, the titles and abstracts of the remaining studies were screened, with those that fulfilled the criteria being chosen for further review. Finally, the full texts of these articles were thoroughly scrutinized to decide whether they were suitable for data extraction. This search sequence is accurately illustrated in a PRISMA flow chart (see Fig 3.1), which displays all studies that were either included or excluded, along with the reasons for exclusion. Articles that did not report required data for meta-analysis were excluded.

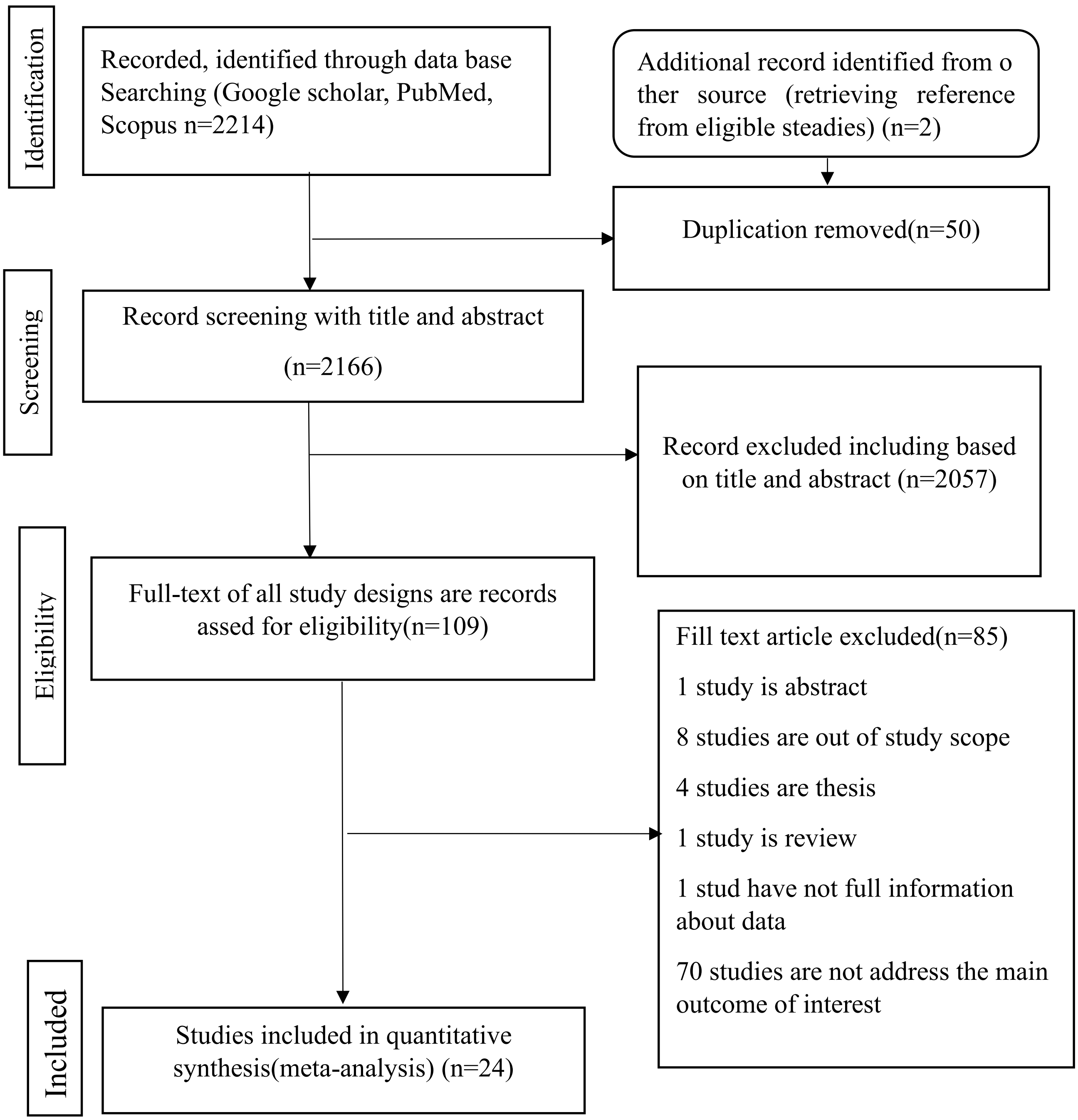

Figure 3.1 flow chart showing the procedure of selecting studies for the systematic review and meta-analysis of factors breast cancer among women in SSA countries ,2000-2023

3.6 Eligibility criteria

Studies were selected based on the following criteria of study population, exposure and outcome of interest.

3.6.1 Inclusion Criteria:

- Studies with cross-sectional, case-control and cohort designs were included,
- Studies published in English from the year 2000 up to march 2023 will be included
- Studies that investigate the risk factors of breast cancer in women in SSA countries.
- Studies conducted on human subjects.

3.6.2 Exclusion Criteria:

- Studies that are not relevant to the topic of breast cancer in women in SSA countries.
- Studies that do not provide sufficient information on the risk factors of breast cancer.
- Studies that are not published in the English language.
- Studies conducted on animal subjects.
- Conference papers, unpublished paper, editorial notes and systematic reviews and meta-analyses were excluded from the study.

3.7 Data extraction

The data extraction was done by using a tool developed by the 2014 Joanna Briggs Institute Reviewers' Manual data extraction form (JBI, 2015). The abstract and full-text were reviewed appropriately. The data extraction includes: author's name, publication year, study period, study design (cross-sectional, case–control and cohort), sample size, study area (country), Sociodemographic characteristics risk factors (e.g., Residence, Marital status, education,), lifestyle risk factors (e.g., Alcohol intake, smoking status, physical exercise), and reproductive risk factors (e.g., Family history of breast, breast feeding status, contraceptive method usage, and menopausal status) were extracted from each article.

3.8 Strategy for data synthesis

In total, twenty-four studies were eligible to extract data using a Microsoft excel spreadsheet and endnote20 were presented in terms of authors' name and publication date, sample size, and other study characteristics. But not all researchers had used the same classification for each predictor or risk factors at their study level. When this kind of event happened, a better inclusive classification system or category was selected. If all these efforts did not work, studies containing unfitted categories for predictors would not be included in the study (Dereje, 2020). Therefore, one cross-sectional, one cohort and twenty-three case-control full-text articles conducted on this study reported from 2000 to march 2023 were used. All twenty-four included full-text articles were chosen to measure associated factors of breast cancer among women in Sub-Saharan African.

3.9 Risk of bias assessment

The studies underwent a rigorous evaluation of their methodology using standardized assessment tools derived from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instruments. We applied JBI's predefined criteria for assessing the quality of primary studies, and studies that met or exceeded a threshold of 60% were considered for inclusion in the meta-analysis. Any disparities or disagreements were resolved through constructive dialogue (JBI, 2015). Quality assessment instruments for each specific study design were provided in **Appendix A-C**. Notably, all of the studies in this analysis demonstrated moderate to high quality standards.

3.10 Data analysis

After data extraction and synthesis, the information was inputted into an Excel spreadsheet and subsequently imported into the R 4.2 version software for in-depth analysis. To evaluate heterogeneity among studies reporting effect size, the I^2 statistic, coupled with the Cochran Q statistic, was utilized. I^2 values of 0%, 25%, 50%, and 75% corresponded to no, low, medium, and high heterogeneity, respectively, at a p-value of 99.4%. A random-effects meta-analysis model was employed to estimate the pooled effect size of risk factors. Visual representation of heterogeneity through forest plots was used. The possibility of publication bias was explored by Egger (Egger et al., 1997) with a p-value threshold of less than 0.05. Additionally, funnel plots were utilized to assess publication bias. If there was publication bias, the Trim and Fill method was employed

(Duval & Tweedie, 2014). A sensitivity analysis was conducted to assess the robustness and reliability of the results. Further details regarding the meta-analysis model are provided below.

3.11 Meta-Analysis:

Meta-analysis is a statistical method used to combine and analyze data from multiple studies to obtain a quantitative summary estimate of the effect size. It aims to provide a more precise and robust estimate of the treatment effect or relationship between variables by pooling the results across studies.

Meta-analysis involves applying statistical models to the effect sizes and associated variances (or standard errors) reported in each study, taking into account the sample sizes and variability of the effect estimates. The most commonly used meta-analytic models are the fixed effects model and the random effects model (Borenstein et al., 2009). Random and fixed effects are two commonly used approaches in the context of meta-analysis to account for the variability between studies. Here are the meanings of random and fixed effects, along with their corresponding statistical formulas.

3.11.1 Fixed Effects

Fixed effects models assume that the true effect size is the same across all studies, and any observed differences in effect sizes are only due to within-study sampling error. The model assumes that there is no between-study heterogeneity beyond what is expected by chance.

The statistical formula for the fixed effects model is

$$Y_i = \theta + e_i \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots 3.1$$

where Y_i represents the observed effect size in study i, θ represents the common true effect size across all studies, and e_i represents the within-study random error; it is assumed to be a normal distribution with a mean of zero and a variance that represents the within-study variability or the sampling error.

Mathematically, we can represent the distribution of e_i as follows:

$$e_{i \sim N(0,\sigma^2)}$$

e_i: The error term for the ith study.

N: Represents a normal (Gaussian) distribution.

0: The mean of the normal distribution, which is assumed to be zero because, in the fixed-effects model, it is assumed that the true effect size θ is constant across all studies.

σ^2: The variance of the ith study. This variance represents the within-study variability and is typically estimated based on the standard error (SE) or confidence interval of the observed effect size Y_i. In this case i represents number of studies = study1, study 2, ⋯, study24

The fixed effects model assigns equal weights to each study, assuming that any observed differences are solely due to sampling error (Borenstein et al., 2009).

3.11.2 Random Effects:

Random effects models assume that the true effect size varies across studies due to both within-study sampling error and between-study heterogeneity. The model incorporates both within-study and between-study variability, allowing for the estimation of the average effect size across studies as well as the variability between studies (Dersimonian & Laird, 1986).

The statistical formula for the random effects model is:

$$Y_i = \theta + u_i + e_i \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots 3.2$$

where Y_i represents the observed effect size in study i, θ: The overall (pooled) effect size or mean effect size, u_i the deviation of the effect size in the ith study from the overall effect size (θ). In the random-effects model, u_i is considered a random variable that follows a normal distribution with mean zero and between-study variance τ^2(Tau-squared). The between-study variance τ^2 represents the extent to which true effect sizes vary between studies. A larger τ^2 indicates more heterogeneity.

e_i: The within-study error or random error, representing the variation within each study. e_i is assumed to be normally distributed with a mean of zero and a within-study variance σ^2(Sigma-squared). σ^2 captures the random sampling error and other sources of variation within each study.

In the random-effects model, it is assumed that the u_i values follow a normal distribution with a mean of zero and a variance of τ^2 (between-study variance). This means that it considers both the within-study variability (σ^2) and the between-study variability or heterogeneity (τ^2) (Cooper et al., 2009).

Mathematically, we can represent the distribution of u_i as follows:

$$u_i \sim N(0, \tau^2)$$

The choice between a fixed-effects model and a random-effects model in meta-analysis depends on several factors, including the characteristics of the studies being analyzed and the research question at hand (Higgins et al., 2003). However, it is generally recommended to consider the random-effects model as the default choice in meta-analysis (Borenstein et al., 2009). The random-effects model accounts for potential heterogeneity among studies, which is often present in meta-analyses due to variations in study design, populations, interventions, or other factors. We used the I^2 statistic to gauge the extent of variability between effect sizes in a meta-analysis. Higher I^2 values indicate substantial heterogeneity, suggesting differences beyond chance between study results. When I^2 is high (e.g., >50% or 75%), indicating notable between-study variability, it favors the use of a random-effects model over a fixed-effects model to appropriately account for and incorporate this observed heterogeneity in the meta-analysis.

In a meta-analysis, one of the relevant issues is the problem of heterogeneity among studies. To check heterogeneity between original studies, we can use statistical methods such as the Cochran's Q test and the I-squared (I^2) statistic. These methods are commonly used in meta-analysis to assess the variability or heterogeneity among the effect sizes or outcomes reported in different studies (Julian & Green, 2008). Here is an overview of how we can use these methods.

In order to estimate Cochran's Q test and the I-squared (I^2) statistic first we got to Calculate individual study weights the meaning of the study weight and method of find it is explained below:

3.11.3 study weights

In meta-analysis, study weights are numerical values assigned to individual studies based on their contribution to the overall meta-analytic estimate. These weights reflect the precision or reliability of each study's effect size estimate and influence the extent to which each study contributes to the pooled effect size (Borenstein et al., 2009). The calculation of study weights depends on the statistical model being used, whether it is a fixed-effects model or a random-effects model, the calculation of study weights for both models as follow:

In a fixed-effects meta-analysis, it is assumed that all studies estimate the same true effect size, and any variation among study estimates is due to sampling error. The study weights in a fixed-effects model are typically based on the inverse of the variance of the effect size estimate.

The formula to calculate the weight (w) for each study in a fixed-effects model is:

$$w = \frac{1}{variance\ of\ of\ effect\ size\ estimate} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots 3.3$$

The inverse of the variance represents the precision of the effect size estimate, and studies with smaller variances (i.e., more precise estimates) are assigned larger weights (Julian & Green, 2008). In a random-effects meta-analysis, it is recognized that there is variation among the true effect sizes across studies due to both sampling error and genuine heterogeneity. The study weights in a random-effects model incorporate both the within-study variance (sampling error) and the between-study variance (heterogeneity).

The formula to calculate the weight (w) for each study in a random-effects model is:

$$w = \frac{1}{(within\ study\ variance\ +between\ study\ variance)} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots 3.4$$

- The within-study variance is typically estimated from the study-specific effect size estimate and its standard error or confidence interval.
- The between-study variance represents the estimated heterogeneity among studies and is obtained from the meta-analysis model itself (e.g., Random effect model) (Julian & Green, 2008).

Then after Perform Cochran's Q test: Cochran's Q test determines whether there is statistically significant heterogeneity among the effect sizes of the studies. It is based on the assumption that the effect sizes are sampled from a common population. A significant Q value indicates heterogeneity. **The formula for Cochran's Q is:**

$$Q= \sum_{i=1}^{n}(w_i((observed\ effect\ size\ in\ the\ i^{th}\ study\ overall\ effect\ size)^2) \cdots\cdots\cdots\cdots 3.5$$

where w is the weight for each study, effect size is the reported effect size for each study, and the overall effect size is calculated using a fixed or random-effects model.

Cochran's Q test follows a chi-square distribution with k-1 degrees of freedom, where k is the number of studies. If Q is statistically significant ($p < 0.05$), it suggests heterogeneity.

From the Cochran's Q test we can calculate the I-squared **(I^2) statistic**: The I^2 statistic quantifies the percentage of total variation across studies that is due to heterogeneity rather than chance. It ranges from 0% to 100% corresponding to no, and high heterogeneity respectively that means higher values indicate greater heterogeneity and vice versa.

The formula for I^2 is:

$$I^2 = \frac{(Q - df)}{Q} * 100\% \quad \cdots\cdots\cdots 3.6$$

where Q is the Cochran's Q statistic and df is the degrees of freedom (k-1) (Higgins et al., 2003).

Finally, the **publication bias was performed**, Publication bias is a well-known issue in research, where studies with statistically significant or "positive" results are more likely to be published, while studies with non-significant or "negative" results are less likely to be published. This can lead to an overestimation of the true effect in a meta-analysis (Duval & Tweedie, 2000).

Publication bias can distort the results of a meta-analysis by overestimating the magnitude or significance of the overall effect size. It can lead to an inaccurate representation of the true underlying effect, as studies with non-significant or negative results may not be included or available in the analysis (Borenstein et al., 2009).

To test for publication bias in meta-analysis, several methods and statistical tests have been developed. In this study the funnel plot approaches (see Appendix D) and Egger test (see Table 4.3) were used in order to test the presence or the absence of publication bias between studies. Funnel plots are scatter plots that display the effect sizes or estimates from individual studies against a measure of their precision (such as standard error or sample size). In the absence of publication bias, the funnel plot should exhibit a symmetric inverted funnel shape, with smaller studies scattered widely around the average effect size, while larger studies tend to cluster near the overall estimate. Asymmetry in the funnel plot can indicate potential publication bias (Sterne & Egger, 2001).

3.11.4 Sensitivity analysis

In this study we have used sensitivity analysis in order to check the robustness and stability of the analysis (see Table 4.3). Sensitivity analysis is a statistical technique used to assess the robustness and stability of the results in a research or statistical analysis. It involves re-evaluating the primary analysis using modified data or statistical approaches to assess whether changing any of the assumptions impacts the combined effect estimate and consequently influences the ultimate findings (Viel & Pobel, 1995).

3.11.5 Trim and Fill methods

The Trim and Fill method is a statistical technique used in the meta-analysis to assess and adjust for potential publication bias. The primary purpose of the Trim and Fill method is to estimate the potential impact of publication bias on the results of a meta-analysis and provide an adjusted effect size that takes into account missing studies that may not have been published due to their results (Duval & Tweedie, 2000).

3.12 Assumptions and method of diagnosis of random effect model

The assumptions of a statistical model are critical for its validity and reliable interpretation. These assumptions represent the conditions that must hold true for the model to provide accurate and meaningful results. They ensure that the model adequately captures the underlying relationships in the data. Violating these assumptions can lead to biased or unreliable estimates. The assumptions of a statistical model are critical for its validity and reliable interpretation. These assumptions represent the conditions that must hold true for the model to provide accurate and meaningful results. They ensure that the model adequately captures the underlying relationships in the data. Violating these assumptions can lead to biased or unreliable estimates.

1. **Independence of Studies:** This assumption implies that the effect sizes or outcomes in the included studies are independent of each other. In other words, the results of one study should not be influenced by the results of another study. To assess independence, carefully review the study selection and data extraction processes to ensure that there is no overlap of data or repeated inclusion of the same study. This assumption is often considered when evaluating the risk of bias in individual studies (Akl & Askie, 2019).

2. **Absence of Publication Bias:** Publication bias occurs when studies with significant or positive results are more likely to be published than studies with non-significant or negative results. We can assess publication bias through methods like funnel plot asymmetry, Egger's test, Begg's test. Asymmetry in the funnel plot or significant results in Egger tests may suggest potential publication bias (Sterne et al., 2011).
3. **Heterogeneity of Study Effects:** The random-effects model explicitly assumes that there is heterogeneity in the true treatment effects across studies. It means that the effect sizes in the studies are not all drawn from the same underlying distribution but are influenced by both a common mean effect and individual study-specific effects. The Q-statistic and its associated p-value from the chi-squared test are used to test for heterogeneity. A significant p-value (typically $p < 0.05$) suggests that there is significant heterogeneity in the effect sizes. Additionally, examining the estimated between-study variance (Tau-squared) can help assess the extent of heterogeneity (Higgins et al., 2003).

3.12 Ethics approval and consent to participate.

This research is a systematic review and a meta-analysis in which data were gathered from published articles from websites, and hence ethical approval has not been obtained from the Institutional Review Board.

4.RESULT AND DISCUSSION

4.1 Result

A total of 2216 articles were identified from the different data bases. After removing duplicate articles, 2166 articles were eligible for title and abstract review. From these articles, 109 articles were eligible for full text review. Finally, using preset inclusion and exclusion criteria only 24 articles were included in this systematic review and meta-analysis study.

4.1.1 Description of included studies

Twenty-four studies met the inclusion criteria for this systematic review and meta-analysis (Table 4.1). Ten SSA countries were included in this study, with the majority from Nigeria, Ethiopia, Sudan, and Central Africa of the Republic: - of this about 23% of the studies were published in the past 10 years. From a total of the 24 studies, 22 were studies based on a case-control study design, one is cross-sectional, and one study was cohort. The cohort studies and cross-sectional study were not used for the meta-analysis of this paper due to the number of such studies being limited. From the total articles included in the study there were a total of 17,321 from different SSA countries who participated in the studies. Of these studies, based on the methodological quality assessment, almost all studies were found to be moderate and above quality. We included all 24 studies in the systematic review and meta-analysis.

Table 4.1: Summary of eligible articles in to pooled to identify risk factors of breast cancer among women in SSA countries

S/N	Frist Autor/year	Title of the study	Study design	Overall quality
1	(Clement et al., 2003)	Obesity and Height in Urban Nigerian Women with Breast Cancer	Case-control	8/10
2	(Hussain et al., 2010)	Role of Some Risk Factors in the Etiology of Breast Cancer in the Sudan	Case-control	8/10
3	(Tomi et al., 2021)	Association of body composition with odds of breast cancer by molecular subtype: analysis of the Mechanisms for Established and Novel Risk Factors for Breast Cancer in Nigerian Women (MEND) study	Case-control	8/10
4	(Larry et al., 2022)	The effect of reproductive, hormonal, nutritional and lifestyle on breast cancer risk among black Tanzanian women: A case control study	Case-control	9/10
5	(Samuel et al., 2022)	Physical activity and the risk of breast cancer among Nigerian women	Case-control	8/10
6	(Samuel et.al, 2022)	Reproductive factors and the risk of breast cancer among Nigerian women by age and estrogen receptor status	Case-control	8/10
7	(Augustin, et al., 2017)	Behavioral risk factors of breast cancer in Bangui of Central African Republic: A retrospective case-control study	Case-control	9/10
8	(Augustin, et al., 2017)	Reproductive risk factors associated with breast cancer in women in Bangui: a case–control study	Case-control	9/10
9	(Mariana et al., 2021)	Risk Factors for Breast Cancer, Overall and by Tumor Subtype, among Women from Mozambique, Sub-Saharan Africa	Case-control	7/10
10	(Henock et al., 2021)	Identifying Risk Factors of Breast Cancer Among Women Attending Selected Hospitals of Addis Ababa City: Hospital-Based Unmatched Case-Control Study	Case-control	9/10
11	(Fatuma et.al, 2021)	Socio-demographic and Hematological Determinants of Breast Cancer in a Tertiary Health Care and Teaching Hospital in Addis Ababa, Ethiopia	Case-control	7/10
12	(Fatuma et al., 2022)	Association of risk factors and breast cancer among women treated at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: a case–control study	Case-control	9/10

13	(D Huo et al., 2008)	Parity and breastfeeding are protective against breast cancer in Nigerian women	Case-control	8/10
14	(Inarie et al ., 2019)	Dietary intake and breast cancer risk in black South African women: The South African Breast Cancer study	Case-control	8/10
15	(Kelenchi e t al., 2013)	Risk Factors Associated with Breast Cancer among Women in Warri and lbadan, Nigeria	Case-control	8/10
16	(Irmgard et al., 2013)	Dietary patterns and breast cancer risk among women in northern Tanzania: a case–control study	Case-control	7/10
17	(Mohamme d et al., 2013)	Investigation of Breast Cancer Risk Factors in northern states of Sudan using Logistic Regression Analysis	Case-control	8/10
18	(Eman et al ., 2008)	Application of Logistic Regression for Incidence of Breast Cancer among Sudanese Females (2005-2008)	Cohort	9/12
19	(Michael et al., 2006)	Case–control study of risk factors for breast cancer in Nigerian women	Case-control	9/10
20	(N.A. Othieno et al., 2015)	Comparative study of breast cancer risk factors at Kenyatta National Hospital and the Nairobi Hospital	Case-control	7/10
21	(Engbang et al., 2020)	Risk Factors for Breast Cancer in the City of Douala: A Case Control Study	Case-control	8/10
22	(Frank et al ., 2014)	Alcohol Consumption and Breast Cancer Risk among Women in Three Sub-Saharan African Countries	Case-control	8/10
23	(Alaaddin et al., 2017)	Developing a risk prediction model for breast cancer: a Statistical Utility to Determine Afnity of Neoplasm (SUDAN-CA Breast)	Cross-sectional	6/8
24	(Lidia et al. , 2021)	Risk Factors Associated with Breast Cancer among Women in Addis Ababa, Ethiopia: Unmatched Case–Control Study	Case-control	9/10

Table 4.2. Summary of identified risk factors of breast cancer among women in SSA countries based on studies included in this study.

S/N	Frist Autor/year	country	Sample size	Statistically significant associated factors
1	(Clement et al., 2003)	Nigeria	507	Women: ● Younger(year) at onset of menarche, (OR = 0.89, 95% CI = 0.81, 0.96), ● Age(year) with OR of 1.07 (95% CI: 1.04, 1.10, p=0.01), height OR of 1.04 (95% CI 1.01, 1.07; p=0.01) and weight was OR of 1.02 (95% CI 1.00, 1.03; p=0.02).
2	(Hussain et al., 2010)	Sudan	250	● Overweight women who were overweight for more than 20 years had a significantly higher risk of breast cancer. ● Physical inactivity was also found to be a risk factor for breast cancer. ● Finally, the age at menarche as well as marital status, were also found to be associated with breast cancer risk.
3	(Tomi et al., 2021)	Nigeria	705	● Higher BMI (AOR: 0.79; 95% CI: 0.67, 0.95) ● weight (AOR: 0.83; 95% CI: 0.69, 0.98) were associated with reduced odds of BC in adjusted models
4	(Larry et al., 2022)	Tanzania	295	● Only old age at menopause had a significant risk, a 2.6-fold (OR = 2.63, 95% CI = 1.01–6.83) increase.
5	(Samuel et al., 2022)	Nigeria	759	● Women who have ever breastfed had significantly reduced odds of breast cancer (OR= 0.52, 95% CI: 0.29, 0.93).
6	(Samuel et al., 2022)	Nigeria	782	● Compared to women in the lowest categories, women in the upper middle category of total PA (adjusted OR-AOR 0.44, 95% CI: 0.27, 0.78) ● Uppermost categories of total non-vigorous PA (AOR 0.26, 95%CI:0.09,0.75), household PA (AOR 0.0.38, 95% CI: 0.20, 0.71) and occupational PA (AOR 0.64, 95% 0.40, 1.02) had a reduced risk of breast cancer.
7	(Augustin et al., 2017)	CAR	522	● women with breast cancer were more likely to have attained illiterate and elementary education level [11.23 (95% CI, 4.65–27.14) and 2.40 (95% CI, 1.15–4.99)], married [2.09 (95% CI, 1.18–3.71)], positive family history [2.31 (95% CI, 1.36–3.91)], fresh fish consumption [4.26 (95% CI, 1.56–11.65)], alcohol [2.53 (95% CI, 1.39– 4.60)], overweight [5.36 (95% CI, 4.46–24.57)] and obesity [3.11(95% CI, 2.39–20.42)]. Similarly, women who, regularly consume charcuterie or fresh fish showed respectively 10.82 and 4.26-times higher BC risk (95% CI, 2.39–48.90, p = 0.002 and 95% CI, 1.56–11.65, p = 0.005) compared to those who do not consume regularly.

				● However, decreased risk of breast cancer was associated with urban residence [0.16 (95% CI, 0.07–0.37)], and physical activity [0.71(95% CI, 0.14–0.84)] and women who use of hormonal contraceptive (OR =0.62 [0.41–0.93).
8	(Augustin et al., 2017)	CAR	522	● Women with breast Ca were more likely to have had an abortion (AOR = 5.41, CI: 3.47–8.44), and to be nulliparous (AOR = 1.98, CI: 1.12–3.49). ● Decreased odds of breast Ca were being employed (AOR = 0.32, CI: 0.19–0.56) associated late menarche (AOR = 0.18, CI: 0.07–0.44), regular menstrual cycles (AOR = 0.44, CI: 0.23–0.81), term pregnancy (AOR = 0.26, CI: 0.13–0.50) and hormonal contraceptive use (AOR = 0.62, CI: 0.41–0.93).
9	(Mariana et al., 2021)	Mozambique	776	● A higher educational level (≥8 vs. 0 schooling years) increased breast cancer risk across all subtypes (overall AOR 1.98; 95% CI, 1.04–3.80) ● Higher weight and BMI were associated with a higher breast cancer risk among postmenopausal women (per 1-kg increase: AOR 1.05; 95% CI, 1.02–1.08; per 1-kg/m2 increase: AOR 1.11; 95% CI, 1.04–1.18, respectively), but were protective in premenopausal women (AOR 0.98; 95% CI, 0.96– 0.99; AOR 0.95; 95% CI, 0.91–0.99, respectively), regardless of subtype.
10	(Henock et al., 2021)	Ethiopia	220	● The results show that physical activity was significantly associated with breast (AOR=0.2, p<0.001). Menopausal status was also significantly associated with breast cancer, with women in menopause having a higher risk of breast cancer than those in perimenopause (AOR=6.8, p=0.008). ● Breastfeeding was found to be significantly associated with breast cancer, with women who had never breastfed having a higher risk of breast cancer than those who had (AOR=3.4, p=0.022). Similarly, BMI was found to be significantly associated with breast cancer, with women with a BMI greater than 25.1 kg/m2 having a higher risk of breast cancer than those with a BMI less than 18.5 kg/m2 (AOR=5.9, p=0.001).
11	(Fatuma et.al., 2021)	Ethiopia	460	● The result shows the mean age was 42.8 + 12.1 years and 39.3 + 11.1 years for cases and controls, respectively. About 43.5% of the cases and 14.8% of the controls were not able to read and write. About 76.1% of the cases and 67.4% of the controls were married. ● The mean values of Hemoglobin, Red Blood cell, Packed Cell Volume for the cases were 13.1 + 1.6g/dl; 4.6 + 0.54x1012/L; and 38.7 + 4.5 %, respectively. These were significantly lower than those of the controls (14.0 + 1.3g/dl, 4.8 + 0.47 x 1012/L, 40.5 +

				3.5%, respectively). Mean platelet count was higher among the cases, whereas total White Blood cell count was almost similar.
12	(Fatuma et al., 2022)	Ethiopia	460	● The odds of breast cancer were higher among women between 40 and 49 years (adjusted OR (AOR): 3.29, 95%CI 1.39 to 7.77), being unemployed (AOR: 4.28, 95%CI 2.00 to 9.16), Weight(<59kg), overweight, early menarche (<12) and milk consumed more than once per week where significantly higher the risk of breast cancer, ● On the other hand, the odds of breast cancer were significantly lower among women who had moderate physical activities.
13	(D Huo et al., 2008)	Nigeria	1488	● The result shows Compared with women with menarche age < 17 years, the adjusted OR for women with menarche age ≥17 years was 0.72 (95% CI: 0.54–0.95, P = 0.02). Parity was negatively associated with risk (P-trend = 0.02. Importantly, breast cancer risk decreased by 7% for every 12 months of breastfeeding (P-trend =0.005).
14	(Inarie et al., 2019)	South African	792	● Fresh fruit consumption showed an inverse association with BC risk (OR=0·3, 95 % CI 0·12, 0·80) in premenopausal women, whilst red and organ meat consumption showed an overall inverse association with BC risk (OR=0·6, 95 % CI 0·49, 0·94 and OR=0·6, 95 % CI 0·47, 0·91).
15	(Kelechi et al., 2013)	Nigeria	266	● The odds of developing breast cancer were four times higher among women who reported daily exposure to fumes from automobiles and electricity generating plants than those who were rarely exposed (0R=4.40, C/=1.25- 15.57) and seven times higher among women who reported occasional exposure to wastes from operating industries than those who were rarely exposed (0R=6.91, C/=2.87- 16.66).
16	(Irmgard et al., 2013)	Tanzania	345	● The result of analysis of study provides OR for the "Fatty Diet" was 1.42 (95% CI 1.08-1.87; P=0.01), indicating that individuals with a higher consumption of milk, vegetable oils and fats, butter, lard, and red meat had a 42% higher risk of the outcome compared to those with lower consumption of these foods. ● Similarly, the OR for the "Fruity Diet" was 1.61 (95% CI 1.14-2.28; P=0.01), indicating that individuals with a higher consumption of fish, mango, papaya, avocado, and watery fruits had a 61% higher risk of the outcome compared to those with lower consumption of these foods.
17	(Mohammed et al., 2013)	Sudan	120	● The results of logistic regression analysis in this study showed that there is no difference in risk factors between cases and controls, so the breast cancer risk factors are same among all Sudanese women. That is the risk factors like Age, marital status, education,

				residence, age at menarche, use contraceptive and family history of breast cancer with respective odds ratio (OR = 2.43,3,1.1,7.21,0.22, 0.27 and 0.37) respectively are risk factors but not significant difference between case and control.
18	(Eman et a l., 2008)	Sudan	110	● The two variables are significant namely, stage and marital status with p-values = (.000), (.074) respectively. ● The OR for the stage shows that those who are at late stages are (.65) times more likely to die compared with those who are at early stages. Those who are single are (1.223) times more likely to die compared with those who are married. 95% confidence interval indicated that the value of OR ranged between (.478, .792), (.981, 1.526) for stage and marital status respectively
19	(Michael et al., 2006)	Nigeri a	500	● Family history of breast cancer (OR = 8.08, 95% CI 1.003–64.95, p = 0.04), education of high school level and above (OR 1.35, 95% CI 1.04–1.74, p = 0.0205), were significant predictors of breast cancer risk ● Breastfeeding was associated with a significant (23%) reduction in breast cancer risk (OR 5 0.77, 95% CI 0.63–0.93, p 5 0.006).
20	(N.A. Othieno et.al., 2015)	Kenya	694	● The results show that the area of residence (p=0.045) diet (p=0.01), and family history of breast cancer (p=0.016), use of hormonal contraceptives, had association with breast cancer occurrence.
21	(Engbang et al., 2020)	Camer oon	1520	● The finding demonstrated that there is a significant association between age ≥ 50 and breast cancer (OR = 2.59; CI = [1.96 - 3.41]), ● Patients who smoked were 4 times more likely to develop breast cancer than those who did not smoke (OR = 4.21 with CI = [2.30 - 7.71]), ● Patients who had been on hormonal contraception were relatively more likely to develop breast cancer than those who had never been on contraception (OR = 1.56 with CI = [0.71 - 1.94]).
22	(Frank et a l., 2014)	Sub-Sahara	4727	● Consumed alcohol (OR = 1.62, 95% CI: 1.33–1.97), Both past (OR = 1.54; 95% CI: 1.19–2.00) and current drinking (OR = 1.71; 95% CI: 1.30–2.23) were associated with breast cancer risk. ● A dose-response relationship was observed for duration of alcohol drinking (P-trend ,0.001), with 10-year increase of drinking associated with a 54% increased risk (95% CI: 1.29–1.84).
23	(Alaaddin et al., 2017)	Sudan	153	● The finding demonstrated that patient, Age (years) (OR=0.098, 95% CI =1.057–1.150), Menarche(years) (OR= − 0.318 ,95% CI= 0.571–0.926), positive family history of BC (OR=1.141, 95% CI= 1.166–8.406) and Vegetables & fruits (servings/week) − 0.265, 0.616–0.956) were significantly related to risk of breast cancer,

				where except positive family of patient the remaining variables are lower the odds of breast cancer according to this finding.
24	(Lidia et a l., 2021)	Ethiop ia	348	• The finding shows that Early onset of menarche (AOR= 4.10; 95% CI: 1.84, 9.15), rural women (AOR= 3.64; 95% CI:1.38, 9.57), utilization of packed foods or drinks (AOR= 2.80; 95% CI:1.52, 5.15), and smoke-dried meat (AOR= 2.41; 95% CI:1.36, 4.27), family history of cancer (AOR= 2.11; 95% CI:1.04, 4.26), overweight and/or obesity (AOR= 2.38; 95% CI:1.31, 4.31), and women with one or less children (AOR= 1.86; 95% CI:1.01, 3.41) were associated factors with breast cancer risk

4.1.2 Model Choice and Diagnostic Checking

Model Choice

Based on Table 4.3, considerable heterogeneity is evident across all variables, as indicated by I^2 values ranging from 35% to 89%. These I^2 statistics suggest substantial to high variability in effect sizes among the included studies for each variable and it supports the utilization of a random-effects model for the meta-analysis. Therefore random-effects model is well-suited for accommodating between-study heterogeneity than that of fixed effect one, enabling the incorporation of this variability into the analysis. This choice allows for the estimation of an overall effect size while considering and accounting for the observed diversity in effect sizes across studies for each variable in the meta-analysis.

Table 4.3 Model choice and diagnostic checking

Variables	I^2	Egger test
Educational level	75%	0.3486
Marital status	80%	0.6220
BMI status	77%	0.1227
Physical Exercise	88%	0.9902
Area of Residence	75%	0.4773
Smoking status	79%	0.7433
Alcohol intake	79%	0.3447
Family history of breast	35%	0.5534
Menopausal status	85%	0.3589
Breast feeding History	84%	0.1351
OCP method user	84%	0.8359
Age at Menarche	89%	0.7905

Model Diagnostic Checking

In this thesis, our statistical analysis relies on several critical assumptions that form the foundation of our model's validity. The first assumption, Independence of Studies, ensures that the results of each study we have included are not influenced by one another, allowing us to treat them as distinct and unrelated. The second assumption, Absence of Publication Bias, was checked by using funnel plot in **(Appendix D)** and non-significant Egger test (see Table 4.3) for each risk factor. Lastly, the Heterogeneity of study effects assumption acknowledges that true treatment effects vary between studies, which our random-effects model accounts for (see Table 4.3 in the I^2 column). Therefore, all assumptions of the random effect model were met in this paper.

4.1.3 Result of random effect Meta-analysis model on risk factors of breast cancer

The random-effects meta-analysis model is a statistical approach used in meta-analytical studies to estimate the average effect size across multiple studies while considering both within-study variability and between-study variability. Unlike the fixed-effects model, which assumes a single true effect size for all studies, it accounts for the possibility that the true effect size might vary among studies due to both random error within studies and genuine differences between studies. This model assumes that the true effect size follows a distribution, allowing for more flexibility and accommodating heterogeneity among studies (Borenstein et al., 2009).

In our finding, we selected for the random-effects meta-analysis model due to observed variations among the effect sizes reported in the studies included. The presentation of I^2 results in **Table 4.3** indicated substantial heterogeneity among true effect sizes of included studies. This choice of using a random-effects model was more suitable than a fixed-effect model when addressing this level of heterogeneity. The random-effects model acknowledges that the true effect sizes might differ not only due to random error within studies but also due to genuine differences between studies. It assumes that the effect size varies across different studies, accommodating this variability. This model incorporates both within-study and between-study variations, providing a more conservative and generalizable estimation of the overall effect size across diverse studies in our meta-analysis and the followings are result of random effect meta-analysis model for each risk factors of breast cancer.

Educational level

In Figure 4.1, a study looked into how the education status of women is associated with breast cancer. Women who cannot read and write well had two-fold higher risk than women who went to university. Women who had less diploma education level had about 1.13 times higher risk of breast cancer than a woman who had university level educational status. When we look at all the information together, the overall risk is higher about 1.36 times, and this is for sure because the 95% confidence interval does not include 1. There is heterogeneity in the results from different studies (about 75% difference), so the random effect model was assumed in analysis. They found a strong connection a score of 2.77, which is quite big) between lower education and the risk of breast cancer. This finding also saw differences between different groups with a score of 4.29. So, it is clear that having less education is linked to a higher chance of getting breast cancer, especially if those who did not finish school. And sensitivity analysis confirms the result's consistency (OR range: 1.32 to 1.39) (see Table 4.4).

Study or Subgroup	Illiterate,Below Diploma Events	Illiterate,Below Diploma Total	University Events	University Total	Weight	Odds Ratio MH, Random, 95% CI
EducationalLevel = Illitrate vs University						
Augustin et.al(2017)	45	79	23	74	4.1%	2.93 [1.51; 5.70]
D Huo et.al.(2008)	191	303	177	305	5.8%	1.23 [0.89; 1.71]
Fatuma et.al.(2021)	100	134	26	88	4.5%	7.01 [3.85; 12.79]
Frank et.al.(2014)	383	711	469	1114	6.4%	1.61 [1.33; 1.94]
Henock et.al(2021)	24	51	62	225	4.3%	2.34 [1.25; 4.36]
Inarie et.al.(2019)	97	168	42	88	4.9%	1.50 [0.89; 2.51]
Kelechi et.al.(2013)	11	34	19	100	3.2%	2.04 [0.85; 4.89]
Lidia et.al.(2021	39	66	84	121	4.3%	0.64 [0.34; 1.19]
Total (95% CI)	**890**	**1546**	**902**	**2115**	**37.6%**	**1.89 [1.17; 3.04]**
Heterogeneity: Tau^2 = 0.3875; Chi^2 = 38.81, df = 7 (P < 0.01); I^2 = 82%						
EducationalLevel = lower than diploma vs University						
Augustin et.al(2017)	106	369	23	74	4.7%	0.89 [0.52; 1.54]
D Huo et.al.(2008)	451	780	177	305	6.1%	0.99 [0.76; 1.30]
Fatuma et.al.(2021)	104	237	26	88	4.8%	1.86 [1.10; 3.15]
Frank et.al.(2014)	1286	2902	469	1114	6.5%	1.09 [0.95; 1.26]
Henock et.al(2021)	62	132	24	37	3.7%	0.48 [0.23; 1.02]
Inarie et.al.(2019)	257	536	42	88	5.2%	1.01 [0.64; 1.58]
Kelechi et.al.(2013)	35	132	19	100	4.3%	1.54 [0.82; 2.89]
Larry et.al.(2022)	52	161	37	121	4.9%	1.08 [0.65; 1.80]
Lidia et.al.(2021	109	161	84	121	4.9%	0.92 [0.56; 1.54]
Mariana et.al(2021)	451	879	149	320	6.1%	1.21 [0.94; 1.56]
N.A. Othieno et.al.(2014)	299	595	38	95	5.3%	1.52 [0.98; 2.35]
Samuel et.al.(2022)	109	205	207	472	5.8%	1.45 [1.05; 2.02]
Total (95% CI)	**3321**	**7089**	**1295**	**2935**	**62.4%**	**1.13 [1.03; 1.24]**
Heterogeneity: Tau^2 = < 0.0001; Chi^2 = 16.27, df = 11 (P = 0.13); I^2 = 32%						
Total (95% CI)	**4211**	**8635**	**2197**	**5050**	**100.0%**	**1.36 [1.10; 1.70]**
Heterogeneity: Tau^2 = 0.1876; Chi^2 = 75.31, df = 19 (P < 0.01); I^2 = 75%						
Test for overall effect: Z = 2.77 (P < 0.01)						
Test for subgroup differences: Chi^2 = 4.29, df = 1 (P = 0.04)						

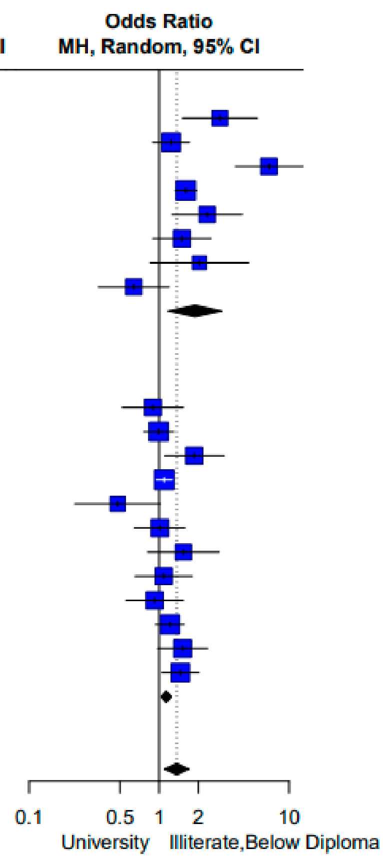

Figure 4.1: Forest plot of effects of educational status on breast cancer among women in SSA countries, 2000-2023.

Marital status

The forest plot in Figure 4.2 illustrates an analysis focused on investigating the association between marital status and the risk of breast cancer. women who are single had a slightly lower risk (OR: 0.69, 95% CI: 0.36-1.31) but the result is not statistically significant. On the other hand, women who are divorced or widowed exhibited a significant reduction in risk (OR: 0.69, 95% CI: 0.55-0.88) compared to married women. When considering all the collected data together, there seems to be an overall decrease in risk (OR: 0.69, 95% CI: 0.46-1.04), but this reduction is not statistically significant. It is important to note that there is substantial variation among the studies (tau^2 = 0.5877, I^2 = 80%), leading to the assumption of a random effect. However, despite this, the test for the overall effect is not statistically significant (z-score: -1.77, p = 0.08), indicating limited evidence of a connection between breast cancer and marital status. The analysis does not reveal substantial differences among categories of marital status (chi-square = 0.00, p = 0.97), and sensitivity analysis demonstrates that the calculated OR for this variable remains consistent (with a range of OR changes between 0.64 and 0.73).

Study or Subgroup	Single,Divorced,Widowed Events	Single,Divorced,Widowed Total	Married Events	Married Total	Weight	Odds Ratio MH, Random, 95% CI
MaritalStatus = single vs marrid						
Augustin et.al(2017)	132	445	42	74	6.7%	0.32 [0.19; 0.53]
Fatuma et.al.(2021)	23	52	175	330	6.5%	0.70 [0.39; 1.27]
Henock et.al(2021)	9	17	101	203	5.2%	1.14 [0.42; 3.06]
Hussain et.al.(2010)	16	24	134	226	5.5%	1.37 [0.56; 3.34]
Kelechi et.al.(2013)	7	14	46	197	4.9%	3.28 [1.09; 9.85]
Larry et.al.(2022)	45	111	59	184	6.7%	1.44 [0.89; 2.36]
Lidia et.al.(2021)	14	72	84	219	6.3%	0.39 [0.20; 0.74]
Michael et.al(2006)	24	60	226	440	6.6%	0.63 [0.36; 1.09]
Mohammed et.al.(2013)	8	57	52	63	5.2%	0.03 [0.01; 0.09]
N.A. Othieno et.al.(2015)	51	107	254	510	6.9%	0.92 [0.60; 1.39]
Samuel et.al.(2022)	36	69	301	626	6.7%	1.18 [0.72; 1.94]
Total (95% CI)	**365**	**1028**	**1474**	**3072**	**67.2%**	**0.69 [0.36; 1.31]**
Heterogeneity: $Tau^2 = 1.0555$; $Chi^2 = 72.72$, df = 10 ($P < 0.01$); $I^2 = 86\%$						
MaritalStatus = Divorsed,widowd vs marrid						
Fatuma et.al.(2021)	32	78	175	330	6.7%	0.62 [0.37; 1.02]
Kelechi et.al.(2013)	12	55	46	197	6.1%	0.92 [0.45; 1.88]
Lidia et.al.(2021)	18	75	84	219	6.4%	0.51 [0.28; 0.92]
N.A. Othieno et.al.(2015)	34	77	254	510	6.8%	0.80 [0.49; 1.29]
Samuel et.al.(2022)	40	91	325	626	6.9%	0.73 [0.47; 1.13]
Total (95% CI)	**136**	**376**	**884**	**1882**	**32.8%**	**0.69 [0.55; 0.88]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.2$, df = 4 ($P = 0.70$); $I^2 = 0\%$						
Total (95% CI)	**501**	**1404**	**2358**	**4954**	**100.0%**	**0.69 [0.46; 1.04]**
Heterogeneity: $Tau^2 = 0.5877$; $Chi^2 = 75.06$, df = 15 ($P < 0.01$); $I^2 = 80\%$						
Test for overall effect: $Z = -1.77$ ($P = 0.08$)						
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 ($P = 0.97$)						

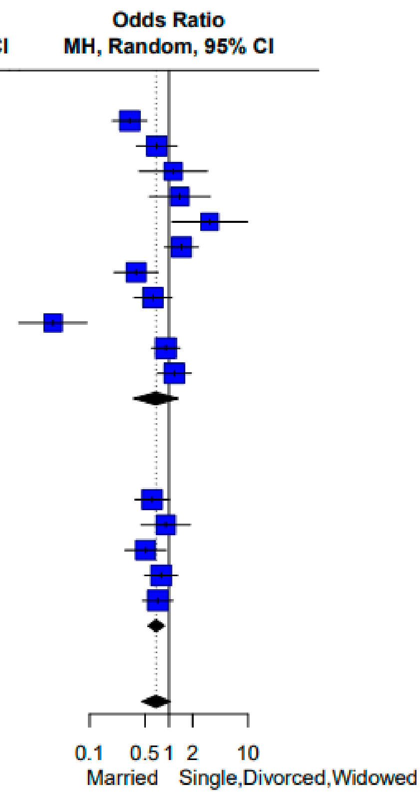

Figure 4.2: Forest plot of effects of marital status on breast cancer among women in SSA countries, 2000-2023

BMI status

The forest plot in Figure 4.3 depicts a meta-analysis assessing the impact of different Body Mass Index (BMI) categories on breast cancer risk. Results reveal inconclusive findings, underweight women show a OR of 1.05 (95% CI: 0.61-1.82), overweight women exhibit an OR of 1.16 (95% CI: 0.84-1.60), similarly obesity women have an OR of 0.73 (95% CI: 0.46-1.17) all of these results are also not statistically significant since it includes the null value 1. The pooled OR of 0.98 (95% CI: 0.76 to 1.23) for all BMI categories combined indicates no significant overall effect, with z-score for the overall effect is -0.25 (p = 0.80), suggesting no statistical significance relation. While there is no significant subgroup difference (chi square = 2.52, p = 0.28), and significant heterogeneity exists (I^2= 77%) and sensitivity analysis (see Table 4.4) obtained OR for this variable was robust (range of OR changes: between 0.91 and 1.01).

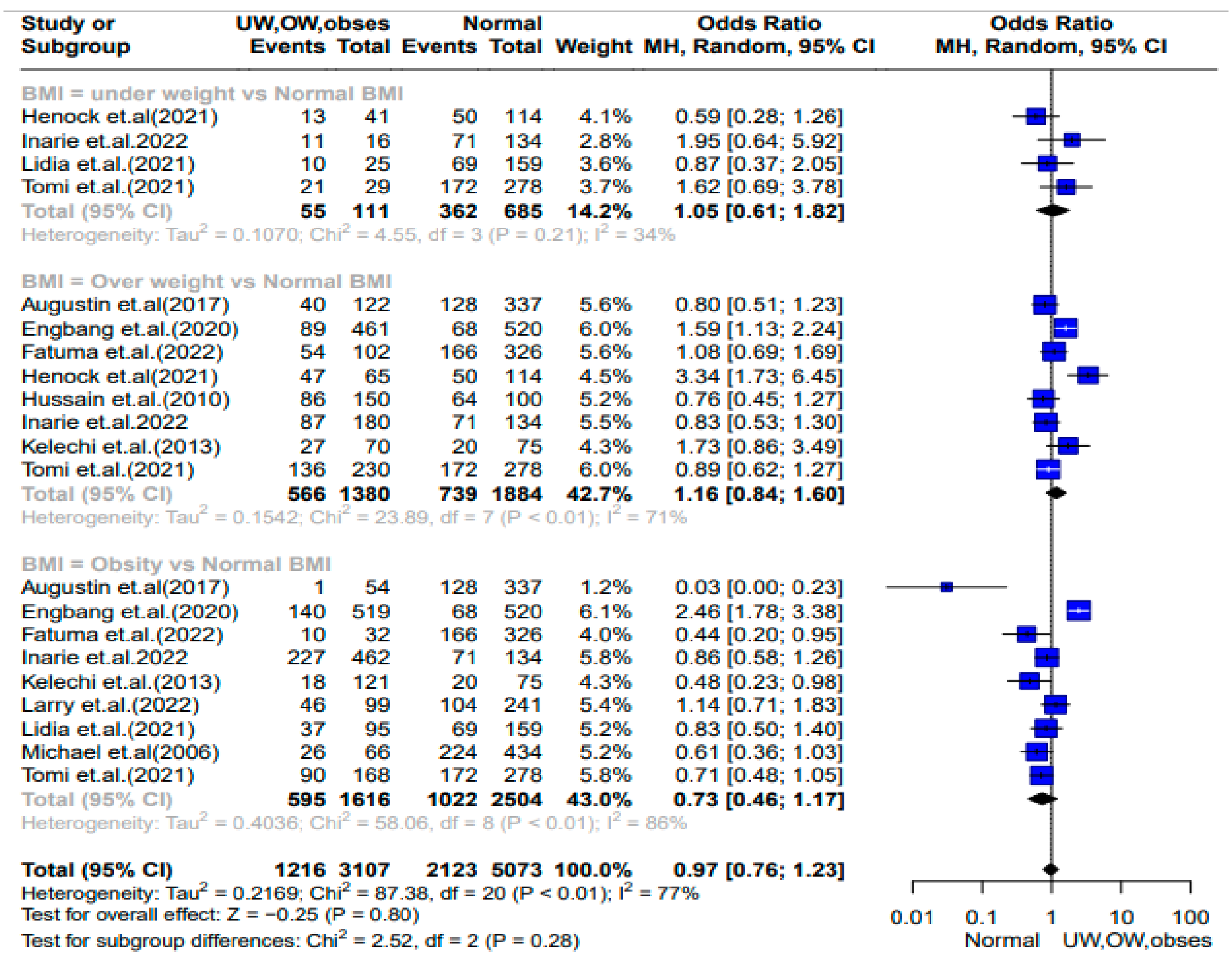

Figure 4.3: Forest plot of effects of BMI on breast cancer among women in SSA countries, 2000-2023.

Because the result of Egger test in (Table 4.4) and forest plot in the Appendix D, revealed publication bias were occurred in risk factor obesity under categories of BMI, for this reason we performed a Trim and Fill analysis to address the potential influence of publication bias, which adjusted for funnel plot asymmetry by adding four hypothetical studies. The adjusted OR was 1.14 with 95% CI (0.6082, 2.1309) and nonsignificant Egger test was occurred (see Table), and although this estimate suggested a positive association, it remained statistically insignificant (p = 0.6852). Heterogeneity remained high (I^2 = 87.2%), and the Q-test for heterogeneity was significant ($p < 0.0001$) see (Table 4.5).

Physical Exercise

Figure 4.4 shows analysis of six studies investigating the link between physical exercise and breast cancer risk reveals a pooled odds ratio of 0.53, implying potential risk reduction with exercise. However, the 95% confidence interval (0.14 to 1.95) includes values both above and below 1, indicating inconclusive evidence and substantial heterogeneity (tau^2 = 2.3767, I^2 = 88%) suggests variability across studies. The z-score of -0.95 (p = 0.34) for the overall effect is not statistically significant which indicates lack of association between breast cancer and physical activities. In sensitivity analysis, overall estimation changed between 0.34 and 0.79 when excluding each study one by one which indicate robustness overall odds ratio.

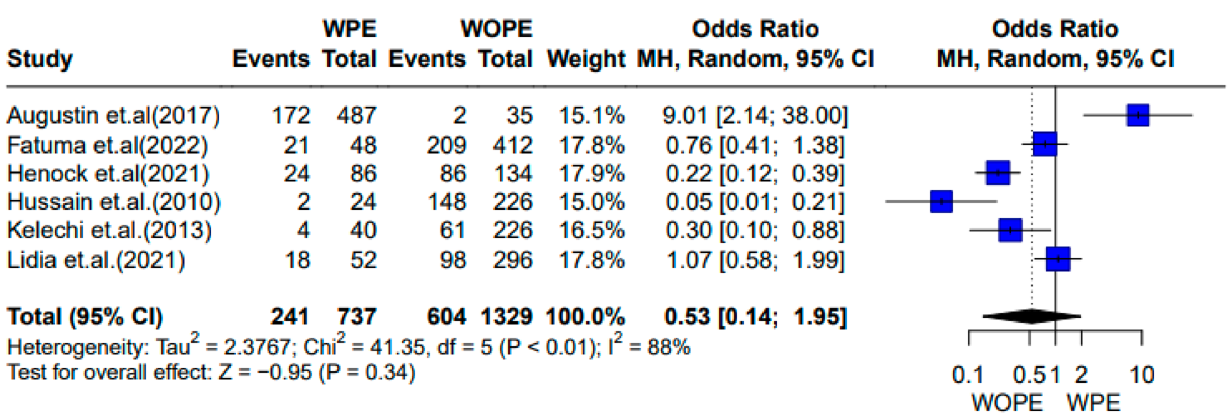

Figure 4.4: Forest plot of effects of physical activity on breast cancer among women in SSA countries, 2000-2023

Area of Residence

Forest plot illustrated in Figure 4.5 demonstrates the correlation between area of residence as risk factors for breast cancer. The analysis of six studies reveals a pooled odds ratio (OR) of 0.54 (95% CI: 0.31-0.95), indicating a significant reduction in breast cancer risk among women residing in urban areas compared to those in rural settings. However, considerable heterogeneity is evident, as shown by the tau^2 of 0.3858, the chi square of 20.37 with 5 degrees of freedom ($p < 0.01$), and an I^2 value of 75%. Despite the variability, the z-score of -2.12 ($p = 0.03$) for the overall effect signifies a statistically significant association and Sensitivity analysis also revealed that the odds ratio (OR) obtained for this variable demonstrated robustness, with a range of OR changes spanning between 0.46 and 0.65 (Table 4.4).

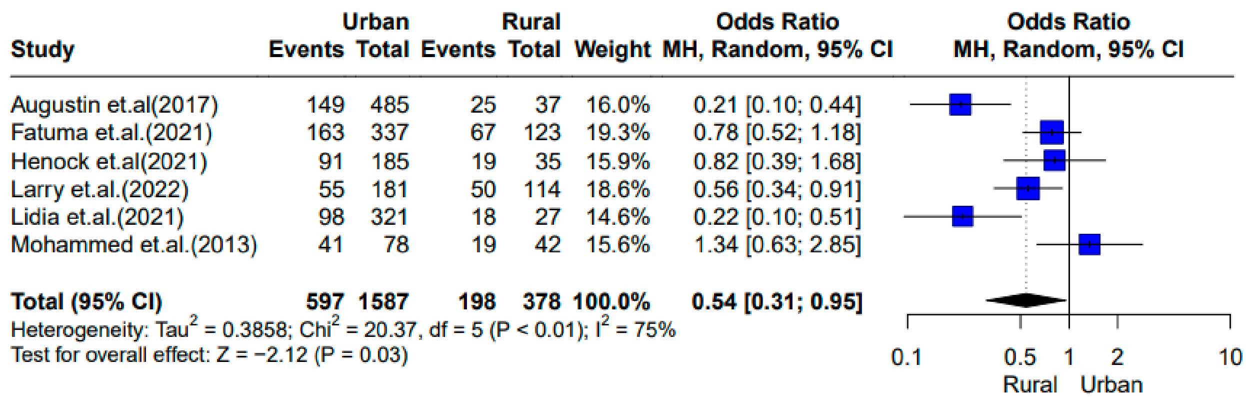

Figure 4.5: Forest plot of effects of residence on breast cancer among women in SSA countries, 2000-2023

Smoking status

The following Figure 4.6 is forest plot output regarding the risk factor of smoking status in relation to breast cancer reveals into the potential association. A total of 6 studies were analyzed, and the pooled odds ratio (OR) was calculated to be 1.91, indicating a higher odds of breast cancer among women who smoke compared to non-smokers. However, the 95% confidence interval (CI) spans from 0.90 to 4.04, indicating uncertainty in the true effect size, on the other hand heterogeneity analysis demonstrated a tau^2 of 0.5320 and an I^2 of 79%, indicating substantial variability among the study results. The test of the overall effect yielded a z-score of 1.696 with a p-value of 0.09, suggesting a lack of statistical significance at the conventional level. Additionally, a sensitivity analysis was performed, which showed that the range of OR changes spanned between 1.49 and 2.96, indicating the robustness of the observed trend.

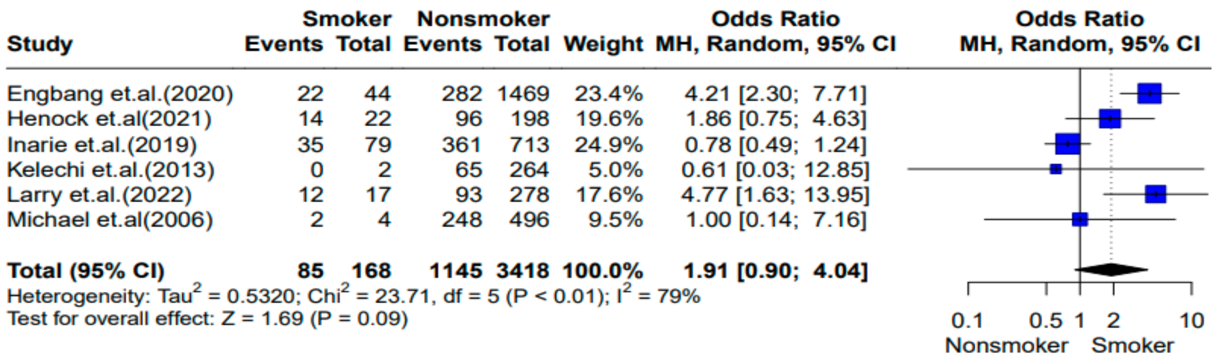

Figure 4.6: Forest plot of effects of smoking status on breast cancer among women in SSA countries, 2000-2023

Alcohol intake

The forest plot illustrated in Figure 4.7 output concerning the risk factor alcohol intake status and its correlation with breast cancer. This analysis comprises 8 studies, culminating in a pooled odds ratio (OR) of 1.47. This indicates that women who engage in alcohol consumption might have a higher odds of breast cancer compared to those who do not consume alcohol with 95% confidence interval (CI) of 1.11 to 1.96 which suggests that the observed effect is statistically significant, and the range does not span the null value of 1, on the other hand the analysis of heterogeneity displays a tau^2 of 0.1229 and an I^2 of 79%, signifying considerable variation across the studies. The overall effect test yields a z-score of 2.64, with a corresponding p-value of 0.01, demonstrating statistical significance at the conventional threshold, moreover, the sensitivity analysis emphasizes the robustness of the observed association, as evidenced by the range of OR changes spanning from 1.36 to 1.59.

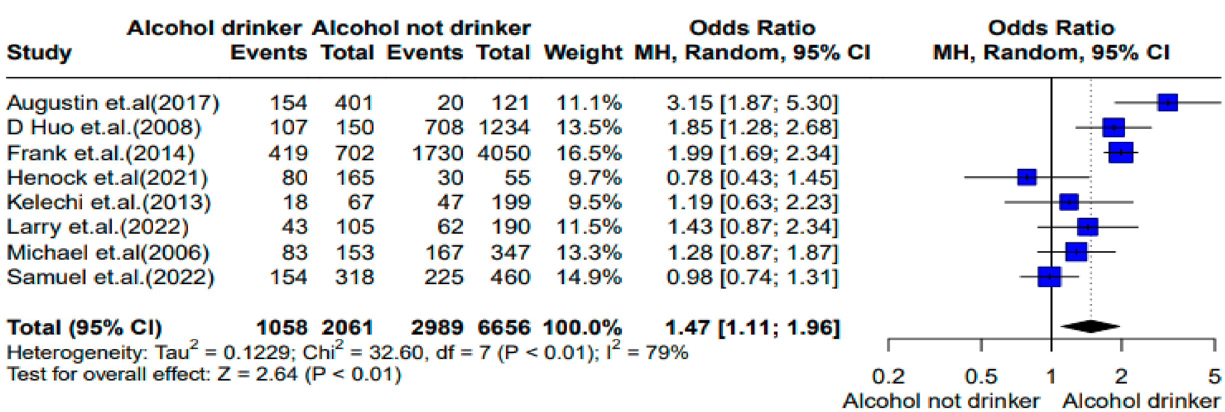

Figure 4.7: Forest plot of effects of alcohol on breast cancer among women in SSA countries, 2000-2023.

Family history of breast cancer

The graphical representation in Figure 4.8, illustrates the forest plot investigating the link between positive family history of breast cancer and the risk of breast cancer compared to those without a family history. The analysis encompasses data from 14 studies, revealing a pooled odds ratio (OR) of 1.87, with a 95% confidence interval (CI: 1.58 to 2. 21). This CI indicates a statistically significant association, as it excludes the value 1. The heterogeneity analysis reveals a tau^2 of 0.0490 and an I^2 of 44%, suggesting a moderate level of variability across studies. The test of the overall effect yields a z-score of 6.81 (p = 0.01), reaffirming the statistical significance, moreover the sensitive analysis indicates robustness of the observed association by ranging OR changes spanning from 1.79 to 1.94. Thus, the findings suggest a strong connection between having a family history of breast cancer and an increased risk of developing breast cancer.

Study	PFHBC Events	PFHBC Total	NFHBC Events	NFHBC Total	Weight	Odds Ratio MH, Random, 95% CI
Augustin et.al(2017)	60	116	114	406	11.4%	2.74 [1.80; 4.19]
Clement. et.al(2003)	19	41	215	466	5.9%	1.01 [0.53; 1.91]
D Huo et.al.(2008)	69	96	750	1292	10.1%	1.85 [1.17; 2.92]
Fatuma et.al(2022)	15	19	215	441	2.1%	3.94 [1.29; 12.06]
Frank et.al.(2014)	159	261	1979	4466	21.2%	1.96 [1.52; 2.53]
Henock et.al(2021)	14	22	96	198	3.1%	1.86 [0.75; 4.63]
Hussain et.al.(2010)	22	36	128	214	4.7%	1.06 [0.51; 2.18]
Inarie et.al.(2019)	25	42	371	750	6.0%	1.50 [0.80; 2.83]
Kelechi et.al.(2013)	4	14	61	252	1.9%	1.25 [0.38; 4.14]
Larry et.al.(2022)	16	26	89	269	3.7%	3.24 [1.41; 7.42]
Lidia et.al.(2021)	23	52	93	296	6.6%	1.73 [0.95; 3.15]
Michael et.al(2006)	15	16	235	484	0.7%	15.89 [2.08; 121.27]
N.A. Othieno et.al.(2015)	104	183	235	507	15.3%	1.52 [1.08; 2.14]
Samuel et.al.(2022)	40	59	339	720	7.3%	2.37 [1.34; 4.16]
Total (95% CI)	**585**	**983**	**4920**	**10761**	**100.0%**	**1.87 [1.58; 2.21]**

Heterogeneity: Tau^2 = 0.0173; Chi^2 = 19.91, df = 13 (P = 0.10); I^2 = 35%
Test for overall effect: Z = 7.32 (P < 0.01)

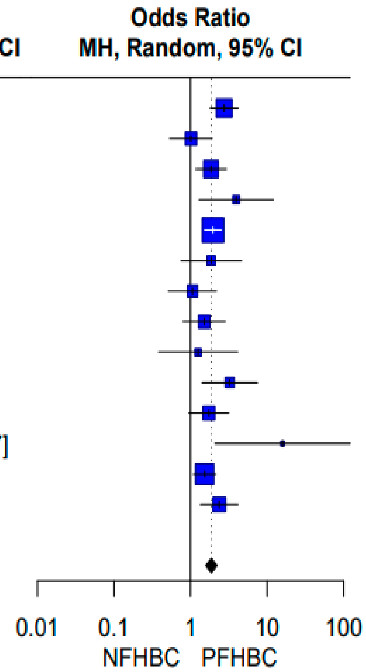

Figure 4.8: Forest plot of effects of family history of breast cancer on breast cancer among women in SSA countries, 2000-2023.

Menopausal status

The forest plot presented in Figure 4.9 offers valuable information about the connection between menopausal status and the risk of developing breast cancer. The analysis incorporates data from 14 studies, resulting in a pooled odds ratio (OR) of 1.36. This OR indicates that postmenopausal status is associated with a 36% higher likelihood of breast cancer compared to premenopausal status. The 95% confidence interval (CI) for the pooled OR spans from 1.02to 1.81, suggesting statistically significant association, moreover overall effect is statistically significant, as indicated by a z-score of 2.08 ($p = 0.04$). On the other hand, analysis reveals some degree of heterogeneity among the studies, with a tau^2 value of 0.2506 and a chi square value of 88.09, along with 13 degrees of freedom ($p < 0.01$) at the same fashion the I^2 value of 85% indicates substantial variability across the studies. Sensitivity analysis further underscores the robustness of the findings, with the range of OR changes spanning between 1.27 and 1.44. These results emphasize the potential association between postmenopausal status and increased breast cancer risk when compared to premenopausal status.

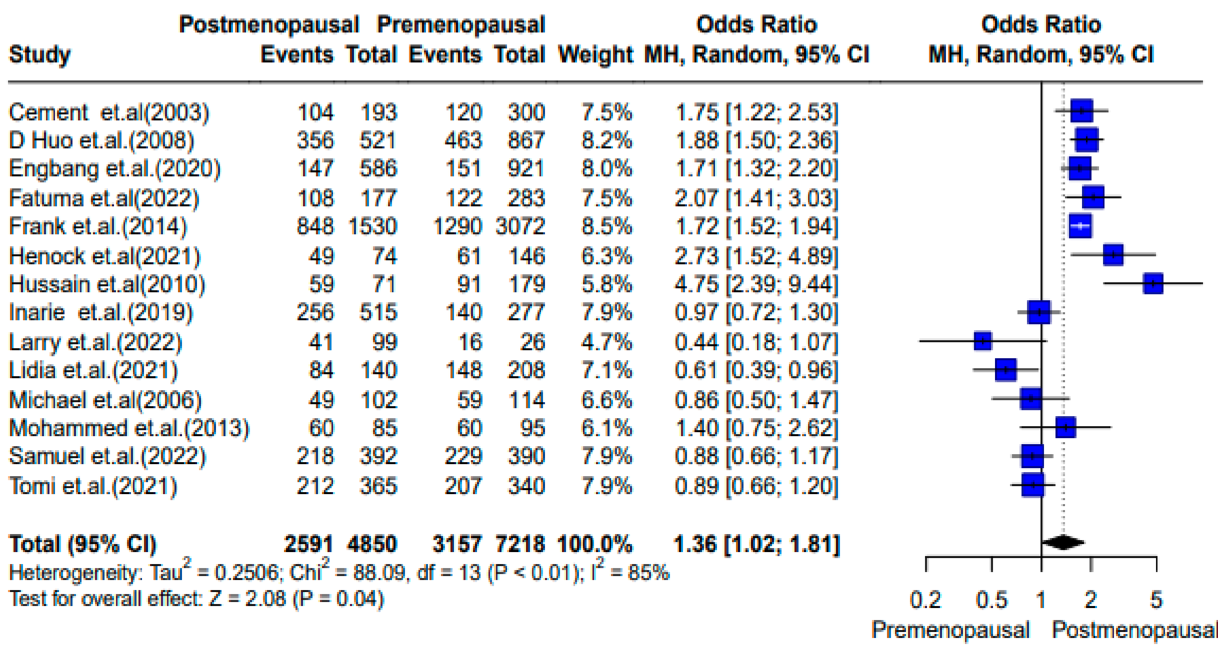

Figure 4.9: Forest plot of effects of menopausal status on breast cancer among women in SSA countries, 2000-2023

Breastfeeding History

The forest plot in Figure 4.10 below output presents an analysis concerning the association between breastfed status and breast cancer risk. The analysis is based on data from 7 studies, resulting in a pooled odds ratio (OR) of 0.72 this OR indicates that women who have ever breastfed are associated with a 28% reduced likelihood of breast cancer compared to those who have never breastfed however the 95% confidence interval (CI) for the pooled OR ranges from 0.43 to 1.19, suggesting a degree of uncertainty in the precise effect estimate since it includes the null value. Heterogeneity is also observed among the studies, with a tau^2 value of 0.3738 and a chi square value of 37.64, alongside 6 degrees of freedom ($p < 0.01$) in the same way I^2 value of 84% suggests substantial variability across the studies. The overall effect is statistically nonsignificant, with a z-score of -1.29 ($p = 0.2$) which indicates lack of association breastfeed and breast cancer. Sensitivity analysis underscores the consistency of the findings, with the range of OR changes spanning between 0.62 and 0.78. These results highlight a potential inverse relationship between breastfed status and breast cancer risk compared to never breastfed individuals.

Study	Ever breastfed Events	Ever breastfed Total	Never breastfed Events	Never breastfed Total	Weight	Odds Ratio MH, Random, 95% CI
Cement et.al(2003)	212	438	15	30	12.9%	0.94 [0.45; 1.97]
Frank et.al.(2014)	1902	2287	219	287	16.8%	1.53 [1.14; 2.06]
Henock et.al(2021)	67	164	43	56	13.4%	0.21 [0.10; 0.42]
Larry et.al.(2022)	96	280	9	15	10.0%	0.35 [0.12; 1.01]
Lidia et.al.(2021)	94	274	22	74	14.7%	1.23 [0.71; 2.16]
Michael et.al(2006)	93	209	116	208	16.2%	0.64 [0.43; 0.94]
Samuel et.al.(2022)	315	658	58	107	16.0%	0.78 [0.51; 1.17]
Total (95% CI)	**2779**	**4310**	**482**	**777**	**100.0%**	**0.72 [0.43; 1.19]**

Heterogeneity: $Tau^2 = 0.3738$; $Chi^2 = 37.64$, df = 6 ($P < 0.01$); $I^2 = 84\%$
Test for overall effect: $Z = -1.29$ ($P = 0.20$)

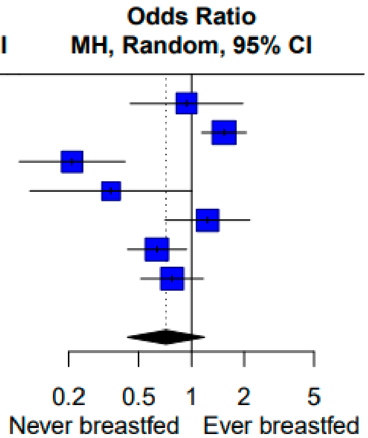

Figure 4.10: Forest plot of effects of breast feed status on breast cancer among women in SSA countries, 2000-2023

Oral contraceptive method (OCP)

Figure 4.11 provided forest plot output regarding the impact of oral contraceptive method on breast cancer risk, particularly comparing women who are users of oral contraceptive method to those who are non-users, the pooled odds ratio (OR) of 0.92 suggests a slight reduction of 8% in the odds of breast cancer for women who are uses oral contraceptive method. However, this effect is not statistically significant as the 95% confidence interval (CI: 0.58 to 1.45) includes the null value of 1 this implies that the observed decrease in odds could be due to random variation. The heterogeneity analysis reveals moderate variability among the studies ($I^2 = 84\%$), and the test of overall effect z-score of -0.35 ($p = 0.72$) further indicates the lack of significant association. Additionally, Sensitivity analysis also performed, with the OR range spanning from 0.81 to 1.10.

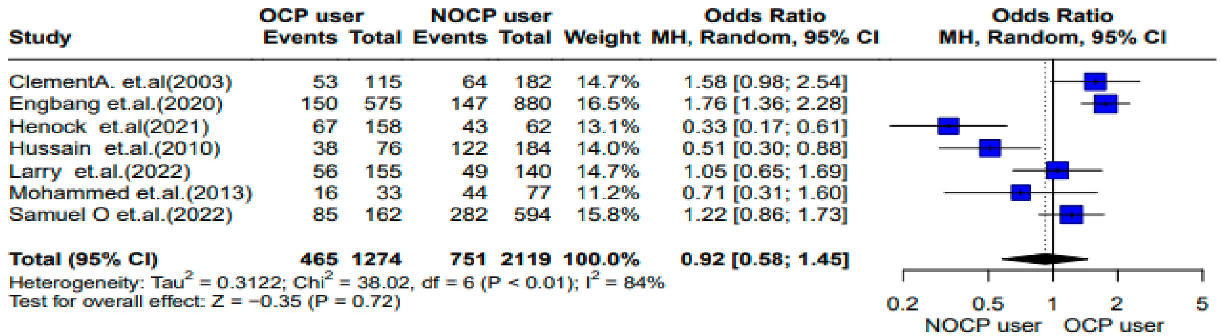

Figure 4.11: Forest plot of effects of oral contraception method on breast cancer among women in SSA countries, 2000-2023.

Since the result of Egger test in (Table 4.4) and forest plot in the Appendix D, revealed publication bias were occurred in risk factor Oral contraceptive method, we performed a Trim and Fill analysis to address the potential influence of publication bias, which adjusted for funnel plot asymmetry and significant Egger test by adding three hypothetical studies. The adjusted OR was 1.4306 with 95% CI (0.8046; 2.5437) nonsignificant Egger test occurred, and although this estimate suggested a positive association, it remained statistically insignificant ($p = 0.2226$). Heterogeneity remained high (I^2 = 89.4%), and the Q-test for heterogeneity was significant ($p < 0.0001$) see (Table 4.5).

Age at Menarche

Below forest plot output illustrates an investigation into the relationship between age at menarche and breast cancer risk. The analysis comprises data from 10 studies, resulting in a pooled odds ratio (OR) of 0.95. This indicates a marginal reduction of 5% in the odds of breast cancer for those with an early age at menarche, yet not statistically significant, breast cancer risk compared to those with an age at menarche above 12 years. The 95% confidence interval (CI) for the pooled OR ranges from 0.0.47 to 1.90, implying a degree of uncertainty in the precise effect estimate. Moreover, the overall effect demonstrates non-significance, with a z-score of 0.16 ($p = 0.88$). Heterogeneity is evident among the studies, with a tau^2 value of 1.0874 and a chi square value of 79.10, accompanied by 9 degrees of freedom ($p < 0.01$) and I^2 value of 89% suggests considerable variability among the studies. Sensitivity analysis highlights the consistency of the findings, with the range of OR changes spanning between 0.80 and 1.13.

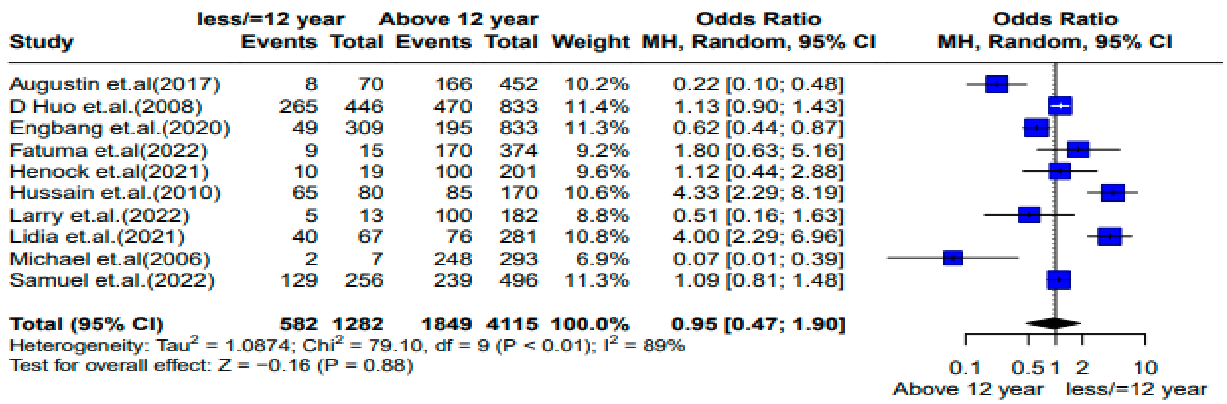

Figure 4.12: Forest plot of effects of age at menarche on breast cancer among women in SSA countries, 2000-2023.

Table 4.4: Summarize estimated Odd ratio, publication bias, and sensitivity analysis breast cancer risk factors

Variables	Study(n)	I^2	X^2	OR (95% CI)	Egger test	Sensitivity analysis (rage of OR)
Education(ref=University)						
Illiterate	8	82	0.01	1.89(1.17,3.04)	0.4963	1.55-2.17
Below diploma	12	32	0.13	1.13 (1.03, 1.24)	0.9522	1.10-1.60
Marital status(ref=married)						
single	11	86	0.01	0.67(0.36,1.31)	0.6439	0.60-0.74
Divorced\widowed	5	0	0.7	0.69 (0.55, 0.88)	0.9577	0.67-0.74
place of residence(ref=rural)						
Urban	6	75	0.01	0.54(0.31,0.95)	0.4773	0.46-0.65
BMI (ref=Normal)						
Underweight	4	34	0.21	1.05(0.61,1.82)	0.2203	0.9-1.33
Overweight	8	71	0.01	1.16 (0.84-1.60)	0.4291	1.03-1.23
Obsess	9	86	0.01	0.73 (0.46-1.17)	0.0133	0.67-0.85
Physical activity (ref=no)						
physical activity (yes)	6	88	0.01	0.53(0.14,1.95)	0.9902	0.34-0.79

smoking(ref=no)						
smoking(yes)	6	79	0.01	1.91(0.9,4.04)	0.7433	1.46-2.96
Alcohol use(ref=no)						
Alcohol use(yes)	8	79	0.01	1.47(1.11,1.96)	0.3447	1.36-1.59
family history of breast cancer(ref=no)						
family history of breast cancer(yes)	14	35	0.1	1.97(1.58,2.21)	0.5534	1.79-1.94
menopausal status(ref=premenopausal)						
postmenopausal	14	85	0.01	1.36(1.02,1.81)	0.3589	1.27-1.44
Breastfeeding history (ref=no)						
Breastfeeding history (yes)	7	84	0.01	0.72(0.43,1.19)	0.1351	0.65-0.78
OCP user(ref=no)						
OCP user(yes)	7	84	0.01	0.92(0.58,1.45)	0.0330	0.81-1.10
Age at menarche(ref=>12)						
<12	10	89	0.01	0.95(0.47,1.90)	0.7905	0.80-1.13

The (Table 4.3) provides a general overview of the meta-analysis. It displays the number of studies included in the analysis for each risk factor, along with the results of the heterogeneity test, the overall pooled effect size with a 95% confidence interval for each breast cancer risk factor, the Egger test, and sensitivity analysis. The forest plot explains most of the information that provided in the above table (Table 4.3).

The Egger test results in the table suggest that the rest of two risk factors (Oral contraceptive method and obesity in BMI categories) there is no publication bias among the studies. This conclusion is drawn because the Egger test values for each risk factor are greater than the p-value threshold (p=0.05), indicating that we cannot reject the null hypothesis, which assumes the absence of publication bias. Furthermore, the funnel plot, as shown in **Appendix 2**, also supports this by indicating symmetry, further suggesting no publication bias among the studies. The two risk factors need additional analysis that is the Trim and Fill method, which is provided in the (see Table. 3.4) below. The sensitivity analysis indicates that the pooled odds ratios for each variable are robust and consistent (Table 4.5).

Table 4.5 Summary of publication bias statistics based on the Trim and Fill analysis

Risk factors	Study(n)	Adjusted OR 95%CI	I^2	X^2	Adjusted Egger test	Number of Added studies
OCP user(ref=no)						
OCP user(yes)	10	1.43 (0.8046;2.5437)	89.4%	0.0001	0.8359	3
BMI (ref=Normal)						
Obsess	13	1.14 (0.6082, 2.1309)	87.2%	0.0001	0.7621	

4.2 Discussion

This systematic review and meta-analysis explore a complex network of socio-demographic, behavioral, and reproductive risk factors associated with breast cancer among women living in SSA. It was found that being illiterate significantly increased the risk of breast cancer, while women who live in urban areas had decreased risk compared to women who live in rural areas. From behavioral risk factors, the study revealed that alcohol consumption heightened the risk of breast cancer. Similarly, among reproductive risk factors, postmenopausal status and a positive family history of breast cancer were significantly linked to an increased risk of breast cancer. Results of this finding reveal the intricate nature of the disease and provide precious understanding into potential opportunities for focused prevention strategies. One of the pivotal observations from this study is the influence of the residence area of women on breast cancer risk. Notably, individuals residing in urban areas exhibited a significantly reduced risk of breast cancer compared to those in rural areas. This interesting result may be attributed to urban lifestyle factors such as access to healthcare, enhanced awareness, and different environmental exposures that could collectively contribute to the observed decrease in risk. This finding was in agreement with a study conducted in Bangui: case-control study (Balekouzou et al., 2017) and in disagreement with study conducted in Ugandan at a Tertiary Hospital (Galukande et al., 2016).

The presence of a positive family history of breast cancer emerged as a powerful risk factor which is almost 2-fold increase the risk of breast cancer. This result is consistent with the previous studies like systematic review and meta- analysis conducted in Iran (Shamshirian et al., 2020) and case control studies conducted in northern Algeria (Mokhtar et al., 2020), and in Tunisia (Msolly et al., 2013). This finding underlines the significance of genetic tendency in breast cancer etiology. It underscores the importance of genetic counseling and early screening for individuals with a family history, as well as highlights the need for public health initiatives to increase awareness among such high-risk populations.

This analysis further revealed the significant association between alcohol consumption and an increased risk of breast cancer. This underscores the importance of addressing modifiable lifestyle or behavioral factors in breast cancer prevention. Public health campaigns aimed at limiting alcohol consumption could potentially play a pivotal role in reducing breast cancer incidence. The finding agreed with many previous studies, a study conducted in united states of America (USA) their finding suggests, alcohol use even at moderate levels (two drinks per day) increases risk for both premenopausal and postmenopausal breast cancer(Cancer Prevention Research Program, et al., 2003); study conducted in Eastern Mediterranean Region (Namiranian et al., 2014), and Sub-Saharan African countries (Frank et al., 2014), unfortunately this finding disagree with some previous conducted studies like systematic review and meta-analysis conducted on Chinese (Gao et al., 2013), study conducted in Iran (Khoramdad et al., 2022), and Uganda (Galukande et al., 2016) this disagreement may be the social life style of population and method of data analysis.

The results of this study showed that educational level is one of the risk factors of breast cancer, and argued that an individual who cannot write or read or generally illiterate an individual has an approximately higher risk of breast cancer than those who get in a higher level of education. This finding agrees with the previous report that was conducted across different countries like (Balekouzou, et al., 2017); (Mokhtar et al., 2020). Conversely this finding is inconsistent with the differing previous report like (Khoramdad et al., 2022). Illiterate individuals face heightened sensitivity to breast cancer compared to university-educated counterparts due to limited healthcare access, knowledge gaps in health behaviors, and socioeconomic disparities. This disparity stems from delayed diagnosis, poor understanding of risk factors, and limited resources. Higher education correlates with informed health choices, healthier lifestyles, and improved socioeconomic status. Bridging this gap requires promoting education, enhancing healthcare accessibility, and raising awareness to reduce the unequal breast cancer risk among different educational backgrounds.

Furthermore, postmenopausal status and elevated breast cancer risk confirms existing research, this finding consistent with the previous report (Henok et al., 2021); and (Fatuma et al., 2022). The heightened breast cancer risk in postmenopausal women, as opposed to their premenopausal counterparts, is mainly attributed to hormonal shifts following menopause. Estrogen, a pivotal hormone for breast tissue development, is primarily produced by the ovaries. Post-menopause, ovarian activity diminishes, leading to reduced estrogen production; however, adipose tissue continues estrogen synthesis through aromatization. Elevated adipose tissue levels in postmenopausal women result in prolonged estrogen exposure, potentially spurring the growth of estrogen-responsive breast cancer cells. This estrogen-driven mechanism finds support in studies like the "Endogenous Hormones and Breast Cancer Collaborative Group" analysis featured in the Lancet, underscoring the connection between postmenopausal estrogen levels and breast cancer risk (Key, 2003).

Conversely this result contradicts with some previous report by (Collaborative Group on Hormonal Factors in Breast Cancer, 2012) that reported that the risk of breast cancer is higher in premenopausal than that of postmenopausal one.

In the analysis of variables linked to breast cancer risk several factors emerged as non-significant in this study, yet their implications should not be dismissed. These variables encompass smoking status, physical exercise, marital status, BMI, breastfed history, age at menarche, and oral contraception methods. While failing to attain statistical significance, the trends they exhibit in relation to breast cancer risk justify comprehensive examination.

By drawing parallels to prior investigations, this study's results find alignment in the existing body of literature. It is worth noting that the absence of a statistically significant association between breast cancer and specific marital statuses, as well as physical exercise observed in our study, is consistent with the results found in another independent research. For instance, according to

Balekouzou et al., (2017) the odds of breast Cancer were 2.09 times higher among married women compared with singles, this indicates the risk of breast cancer is lower for single women than that of married women. In similar way several researchers argued that physical exercise was inversely related with breast cancer (Gao, et al., 2013); (Balekouzou, et al., 2017) and (Laamiri et al., 2016) have noted similar risk-reducing patterns associated with certain marital statuses and active lifestyles. The convergence of these results underlines the potential influence of these variables on breast cancer risk, regardless of statistical significance.

Furthermore, this study's alignment with established research extends to the impact of smoking on breast cancer risk. While observed association did not reach statistical significance, the consistent elevation in risk resonates with the findings of several studies (Khoramdad et al., 2022; Michael et al., 2017) and (Larry et al., 2022). This consistency across studies reinforces the robustness of the smoking-breast cancer connection, underscoring its importance even when statistical thresholds are not met in a particular study.

In addition, variables such as early age of menarche, breastfed history, and oral contraception methods reveal trends in this finding that correspond to existing hypotheses. Although statistical significance was not achieved in this study, these trends align with the statements of (Romieu et al., 2021) argued that reproductive variables like age of menarche were statistically significantly associated with the risk of breast cancer among all women, nor in pre or in post-menopausal women separately. At the same fashion, meta-analysis conducted by (Zhou et al., 2015) based on their pooled results suggested that breastfeeding was inversely associated with the risk of breast cancer, and a systematic review and meta-analysis conducted by (Kanadys et al., 2021) yielded interesting findings, their analysis suggested that ever-users of oral contraceptives was 1.01 (95% CI, 0.95–1.07), compared with never-users, who have postulated the potential roles of these factors in shaping breast cancer risk. This collective alignment across studies emphasizes the value of considering these non-significant variables within the broader context of breast cancer research.

Despite these nonsignificant variables, the convergence between this findings and previous research strengthens the plausibility of the observed trends. As a result, this study underscores the need for a comprehensive perspective when interpreting non-significant variables, as they can contribute to a more nuanced understanding of breast cancer risk factors.

5.CONCLUSION AND RECOMMENDATION

5.1 Conclusion:

In this study, we started on a comprehensive systematic review and meta-analysis to clarify the risk factors associated with breast cancer among women in Sub-Saharan African countries by employing the random effect meta-analysis model. This investigation revealed five prominent risk factors: Educational level, residence, alcohol consumption, family history of breast cancer, and menopausal status. On the other hand, breastfeed, early age at menarche, physical exercise, BMI, and oral contraception use had no statistically significant associations with breast cancer. Although their effects on risk were not statistically significant, these factors may still play nuanced roles that justify further exploration.

Notably, the non-significant findings surrounding smoking indicated that while it may influence breast cancer risk, this study did not find a conclusive link. Therefore, there is an opportunity for further exploration in this field.

5.2 Recommendations:

Based on this finding, we offer customized recommendations for various stakeholders. For patients, heightened awareness about significant risk factors like educational level, residence, alcohol intake, family history, and menopausal status can empower informed decision-making. It is crucial to adopt healthy lifestyle choices and seek regular check-ups to detect potential risks early. For healthcare providers, understanding these risk factors can guide personalized patient care and timely interventions. They can educate patients on mitigating modifiable risks like alcohol consumption and encourage adherence to regular screenings.

Stakeholders and policymakers should allocate resources to enhance breast cancer education campaigns targeting the identified risk factors, particularly in Sub-Saharan African countries. Additionally, we acknowledge the challenge of database accessibility faced during this investigation and due to limitation of data, we cannot perform subgroup meta-analysis and meta-regression in order to address source of heterogeneity between included studies. Finally, we recommend future researchers to overcome this limitation and expand the study's scope by accessing additional databases like Web of Science and EMBASE and other electronic databases.

This could lead to the opportunity to get more published studies and comprehensive understanding of breast cancer risk factors and refine preventive strategies. To sum up, this investigation illuminates the complex area of breast cancer risk elements within Sub-Saharan African nations.

Limitation of the study

The limitations of this systematic review and meta-analysis lie in the constraints of available data sources, particularly the lack of access to electronic databases like Web of Science and Embase, which may have resulted in an incomplete collection of relevant studies. Additionally, due to limitation of data, in this study we do not perform subgroup analysis of region, study design, study population and other characteristics of studies and also, we cannot perform meta- regression interims of publication year and sample size in order to know the source of heterogeneity. Moreover, the inability to access certain databases may have excluded potentially valuable studies, which could have enriched the overall analysis. These limitations highlight the need for further research, enhanced data accessibility, and increased attention to the underexplored facets of breast cancer risk factors in this region to provide a more comprehensive understanding.

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APPENDIX

Appendix A. JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies

Reviewer --Date ----------------------------
Author --Year----------------- Record Number------------

1. Were the criteria for inclusion in the sample clearly defined? Yes □ No □ Unclear □ Not applicable □

2. Were the study subjects and the setting described in detail? Yes □ No □ Unclear □ Not applicable □

3. Was the exposure measured in a valid and reliable way? Yes □ No □ Unclear □ Not applicable □

4. Were objective, standard criteria used for measurement of the condition? Yes □ No □ Unclear □ Not applicable □

5. Were confounding factors identified? Yes □ No □ Unclear □ Not applicable □

6. Were strategies to deal with confounding factors stated? Yes □ No □ Unclear □ Not applicable □

7. Were the outcomes measured in a valid and reliable way? Yes □ No □ Unclear □ Not applicable □

8. Was appropriate statistical analysis used? Yes □ No □ Unclear □ Not applicable □

Overall appraisal: Include □ Exclude □ Seek further info □ Comments (Including reason for exclusion)
……………………………………………………………………………………………………
…………………………………………………………………………………………………

Appendix B. JBI Critical Appraisal Checklist for Case Control Studies

Reviewer ---Date --------------------------
Author---Year --------------Record Number-------------

1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls? Yes□ No□ Unclear □ Not applicable □

2. Were cases and controls matched appropriately? Yes□ No□ Unclear □ Not applicable □

3. Were the same criteria used for identification of case and controls? Yes□ No□ Unclear □ Not applicable □

4. Was exposure measured in a standard, valid and reliable way? Yes□ No□ Unclear □ Not applicable □

5. Was exposure measured in the same way for cases and controls? Yes□ No□ Unclear □ Not applicable □

6. Were confounding factors identified? Yes□ No□ Unclear □ Not applicable □

7. Were strategies to deal with confounding factors stated? Yes□ No□ Unclear □ Not applicable □

8. Were outcomes assessed in a standard, valid and reliable way for cases and controls? Yes□ No□ Unclear □ Not applicable □

9. Was the exposure period of interest long enough to be meaningful? Yes□ No□ Unclear □ Not applicable □

10. Was appropriate statistical analysis used? Yes□ No□ Unclear □ Not applicable □

Overall appraisal: Include□ Exclude □ Seek further info □
Comments (Including reason for exclusion) ---

Appendix C. JBI Critical Appraisal Checklist for Cohort Studies

Reviewer --Date-----------------
Author---Year--------------Record Number-------------------
Yes □ No □ Unclear □ Not applicable □

1) Were the two groups similar and recruited from the same population? Yes □ No □ Unclear □ Not applicable □

2) Were the exposures measured similarly to assign people? Yes □ No □ Unclear □ Not applicable □

3) to both exposed and unexposed groups? Yes □ No □ Unclear □ Not applicable □ 4) Was the exposure measured in a valid and reliable way? Yes □ No □ Unclear □ Not applicable □

5) Were confounding factors identified? Yes □ No □ Unclear □ Not applicable □

6) Were strategies to deal with confounding factors stated? Yes □ No □ Unclear □ Not applicable □

7) Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? Yes □ No □ Unclear □ Not applicable □

8) Were the outcomes measured in a valid and reliable way? Yes □ No □ Unclear □ Not applicable □

9) Was the follow up time reported and sufficient to be long enough for outcomes to occur? Yes □ No □ Unclear □ Not applicable □

10) Was follow up complete, and if not, were the reasons to loss to follow up described and explored? Yes □ No □ Unclear □ Not applicable □

11) Were strategies to address incomplete follow up utilized? Yes □ No □ Unclear □ Not applicable □

12) Was appropriate statistical analysis used? Yes □ No □ Unclear □ Not applicable □

Overall appraisal: Include□ Exclude □ Seek further info□

Comments (Including reason for exclusion) ---

Appendix D Funnel plot of risk factors of breast cancer

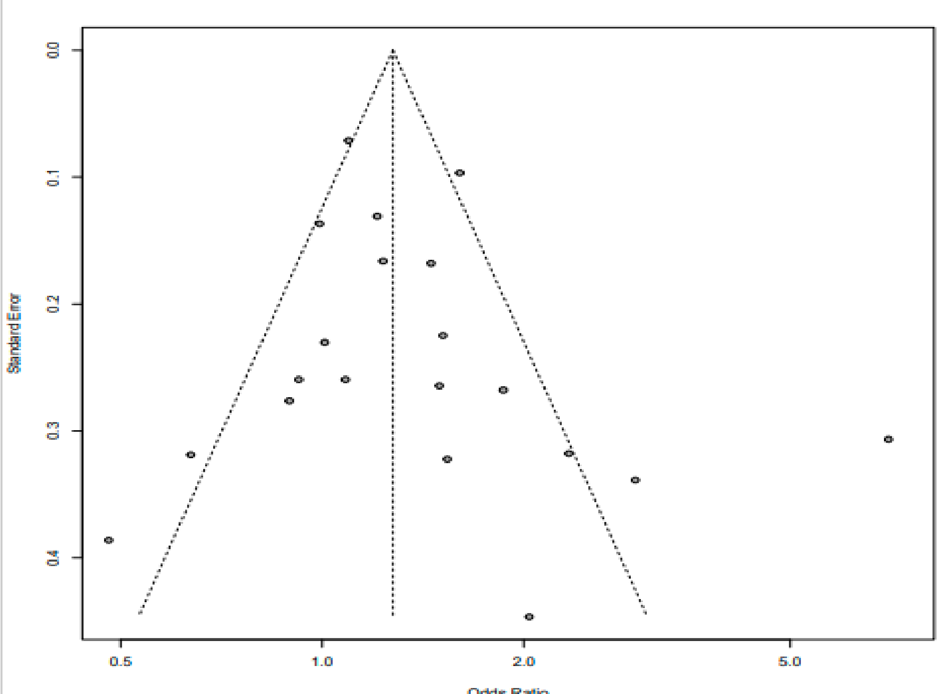


Figure 1 Funnel plot of Education level

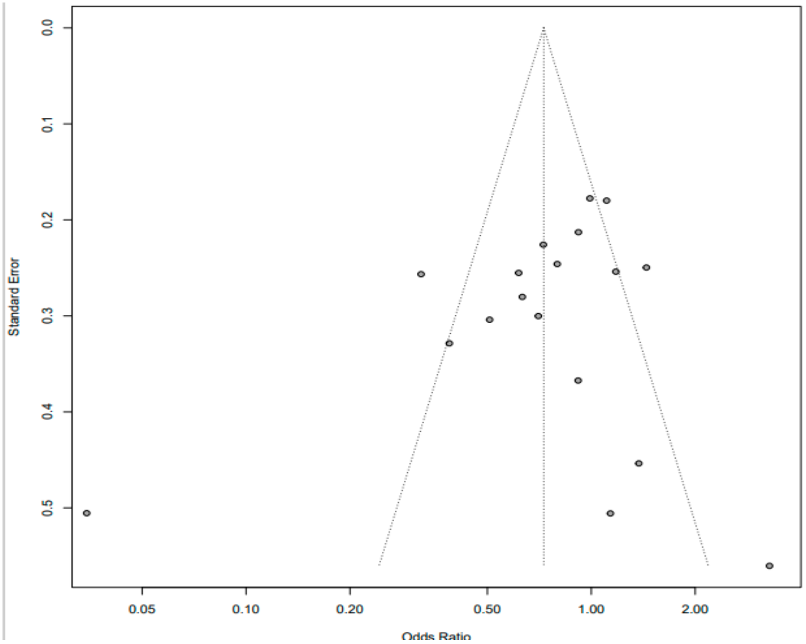


Figure 2 Funnel plot of Marital status

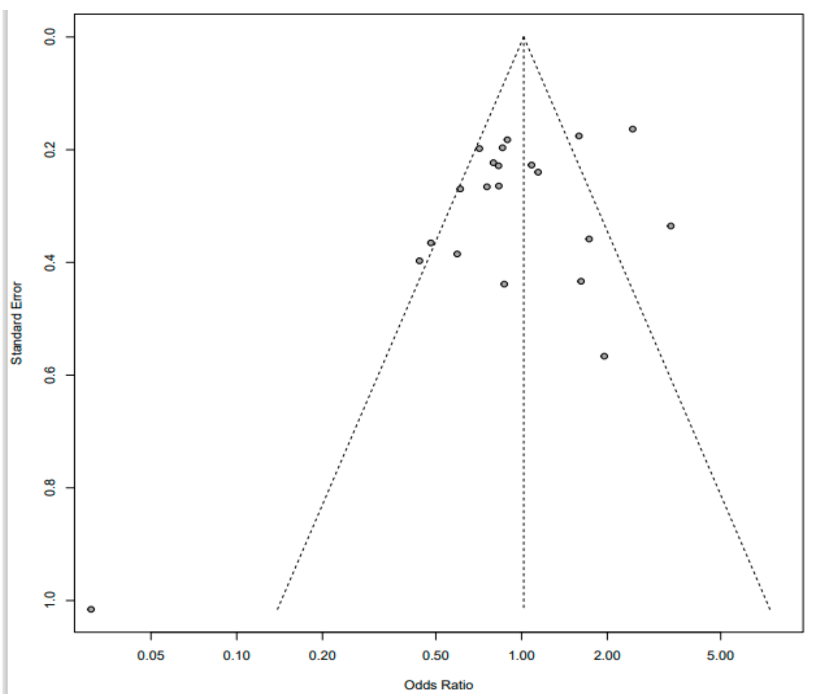
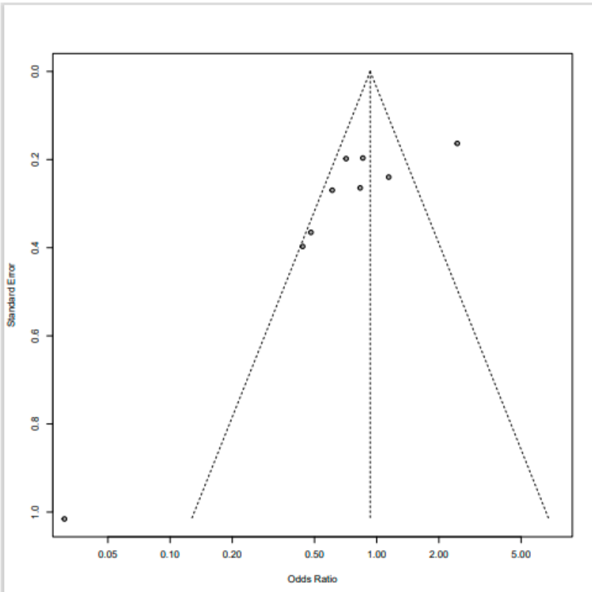
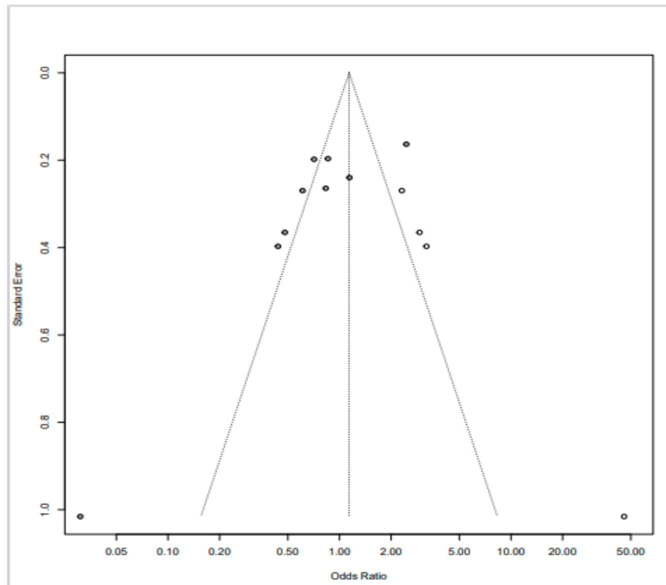


Figure3: Funnel plot of body mass index (BMI)





Before Trim and Fill method apply After Trim and Fill method apply

Figure 3.1: Funnel plot of obesity

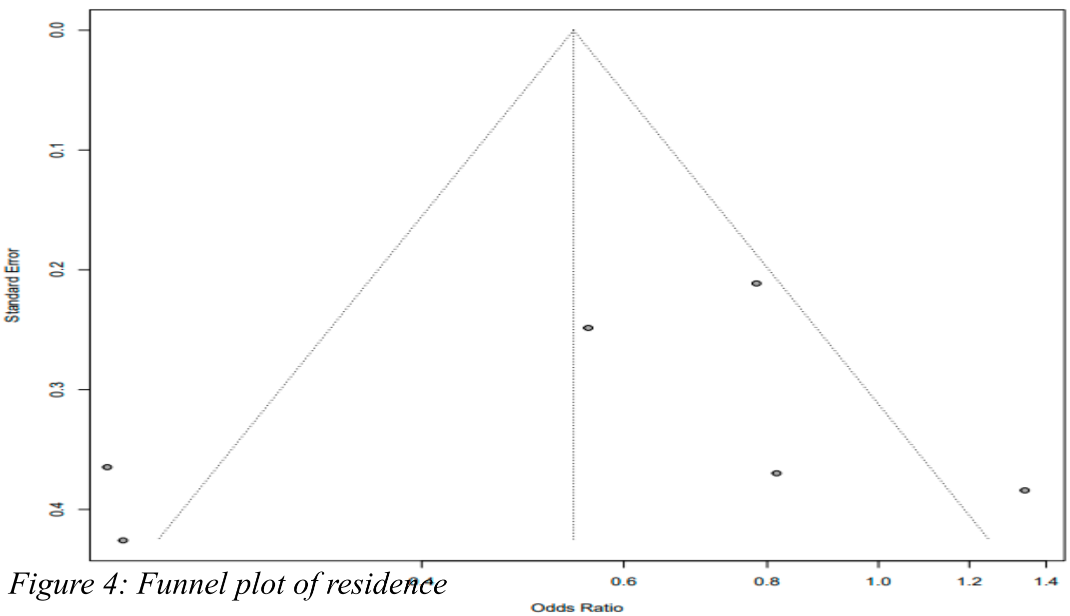


Figure 4: Funnel plot of residence

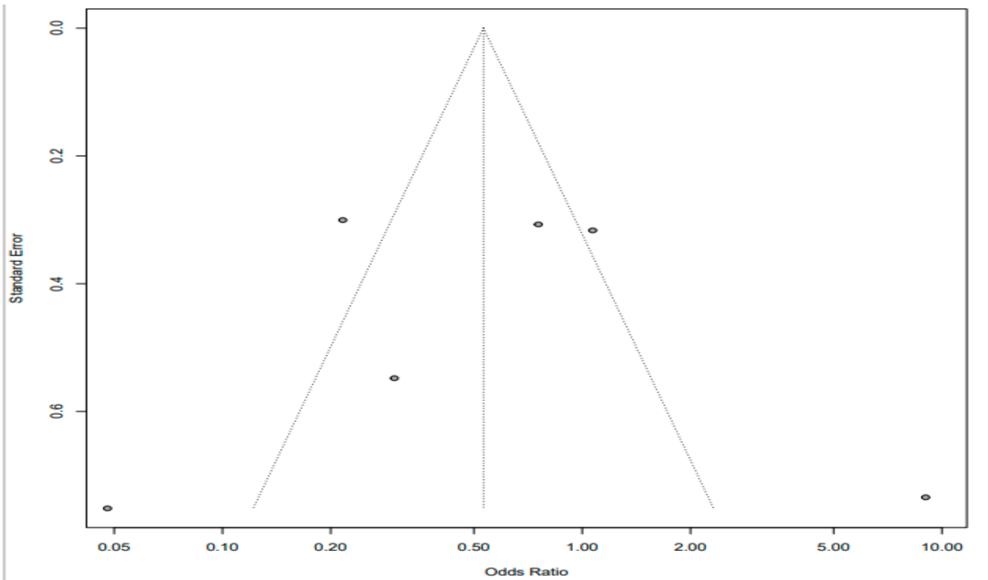


Figure5: Funnel plot of physical exercise

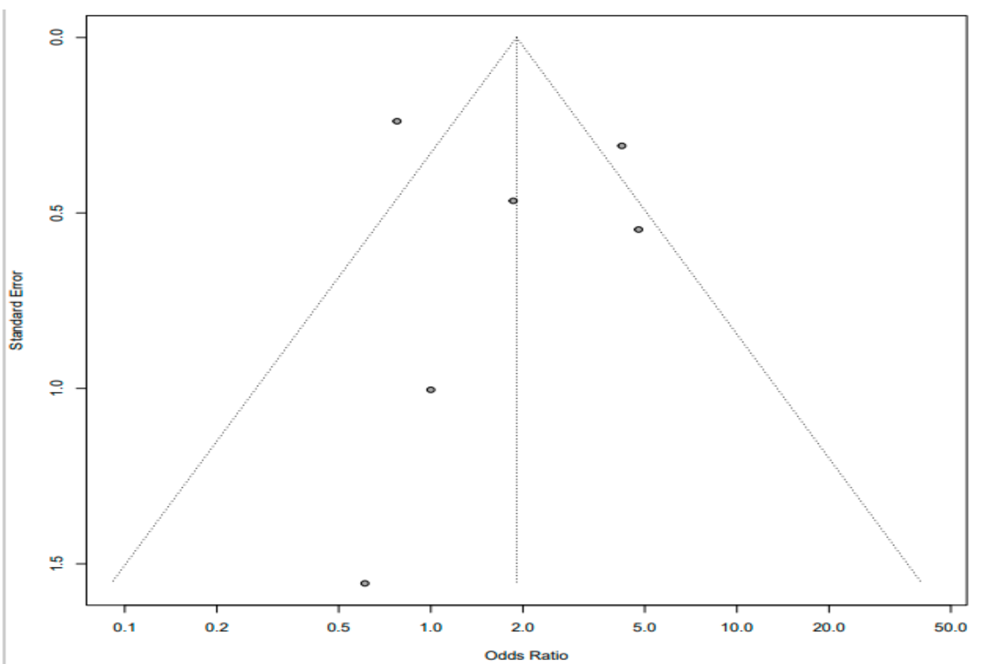


Figure6: Funnel plot of smoking status

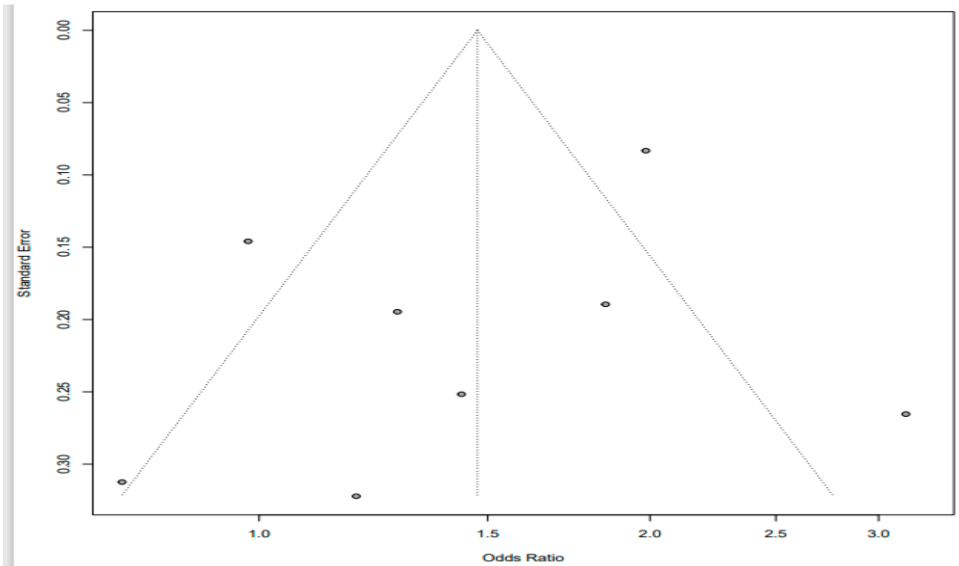


Figure 7: Funnel plot of Alcohol intakk

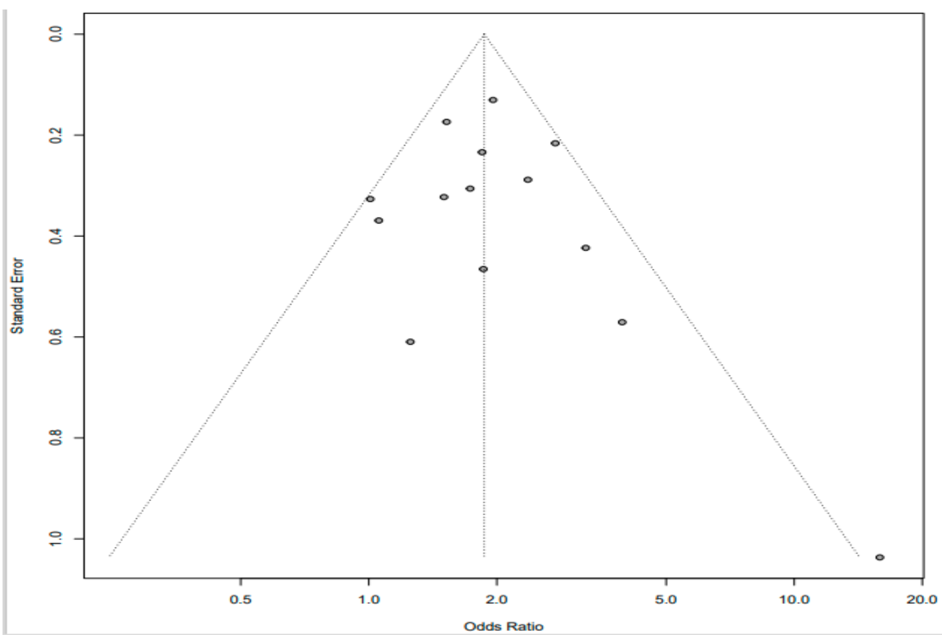
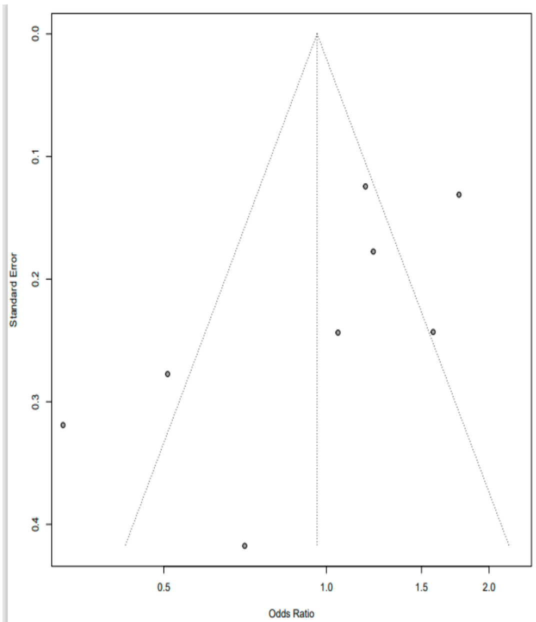
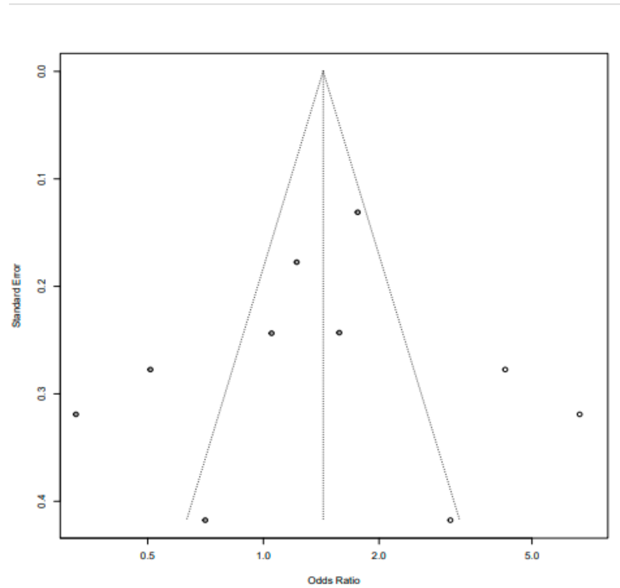


Figure 8: Funnel plot of family history of breast cancer





Before Trim and Fill method apply After Trim and Fill method apply

Figure9: Funnel plot of oral contraception (OCP) method uses

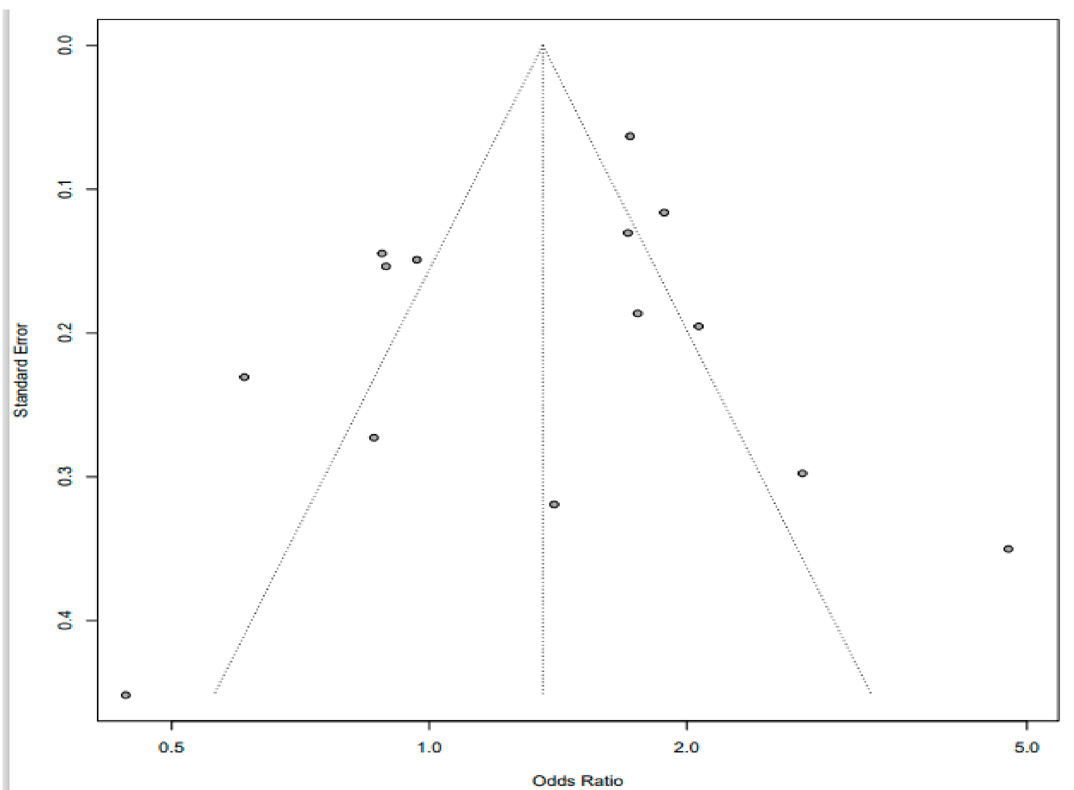


Figure10: Funnel plot of menopausal status

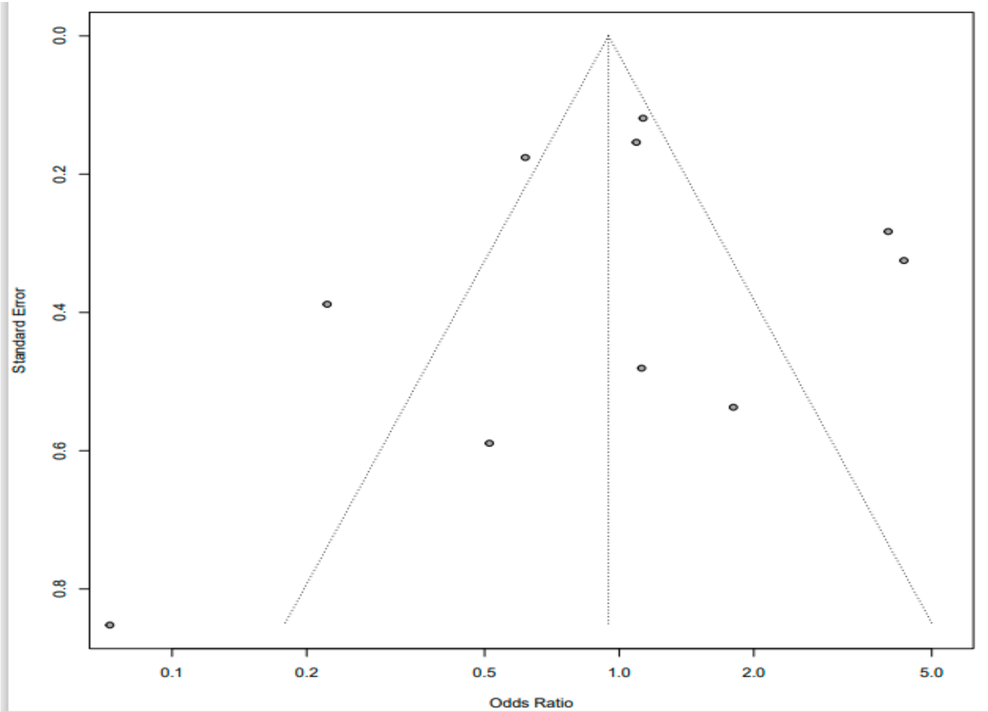


Figure 11: funnel plot of age at menarche

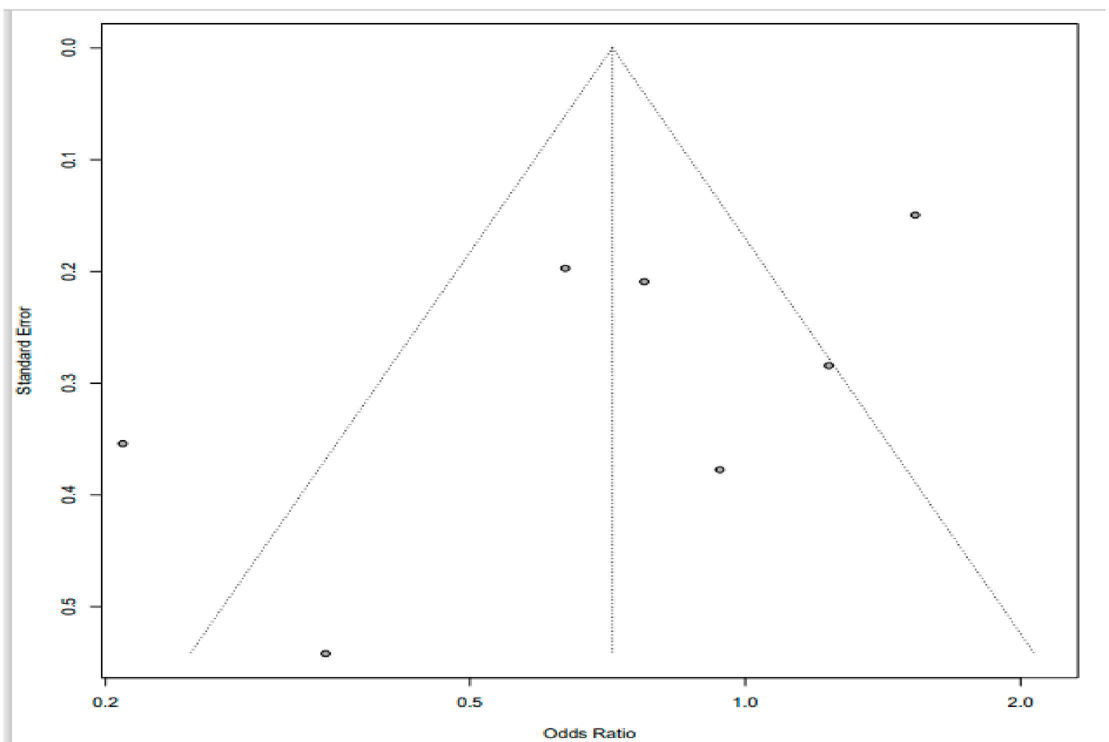


Figure 12: Funnel plot of breast feeding