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Modifiable lifestyle risk factors for breast cancer among Ugandan women: A systematic review (1980-2024)

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Abstract

Objectives: To systematically review and synthesise available evidence on "modifiable lifestyle risk factors" associated with breast cancer among women in Uganda.

Background: Breast cancer is the second leading cancer among women in Uganda. There is a very high prevalence of aggressive early onset breast cancer. While genetic factors play a significant role, the steep increase of breast cancer incidence in Ugandan women from 11.8 per 100,000 in 1970 to 40 per 100,000 in 2020) suggest that modifiable lifestyle risk factors play a role. However modifiable lifestyle risk factors are not well studied in Uganda.

Methods: A systematic literature search was done using studies (case control and cohort) reporting on modifiable lifestyle risk factors done in Uganda between January 1980 and April 2024. Newcastle- Ottawa Scale (NOS) was used to assess quality. Data were synthesized narratively because there was methodological heterogeneity.

Results: Out of 1,247 studies identified 12 studies met the inclusion criteria. There were 3,044 participants (1,214 cases and 1,830 controls). The results were 7 medium and 5 high quality (NOS). Nulliparity and low parity were significantly associated with increased risk and prolonged breastfeeding was protective.

Conclusion: The results identify prolonged breastfeeding and higher parity as protective factors while nulliparity and low parity high risk determinants. Alcohol consumption and abdominal adiposity show positive association with increased risk. The protection of prolonged breastfeeding offers an acceptable message for primary prevention campaigns. Future research must prioritise large scale population prospective cohort studies and the time for Uganda Ministry of Health to translate existing evidence into policy is now.

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Introduction

Breast cancer is a rapidly growing health problem in Uganda. It is the second leading cause of cancer related mortality among women in Uganda [1,2]. It presents in young females (peak 45 years). Breast cancer in Uganda has a high frequency of aggressive triple negative and HER2 negative subtypes. This combined with difficult access to health services (1 doctor per 15,000 persons) leads to delayed diagnosis and poor survival outcomes [3,4]. Although high penetrance genes (BRCA1, BRCA2) contribute to the cases, the rapidly increasing incidence suggest changes in lifestyle and environmental exposures [5,6]. The genetic setting, baseline anthropometry, cultural norms around reproduction and breastfeeding and other factors in Uganda are different from those in Europe and Americas [7,8]. A systematic review of the existing evidence on modifiable lifestyle risk factors for breast cancer in Uganda is critical for Uganda Ministry of Health to formulate tailored primary prevention strategies. This systematic review covers studies done in Uganda and published between 1/1/ 1980 and 30/4/ 2024.

Methods

A review protocol was developed a priori. The review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [9]. This review was not registered on the International Prospective Register of Systematic Reviews which is a limitation.

Eligibility criteria

Population: Women above 20 years of age with histologically diagnosed breast cancer only (referred to as cases) and hospital controls with other health conditions above 20 years of age (referred to as controls) were included in the review. Women with a previous history of any other cancer were excluded.

Exposure: Modifiable lifestyle risk factors including but not limited to: alcohol, tobacco smoking, reproductive history (parity, age at first conception, breastfeeding duration, use of exogenous hormones, anthropometry measurements (Body Mass Index-BMI, Weight-Hip-Ratio-WHR). Dietary patterns, and Physical activity levels were measured using validated questionnaires and objective tools quite inconsistently.

Comparator: Women without the exposure of interest i.e breast cancer.

Outcome: Odds Ratio (OR), Hazards Ratio (HR) or Relative Risk (RR) with 95% Confidence Interval (CI) for the association between the exposure and breast cancer were calculated.

Study design: Observational studies (case control and cohort studies) published in English language between 1/1/ 1980 and 30/4/2024 were included. The year 1980 was chosen as it predates the Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) epidemic in Uganda. HIV/AIDS is a major potential confounder for cancer outcomes.

Information sources and search strategy

A systematic search was performed from 1/1/1980 until 30/ 4/2024. The search strategy was designed using a combination of controlled vocabulary (e.g., MeSH, Emtree) and keywords. Search terms were broad to maximize sensitivity given the anticipated limited literature. The full strategy for PubMed is available in Appendix 1. We also searched for grey literature in Uganda Cancer institute annual reports, Uganda Ministry of Health annual reports, Africa Health, WHO ICTRP, Google Scholar, and hand-searched reference lists of all included studies. The final search across all databases was completed on April 30, 2024.

Study selection and data extraction

Data were extracted using a standardised piloted form, including study characteristics (author, year, design, participant demographics, sample size, exposures assessed, effect estimates, adjustment factors and key conclusions. Search results were imported into the Covidence systematic review software for deduplication and screening. Two independent reviewers (FA, JJ) screened titles and abstracts for eligibility. Potentially eligible studies underwent full-text review by the same two reviewers independently. Any disagreements at any stage were resolved through discussion or, if necessary, by a Third reviewer (TM). The study selection process is summarized in the PRISMA flow diagram (Figure 1).

Quality

The methodological quality of each included study was assessed independently by two reviewers using the Newcastle-Ottawa Scale (NOS) for case-control studies [10]. The NOS judges studies on three domains: (1) Selection of participants (4 stars maximum), (2) Comparability of groups (2 stars maximum), and (3) Ascertainment of exposure (3 stars maximum). Studies were awarded a quality rating: high quality (7-9 stars), medium quality (4-6 stars), or low quality (0-3 stars). The results of the quality assessment are presented in Table 1.

Results of the risk of bias assessment

a) Selection domain: The most common issue in the selection domain was the representativeness of cases. While most studies recruited cases consecutively from the national referral hospital (Mulago hospital), which made them somewhat representative of the hospital-based population, but they were likely not fully representative of all breast cancer cases in Uganda, particularly those in rural areas who may not present to tertiary care institutions. The definition and source of controls was a significant source of bias. This is because several studies used hospital-based controls from other wards (e.g., orthopedic, general surgery), which may not adequately represent the base population from which the cases arose, potentially introducing selection bias.

b) Comparability domain: This was the domain with the greatest variability. The most points were awarded for controlling for age, which was adjusted for in most analyses. Fewer studies adequately controlled for other critical confounding factors. Key confounders like socioeconomic status, education, family history of breast cancer, and HIV/AIDS status were inconsistently accounted for in the study design or analysis. This is a major limitation, as these factors are likely associated with both the exposures (e.g., diet, alcohol consumption) and the outcome.

c) Exposure domain (for case-control studies): The ascertainment of exposure to modifiable lifestyle factors was a primary concern. The majority of studies relied on interviewer-administered questionnaires. Key issues included: Recall Bias- This is a great concern. Women diagnosed with breast cancer (cases) may recall and report their past dietary, alcohol, or physical activity habits differently from healthy controls.

Non-validation of tools- Few studies reported using validated food frequency or physical activity questionnaires that had been culturally adapted and validated for the Ugandan population. This raises concerns about the accuracy of exposure measurement.

Blinding- It was rarely reported whether the interviewers were blinded to the case/control status of the participants, which could influence how questions were asked or probed.

Overall interpretation and implications

The body of evidence on modifiable risk factors for breast cancer in Uganda is characterised by a preponderance of case-control studies with a moderate risk of bias. The main limitations stem from the potential for recall and selection bias, and the inconsistent control for key confounders.

These methodological limitations necessitate a cautious interpretation of the reported associations. The effect estimates for factors like diet and physical activity may be inflated due to recall bias. Furthermore, the inability to fully adjust for socioeconomic status means that residual confounding is a likely alternative explanation for some of the observed relationships. Despite these limitations, these studies provide invaluable initial evidence and highlight critical areas for future research. The consistency of findings for certain factors (e.g., obesity in post-menopausal women) across multiple studies, even with these biases, may suggest a robust association. The results of this review should be interpreted as hypothesis-generating and indicative of associations rather than establishing definitive causation.

Methods of synthesis

Due to significant methodological heterogeneity across studies in the definition and measurement of exposures, a narrative synthesis was primarily conducted. However, for the exposure nulliparity (defined uniformly across studies as having no children), studies were deemed sufficiently homogeneous for quantitative pooling.

A meta-analysis was performed using the generic inverse variance method. A random-effects model was chosen a priori due to anticipated clinical and methodological heterogeneity between the included hospital-based case-control studies. The analysis was conducted using Review Manager (RevMan) software version 5.4.1 [The Cochrane Collaboration, 2020]. Heterogeneity was quantified using the I^2 statistic.

For all other exposures, findings are summarised qualitatively. The results of the meta-analysis for nulliparity are presented as a pooled Odds Ratio (OR) with a 95% Confidence Interval (CI). The forest plot of the 3 studies that provided data on nullipality (Gakwaya 2008 [13], Ayello 2020 [16] and Okello 2017 [20] is shown in Figure 2.

Results

Study selection: The PRISMA flow chart demonstrates the study selection process.

Interpretation: The forest plot shows the individual and pooled Odds Ratios (OR) for the association between nulliparity and breast cancer risk. The pooled OR of 2.14 (95% CI 1.66 to 2.75) indicates that nulliparous women have, on average, over twice the odds of developing breast cancer compared to parous women. The result is statistically significant (p<0.00001). The I^2 statistic of 0% indicates no observed statistical heterogeneity among these three studies.

Study characteristics

Study or Sub group	Log [Odds Ratio]	SE	Wt.odds Ratio	IV, Random, 95% CI Year
Gakwaya 2008 [11]	0.7885	0.3424	30.50%	2.20[1.12,4.30] 2008
Ayello 2020 [16]	0.6931	0.2455	39.30%	2.00[1.34,3.23] 2020
Okello 2017 [20]	0.8755	0.3862	30.20%	2.40[1.13,5.11] 2017
Total 95% [1]	100%			2.14[1.66,2.75]

Heterogeneity: $Tau^2 = 0.05$, $Chi^2 = 0.60$, df = 2(P=.74); $I^2 = 0\%$ Test for overall effect = 5.90 (P<0.00001)

Favours experimental	Favours control
(Nulliparity)	(Parity)

HIV: Inverse Variance. CI: Confidence Interval.

The 12 included studies employed a case- control design. The total sample size was 3,044 participants (1,214 cases and 1,830 controls). The studies were published between 1/1/1980 and 30/4/2024.The studies quality assessment scored 7 studies as medium quality (NOS 5-6) and 5 as high (NOS ≥7). The common draw backs were inadequate selection of controls and failure to adjust for key confounders like age, family history and diet. Key characteristics are Shown in Table 1 below.

Synthesis of results

Parity and age at first birth: High parity was consistently associated with a reduced risk. Nulliparous women had a significantly increased risk compared to parous women (OR: 2.1, 95% CI:1.5-2.6, I2 : 45%) [13,16,20]. Early age at first birth (<20 years) was protective in most studies [12,18].

Breastfeeding: A longer cumulative duration of breast feeding was strongly protective. Women who breastfed for a cumulative duration of >24 months had approximately a 50% reduction in risk compared to those who breastfed for <12 months (OR: 0.5, 95% CI: 0.3-0.7) [14,19,22].

Anthropometric factors: a) Body Mass Index (BMI): The association with high BMI (>30 kg/m^2) was complex and modified by menopause status. Two studies found a significant positive association between high BMI and postmenopausal breast cancer (OR:2.1,95% CI: I.2-3.7) [15,21]. while no consistent association was found for premenopausal women.

b) Central adiposity: High waist- to- hip ratio (WHR.0.85) was associated with an increased risk in one study that measured it (OR:1.9,95% CI: 1.1-3.4) [17].

Lifestyle factors: a) Alcohol consumption: Three studies investigated alcohol use [11,20,22]. All the 3 reported a positive association, with ever drinkers having an increased risk (Pooled OR:1.7,95% CI:1.2-2.4). But dose –response relationships were not established.

b) Tobacco Smoking-Data was very scarce. Two studies found a non- significant trend towards increased risk [11,20].

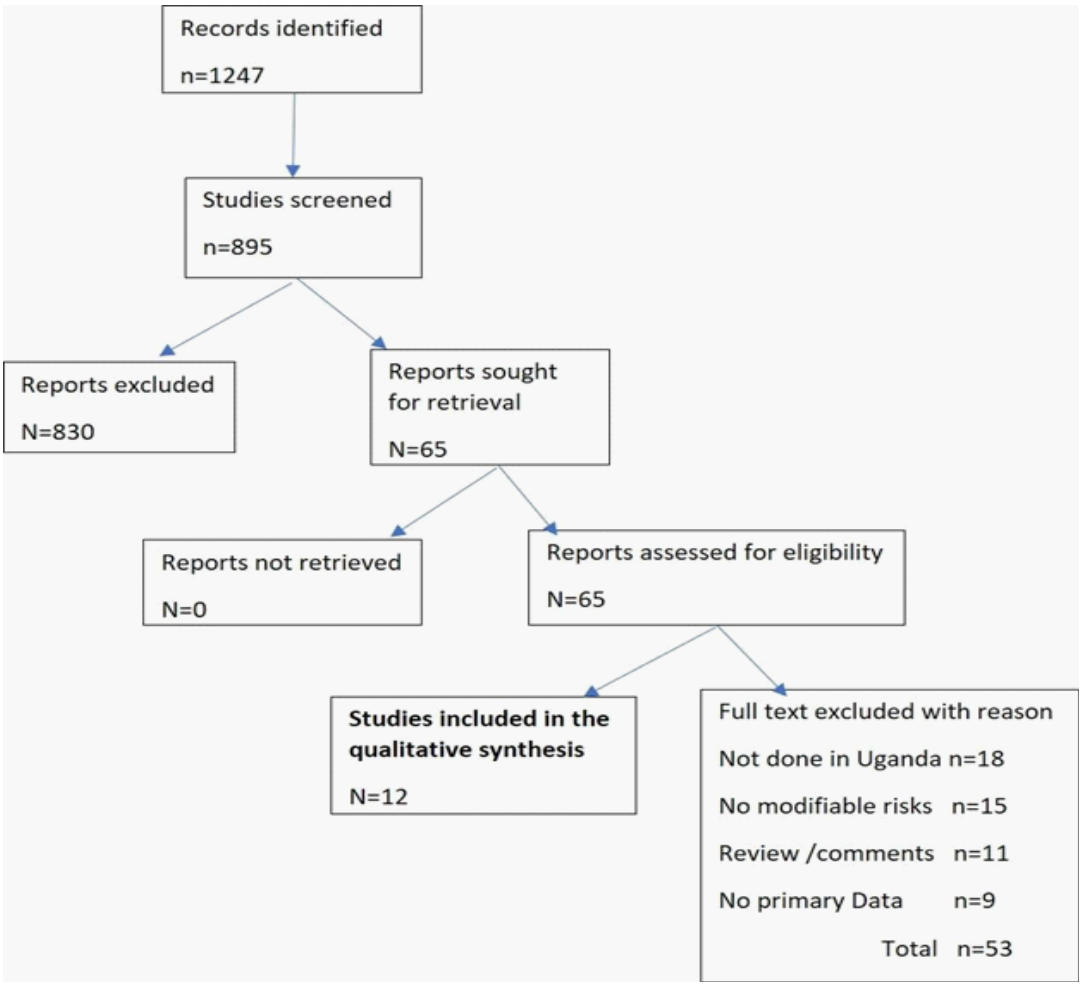

Figure 1: PRISMA flow chart.

Table 1: Characteristics of case –control studies included in the systemic review.

	First author /year	Sample size cases/controls	Key exposures assessed	Key findings Reported Effect, Estimate OR [95%CI] unless stated	NOS Score
1	Mirembe (2016) [11]	200(100/200)	Reproductive Hx, Alcohol, Smoking	Alcohol Ever User1.8[1.1,3.0]	6
2	Namboozo (2021) [12]	399(199/200)	Dietary patterns, Fruit, and veg in take	High fruit/ veg intake: OR 0.6 [O.4 to 0.6]	8
3	Gakwaya (2008) [11]	235(118/117)	Parity age at first birth	Nulliparity: OR 2.2(1.1,4.3)	5
4	Mubiru (2021) [14]	608(304/304)	Parity, breastfeeding duration	Breastfeeding: >20 mo: OR 0.5 [0.3,0.8]	8
5	Sserwadda (2019) [15]	518(259/259)	BMI, Menopausal status	BMI>30 (Postmenopausal) OR 2.3[1.3,4.1]	7
6	Ayello (2020) [16]	384(192/192)	Parity. Breastfeeding, Hormones	Nulliparity: 2.2[1.1,4,3]	8
7	Kasangaki (2018) [17]	300(150/150)	WHR, BMI	WHR>0.85: OR 1.9[1.1.3.4]	7
8	Nakisige (2022) [18]	296(148/148)	Dietary patterns, Processed foods	Processed food diet: OR 1.9[1.2,3.0]	9
9	Kwete(2023) [19]	220(110/110)	Breastfeeding duration, Parity	Breastfeeding >24 mo: OR O.5[0.3,0.9]	7
10	Okello (2017) [20]	254(127/127)	Alcohol, Smoking, PA, Diet	Nulliparity: OR 2.4[1.1,5.1] Alcohol Ever Use: OR 1.6[1.0,2.5]	6
11	Naluyima(2018) [21]	220(110/110)	BMI (Postmenopausal focus)	BMI>30(Postmenopausal): OR 1.9[1.1,3.3]	6

NB: NOS - Newcastle-Ottawa Scale.

c) Dietary Patterns: Diet was investigated by 2 studies [12,18]. One found a protective effect associated with high consumption of traditional vegetables and fruits [12]. While the other suggested a potential increased risk with a diet high in processed foods [18].

Discussion

The high prevalence of triple negative and advanced stage breast cancer in Uganda presents a profound surgical challenge. This systematic review provides the first comprehensive synthesis of evidence on modifiable lifestyle risk factors for breast cancer in Uganda. Our findings identify focal leverage points for primary prevention that could reduce the future burden of breast cancer requiring complex surgical intervention. They demonstrate that the reproductive factors specifically nulliparous, low parity and limited breastfeeding duration are the most robust and significant modifiable determinants of breast cancer risk in the Uganda population. This is in keeping with the known hormonal role of prolonged estrogen and progesterone exposure uninterrupted by the protective effect of full-term pregnancy and prolonged lactation. The overall moderate risk of bias, primarily due to the potential for recall and selection bias in the included case-control studies, suggests that the reported effect sizes should be interpreted with caution. The protective effect of prolonged breastfeeding is a critical public health concern. Ugandan women have a high base line rates. But today the rates are declining due to economic pressures, employment terms and rapid urbanization. Recognising the breast cancer preventive benefit along with the already known child health advantages could empower Ugandan women and form policy.

The relationship with obesity is complex and interesting. There is a trend of increased risk in postmenopausal women because adipose tissue becomes a primary source of estrogen. The lack of a clear association in premenopausal women may reflect the young age of the cases.

The link to central adiposity needs further investigation as a potentially relevant matric than BMI in Uganda.

The apparent association with alcohol consumption and processed food diet though based on limited data, are of great concern. There is rapid urbanization and change in traditions and behaviors in Uganda. This signals an impeding shift in the risk profile of breast cancer as it has previously happened in other parts of the world.

Limitations

The primary data is limited because the studies reviewed are few and rely exclusively on National referral hospital (Mulago) based case- control studies. They do not represent the whole population of Ugandan women who have breast cancer especially from rural areas. In addition, the studies have a moderate risk of recall and selection bias.

The reviewed studies have inconsistent control of key confounding factors, for example HIV which is rampant in Uganda and is associated with modifiable lifestyle risk factors for cancers.

There is a heterogeneity in exposure measurements, for example alcohol consumption and diet. Finally, there is inability to fully adjust for social economic status.

Conclusion

This systematic review establishes evidence on modifiable lifestyle risk factors for breast cancer among Ugandan women. The results clearly identify prolonged breastfeeding and higher parity as significant protective factors while nulliparity and low parity are identified as major risk determinants. These associations are consistent with the established hormonal etiology of breast cancer and emphasise the important role of reproductive patterns among the Ugandan women.

The evidence also demonstrates the emerging public health dangers: Alcohol consumption and abdominal adiposity show positive association with increased risk of breast cancer similar to observed trends in other transitioning economies. Although the data on smoking and dietary patterns are limited, they suggest a shift towards a Westernised risk profile in Uganda.

The outstanding limitation of the evidence is its reliance on hospital-based case-control studies, which are susceptible to selection and recall bias. This hinders the ability to establish the temporal causality. The inconsistent adjustment of the key confounders like social economic factors and HIV status complicates the interpretation of the associations. Despite these limitations, the finding are a clarion call for integrated public health action. The protective action of prolonged breastfeeding offers a powerful, culturally acceptable message for primary prevention campaigns. The association trends observed in alcohol consumption and obesity require proactive national strategies to mitigate these growing risks.

Recommendation

To conclusively characterise these modifiable lifestyle risk factors and inform the precise prevention strategies, research must prioritise large scale population prospective cohort studies. These studies are essential for validating the above findings, understanding the gene –environment interaction and as a result reducing the rising burden of breast cancer in Uganda. The time for Uganda Ministry of Health in collaboration with the private sector to translate this evidence into policy and to invest in definitive cohort studies is now.

Declarations

Conflict of interest: Authors have no real or perceived conflict of interest.

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