



OPEN Prevalence and genotypic distribution of high-risk human papillomavirus in primary breast tumors in Western Uganda: a case-control study

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Although in vitro studies have demonstrated that HPV can immortalize mammary epithelial cells, its contribution to breast carcinoma development in living organisms remains debatable. Reports on HPV detection in breast tumors vary widely across regions, and data from East Africa are limited. This study investigated the prevalence and genotypic distribution of high-risk HPV in breast tumors in Western Uganda. This retrospective case-control study was conducted using archived formalin-fixed paraffin-embedded tissue specimens from 66 breast carcinomas (cases) and 42 fibroadenomas (controls) diagnosed between 2012 and 2018 at Mbarara Regional Referral Hospital. High-risk HPV DNA was detected using real-time polymerase chain reaction (rRT-PCR), and genotyping was performed using the AmpliSens HPV HCR genotype-titre-FRT PCR kit. To validate the assay, cervical squamous cell carcinoma samples served as technical controls. Associations between HPV prevalence and breast carcinoma were assessed using chi-square tests and odds ratios. High-risk HPV DNA was detected in 25 of 108 breast tumor specimens (23.1%). The prevalence of HPV was 24.2% (16/66) in breast carcinomas and 21.4% (9/42) in fibroadenomas, with no statistically significant difference between cases and controls ($p = 0.735$; OR = 1.17, 95% CI: 0.46–2.97). Detected HPV genotypes included 16, 18, 33, 39, 45, 51, 56, and 58. HPV genotype 39 was the most frequently detected genotype in both breast carcinomas (50% of HPV-positive cases) and fibroadenomas (44.4% of HPV-positive cases). High-risk HPV was detected in all cervical cancer control specimens, confirming assay validity. These findings indicate that although high-risk HPV DNA was detected in breast tissue in this population, its presence alone does not support a primary causal role in breast carcinogenesis. Further studies incorporating viral load and transcriptional activity are needed to clarify the biological relevance of HPV in breast tissue.

Keywords Breast, Cancer, Human Papillomavirus, Western Uganda

Breast carcinoma is the most common malignancy and leading cause of cancer-related deaths in women^{1,2}. Approximately 2 million new cases and over 684,996 deaths were recorded in 2023^{2,3}. In East Africa, incidence and mortality rates remain high at 30.4 and 15.6 per 100,000 women, while in Uganda incidence has nearly tripled over the past four decades and is estimated to increase by 57.7% by 2030^{4–6}.

Breast carcinoma is a multifactorial disease associated with reproductive, hormonal, lifestyle, environmental, and genetic risk factors. These include age, parity, breastfeeding practices, hormonal exposure, alcohol consumption, smoking, and inherited mutations such as BRCA1 and BRCA2^{6,7}. However, a substantial proportion of breast carcinoma cases have no clearly identifiable etiologic factors, suggesting that additional

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contributors to breast carcinogenesis remain unrecognized⁸. Infectious agents have been implicated in the development of several human malignancies and may account for approximately 15% of cancers globally¹³, raising interest in their potential role in breast carcinoma.

Human Papillomavirus (HPV) is a well-known oncogenic virus³. The high-risk HPV genotypes include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. These are strongly associated with malignant transformation of the uterine cervix, vulva, anus, and oropharynx^{9,10}. At the molecular level, HPV oncogenes E6 and E7 promote carcinogenesis through inactivation of the tumor suppressor proteins p53 and retinoblastoma (Rb), leading to genomic instability and uncontrolled cellular proliferation^{10–12}. Experimental studies have demonstrated that HPV can immortalize normal human mammary epithelial cells in vitro, providing biological plausibility for a potential role of HPV in breast tumorigenesis¹¹.

HPV DNA has been detected in breast carcinoma specimens from multiple geographic regions, including Europe, Asia, Africa, Australia, and South America. Reported prevalence rates vary widely, and several studies have failed to detect HPV in breast carcinoma tissues¹³. These variations may reflect geographic differences in HPV prevalence and population-specific factors^{13,14}.

Importantly, HPV DNA has also been detected in benign breast lesions such as fibroadenomas in some studies^{1,14,15}. Fibroadenomas are common benign breast tumors, particularly in younger women. Although non-malignant, the detection of HPV in these lesions suggests that HPV infection, if biologically relevant, may occur early in breast tissue rather than being confined to invasive carcinoma^{14,15}.

Data on HPV prevalence and genotype distribution in breast tumors from East Africa are scarce, and no prior study has specifically evaluated the association between high-risk HPV infection and breast carcinoma in Western Uganda. Therefore, this study aimed to determine the prevalence and genotype distribution of high-risk HPV in breast carcinomas and fibroadenomas in Western Uganda and to assess whether an association exists between HPV infection and breast carcinoma.

Methods

Study design and setting

This retrospective case-control study was conducted at the Department of Pathology, Mbarara University of Science and Technology (MUST), in collaboration with MBN Laboratories, Kampala, Uganda. Archived formalin-fixed paraffin-embedded (FFPE) breast tissue specimens were retrieved from the histopathology archives of Mbarara Regional Referral Hospital (MRRH).

MRRH is a public tertiary referral hospital serving multiple districts in Western Uganda, including Mbarara, Bushenyi, Isingiro, and surrounding regions. It functions as a major referral center, receiving patients from lower-level health facilities and providing specialized diagnostic pathology services to a large catchment population.

Study population and sample collection

The study population comprised archived FFPE tissue blocks from patients diagnosed with breast carcinoma (cases) and fibroadenoma (controls) between January 2012 and December 2018. Primary breast carcinoma specimens included invasive ductal carcinoma, invasive lobular carcinoma, and ductal carcinoma in situ.

Fibroadenomas were selected as benign controls because histologically normal breast tissue was not routinely archived at the study site, and fibroadenomas represent commonly encountered benign breast lesions.

Specimens were included if they were adequately processed and preserved. Poorly processed or damaged tissue blocks were excluded. Proportionate stratified random sampling was used to ensure representative selection of both breast carcinoma and fibroadenoma specimens from the available archive.

Sample size

The sample size was calculated using the formula for estimation of a single proportion¹⁶.

$$n = Z^2 P (1 - P) / r^2.$$

where $Z = 1.96$ at a 95% confidence level, $P = 0.16$ (based on a reported HPV prevalence of 16% among breast tumors⁸ and $r = 0.08$ as the margin of error).

The minimum estimated sample size was 81 specimens. To account for potential tissue degradation, the sample size was increased, yielding a final target sample size of 108 specimens.

Sample selection and allocation

A total of 141 archived breast specimens (85 breast carcinomas and 56 fibroadenomas) were available during the study period. Breast carcinomas and fibroadenomas therefore represented approximately 60% (85/141) and 40% (56/141) of the archived specimens, respectively.

Proportionate stratified random sampling was used to ensure representation of both diagnostic categories based on their relative distribution in the archive. Accordingly, 66 breast carcinoma specimens and 42 fibroadenoma specimens were randomly selected from their respective strata to achieve the final study sample of 108 specimens. Within each stratum, simple random sampling was performed using computer-generated random numbers as shown in Fig. 1.

DNA extraction

Archived breast tissue specimens had been previously processed for routine histopathological diagnosis, including fixation in 10% neutral buffered formalin, paraffin embedding, and sectioning for hematoxylin and eosin (H&E) staining. Histological diagnosis was confirmed prior to molecular analysis.

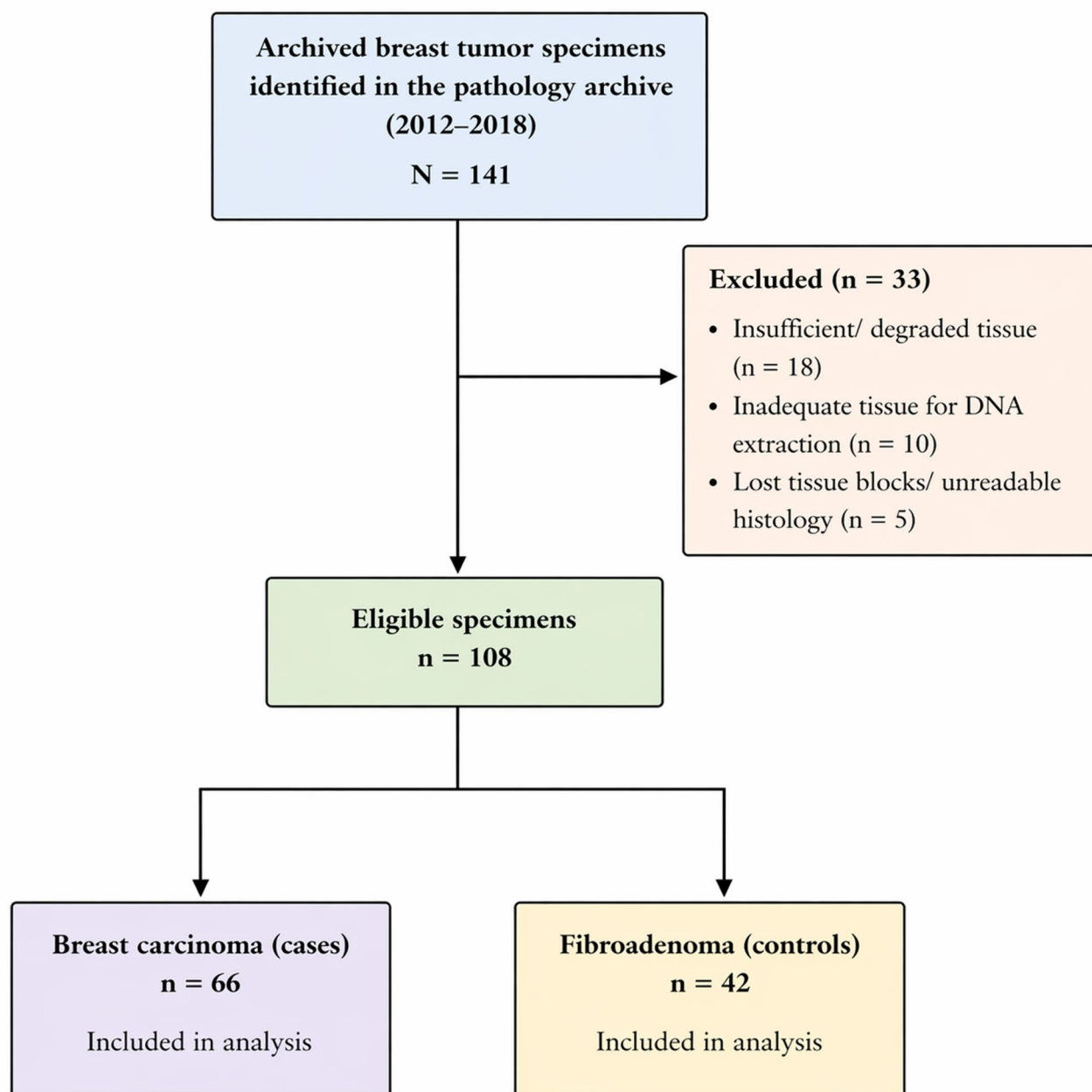


Fig. 1. Flow diagram of sample identification and selection from archived breast tissue specimens (2012–2018). Of 141 specimens retrieved (85 breast carcinomas, 56 fibroadenomas), 108 were included following proportionate stratified random sampling, comprising 66 breast carcinoma cases and 42 fibroadenoma controls.

For DNA extraction, four 10 µm sections were subsequently cut from each formalin-fixed paraffin-embedded (FFPE) tissue block using a fresh microtome blade for each specimen to minimize cross-contamination. Sections were deparaffinized using xylene followed by graded ethanol washes. DNA was extracted using a standard phenol-chloroform method, which is well established for the recovery of amplifiable DNA from FFPE tissues¹⁴. DNA integrity and suitability for PCR amplification were assessed using β-globin gene amplification as an internal control.

HPV detection and genotyping

High-risk HPV DNA was detected using real-time polymerase chain reaction (PCR). Genotyping was performed using the AmpliSens HPV HCR genotype-titre-FRT PCR kit, which detects high-risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. The assay targets the E6 and E7 oncogenes of these genotypes, as specified by the manufacturer.

Archived FFPE cervical squamous cell carcinoma specimens were included as positive technical controls and were processed using the same DNA extraction and PCR protocols as the breast tissue specimens.

Quality control

Strict contamination-prevention measures were applied throughout laboratory procedures. Separate microtome blades were used for each tissue block. Additionally, work surfaces were cleaned between samples. Histological diagnoses were reconfirmed by pathologists using hematoxylin and eosin-stained sections prior to molecular analysis.

Statistical analysis

Data were analyzed using STATA version 13 (StataCorp, College Station, TX, USA). Categorical variables were summarized as frequencies and proportions. The prevalence of high-risk HPV in breast carcinoma and fibroadenoma specimens was compared using the chi-square test. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the association between HPV infection and breast carcinoma. A p-value of <0.05 was considered statistically significant.

Ethical considerations

Ethical approval for this study was obtained from the Mbarara University of Science and Technology Research Ethics Committee (MUST-REC) (Approval No. 15/10–17). Administrative permission to access archived breast tissue specimens and conduct the study was granted by Mbarara Regional Referral Hospital.

The study used archived formalin-fixed paraffin-embedded (FFPE) breast tissue blocks retrieved from the pathology archives. All specimens were de-identified prior to analysis. The requirement for individual informed consent was waived by the Research Ethics Committee because the study involved retrospective analysis of anonymized archived tissue specimens and posed minimal risk to participants.

All methods were performed in accordance with relevant institutional guidelines and regulations and with the principles of the Declaration of Helsinki.

Results

Study population and specimen characteristics

A total of 108 archived breast tissue specimens were analyzed, comprising 66 breast carcinoma cases (61.1%) and 42 fibroadenoma controls (38.9%). Among breast carcinoma cases, invasive ductal carcinoma was the predominant histological subtype (60/66; 90.9%), followed by ductal carcinoma in situ (3/66; 4.5%) and invasive lobular carcinoma (3/66; 4.5%).

Distribution of high-risk HPV by demographic characteristics

Among breast carcinoma cases, high-risk HPV was detected predominantly in women aged 30 years and above. HPV-positive cases were identified across several districts in Western Uganda. However, HPV prevalence did not differ significantly by age group ($p=0.382$) or district of residence ($p=0.893$).

Among fibroadenoma controls, HPV was detected primarily in patients under 30 years of age. However, HPV prevalence did not differ significantly by age group ($p=0.288$) or district of residence ($p=0.360$) (Table 1).

Prevalence of high-risk HPV in breast carcinomas and fibroadenomas

High-risk HPV DNA was detected in 25 of 108 breast tumor specimens (23.1%). Among breast carcinoma cases, 16 of 66 specimens (24.2%) were HPV-positive, compared with 9 of 42 fibroadenoma controls (21.4%).

Characteristic	Breast Carcinoma (n = 66)			Fibroadenoma (n = 42)		
	Total cases (N)	HPV positive n (%)	p-value	Total cases (N)	HPV positive n (%)	p-value
Age (years)			0.382			0.288
< 18	0	0 (0.0)		11	4 (36.4)	
18–29	3	0 (0.0)		28	5 (17.9)	
30–49	26	5 (19.2)		3	0 (0.0)	
≥ 50	37	11 (29.7)		0	0 (0.0)	
District			0.893			0.360
Mbarara	29	7 (24.1)		21	4 (19.1)	
Bushenyi	12	3 (25.0)		6	3 (50.0)	
Isingiro	3	0 (0.0)		4	0 (0.0)	
Other districts	22	6 (27.3)		11	2 (18.2)	
Total	66	16 (24.2)		42	9 (21.4)	

Table 1. Demographic characteristics and row-wise HPV prevalence among breast carcinoma and fibroadenoma cases. Values are presented as number (row percentage). P-values were calculated using the chi-square test.

Genotype	Overall n (%)	Ductal carcinoma in situ(N=3) n (%)	Invasive ductal carcinoma(N=60) n (%)	Invasive lobular carcinoma(N=3) n (%)
GT 16	2 (3.0)	0 (0.0)	2 (3.3)	0 (0.0)
GT39	8 (12.1)	0 (0.0)	8 (13.3)	0 (0.0)
GT45	3 (4.6)	0 (0.0)	3 (5.0)	0 (0.0)
GT33	2 (3.0)	0 (0.0)	2 (3.3)	0 (0.0)
GT56	1 (1.5)	0 (0.0)	1 (1.7)	0 (0.0)
GT51	1 (1.5)	0 (0.0)	0 (0.0)	1 (33.3)
GT58	3 (4.6)	0 (0.0)	3 (5.0)	0 (0.0)

Table 2. Distribution of High-risk HPV genotypes in breast carcinoma specimens.

Genotypes	Overall n (%)	Breast carcinoma (N=66) n (%)	Fibroadenoma (N=42) n (%)	p-value *
GT16	3 (2.8)	2 (3.0)	1 (2.4)	1.000
GT18	1 (0.9)	0 (0.0)	1 (2.4)	0.389
GT39	12 (11.1)	8 (12.1)	4 (9.5)	0.762
GT45	3 (2.8)	3 (4.6)	0 (0.0)	0.280
GT33	2 (1.9)	2 (3.0)	0 (0.0)	0.520
GT56	5 (4.6)	1 (1.5)	4 (9.5)	0.073
GT51	1 (0.9)	1 (1.5)	0 (0.0)	1.000
GT58	3 (2.8)	3 (4.5)	0 (0.0)	0.280

Table 3. Distribution of high-risk HPV genotypes in breast carcinoma and fibroadenoma specimens.

There was no statistically significant difference in HPV prevalence between breast carcinoma and fibroadenoma specimens ($\chi^2 = 0.114$; $p = 0.735$). The odds ratio for the association between HPV infection and breast carcinoma was 1.17 (95% CI: 0.46–2.97).

Distribution of high-risk HPV genotypes

High-risk HPV genotypes detected in breast carcinoma specimens included types 16, 33, 39, 45, 51, 56, and 58 (Table 2). Among the 16 HPV-positive cases, genotype 39 was the most frequently identified type, detected in 8 cases (50.0%). Genotypes 45 and 58 were each detected in 3 cases (18.8%), while genotypes 16 and 33 were identified in 2 cases each (12.5%). Genotypes 51 and 56 were each detected in 1 case (6.3%). Multiple high-risk HPV genotype infections were identified in 5 of 25 HPV-positive specimens (20.0%). HPV-positive cases were observed across invasive ductal carcinoma, invasive lobular carcinoma, and ductal carcinoma in situ subtypes.

Multiple high-risk HPV genotype infections were identified in 5 of 25 HPV-positive specimens (20.0%). The observed co-infection patterns included HPV39 + 56, HPV33 + 58, HPV39 + 45 ($n = 2$), and HPV16 + 39.

Among HPV-positive fibroadenoma specimens ($n = 9$), genotype 39 was detected in 4 cases (44.4%), with genotypes 16, 18, and 56 also identified. No statistically significant difference in genotype distribution was observed between breast carcinoma and fibroadenoma specimens (Table 3).

HPV detection in cervical cancer technical controls

All archived cervical squamous cell carcinoma specimens included as technical controls tested positive for high-risk HPV DNA, confirming the validity of the HPV detection and genotyping assays. HPV genotype 39 was the most frequently detected genotype among cervical cancer controls (50%), followed by genotype 45 (33%) and genotypes 16, 18, 35, and 56 (each 16.7%).

Discussion

In this study, high-risk human papillomavirus (HPV) DNA was detected in both breast carcinomas and fibroadenomas in Western Uganda. However, no statistically significant association was observed between HPV infection and breast carcinoma.

The overall prevalence of high-risk HPV in breast tumors was 23.1%, with detection rates of 24.2% in breast carcinomas and 21.4% in fibroadenomas. Comparable prevalences have been reported in studies from Europe, Africa, and Asia that used PCR-based detection methods in formalin-fixed paraffin-embedded breast tissue specimens^{1,17–19}. In contrast, studies from Italy, Greece, Denmark, and India that reported no HPV detection differed in methodological aspects such as primer design, genomic targets, and DNA extraction protocols^{21–23}. Variations in assay sensitivity, tissue preservation, and contamination control may also contribute to inconsistent findings^{20–22}. Such variation across studies likely reflects geographic differences in HPV prevalence, population characteristics, and differences in laboratory detection methods²³.

Although high-risk HPV was identified in a proportion of breast carcinomas, the absence of a significant difference between malignant and benign lesions suggests that HPV infection alone may be insufficient to drive

malignant transformation in breast tissue. Similar observations have been reported in other case-control studies where HPV was detected in both breast carcinoma and benign breast lesions without a clear association with malignancy^{14,22,24,25}. This pattern is consistent with the concept of HPV acting as a passenger virus, present in breast tissue without directly driving oncogenic transformation^{13,26}.

A notable finding of this study was the predominance of HPV genotype 39, which accounted for approximately half of all HPV-positive breast carcinoma and fibroadenoma cases. This contrasts with findings from several regions where HPV genotypes 16 and 18 predominate in breast tumors^{2,27,28}. However, our results are consistent with a study from the United Kingdom that similarly reported HPV genotype 39 as the most frequently detected genotype in breast carcinoma specimens¹⁹. The consistent detection of genotype 39 in both breast tumors and cervical cancer control specimens suggests that this genotype may be relatively common in the Western Ugandan population.

The detection of high-risk HPV DNA in fibroadenoma specimens needs careful consideration. Fibroadenomas are common benign fibroepithelial tumors, particularly among younger women, and are generally not considered premalignant lesions²⁹. The presence of HPV in these lesions raises the possibility that HPV infection may occur early in breast tissue and persist without necessarily leading to malignant transformation^{29,30}. Alternatively, HPV detection in fibroadenomas may represent incidental infection of breast epithelium without biological relevance¹⁵. Longitudinal studies would be required to determine whether HPV-positive fibroadenomas confer an increased risk of progression to breast carcinoma.

Given the potential for contamination and false-positive results in HPV studies, methodological rigor is essential. In this study, archived cervical squamous cell carcinoma specimens were included as technical controls, and high-risk HPV DNA was detected in all control samples, confirming the validity of the detection and genotyping assays.

This study has several limitations. Fibroadenomas were used as controls because histologically normal breast tissue was not available, which may have limited comparisons with truly normal tissue. The sample size was modest, reducing statistical power and limiting subgroup analyses. In addition, data on key breast carcinoma risk factors, including hormonal exposure, BRCA1/BRCA2 mutation status, and lifestyle factors, were not available, precluding stratified analyses. Functional assays to assess viral activity, such as in situ hybridization or viral transcription analysis, were also not performed.

Despite these limitations, this study provides baseline data on the prevalence and genotype distribution of high-risk HPV in breast tissue from a previously unstudied population.

Future studies should incorporate functional assays to determine whether detected HPV DNA reflects active infection within tumor cells. Larger studies that include histologically normal breast tissue and detailed patient-level data will be important to clarify the relationship between HPV and breast carcinoma. The role of multiple HPV infections also warrants further investigation. Multi-center studies may help assess geographic variation in HPV prevalence.

Conclusion

High-risk HPV DNA was detected in both breast carcinomas and fibroadenomas in Western Uganda, with genotype 39 being the most frequently identified type. The similar prevalence observed in malignant and benign lesions suggests that high-risk HPV infection is unlikely to play a primary causal role in breast carcinogenesis in this population.

Data availability

Supporting data can be obtained by contacting either the first or last author.

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Author contributions

AB, RK, PPN, HT, FS, ST, ES, MY, RA, ADA, OA contributed to the conception, drafting, and have approved the final version of this manuscript for submission.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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