

Breast cancer in Trinidad and Tobago: Etiopathogenesis, histopathology and receptor study

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ABSTRACT

Background: Breast Carcinoma (BCa) is the leading cause of cancer among females in Trinidad and Tobago (TnT). This twin-island has a diversified population of 1.3 million individuals that display and are exposed to a variety of lifestyle choices that have been linked to the development of BCa. Therefore, this study aimed to identify the risk factors that influence the development of BCa, analyze the common histopathological details, and categorize BCa based on receptor study. **Methods:** Cancer information for 120 BCa cases at Eric Williams Medical Sciences Complex from 2012 to 2019 was retrieved, analyzed, and statistically estimated. The clinical details were categorized based on data tabulations, and histological assessment was performed to identify specific features. The receptor analysis was classified based on estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor-2 (HER-2neu) staining intensity. A descriptive data analysis and comparison were statistically evaluated in all these cases. **Results:** Epidemiological factors influencing the development of BCa were age with a peak of 56–65 years 27.5% (n = 33), ethnicity predominated in Indo-Trinidadians 48.33% (n = 58), and marital status primarily in unmarried/single/widowed patients 55% (n = 66). Infiltrating ductal carcinoma was the principal histopathological type 91.66% (n = 110). Receptor analysis revealed ER/PR + HER-2neu as the most common type 40% (n = 18) for therapeutic surveillance. **Conclusion:** This study highlights various epidemiological factors that influence the development of BCa among females in TnT. Histopathological analysis and receptor studies would provide a useful link between the tumor behavior and its prognosis.

Keywords: Breast cancer, histopathology, lifestyle, receptor study, risk factors, screening

Introduction

Globally breast carcinoma (BCa) is the leading cause of cancer in females. Globocan 2018 revealed that BCa stands jointly first along with lung cancer in terms of percentages of new cancer

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Received: 01-04-2021

Revised: 13-07-2021

Accepted: 15-07-2021

Published: 27-12-2021

Access this article online

Quick Response Code:



Website:
www.jfmpc.com

DOI:
10.4103/jfmpc.jfmpc_627_21

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How to cite this article: Umakanthan S, Bukelo M, Chattu VK, Maharaj R, Khan NN, Keane K, et al. Breast cancer in Trinidad and Tobago: Etiopathogenesis, histopathology and receptor study. J Family Med Prim Care 2021;10:4438-45.

cases worldwide in 2018.^[1] The age-standardized incidence of BCa globally is 46.3%, and in the Caribbean, it is higher at 50.2%. The Caribbean mortality rate is higher at 18.1% than global mortality at 13%.^[2] In the Caribbean region, the incidence and mortality were the highest in the Bahamas and the lowest in Haiti.^[3,4] The previous literature data about BCa in Trinidad and Tobago (TnT) has been valuable in determining the BCa association with ancestry, geography, and mortality.^[5-7] However, there has been no study detailing the histopathology and receptor analysis of BCa in TnT.

BCa carcinogenesis is a widely researched area seeking detailed confirmation on various etiological factors. Histopathological variation has posed a constant challenge in identifying and selecting available treatment options.^[8] Receptor analysis of BCa has been an integral aspect of treatment outcome and prognosis.^[9]

The Republic of TnT is the southernmost Caribbean island country with the third-highest GDP per capita in the Americas. The country has the second-highest BCa mortality rate in the Caribbean. It has a total population of 1,328,019, with a female population of 674,607.^[10] As per our knowledge, this study is the first of its kind in ToT to determine the serial link between epidemiological risk factors, histopathologic characteristics, and receptor analysis of Breast Cancer.

Materials and Methods

Study design

This is a hospital-based retrospective cohort study. The cases were retrieved by searching the archival records from the medical records section and paraffin tissue blocks from the pathology department from 2012 to 2019. A total of 120 adult female cases were reviewed.

Study location

This study was conducted at the histopathology department, Eric Williams Medical Sciences Complex (EWMSC), North Central Regional Health Authority (NCRHA), and the University of the West Indies (UWI), Mount Hope located in Trinidad, West Indies.

Ethical approval and consent

Ethical approval was granted by the Campus Research and Ethics Committee, UWI (Ref: CEC430/01/18), and by the public health observatory at the NCRHA, Trinidad. This study was carried out on archival tissue blocks and by searching medical records. Telecommunication mode was undertaken for follow-up criteria. This study posed no risk to the patients and their families/relatives/community. Data records were accessible only to the investigators and were stored using code numbers in password-protected personal computers.

Exclusion and inclusion criteria

Case records without tissue blocks were excluded.

Slide preparation

The retrieved tissue blocks were cut at 3–5 μm using a rotary microtome. The slides were fixed at 70°C for 2 h and stained using hematoxylin and eosin. The stained slides were observed, analyzed, and reported by consultant pathologists.

Tumor classification

Nottingham modification of Bloom–Richardson system (NMBR) grading system and WHO guidelines were followed to accomplish tumor grading and histologic classification.

Data analysis

Statistical package for the social sciences was used for descriptive analysis calculations of estimates, frequency, and percentage for all the retrieved data.

Results

A total of 120 cases of BCa were retrieved with complete clinical details and histologically identified from January 2012 to December 2019.

Demographics

The patients' age varied between 24 and 86 years. The peak incidence was 56–65 years with a frequency of 33 patients ($n = 27.5\%$). A majority of cases were in the age of 56–75 years [Table 1].

Indo-Trinidadians constituted the majority, 48.33% ($n = 58$), among the diverse population groups seen in Trinidad. Trinidad's Eastern region presented with the highest number of BCa cases ($n = 69$), followed distantly by the Central region ($n = 28$). Unmarried/single/widowed ($n = 66$) and unemployed ($n = 65$) were predominantly affected by BCa [Table 1].

Risk factors

The risk factors were analyzed individually and the following results were obtained [Table 2]: Menarche in years, 12 years: 41.6% ($n = 50$); number of pregnancies: one to two births, 40% ($n = 48$); age in years when first live birth: 20–24 years, 36.6% ($n = 44$); had taken oral contraceptive pill (OCP): 60% ($n = 72$); family history of BCa: 55.8% ($n = 67$); overweight (BMI > 25 kg/m^2): 42.5% ($n = 51$); alcohol intake: 38.3% ($n = 46$); pre-existing chronic disorders: hypertension, 51.66% ($n = 62$); diabetes mellitus: 34.16% ($n = 41$); cardiovascular disorders: 26.66% ($n = 32$); and reproductive diseases: 19.16% ($n = 23$).

Histopathological analysis

The most common histologic variant among 120 BCa cases was infiltrating ductal carcinoma (IDC): (110 cases; 91.66%). Other minor variants were infiltrating lobular carcinoma (ILC): (4 cases; 3.33%), mucinous/colloid carcinoma (4 cases; 3.33%), and medullary carcinoma (2 cases; 1.66%) [Table 3].

Tumor grading revealed grade 2 NMBR in 76 cases (63.33%), followed distantly by grade 3 in 32 cases (26.66%) and grade 1 in 12 cases (10%), respectively [Table 3].

Other relevant histologic findings [Table 3] were as follows: Ductal carcinoma in-situ (DCIS) present in 65 cases (54.16%), comedo pattern of DCIS in 98 cases (81.66%), high-grade DCIS in 66 cases (55%), lymph node involved in 72 cases (60%), lymphovascular invasion seen in 32 cases (26.66%), necrosis seen in 12 cases (10%), calcification present in 4 cases (3.33%), and nipple and areola involvement in 12 cases (10%).

Receptor studies

Immunohistochemical studies were conducted on 45 cases [Table 4]. Eighteen cases (40%) revealed ER, PR positive, and HER-2neu negative (Luminal A), followed by triple-negative tumors in 14 cases (31.11%).

ER/PR positive were tumors that exhibited 10%–75% nuclear staining [Figures 1 and 2]. HER-2neu positive were tumors with

strong complete membrane staining (3+) in >10% of the tumor cells [Figure 3].

Discussion

Breast cancer is the most common type of cancer among women in Trinidad and Tobago. This is mainly attributed to dietary patterns, physical inactivity, overweight, alcohol abuse, and a higher prevalence of carcinogenic viruses in the Caribbean populations.^[11]

In our cohort study, the highest incidence of BCa was seen in the age group of 56–65 years (27.5%), followed by 66–75 years (25%). There was a sudden decline in incidence in the age group above 75 years (8.33%). This surge is similar to the incidence rates found in western countries and has been influenced by comorbidities, hormone replacement treatment (HRT), and lifestyle changes. Younger patients with BCa were associated with a positive family history of BCa. It was found that the 5-year survival rate was lowest in the < 75-years age group.^[12,13]

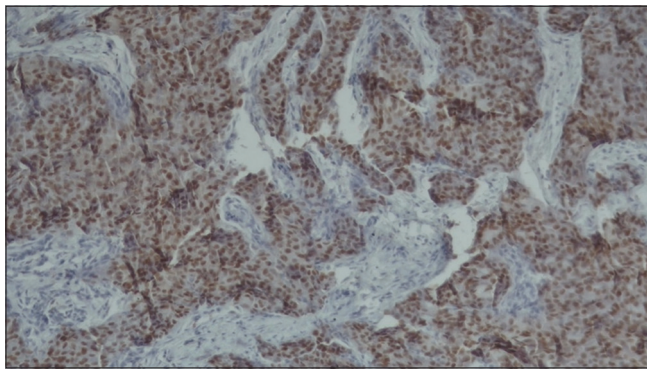


Figure 1: ER-positive tumor cells (x40)

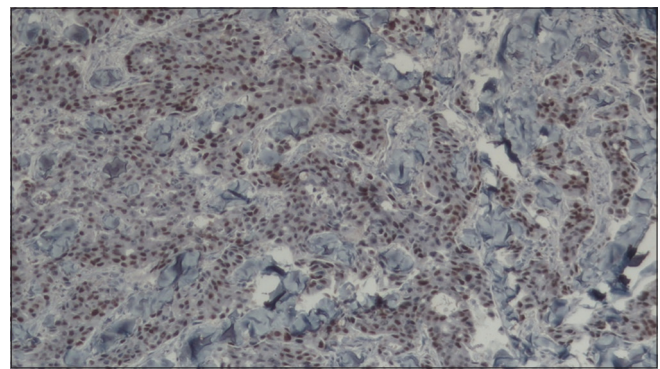


Figure 2: PR positive tumor cells (x40)

Table 1: Summary of the demographics of 120 adult women breast cancer patients at the EWMSC from 2012-2019

Demographic Characteristics	Frequency	Percentage
Age in years	35 and below	8 (6.6%)
	36-45	19 (15.83%)
	46-55	20 (16.66%)
	56-65	33 (27.5%)
	66-75	30 (25%)
	76 and above	10 (8.33%)
Ethnicity	Afro-Trinidadian	32 (26.66%)
	Indo-Trinidadian	58 (48.33%)
	Mixed	30 (25%)
Geographical location of residence	East	69 (57.5%)
	Central	28 (23.33%)
	South	18 (15%)
	Tobago	5 (4.16%)
Marital status	Currently married	54 (45%)
	Unmarried/single/widowed	66 (55%)
Employment status	Employed	55 (45.83%)
	Unemployed (housewives)/retired	65 (54.17%)
The mean duration of the number of days being absent from work	172 days	

Table 2: Established risk factors for breast cancer in 120 female adult breast cancer patients of the EWMSC

	Risk Factor	Frequency (%)
Menarche in years	10 and below	16 (13.3%)
	11	26 (21.6%)
	12	50 (41.6%)
	13	13 (10.83%)
	14 and above	15 (12.5%)
Number of pregnancies resulting in live births or full-term stillbirths	Never pregnant	18 (15%)
	One to two births	48 (40%)
	Three to four births	39 (32.5%)
	Five or more births	15 (12.5%)
Age in years when first live birth or full-term stillborn occurred	19 and below	30 (25%)
	20-24	44 (36.6%)
	25-29	16 (13.3%)
	30 and above	30 (25%)
Oral contraceptive pill (OCP) use for more than 2 months	Y	72 (60%)
	N	48 (40%)
Family history of breast cancer	N	27 (22.5%)
	Y	67 (55.8%)
	Did not know/unsure	26 (21.6%)
Body Mass Index (BMI)	Underweight (BMI: 18.49 and below)	2 (1.6%)
	Normal (BMI: 18.5-24.99)	44 (36.6%)
	Overweight (BMI: 25-29.99)	51 (42.5%)
	Obese (BMI: 30 and above)	23 (19.1%)
Alcohol consumption	Y	46 (38.5%)
	N	74 (61.5%)
Tobacco use	Yes	11 (9.1%)
	Sporadic	3 (2.5%)
	Previous smoker	5 (4.1%)
	No	101 (84.1%)
Exercise tolerance	Poor	4 (3.3%)
	Fair/Adequate	37 (30.8%)
	Good	64 (53.3%)
	Excellent	15 (12.5%)
Pre-existing medical conditions	Diabetes Mellitus Type 2	41 (34.2%)
	Hypertension	62 (51.7%)
	CV/PV diseases such as MI and DVT	32 (26.7%)
	Cerebrovascular diseases such as strokes	9 (7.5%)
	Asthma	9 (7.5%)
	Osteoarthritis	23 (19.2%)
	Psychiatric disorders	2 (1.7%)
	Sickle cell anemia	2 (1.7%)
	Reproductive issues such as leiomyomas, ovarian cysts, and PCOS	23 (19.2%)
	GI disorders such as ulcers, cholecystitis	18 (15%)
	Ophthalmic and ENT problems such as cataracts, glaucoma, and chronic sinusitis	9 (7.5%)
Nervous system issues	4 (3.3%)	

TnT is a twin-island with diverse population groups composed of East Indians (37%), Africans (31%), and mixed ancestry (24%). In our study, BCa was highest among Indo-Trinidadians (45.83%) compared to Afro-Trinidadians.^[7] This likely disparity between these two ethnic groups was due to different diet patterns, physical inactivity, high BMI, alcohol intake, high use of HRT, and late parity among Indo-Trinidadians, as shown in a previous study.^[8] Afro-Trinidadians showed higher breast density, late presentation of advanced-stage disease, and ER-negative tumors. These racial differences in the occurrence and

diagnosis of BCa and socioeconomic status were similar in other population-based studies in North America, Europe, and Asia (Japan, China, and India).^[14,15] BCa was higher in unmarried/separated/widowed women compared to married women. This finding is similar to previously published studies and has been attributed to different underlying factors such as genetic risk, hormone levels, immune status, psycho-social factors, and pursuance for attending BCa screening and early detection of cancer.^[16,17] The overall disease-free 5-year survival rate was higher in married BCa patients than in unmarried/separated/widowed BCa women.^[18]

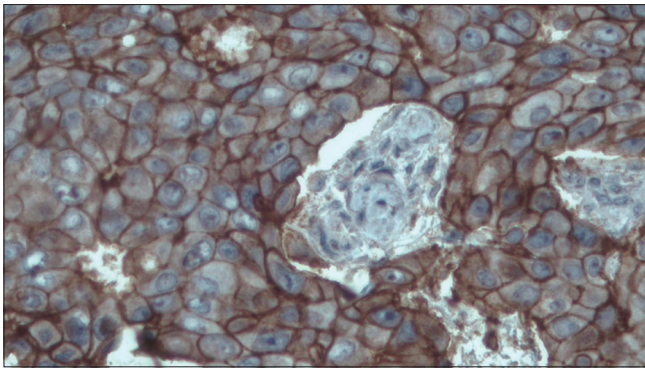


Figure 3: HER-2neu expressed as strong membrane staining (3+)

Table 3: Histopathological features of breast carcinoma specimen in 120 adult females of the EWMSC

Histological Features		Frequency (%)
Histological type of invasive carcinoma	Infiltrating ductal carcinoma	110 (91.7%)
	Infiltrating lobular Ca	4 (3.3%)
	Mucinous/Colloid	4 (3.3%)
	Medullary	2 (1.7%)
Grading of invasive carcinoma	Grade 1	12 (10%)
	Grade 2	76 (63.3%)
	Grade 3	32 (26.7%)
Presence of DCIS	Present	65 (51.2%)
	Not present	55 (45.8%)
Histological type of DCIS	Comedo	98 (81.7%)
	Non-comedo	9 (7.5%)
	Solid	7 (5.8%)
	Micropapillary	2 (1.7%)
	Papillary	3 (2.5%)
	Mixed	1 (0.8%)
Grading of DCIS	High	66 (55%)
	Intermediate	40 (33.3%)
	Low	14 (11.7%)
Presence of LCIS	Present	8 (6.7%)
	Not present	112 (93.3%)
Lymph node involvement	Y	72 (60%)
	N	48 (40%)
Lymphovascular Emboli	Present	32 (26.7%)
	Not present	88 (73.3%)
Necrosis	Present	12 (10%)
	Not present	108 (90%)
Calcification/microcalcification	Present	4 (3.3%)
	Not present	116 (96.7%)
Nipple involvement	Y	12 (10%)
	N	108 (90%)

Table 4: Receptor analysis of breast carcinoma specimen in 45 adult females of the EWMSC

Receptors	Frequency (%)
ER + PR + HER-2 Neu -	18 (40%)
ER - PR - HER-2 Neu -	14 (31.1%)
ER + PR - HER-2 Neu -	4 (8.9%)
ER + PR - HER-2 Neu +	5 (11.1%)
ER - PR - HER-2 Neu +	2 (4.4%)
ER + PR + HER-2 Neu +	2 (4.4%)

Around 45.83% (55 cases) of employed individuals had BCa. The mean duration of the number of days been absent from work was 172 days. As detailed in other studies, our study exhibited multiple similar significant factors related to these patients in returning to work. These were mainly counseling, rehabilitation services provided, younger age group, tumor bilaterality, family support, government leave allowance and financial insurance support, sick leave duration, and flexible working arrangements.^[19] However, the flipside of BCa survivors was that almost 33% of cancer survivors had to quit working or lost their job over 15 months post-diagnosis. The previous studies showed similar employment outcome predictors among BCa survivors.^[20,21] Reproductive state is dependent on ovarian activity exhibited by menarche at its onset and menopause at its cessation.^[22] In our study population, menarche at 12 years constituted 41.6% (n = 50) and menopause at 55 years and above 36.6%. Early menarche (<11 years) and late menopause (>55 years) are associated with a higher risk of BCa and more so for ER-positive tumors.^[23,24]

Patients with a positive family history of BCa had a significantly higher risk outcome, as observed in other studies.^[25] BMI of 25–29.99 constituted 42.5% (n = 51) in our study.^[26] Obesity is also a risk factor for developing poor outcome variants of BCa, such as triple-negative types mainly attributed to pro-inflammatory mediators such as TNF α and IL-6. JAK2/STAT3 is a lipid metabolism regulator considered to make the breast cancer cell more chemoresistant.^[27] Alcohol and tobacco have been considered to relatively increase the risk of BCa. However, in our study, both these factors showed negligible effect on the incidence of BCa.^[28,29] Hypertension is shown to affect survival rates in patients with metastatic BCa. In our study, 51.66% (n = 62) patients had hypertension, demonstrating a strong linkage between hypertension and BCa. However, further analysis needs to be done on the role of anti-hypertensive and its relation to BCa incidence.^[30] Histological classification of breast carcinoma is based on architectural growth patterns and is classified into ductal and lobular.^[31] IDC is the most common histologic type of BCa in our study (91.66%), similar to the worldwide trend.^[32] ILC, mucinous carcinoma, medullary carcinoma, and primary breast osteosarcoma constituted the remainder of the other minor histologic types. Mucinous carcinoma in the breast has a better prognosis than mucinous carcinoma occurring in other primary sites as they are less likely to involve the lymph nodes and are more treatment responsive.^[33,34] Based on the NMBR grading system, 63.33% (n = 76) of BCa were of grade 2 and 26.66% (n = 32) were of grade 3. This trend was similar to previous studies done by Agbo *et al.*^[35] and Titiloye *et al.*^[36] The Asian, North American, and Western European populations have wider access to BCa screening programs, thereby enhancing the chances for detecting BCa at an early stage compared to African countries, which lack regular cancer screening programs.^[14-16]

DCIS was present in the majority of 54.16% (n = 65) cases. DCIS is a noninvasive intraductal epithelial cell proliferation confined to the ducts and is considered a precursor lesion for IDC.^[36] The occurrence was more in patients with

positive family history, low parity, overweight (high BMI), and alcoholics. These factors were identified in our cohort and were in line with studies done in North America, Europe, and the Asian population.^[14-16] African-Trinidad population with DCIS showed more occurrence in the older age group than Indo-Trinidadians. These statistical occurrences based on race and other risk factors were reported by Bailes *et al.*^[37] Williams *et al.*^[38] and Di Saverio *et al.*^[39] DCIS is further classified into comedo, solid, cribriform, micropapillary, and mixed subtypes based on the architectural proliferation. Comedo pattern of DCIS is composed of highly pleomorphic cells with prominent nuclei compared to uniform, mildly pleomorphic cells with monotonous nuclei exhibited in low-grade DCIS. As seen in our study, the increased detection of DCIS among elderly women is possibly due to better screening programs, mammography facilities before undertaking biopsy, and long-term use of postmenopausal estrogen. These similar correlating factors were also documented in epidemiological studies done by Kerlikowske,^[40] Yoo *et al.*^[41] and Oda *et al.*^[42] Necrosis 10% (n = 12) and microcalcification 3.33% (n = 4) were incidental findings in our study. None of these cases had a prior history of trauma, radiotherapy, and reduction mammoplasty or breast infection. Receptor studies on 45 BCa cases revealed ER/PR + HER-2neu – (Luminal A) as the predominant pattern followed by triple-negative cases. Immunohistochemical classification of BCa has been proven to be an effective prognostic and therapeutic tool.^[43] However, there have been numerous troubles shooting features experienced in varying qualities for these receptor studies owing to fixation, antigen retrieval, and differences in staining methods observed in various laboratories.^[44,45]

The primary care physicians (PCPs) play a vital role in detecting important predictors of BCa. They are involved in various stages in BCa patient care that involves cancer detection, diagnosis, treatment aspects, and the recovery phase.^[46] PCPs in TnT are mainly involved in the cancer detection, diagnosis recovery phase as BCa are usually detected during the patient's routine visits to the PCPs either in health care centers or in their private clinics.^[47] PCPs' role in BCa patients is further stretched in high-risk cases when the PCPs spread the knowledge of risk factors, prognostic perception, and further actions by PCPs to refer, counsel, and/or treat high-risk women.^[48] The PCPs' role in attaining a confirmatory family history during BCa diagnosis and prognosis is very high in TnT as the health care centers usually hold patients' vital records throughout their visits along with their families.^[47] The role of attaining the family history is useful during the molecular evaluation of BCa (e.g. BRCA genetic studies) along with detection for other related cancers (especially, ovarian cancers) within the BCa patients.^[49]

Limitations

The main limitation of this study is that it included only one of the five regional health authorities across the country, limiting the number of patients who participated in the study. Involving

all the hospitals under the five regional health authorities spread across the island would have achieved a bigger sample size. However, due to the time constraints and administrative issues, we had to limit to one region.

Conclusions

This study provided useful information on breast tumor characteristics; risk factors and trends in factors such as age, ethnicity, and geographical location; and their contributions to the development of breast cancer. Women were diagnosed later in life with the mean age of 56–65 years. Indo-Trinidadians had a slightly higher incidence of breast cancer compared with their Afro-Trinidadian counterparts. Most women in this study were from East Trinidad, which had the highest concentration of Afro-Trinidadians compared to Central with most the Indo-Trinidadians.

Elevated BMI (over 25) rates and comorbidities such as hypertension and diabetes mellitus may have increased susceptibility to developing breast cancer. Risk factors such as early menarche, late menopause, nulliparity, and oral contraceptive use, while evident, appear to play a less significant role in breast cancer incidence.

Histological patterns of breast tumors followed the global trend. Invasive/IDC and high-grade comedo DCIS were predominant characteristics, with the highest proportion of the subjects having grade 2 stage at diagnosis. However, limited immunohistochemistry performed means that there is limited application of molecular profiles, which is vital to effective prognosis and treatment.

As BCa is the predominant cancer type among TnT women, our study's epidemiological findings can be a useful guide for implementing various cancer prevention strategies and changing lifestyle choices among the population. It can also provide a guiding tool to escalate the efforts in the ongoing national cancer screening programs. This study's unique histopathological analysis and receptor studies can be vital for future cancer surveillance among BCa patients, thereby improving overall survival.

Ethical approval and consent

Ethical approval was granted by the Campus Research and Ethics Committee, UWI (Ref: CEC430/01/18), and the public health observatory at the NCRHA, Trinidad.

Acknowledgements

The authors wish to thank the Public Health Unit, Medical Records section, Department of Histopathology and Department of Clinical Surgical Sciences at the Eric Williams Medical Sciences Complex, North Central Regional Health Authority, and The University of the West Indies for assisting in data collection, block retrieval, and histopathological report collection.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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