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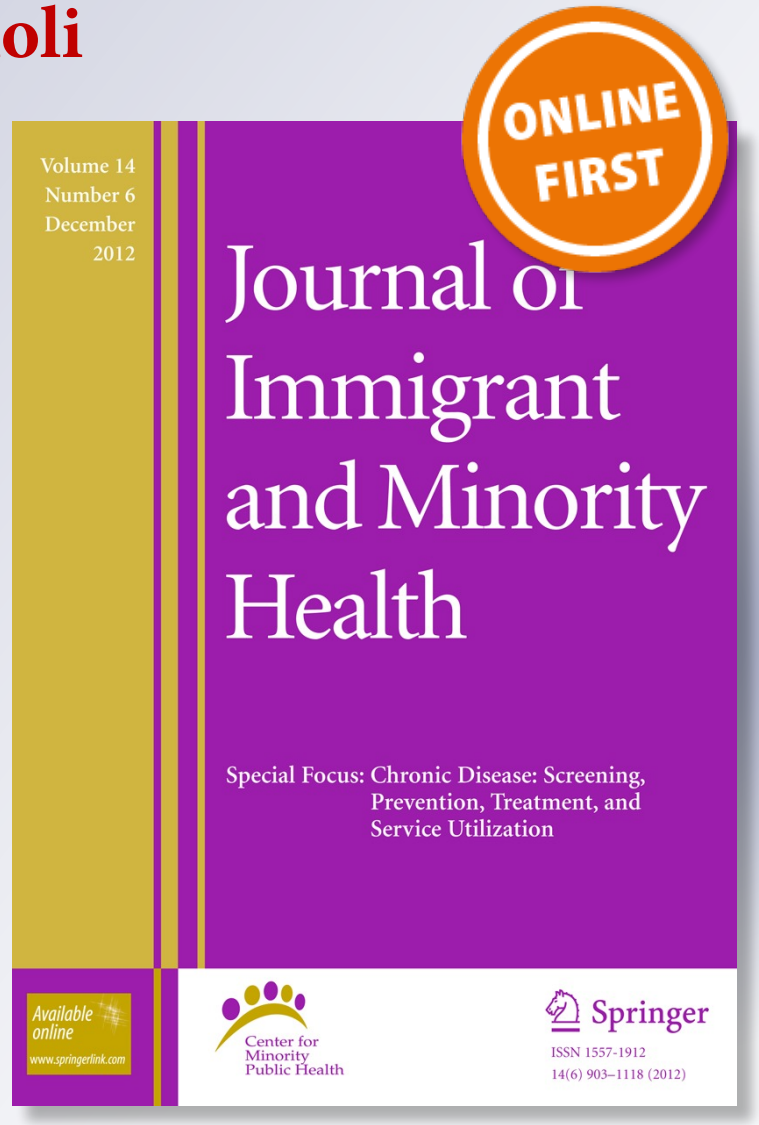

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ORIGINAL PAPER

Breast Cancer Diagnosis from Screening in Trinidad and Tobago: Opportunities for Cancer Prevention

Marlon D. Joseph · Lorna Thorpe · Carey Annandsingh · George Laquis · Joycelyn Lee Young · Jamie Kwasniewski · Roy Lee · Emanuela Taioli

Abstract Trinidad and Tobago (TT) experiences the highest breast cancer mortality in the Caribbean; the distribution of traditional breast cancer risk factors in this population has not been analyzed. Data on women who underwent breast cancer screening at the TT Cancer Society between January 2009–December 2011($N = 2{,}689$) were retrospectively collected. The screening detected 131 incident breast cancers; variables significantly associated with breast cancer diagnosis were, a positive family history of breast cancer (adjusted odds ratio [OR_{adj}]: 1.55; 95 % CI 1.00–2.41), presence of symptoms (OR_{adj}: 1.91; 95 % CI 1.25–2.92), and previous breast surgery (OR_{adj}: 1.67; 95 % CI 0.97–2.88). Breast cancer was significantly associated with increased breast density. Among healthy women, breast density was positively associated with nulliparity (OR_{adj}: 1.46, 1.37, 2.52 respectively for density level 2, 3 and 4 vs. 1) and previous breast surgeries (OR_{adj}: 2.27, 3.09 and 4.13 respectively for density level 2, 3 and 4 vs. 1). This analysis confirms that breast density is an important predictor of newly diagnosed breast cancer in this Caribbean population. Screening is still a diagnostic tool rather than a preventive measure in TT.

Keywords Caribbean populations · Mammography · Breast density · Epidemiology · Trinidad

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Introduction

Trinidad and Tobago (TT) is the second largest of the English-speaking Caribbean countries with a heterogeneous population of approximately 1.3 million. In 2010, roughly 40 % of the population was of African descent, 40 % of Indian sub-continent descent, and the remaining 20 % of mixed ancestry, White, Asian and Amerindian ethnicity [1]. The Cancer Registry of TT estimates that during the period 2000–2002 breast cancer represented 30 % of all new female cancer cases, and 24 % of all female cancer related deaths. While the breast cancer age-standardized incidence rate in TT is low relative to high risk groups, such as African American women (40.0 per 100,000 TT women vs. 121.0 per 100,000 African American women in 2002) [2, 3], breast cancer mortality rates in TT are high and comparable (36.2 per 100,000 TT women vs. 31.6 per 100,000 African American women [3, 4]. Age-standardized mortality rates for breast cancer in TT have been increasing over the past 35 years (14.9 per 100,000 women in 1970 rising to 24.4 per 100,000 women by 2004) [5]. In 2002, the Pan American Health Organization (PAHO) reported that the age-standardized breast cancer mortality rate for women aged 25–74 years old in TT was the highest in the Caribbean, and the fourth highest in the Americas [4].

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Despite the high breast cancer mortality in TT, the distribution of traditional breast cancer risk factors has never been studied in this population, nor the methods utilized for breast cancer early detection have been described [4, 5]. For example, the role of mammographic density in breast cancer risk has been extensively studied in white women [6], but little is known of the association between breast density and breast cancer risk, or of the characteristics associated with breast density in women of African descent.

A recent study showed that women who reside in TT were more likely to be diagnosed with breast cancer at a later stage and more likely to die from the disease compared to Caribbean women living in the US [7]. The National Oncology Programme (NOP) is a major component of the Government of TT's commitment to address this public health challenge. The main focus of the NOP is treatment, education, awareness, prevention, screening for early diagnosis, and palliative care [8]. All citizens of TT are entitled to cancer care and treatment free of charge; however a doctor must refer patients before they can access cancer treatment. The effectiveness of these programs in reducing breast cancer mortality has not been assessed, and it is not clear whether the public campaigns are successful in identifying high-risk subgroups to be the target of intensive preventive programs such as screening. Breast cancer screening is opportunistic and performed at no cost at public hospitals and for a fee at private medical facilities. The Trinidad and Tobago Cancer Society (TTCS), a non-profit organization, plays a major role in screening for various cancers including breast cancer.

The present study was designed in collaboration with TTCS with several purposes: [1] assess the annual rates of screening-diagnosed breast cancer, [2] identify factors predicting the occurrence of breast cancer in this population, [3] describe the characteristics of the newly diagnosed cases and [4] describe personal and behavioral factors associated with breast density. This approach is a key preliminary step for subsequently designing an effective strategy for managing and controlling the public health burden of breast cancer in TT.

Methods

Study Setting and Population

The TTCS is a non-profit organization established in 1972, which routinely offers screening for breast cancer, prostate cancer, cervical cancer and colon cancer. The data collected for this study refer to participants who underwent breast cancer screening at TTCS during the period January 2009–December 2011($N = 2{,}689$). A five-member data collection team from the National Institute of Higher Education, Research, Science and Technology (NIHERST) extracted data from the mammography reports, biopsy reports and patient registration forms at TTCS from January 2012–April 2012 under the supervision of the TTCS clinical operations manager. The five team members met with the PI of this project (MJ) in order to be trained and standardized in data retrieval and data entry. All entries were double entered and verified; all personal identifiers were removed before entering the data in the dataset. At the time of data analysis, data quality was further verified with logical checks. The CUNY University Integrated Internal Review Board approved the study; a waiver to obtain informed consent was approved for this research, and HIPAA authorizations were waived for all subjects.

One hundred and seven participants who reported a prior history of breast cancer and/or prior mastectomy were excluded; therefore, the final study population consisted of 2,582 women who utilized the services at TTCS.

Variables Definitions

Women were defined as being newly diagnosed with breast cancer when a biopsy report confirmed the presence of the malignant neoplasm suggested by the mammography. Each mammography is accompanied by a medical form including demographics, reproductive variables, self-report symptoms, breast health history, and administrative information such as the year the screening was performed, previous mammography before this screening.

Breast density data was extracted from digital mammography reports and categorized according to the breast imaging and reporting data system (BI-RADS) classification system into four levels: BI-RAD type 1-glandular is <25 % of the breast tissue, BI-RAD type 2-scattered fibro-glandular tissues ranging from 25 to 50 % of the breast tissue, BI-RAD type 3-heterogeneously dense fibro-glandular tissue ranging 51–75 % of the breast tissue, BI-RAD type 4 fibro-glandular tissues accounts for more than 75 % of breast tissue [9].

Mammography measurements were performed at TTCS by a three-member team of radiologists using Siemens MAMMOMAT 3000 Nova equipment acquired by the TTCS in 2007. The digitized images were read using the Siemens Syngo Imaging XS. Each woman was assigned to a single breast density category based on readings from both breasts; as a conservative measure, a less dense code superseded a more dense code.

Statistical Analyses

Self-reported symptoms were re-coded into a general category called "symptoms" (yes or no). A comprehensive variable was created to account for breast health history; women who reported prior surgery, and/or prior breast

biopsy, and/or breast cyst aspiration were categorized as "yes" for a significant breast health history. Women who did not undergo any of the above-mentioned procedures were categorized as health history "no".

Descriptive statistics of the study population were calculated and stratified according to the presence of a new diagnosis of breast cancer or not; statistical significance was calculated by Wald χ^2 test, Fisher's exact test and Cochran Armitage trend test where appropriate. α was set at <0.05 level.

Logistic regression was used to examine the associations between a new diagnosis of breast cancer and personal, behavioral risk factors. Crude and adjusted odds ratios for a new diagnosis of breast cancer along with their 95 % confidence intervals were calculated. The multivariate model included variables chosen a priori: age, race/ethnicity, breast density, menopausal status, parity, family history of breast cancer. Other variables such as the presence of symptoms, having had a prior mammography, and having had prior breast surgery, biopsy, aspiration were included in the final model since a more than 10 % change in odds ratios was observed between the univariate and multivariate analyses.

Determinants of breast density among healthy women were also assessed using logistic regression. SAS software version 9.2 (SAS Institute Inc., SAS Campus Drive, Cary, NC, 27513, USA) was used for statistical analyses.

Results

The mammography screening detected 131 new breast cancer cases out of 2,582 screened women (Table 1); the cumulative incidence of breast cancer diagnosed at TTCS in 2009 was 35.2 per 1,000 women screened, in 2010 it was 57.2 per 1,000 women, and in 2011 58.3 per 1,000 women.

The majority of women were in the age group 40–59 years. Participants were largely of African ancestry, but four other ethnic groups were also represented (mixed, East Indian, White, Asian and other); 33 % of participants had missing data on ethnicity. Roughly half of the women were either married or in a common-law relationship. Two-thirds of the women could be classified as Post-menopausal; a small percentage of women reported a prior hysterectomy. Most of the screened women had children; of these, 66 % had their first child between the ages of 18–30 years. Half of the cases went to the screening because of symptoms, while this figure was much lower (33 %) among women who turned out with a normal mammogram. Almost 20 % of newly diagnosed breast cancers had a previous biopsy, surgery or cysts aspiration, compared to 12 % of the women with a normal mammogram. Approximately 2 % of the

Table 1 Description of women who utilized mammography services at Trinidad and Tobago Cancer Society, 2009–2011

Variable	Healthy women $N = 2,451$	Incident breast cancer $N = 131$	Odds ratio	95 % CI	
				Lower	Upper
Age (years)					
18–39	128	10	1.00	Reference	
40–49	875	47	0.69	0.34	1.4
50–59	880	35	0.51	0.25	1.05
60–69	411	21	0.65	0.3	1.43
≥70	131	16	1.56	0.68	3.57
Missing	26	2	0.98	0.2	4.76
Marital status					
Single, separated, widowed, divorced	1,046	62	1.00	Reference	
Married, common law	1,350	66	0.82	0.58	1.17
Missing	55	3	0.92	0.28	3.02
Ethnic group					
African ancestry	834	49	1.00	Reference	
White	42	3	1.22	0.36	4.06
East Indian	241	14	0.99	0.54	1.82
Mixed	492	24	0.83	0.5	1.37
Asian and other	24	1	0.71	0.09	5.35
Missing	818	40	0.83	0.54	1.28
Post-menopausal					
No	541	35	1.00	Reference	
Yes	1,594	80	0.78	0.52	1.17
Missing	316	16	0.78	0.43	1.44
Family history of breast cancer					
No	1,772	88	1.00	Reference	
Yes	585	40	1.38	0.94	2.02
Missing	94	3	0.64	0.2	2.07
Previous hysterectomy					
No	1,947	99	1.00	Reference	
Yes	122	5	1.3	0.85	2.01
Missing	81	4	0.97	0.35	2.7
Pregnancy history					
No children	408	20	1.00	Reference	
Yes	2,004	109	1.11	0.68	1.81
<18 years	165	16	**1.98**	**1.00**	**3.91**
18–30 years	1,615	80	1.01	0.61	1.67
>30 years	224	13	1.18	0.58	2.43
Missing	39	2	1.05	0.24	4.64

One-hundred and seven participants were excluded from final analysis because they had a prior diagnosis of breast cancer. In bold are marked the statistically significant results

CI confidence intervals

women reported having had cancer other than breast cancer in the past (Table 2).

Breast density categorization differs between cases and healthy women; categories 1 and 2 were more represented among women with normal mammograms (77 %), while highly dense breasts (category 4) were more frequent among newly diagnosed breast cancer cases than among healthy women (9.9 vs. 5 %).

In univariate analysis, increasing breast density was significantly associated with increased odds of being diagnosed with breast cancer. Women who were classified as BI-RAD type 4, the densest classification, were 2.5 times more likely to be diagnosed with breast cancer compared to those classified as BI-RAD type 1, the least dense category. There was a significant positive trend for new diagnosis of breast cancer as breast density increased (p value = 0.01). Women who reported symptoms were two times more likely to be diagnosed with breast cancer compared to those who did not report symptoms. Women who reported prior breast surgery/breast biopsy/breast cyst aspiration were almost two times more likely to be diagnosed with breast cancer compared to those that did not report prior breast health surgery/biopsy/aspiration.

At multivariate analysis (Table 3), variables significantly associated with breast cancer diagnosis were a positive family history of breast cancer, presence of symptoms, previous breast surgery, and increased breast density. The relative odds of breast cancer with BI-RAD type 4 were 3.15 (95 % CI 1.43–6.93) compared to those

Table 2 Description of breast health history in women who utilized mammography services at TTCS, 2009–2011

Variable $N = 2583$	Healthy women	Breast cancer	Odds ratio	95 % CI	
				Lower	Upper
Previous mammography					
Yes	1,576	76	1.00	Reference	
No	857	53	1.28	0.89	1.84
Missing	18	2	2.30	0.50	10.11
Breast density[a]					
BI-RAD type 1	701	29	1.00	Reference	
BI-RAD type 2	1,185	36	1.14	0.72	1.81
BI-RAD type 3	364	22	1.46	0.83	2.58
BI-RAD type 4	126	13	**2.50**	**1.26**	**4.93**
Missing	75	11	**3.55**	**1.70**	**7.38**
Breast symptoms					
No	1,505	58	1.00	Reference	
Yes	936	73	**2.02**	**1.42**	**2.89**
Missing	10	0	–	–	–
Previous breast biopsy, surgery, cyst aspiration					
No	2,094	103	1.00	Reference	
Yes	296	25	**1.9**	**1.20**	**3.00**
Missing	88	3	0.69	0.22	2.23

In bold are marked the statistically significant results

[a] Cochran armitage trend test $p = 0.01$

Table 3 Multivariate model predicting new diagnoses of breast cancer from screening-TTCS, 2009–2011

Variable (compared to baseline; $N = 2,582$)	Odds ratio[a]	95 % CI	
		Lower	Upper
Age (years)			
18–39	1.00	Reference	
40–49	1.05	0.43	2.63
50–59	0.78	0.23	2.71
60–69	1.31	0.36	4.73
≥70	2.86	0.78	10.53
Ethnic group			
African	1.00	Reference	
White	1.42	0.4	5.00
East Indian	0.98	0.47	2.04
Mixed	0.79	0.43	1.44
Asian and other	0.76	0.09	6.18
Missing	0.73	0.44	1.20
Post-menopausal			
Yes	0.99	0.41	2.41
Family history			
Yes	**1.55**	**1.00**	**2.41**
Hysterectomy			
Yes	1.15	0.68	1.95
Breast density classification			
BI-RAD type 1	1.00	Reference	
BI-RAD type 2	1.08	0.65	1.80
BI-RAD type 3	1.33	0.67	2.66
BI-RAD type 4	**3.15**	**1.43**	**6.93**
Children			
No	1.23	0.68	2.22
Symptoms			
Yes	**1.91**	**1.25**	**2.92**
Previous mammography			
No	0.73	0.46	1.16
Previous breast surgery			
Yes	1.67	0.97	2.88

CI Confident intervals

[a] Odds ratio adjusted for age, ethnic group, menopausal status, family history of breast cancer, breast density, parity, previous breast surgery. In bold are marked the statically significant results

classified as BI-RAD type 1. Reported symptoms were significantly associated with breast cancer (OR_{adj}: 1.91; 95 % CI 1.25–2.92). A positive family history for breast cancer yielded an OR for breast cancer of 1.55 (95 % CI 1.00–2.41).

There were no statistically significant associations between breast cancer diagnosis and race/ethnicity, menopausal status, parity, hysterectomy, and prior breast screening.

Determinants of Breast Density

The analysis was restricted to women who had a normal mammogram (Table 4). In each breast density category, age was inversely associated with breast density, and so was post-menopausal status. Breast density was positively associated with nulliparity (OR: 1.46, 1.37, 2.52 respectively for breast density category 2, 3 and 4 vs. 1) and previous breast surgeries (OR: 2.27, 3.09 and 4.13 respectively for breast density category 2, 3 and 4 vs. 1).

Discussion

The present study was conducted on more than 2,500 women derived from a mammography screening at TTCS during the period 2009–2011; 131 new cases of breast cancer were diagnosed in this period, approximately 5 % of the adult female population screened.

Traditional risk factors such as age, post-menopausal status and parity were not significant predictors of breast cancer diagnosis in this Caribbean population; family history for breast cancer was confirmed as a risk factor [10]. It is possible that some form of selection bias occurs in this population, and that younger women with a family history of breast cancer are disproportionately utilizing the screening services; another explanation for these results may be the presence of a more aggressive breast cancer type, characterized by specific genetic/biological markers that cluster in families and whose effect on breast cancer risk is overwhelming in comparison to the effect of reproductive factors. Among women who were newly diagnosed with breast cancer at TTCS, roughly half were

Table 4 Predictors of breast density in breast cancer free women who utilized mammography services at TTCS in 2009–2011

Variable (compared to BI-RAD type 1) $N = 2{,}451$	BI-RAD type 2			BI-RAD type 3			BI-RAD type 4		
	Odds ratio**	95 % CI		Odds ratio**	95 % CI		Odds ratio**	95 % CI	
		Lower	Upper		Lower	Upper		Lower	Upper
Age (years)									
18–39	1.00	Reference		1.00	Reference		1.00	Reference	
40–49	0.96	0.45	2.05	0.68	0.29	1.58	0.56	0.21	1.50
50–59	1.00	0.42	2.39	0.46	0.17	1.27	0.36	0.09	1.41
60–69	**0.54**	**0.23**	**1.31**	**0.14**	**0.05**	**0.42**	**0.12**	**0.03**	**0.55**
≥70	**0.50**	**0.20**	**0.67**	**0.12**	**0.03**	**0.43**	**0.05**	**0.01**	**0.60**
Ethnicity									
African ancestry	1.00	Reference		1.00	Reference		1.00	Reference	
Asian and other	1.87	0.54	6.48	**11.66**	**2.91**	**46.63**	7.10	0.52	96.23
White	1.42	0.63	3.21	2.70	0.87	9.00	2.96	0.32	27.07
East Indian	1.11	0.75	1.65	1.39	0.76	2.49	2.16	0.91	5.14
Mixed	1.09	0.80	1.48	1.26	1.79	2.01	1.51	0.72	3.16
Missing	**1.40**	**1.08**	**1.82**	**1.49**	**1.00**	**2.24**	**1.89**	**1.00**	**3.57**
Menopausal									
Yes	**0.41**	**0.25**	**0.67**	**0.35**	**0.19**	**0.64**	**0.21**	**0.08**	**0.53**
Full term pregnancies									
No	**1.46**	**1.05**	**2.02**	1.37	0.87	2.16	**2.52**	**1.37**	**4.62**
Family history of breast cancer									
Yes	0.96	0.75	1.23	0.86	0.58	1.27	1.08	0.60	2.00
Previous breast biopsy, surgery, cyst aspiration									
Yes	**2.27**	**1.54**	**3.34**	**3.09**	**1.81**	**5.24**	**4.13**	**1.90**	**8.92**

CI confidence intervals

** Model adjusted for age, ethnicity, menopausal status, family history of breast cancer, children, previous breast surgery. In bold are marked the statistically significant results

under the age of 50 years. It appears that women in TT are more likely to be diagnosed with breast cancer at a younger age compared to American women. These results are consistent with previous data showing that breast cancer affects TT women at a younger age than that traditionally observed in other populations, and supports the hypothesis of a more aggressive form of the disease [4]. In the United States, according to the Surveillance Epidemiology and End Results (SEER) [3] data for the years 2005–2009, the median age at diagnosis for breast cancer was 61 years, and only 25 % of the cases were diagnosed under the age of 50 years. Cancer is the leading cause of death before age 65 in females in TT, and this is largely attributed to the earlier age of onset. In 1994, breast cancer accounted for 16 % of all female deaths under age 65 [11]. Further investigations into the possible causes of the observed early breast cancer onset in TT are warranted. Possible explanations may be more aggressive breast cancer phenotypes [7], constitutionally different breast tissue composition, as suggested by the breast density profile of TT women reported here, or environmental exposures to specific carcinogens at early ages. Ad hoc studies are needed to assess the relationship between age at diagnosis and stage in TT women compared to US born women, together with in-depth studies of the biological characteristics of the cases ascertained by the screening. Other important breast cancer risk factors that should be considered in this analysis are diet, smoking habits and alcohol consumption. Unfortunately, these factors were not available in this data set.

This analysis confirms that breast density is a significant predictor of newly diagnosed breast cancer, and this result holds true after adjustment for several confounding factors. Our results are consistent with prior studies measuring the association of breast density and breast cancer diagnosis after digital mammography, showing that mammographic density is one of the stronger predictors of breast cancer risk [10, 12], and that risk models including breast density may be utilized to identify women at high risk for breast cancer [13]. A comprehensive meta-analysis and a pooled analysis corroborate the results reported here [6, 14]. A positive association between breast density and breast cancer risk has been reported in both pre-menopausal and post-menopausal women, and in both tumor symptomatic and asymptomatic populations, similar to what was observed in the present study [15]. Despite the growing research on mammographic density, most studies have not included women of African descent, Caribbean women and other ethnic minority groups, but have instead focused on White women.

The present study also reports on factors associated with breast density in a large population of healthy Caribbean women, and shows that breast density is associated with younger ages, with pre-menopausal status, and nulliparity. Previous research in predominantly white populations has consistently shown associations between high mammographic density and younger age, nulliparity, later age at first birth and pre-menopausal status [12, 16, 17]. Breast density is reported by others to be inversely associated with both age and body mass index (BMI) [16]. One limitation of the present study is the unavailability of BMI data for the study sample; therefore this association could not be tested, nor could the analyses be adjusted for BMI.

Very few studies have compared breast density patterns among African American women or Caribbean women with conflicting results [17, 18]. A study including 207 African American women found that they had lower breast density compared to non-Hispanic white women [17]; however, another study reported that 883 African American women had a higher average breast density than non-Hispanic white women [18]. One study conducted in the United Kingdom (UK) found that Afro-Caribbean women had lower mammographic density than white women, but had higher mammographic density than South Asian women living in the UK [19]. Another study examined the association of mammographic density and menstrual and reproductive factors, and found no significant differences in breast density among African American, white and Caribbean women living in New York City [20].

Most of the women who screened at the TTCS reported symptoms upon registration, and those with symptoms were nearly 2 times more likely to be diagnosed with breast cancer compared to those who did not report symptoms. This confirms that screening in TT is still a diagnostic tool and can be classified as an opportunistic rather than a preventive program [21].

The present study is the first of its type in TT; among its strengths are the large sample size and the comprehensive nature of the data collection. However, the study carries several limitations: personal and behavioral characteristics are self-reported, thus responses may influenced by recall bias. Race was self defined by the participants, and information on the degree of racial admixture is not available. Women underwent screening on a voluntary basis, thus some form of selection bias may be present, as suggested by the fact that the majority of women presented with symptoms. The type of selection may have influenced the type of cancer cases identified by the screening, and as a consequence may have influenced the strength of the associations observed here.

In conclusion, early breast cancer detection is the foundation for reducing breast cancer morbidity and mortality. Breast cancer is a significant burden on Trinidad and Tobago both emotionally and economically. Policies to increase efforts to screen high-risk groups together with educational programs towards the general population of women should be considered by the government. Public

health interventions should be coupled with research efforts aimed at better understanding the role of breast density, the distribution of classical risk factors and the biology of breast cancer in this population.

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