original reports

Breast Cancer Research in the Caribbean: Analysis of Reports From 1975 to 2017

abstract

Purpose **Breast cancer is among the leading causes of death resulting from cancer in Caribbean women. Studies examining exogenous and genetically predetermined endogenous risk factors are critical to define breast cancer susceptibility in Caribbean women. The purpose of this systematic review is to assess the existing scientific literature in the last 42 years (1975 to 2017) to describe the body of research generated for the population of this region and determine future research directions.**

Methods **We selected published research articles using a combination of definite keyword searches in PubMed. Only articles presenting the Caribbean population as the focus of their research objectives were included in this analysis.**

Results **Studies on breast cancer in the Caribbean are limited. A majority of publications on Caribbean populations were descriptive, focusing on cancer trends and clinicopathologic factors. High incidence and mortality rates for breast cancer are reported for the region, and there seem to be some differences between countries in the frequency of cases according to age at presentation. A limited number of epidemiologic, behavioral, and genetic and molecular studies were conducted in more recent years.**

Conclusion **A regional strategy for cancer registration is needed for the Caribbean to address possible underestimates of breast cancer incidence. Furthermore, behavioral, molecular, genetic, and epidemiologic investigations of breast cancer are critical to address the concerns related to currently described high incidence and mortality rates in the Caribbean.**

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INTRODUCTION

Recent reports reveal that breast cancer (BC) is a leading cause of death resulting from cancer in women in Caribbean nations.[1] On the basis of estimates by the WHO, geographic variations in BC incidence and mortality are reported among Caribbean nations.[2] Population-based studies suggest that BC susceptibility may be associated with aging, reproductive history, and lifestyle factors.[3-7] Since the 1990s, research has demonstrated that beyond the previously identified risk factors, familial clustering of BC points toward genetic risk factors, such as mutations in *BRCA1* and *BRCA2* genes.[8] The biologic heterogeneity of BC has also been highlighted through molecular profiling,[9-12] with four identified molecular profiles (basal-like, human epidermal growth factor receptor 2 [HER2]/neu [ie, HER2 positive], luminal A, and luminal B), characterized by distinct signatures and clinical outcomes.

As compared with research in other countries, BC research in Caribbean populations is still limited and requires stronger focus and development. Progress in such research would be significant because Caribbean populations are ethnically and culturally diverse (mixed genetic origins of predominantly African descent). Today, a gap exists in research investigating the epidemiology, clinicopathologic features, genetic determinants, and molecular classifications of BC in these populations. The African Caribbean Cancer Consortium seeks to build research capacity in the Caribbean to further investigation of factors associated with BC trends. We examined BC incidence and mortality in the Caribbean. We also analyzed 43 years of population-based studies (1975 to 2017) of BC and associated risk factors in Caribbean countries and discuss future regional research strategies.

METHODS

Literature Review and Inclusion and Exclusion Criteria

This analysis includes relevant publications in PubMed from inception to January 2017 using

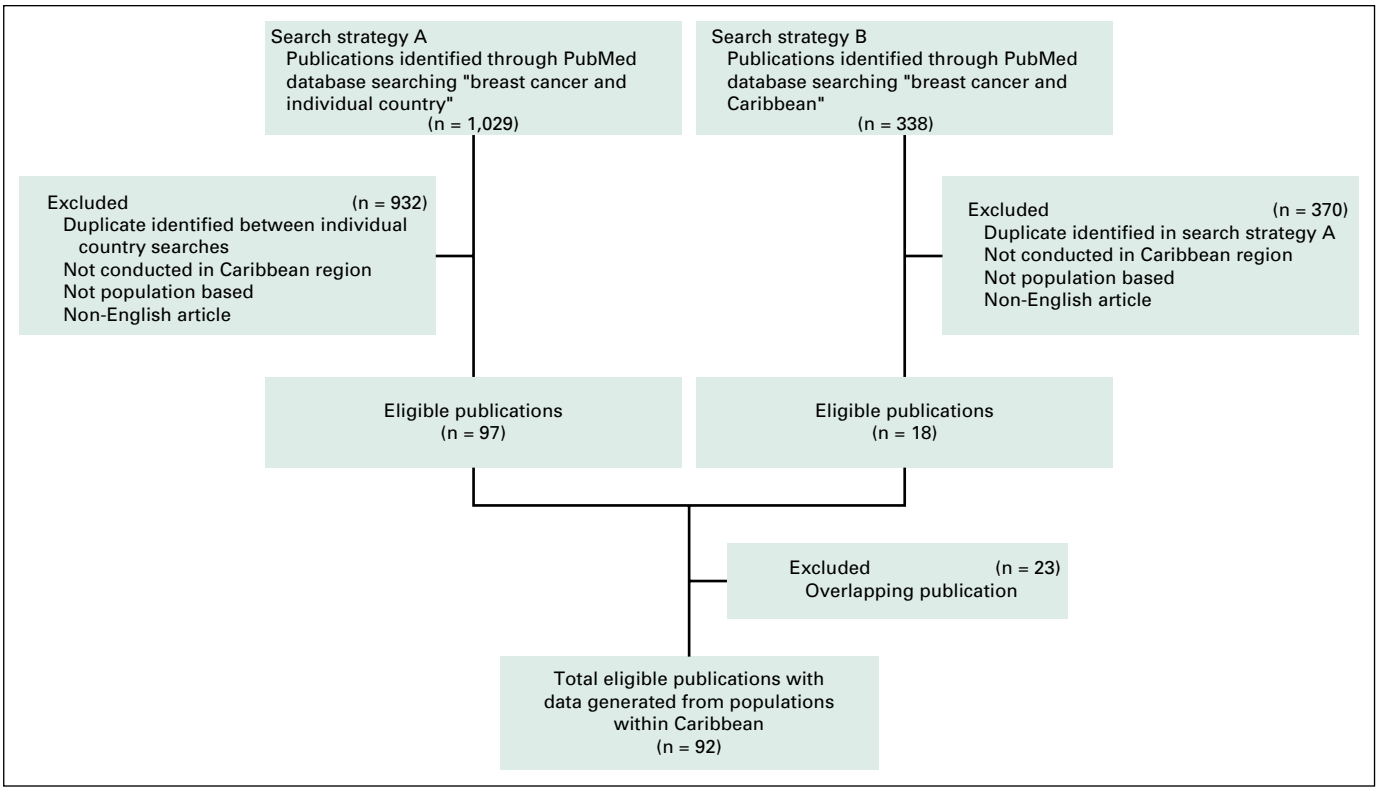

Fig 1. Flow diagram of study selection criteria.

the search terms "breast cancer and Caribbean" and "breast cancer and [individual country name]" for all Caribbean countries (Appendix). The bibliographies of several review articles were examined to identify additional publications that might have been missed by our PubMed search.

Abstracts and full texts were reviewed by three independent reviewers and cross-referenced to address discrepancies and confirm eligibility for inclusion. For overlapping studies, the publication with the largest population and/or most complete information was included. All population-based analyses (case-cohort, cross-sectional, case-control, qualitative, and other observational studies) of BC in a Caribbean population were considered. Studies comparing Caribbean data with those on other populations in different geographic regions were included, but only data on indigenous Caribbean women are reported. Studies conducted in basic science or immigrant Caribbean populations and non-English articles were excluded. Screening prevalence rates in Caribbean women were reported in our previous review[13] and therefore were excluded from this analysis, with the exception of publications that reported factors associated with screening. On the basis of these inclusion and exclusion criteria, data from 92 publications were included in this analysis (Fig 1).

Data Collection

From each publication, first author, publication year, topic of research focus, study sample size, and reported key findings were abstracted. The number of publications by country was examined, and countries were categorized as high (≥ 10 publications), intermediate (five to nine publications), or low (one to four publications).

For estimates of BC incidence and mortality, GLOBOCAN 2012[2] was used for the Caribbean and other world regions (for comparison). Incidence trends by age were also examined for each Caribbean nation and compared with world incidence trends. All incidence and mortality rates are reported as age standardized to the world population.

RESULTS

Estimated Incidence and Mortality of BC in Caribbean Populations

In all geographic regions, BC incidence was higher than mortality (Fig 2). The lowest BC incidence and mortality rates are estimated in Haiti

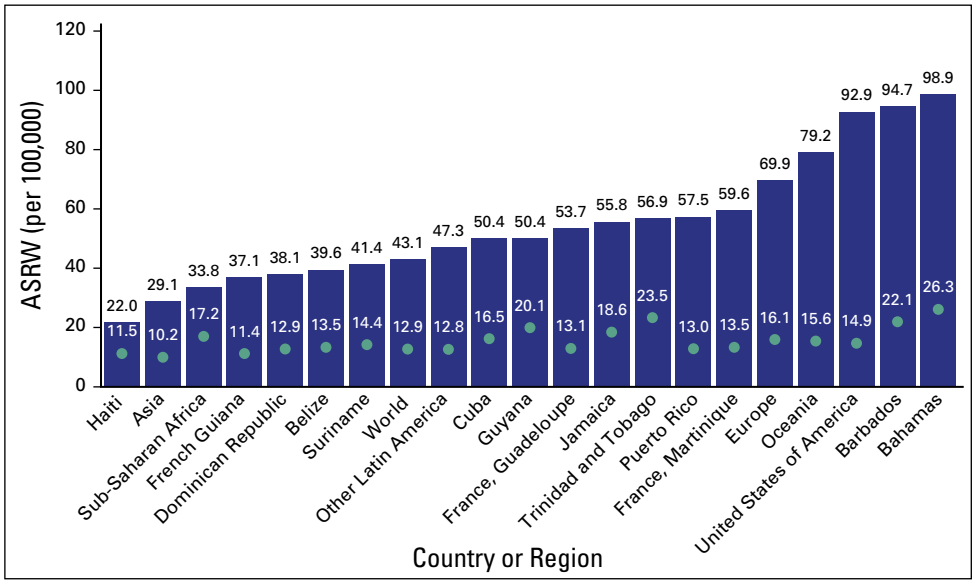

Fig 2. Age-standardized incidence (bars) and mortality rates (circles) of breast cancer per 100,000 per year for individual Caribbean countries, the world, and US and other Latin American countries. Data adapted.[2] ASR(W), rate age standardized to the world population.

(22.0 and 11.5 per 100,000, respectively) and the highest in the Bahamas (98.9 and 26.3 per 100,000, respectively). When age-specific incidence was examined, a majority (11 [79%] of 14) of Caribbean countries had peaks in BC incidence that were similar (age, 65 to 69 years) or at an older age (age, 70 to 74 years) than world estimates (peak at age 65 to 69 years). Among these Caribbean countries, Suriname, the Bahamas, and Guadeloupe had a second peak in BC incidence at < 60 years of age (age 45 to 49, 50 to 54, and 55 to 59 years, respectively). Only French Guiana, Dominican Republic, and Belize had a peak in BC incidence at a younger age (age 55 to 59 years).

Status of BC Research in Caribbean Populations

From 1975 to 2017, 92 publications on BC research in the Caribbean region were identified, with an increase in frequency from the 1990s (Fig 3). Most articles focused on epidemiologic trends and clinicopathologic features. It was not until 2007 that an expansion of research focus was observed (Fig 3). Sixteen (53%) of 30 Caribbean countries were documented in publications focusing on BC in native Caribbean women, with a majority having intermediate to low numbers of publications (Fig 4).

A majority (82 [89.1%] of 92) of publications involved one or more Caribbean coauthors, and

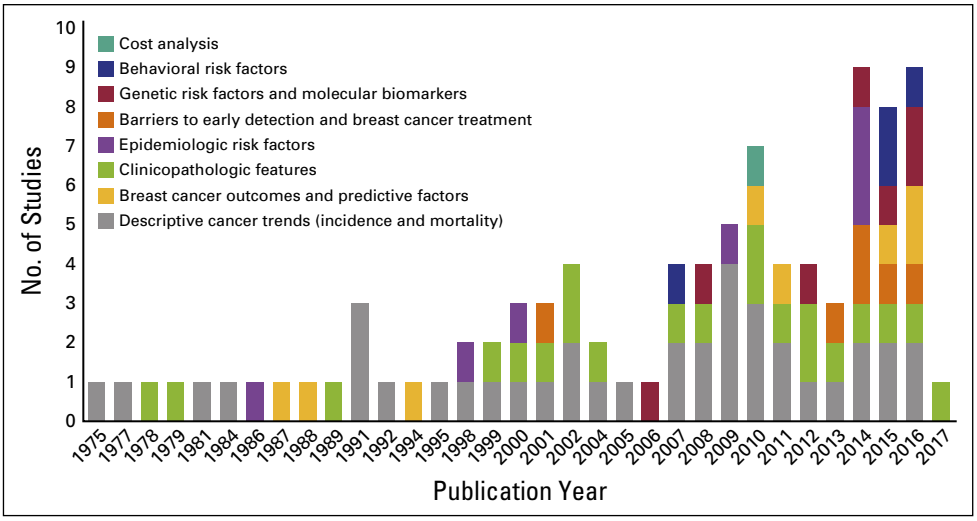

Fig 3. Distribution of breast cancer publications by research focus over time: 1975 to 2017.

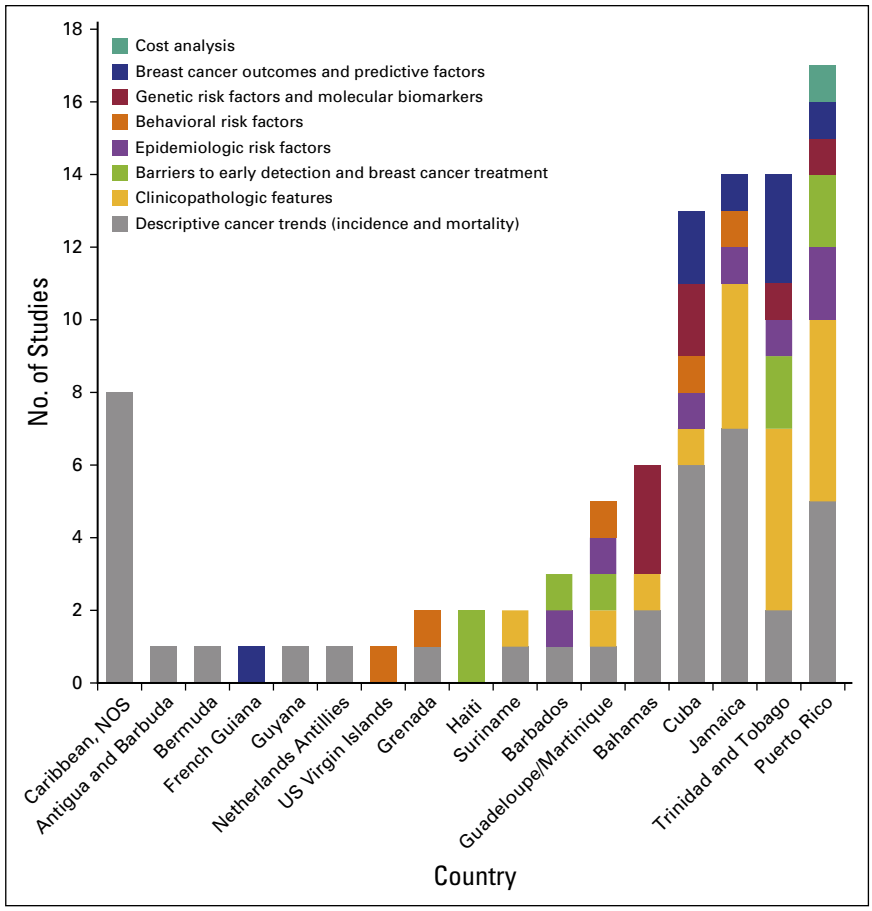

Fig 4. Distribution of studies according to country. NOS, not otherwise specified.

many involved coauthors in other geographic regions. Most Caribbean researchers were the first author (66 [80.5%] of 82) on each publication, and a smaller proportion (61 [74.4%] of 82) were the corresponding author.

Key Findings From Caribbean BC Studies

Key findings of BC research in the Caribbean are summarized in Table 1. Sample size in these publications ranged from 16 to 9,389 women.

Descriptive cancer trends (incidence and mortality). Eight publications from 1992 to 2016 described regional analyses of epidemiologic trends in incidence and/or mortality.[1,14-20] All of them suggested that BC was both the leading cancer site and cause of death resulting from cancer. Similar findings, using data from pathology databases or hospital or national cancer registries, were also published[21-50] and highlighted: earlier age at diagnosis in Barbados (age 50 to 54 years) in contrast to US black women (age 75 to 79 years)[24]; increasing BC incidence in Jamaica from 1958 to 1992,[34,36] followed by relatively stable incidence rates from 1993 to 2007[37,39,40]; lower BC incidence in Puerto Rico from 1969 to 2003 in comparison with mainland United States[46,47] and higher incidence and mortality rates in areas with high socioeconomic status[43]; similarly, from 1994 to 2003, lower BC incidence in Suriname than in the United States[48]; and increasing BC mortality in Trinidad and Tobago (henceforth, Trinidad) from 1970 to 2003,[49] with geographic residence and African ancestry emerging as strong predictors of BC incidence and mortality.[50]

Clinicopathologic features. Eighteen publications described clinicopathologic features of women from seven Caribbean countries (the Bahamas, Cuba, Guadeloupe, Jamaica, Puerto Rico, Suriname, and Trinidad).[51-67,105] The most common histologic type was infiltrating ductal carcinoma. For countries that reported staging data, stage ≥ 2 at presentation was reported in the Bahamas,[51] Jamaica,[54,56] and Trinidad.[67] In contrast, one study in Puerto Rico reported that 88.9% of patients presented with stage I to III and T1/T2 BC.[60] Multiple studies of hormone receptor status

Table 1. Key Findings From BC Research Studies of Caribbean Populations

First Author	Country	Year of Publication	Study Size	Key Findings
Descriptive cancer trends (incidence and mortality)				
Brooks[14]	Caribbean, NOS	1992	NA	NA
Ivey[15]	Caribbean, NOS	2008	NA	BC among leading causes of death resulting from cancer in 21 Caribbean countries
Luciani[16]	Caribbean, NOS	2013	2,695 cases	In 16 Caribbean countries, top five countries with highest age-standardized mortality rates (2004-2008) for BC are St Vincent and the Grenadines, the Bahamas, St Kitts/Nevis, Trinidad and Tobago, and Antigua/Barbuda
Razzaghi[1]	Caribbean, NOS	2016	3,773 cases	From 2003 to 2013, for all Caribbean countries, BC was leading cause of death resulting from cancer, accounting for 21.8% of deaths resulting from cancer in women (highest: Cayman Islands, 29.7%; the Bahamas, 28.8%; lowest: Belize, 14.0%; Suriname 16.1%)
Robles[17]	Caribbean, NOS	2002	NA	Relatively high mortality/incidence ratios; BC cases not being adequately managed in many Latin America and Caribbean countries
Bosetti[18]	Caribbean, NOS	2005	1,350 cases	Among two Latin Caribbean countries from 1970 to 2000, similar mortality rates observed in Cuba (28.22%) and Puerto Rico (27.96%) for women age < 65 years, with Cuba having stable mortality rates
Chatenoud[19]	Caribbean, NOS	2014	1,695 cases	Among two Latin Caribbean countries from 2005 to 2009, similar mortality rates observed in Cuba (14.89%) and Puerto Rico (12.57%), with Cuba having stable mortality rates
Di Sibio[20]	Caribbean, NOS	2016	1,934 incident cases 5,101 case deaths	For Latin Caribbean and South American Caribbean countries (2003-2008), BC was leading incident female cancer in Belize and second leading cause of death resulting from cancer in Belize and Cuba
Simon[21]	Antigua and Barbuda	1991	139 incident cases 149 case deaths	BC is main cancer diagnosed (23.1%) and cause of death among these (18.2%)
Brathwaite[22]	Bahamas	1984	NA	NA
Brathwaite[23]	Bahamas	2007	358 incident cases 178 case deaths	BC is most frequent female cancer (45.3%) and most frequent cause of death among these (19.2%)
Hennis[24]	Barbados	2009	396 cases	Incidence peaked at earlier age among Barbadian women (age 50-54 years) in contrast to African American women (age 75-79 years)
Dallaire[25]	Bermuda	2009	NA	BC is most frequent cancer in women
Martín[26]	Cuba	1998	8,579 cases	BC is among top five cancers in incidence and mortality (1986-1990)
Graupera Boschmonar[27]	Cuba	1999	2,371 cases	3-year survival rate for BC in Cuba, 61% (1988-1989)
Galán[28]	Cuba	2009	2,445 cases	BC is leading cancer in incidence (2001-2003) and second leading cause of death resulting from cancer in women (2005-2007)
Garrote[29]	Cuba	2011	NA	5-year age-standardized relative survival for BC, 69% (1994-1995)

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Table 1. Key Findings From BC Research Studies of Caribbean Populations (Continued)

First Author	Country	Year of Publication	Study Size	Key Findings
Domínguez[30]	Cuba	2014	NA	Unfavorable trend in disability-adjusted life-years seen for BC between 1990 and 2006 in Cuban women of childbearing age
Shai[31]	Cuba	1991	NA	Lower BC mortality compared with US women
Asulin[32]	Grenada	2004	NA	BC among top four frequently diagnosed cancers and most frequent cause of mortality in women
Best Plummer[33]	Guyana	2009	589 cases	Among women, Indo-Guyanese presented with most cases of BC (45%) compared with Afro-Guyanese women
Harris[34]	Jamaica	1977	NA	Upward annual incidence trend observed from 1958 to 1974; BC conforms to Western pattern with regard to shape of age-specific incidence curve and stage of presentation; no obvious histologic differences between BC in Africa, Jamaica, and United States
Brooks[35]	Jamaica	1991	2,837 cases	In women, 24.1% of cancers occurred in breast (1958-1987)
Brooks[36]	Jamaica	1995	582 cases	From 1988 to 1992, increase in female BC (crude rate, 36.0; ASR, 47.1)
Hanchard[37]	Jamaica	2001	627 cases	From 1993 to 1997, in women, leading cancer site was breast (627 [26.7%] of 2,344); incidence remained relatively stable (ASR, 43.2 *v* 47.1 per 100,000 per year)
Blake[38]	Jamaica	2002	291 cases	BC among leading cancer mortality sites in women
Gibson[39]	Jamaica	2008	639 cases	From 1998 to 2002, in women, leading cancer site was breast (639 [27.1%] of 2,350); incidence remained relatively stable (ASR, 43.2 *v* 40.1 per 100,000 per year)
Gibson[40]	Jamaica	2010	720 cases	From 2003 to 2007, in women, leading cancer site was breast; incidence remained relatively stable (ASR, 40.1 *v* 43 per 100,000 per year)
Dieye[41]	Martinique	2007	1,568 cases	BC most common cancer diagnosed in women
Freni[42]	Netherlands Antilles	1981	338 cases	Cancer in women most frequently found in breast
Torres-Cintrón[43]	Puerto Rico	2012	NA	Incidence and mortality rates for BC higher for areas with highest socioeconomic position
O'Neil[44]	Puerto Rico	2015	9,389 cases	Average annual incidence of BC among women, 84 per 100,000 women (2007-2011)
Nazario[45]	Puerto Rico	2000	4,289 cases	Lifetime risk of BC seems to be increasing in Puerto Rico
Martínez[46]	Puerto Rico	1975	871 cases	From 1969 to 1971, age-specific incidence of BC lower in Puerto Rico compared with United States
Ortiz[47]	Puerto Rico	2010	NA	From 1992 to 2004, BC incidence lower than in United States and other ethnic groups, but mortality is similar
van Leeuwaarde[48]	Suriname	2011	421 cases	From 1994 to 2003, BC incidence in Suriname is low compared with that in Western world, but advanced stage at diagnosis; 5-year OS, 79%
Naraynsingh[49]	Trinidad and Tobago	2010	2,689 cases	From 1970 to 2004, BC mortality continued to increase over 35-year period in Trinidad and Tobago
Warner[50]	Trinidad and Tobago	2015	3,767 cases	From 1995 to 2007, West African ancestry and geographic residence seemed to be strong predictors of BC incidence and mortality rates

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Table 1. Key Findings From BC Research Studies of Caribbean Populations (Continued)

First Author	Country	Year of Publication	Study Size	Key Findings
Clinicopathologic features				
Mungrue[51]	Bahamas	2016	270 cases	Ductal carcinoma was most common; most cancers occurring at grade ≥ 2 and presenting as late stage (stage ≥ II); New Providence had highest occurrence of BC among all islands of the Bahamas
Alvarez Goyanes[52]	Cuba	2010	1,509 cases	72% of tumors expressed some level of hormone dependency; 53% were ER positive and 49% were PR positive (ER positive/PR positive, 38%; ER negative/PR negative, 28%; ER positive/PR negative, 23%; ER negative/PR positive, 11%)
Deloumeaux[53]	Guadeloupe	2017	1,275 cases	ER positive/PR positive, 65.1%; ER negative/PR negative, 20.1%; TNBC accounted for 14% of all cases and was more frequent in patients age < 40 years; 5-year survival, 84.9% (survival was higher for HR positive/HER2/neu positive and HR positive/HER2/neu negative subtypes and lower for HR negative/HER2/neu positive subtype and TNBC)
Pott[54]	Jamaica	1978	NA	Considerable number of patients with stage II and III disease; histologic type most frequently seen is infiltrating duct carcinoma
Shirley[55]	Jamaica	2008	NA	NA
Shirley[56]	Jamaica	2010	762 cases	Patient presentation at relatively advanced stages of disease
Alfred[57]	Jamaica	2012	243 cases	ER positive, 63%; ER negative, 37%; ER-negative group was older
Peredo[58]	Puerto Rico	2001	143 cases	28 overexpressed HER2/neu (19.6%); of HER2/neu-negative patients, 30 (26%) of 114 were ER negative compared with nine (33%) of 27 (P = .464); in progesterone specimens negative for HER2/neu, 44 (39%) of 114 were HER2/neu negative *v* 15 (56%) of 27 (P = .108)
Colón[59]	Puerto Rico	2002	309 cases	ER positive, 65.9%; PR positive, 51.8%; HER2/neu, 27.8%
Giraldo-Jiménez[60]	Puerto Rico	2012	54 cases	51 had stage I to III presentation; T1/T2 tumors were found in 88.9% and absence of nodal involvement in 68.5%; 5-year OS and PFS were 81% and 80%, respectively
Ortiz[61]	Puerto Rico	2013	663 cases	17.3% of BC cases were TN; 61.8% were luminal A; 13.3% were luminal B; 7.5% were HER2 overexpressed; TN subtype and HER2-positive tumors were associated with decreased survival
Agosto-Arroyo[62]	Puerto Rico	2015	487 cases	Molecular categories were 66%, 10%, 9%, and 15% for luminal A, luminal B, HER2, and TN groups, respectively
Brathwaite[63]	Suriname	1979	242 cases	Mean age, 55.1 years; histologic types included scirrhous (40.9%), unclassified infiltrating duct (41.3%), medullary (4.5%), infiltrating comedo (3.7%), infiltrating lobular (3.3%), undifferentiated (2.5%), intraduct (1.2%), sarcoma (1.6%), and infiltrating papillary (0.8%)
Raju[64]	Trinidad and Tobago	1989	NA	Multiparous, 85%; average of four children, and 92% of them breast fed; infiltrating duct carcinoma most frequent histologic diagnosis; LC seen in 1% of cases

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Table 1. Key Findings From BC Research Studies of Caribbean Populations (Continued)

First Author	Country	Year of Publication	Study Size	Key Findings
Jack[65]	Trinidad and Tobago	2000	111 cases	Infiltrating duct carcinoma, 32%; IDC, 29%; adenocarcinoma, 12%; and LC and papillary carcinoma, 27%
Rao[66]	Trinidad and Tobago	2002	103 cases	ER positive, 54%; PR positive, 46%; c-erbB-2, 63%; ER negative/PR negative, 41%
Mungrue[67]	Trinidad and Tobago	2014	640 cases	Stage IIA BC most common presenting stage (n = 154; 24%); IDC most common histologic type (n = 429; 67%)
Dindyal[68]	Trinidad and Tobago	2004	299 cases	IDC most commonly occurring histologic type (70%), with ILC accounting for 17%; Afro-Caribbean women twice as likely to develop IDC and ILC compared with Indo-Caribbean women; less common (medullary, 4%; papillary, 2%; and mucinous adenocarcinoma types, 3%) and other rare histologic types (< 4%) were squamous, tubular, and comedo carcinomas, sarcoma, mesenchymal chondrosarcoma, and phyllodes tumor
Epidemiologic risk factors				
Nemesure[69]	Barbados	2009	222 cases 454 controls	In some but not all patients, body size factors play role in BC risk; older age may affect these relationships
Fernández[70]	Cuba	1986	438 cases 449 controls	Older age, late menarche, and late parity associated with BC
Kadhel[71]	Guadeloupe/ Martinique	2014	1,494 cases	Largest numbers of expected cases occurring in women between ages 45 and 54 years
Brady-West[72]	Jamaica	2000	120 cases	Risk factors: early menarche (5.5%), nulliparous (30%), first live birth after age 30 years (5%), ≥ one affected first-degree relative (12.5%); 54% of patients possessed no risk factors examined in this study, 36% had single risk factor, and 10% had two risk factors; larger studies should be encouraged to identify additional risk factors and degree to which published predictive variables are applicable
Santiago[73]	Puerto Rico	1998	18 cases 18 controls	Nonsignificant positive associations between total fat and different components of dietary fat and postmenopausal BC
Morales[74]	Puerto Rico	2014	465 cases 661 controls	ER positive, 75%; PR positive, 66.9%; HER2/neu negative, 76.8%; increased risk factors for BC: low DRC, age > 61 years, family history of BC, low education level; decreased risk factors for BC: endometriosis, parity at early age, higher parity, hysterectomy age < 50 years, multivitamin and calcium intake, and longer duration of breastfeeding
Joseph[75]	Trinidad and Tobago	2014	131 cases 2,415 controls	Analysis confirms that breast density is important predictor of newly diagnosed BC in this Caribbean population
BC outcomes and predictive factors				
Naraynsingh[76]	Trinidad and Tobago	2011	331 cases	Early hospital discharge after BC surgery is feasible option for most patients and can be safely implemented even in resource-limited setting where cost containment is essential

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Table 1. Key Findings From BC Research Studies of Caribbean Populations (Continued)

First Author	Country	Year of Publication	Study Size	Key Findings
Camacho-Rivera[77]	Trinidad and Tobago	2015	2,614 cases	Advanced-stage disease and negative HRS independently significantly associated with poorer survival outcome
Taioli[78]	Trinidad and Tobago	2010	3,710 cases	Study suggests that biologic, behavioral, environmental, and clinical factors play significant roles in observed difference in BC outcomes in women of Afro-Caribbean descent
Roué[79]	French Guiana	2016	269 cases	Place of birth, mode of diagnosis, tumor stage at diagnosis, histologic type, and HRS associated with BC-specific survival
Skoog[80]	Cuba	1987	296 cases	Axillary lymph node status and ER cellular content most important prognostic factors
Ríos[81]	Cuba	1988	225 cases	ER and EGFR receptor status lead to increased prognostic predictive capacity; patients with ER-positive EGFR-positive disease have relapse rates similar to those with ER-negative disease and are thus high-risk patients; patients with ER-positive EGFR-negative disease have good prognosis
Walters[82]	Jamaica	1994	62 cases	Clinical staging inadequate for management of stage I BC; consistent pathologic staging, use of other prognostic predictors, and systemic therapy on more widespread scale may help improve clinical outcome
Behavioral risk factors				
Gibbon[83]	Cuba	2011	250 cases	Drawing on qualitative data examining health beliefs in relation to BC, findings presented here suggest that although family history may be perceived as risk factor for many diseases (not just BC), genetic risk has little meaningful resonance for many participants
Delpech[84]	Grenada	2015	110 controls	Motivation to perform BSE associated with younger age and church attendance; perceived susceptibility associated with marital status and frequency of church attendance; perceived benefit associated with marital status, church attendance, and frequency of attendance
Menvielle[85]	Guadeloupe/ Martinique	2016	4,054 controls	Higher BC screening participation reported among participants having hot water at home and having visited GP during last year
Anakwenze[86]	Jamaica	2015	246 controls	Greatest post-test improvements among items measuring knowledge of BC screening tests and risk factors; use of theory-based educational intervention positively influenced knowledge of BC risk factors, symptoms, and types of screening and increased screening rates in screening-naïve women
Tirado-Gómez[87]	Puerto Rico	2016	50 cases	Low levels of physical activity being practiced by group of Puerto Rican BC survivors, despite fact that many of them had access to exercise equipment and facilities
Underwood[88]	US Virgin Islands	2007	178 controls	Provider communication significantly influenced BC screening practices and receptivity to BC risk management of study participants; participants who reported having had discussions with health care providers about their BC risk were more likely to express willingness to consider risk management strategies

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Table 1. Key Findings From BC Research Studies of Caribbean Populations (Continued)

First Author	Country	Year of Publication	Study Size	Key Findings
Barriers to early detection and BC treatment				
Peltzer[89]	Barbados/ Grenada	2014	517 controls	Among university students in Barbados, most frequently cited risk factors were genetics, stress, and smoking; in Grenada, most frequently cited risk factors were genetics, smoking, and dietary fat/ overweight
Kadhel[90]	Guadeloupe/ Martinique	2016	115 cases	In BC survivors, most frequently cited risk factors were stress, genetic causes, and poor diet
Sharma[91]	Haiti	2013	123 cases	Interventions needed to educate patients on recognition of initial BC signs and symptoms and address cost concerns by providing care free of charge and/or advertising that existing care is already free
O'Neill[92]	Haiti	2015	61 cases	Despite receiving free care, > two thirds of participants spent > 40% of their potential household income on out-of-pocket expenses
Chirikos[93]	Puerto Rico	2007	1,450 cases	Previously underserved women being treated for BC at rate roughly on par with other patients
Sánchez Ayéndez[94]	Puerto Rico	2001	500 controls	Referral from physician most important factor for mammogram compliance
Modeste[95]	Trinidad and Tobago	1999	265 controls	Barriers to early detection identified were low level BSE, infrequent clinical breast examinations as part of regular care, unavailability of mammography services on Tobago, cost of screening, and difficulty of traveling to Trinidad for mammography
Gosein[96]	Trinidad and Tobago	2014	314 controls	76.8% of participants knew that family history of BC was risk factor; obesity and alcohol consumption were less well- known risk factors, with only 29.3% and 12.4% agreeing, respectively; nearly two-thirds (63.7%) incorrectly believed breast trauma to be risk factor
Genetic risk factors and molecular biomarkers				
Akbari[97]	Bahamas	2014	214 cases	Approximately 27% of unselected BC cases attributable to mutation in *BRCA1* or *BRCA2*
Trottier[98]	Bahamas	2015	202	To offer genetic testing to relatives of patients with BC with *BRCA* mutations, direct contact by genetic counselor preferable to using proband as intermediary
Trottier[99]	Bahamas	2016	1,847 controls	*BRCA* mutations were found in 2.8% (20 of 705) of unaffected women with family history of BC/ovarian cancer and 0.09% (one of 1,089) of unaffected women without family history; 38% of unaffected women with known *BRCA* mutation carried same mutation
Rodriguez[100]	Cuba	2008	307 cases	2.6% *BRCA1/2* prevalence (10% familial cases, 10% age < 40 years)
Llanes-Fernández[101]	Cuba	2006	23 cases	23 BC samples exhibited strong expression of IL-10; IL-10 associated with some poor-prognosis tumor makers

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Table 1. Key Findings From BC Research Studies of Caribbean Populations (Continued)

First Author	Country	Year of Publication	Study Size	Key Findings
Dutil[102]	Puerto Rico	2012	23 cases	Six different deleterious mutations observed, including one mutation in *BRCA1* and five mutations in *BRCA2*; three recurrent mutations (*BRCA1* del exon1-2, *BRCA2* 4150G>T, and *BRCA2* 6027del4) account for > 70% of all *BRCA* mutations observed in this study population
Donenberg[103]	Trinidad and Tobago	2016	268 cases	28 (10.4%) of 268 patients had mutation in *BRCA1*, *BRCA2*, or *PALB2*; majority were *BRCA1* and *BRCA2* mutations
Cost analysis				
Ortiz-Ortiz[104]	Puerto Rico	2010	209 cases	Death resulting from BC among factors contributing most to productivity loss

Abbreviations: BC, breast cancer; BSE, breast self-examination; DRC, DNA repair capacity; EGFR, epidermal growth factor receptor; ER, estrogen receptor; GP, general practitioner; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HRS, hormone receptor status; IDC, invasive ductal carcinoma; IL, interleukin; ILC, invasive lobular carcinoma; LC, lobular carcinoma; NA, not available; NOS, Not otherwise specified; OS, overall survival; PFS, progression-free survival; PR, progesterone receptor; TN, triple negative.

(HRS) were conducted in Puerto Rico (four of five studies), whereas only a single study each was conducted in Cuba, Guadeloupe, Jamaica, and Trinidad. No studies of HRS were reported in the Bahamas or Suriname. The frequencies of estrogen receptor (ER) –positive and/or (progesterone receptor (PR) –positive BC were similar for patients in Puerto Rico (ER positive, 65.9%; PR positive, 51.8%), Guadeloupe (ER positive/PR positive, 65.1%), and Jamaica (ER positive, 63%) and slightly higher than the frequencies for patients in Cuba (ER positive, 53%; PR positive, 49%) and Trinidad (ER positive, 54%; PR positive, 46%).[52,53,57,59,66] The prevalence of triple-negative BC was reported only for patients with BC in Guadeloupe (14%) and Puerto Rico (17.3%).[53,61]

Case-control[69,70,73-75] and cohort analyses[71,72] were reported in six Caribbean countries, and common risk factors were identified: older age, late menarche, late parity, null parity, body size, family history, low DNA repair capacity, and low education level. However, the study in Jamaica noted that 54% of patients with BC did not have these common risk factors.[72] Moreover, a higher percentage of cases were diagnosed in women between the ages of 45 and 54 years in Guadeloupe and Martinique.[71]

BC outcomes and predictive factors. Factors associated with BC outcomes were reported in four Caribbean countries (Cuba, French Guiana, Jamaica, and Trinidad). In accordance with the literature, negative HRS, advanced stage at diagnosis, positive lymph node status, and histologic type (infiltrating ductal carcinoma) were associated with poor prognosis or survival.[76-82] Survival rates for patients with BC in Trinidad and Guyana were lower as compared with Caribbean-born patients with BC living in the United States (Brooklyn, NY).[78] In Jamaica, one study reported that clinical staging was inadequate for the management of stage I BC and highlighted a need for consistent pathologic staging as well as use of other prognostic predictors to improve clinical outcomes in BC.[82]

Behavioral risk factors. Seven Caribbean countries contributed to six publications on behavioral factors relevant to BC.[83-88] Screening was associated with younger age and church attendance in Grenada[84] and general practitioner visits and provider communication in Guadeloupe and Martinique and the US Virgin Islands.[85,88] In Grenada, perceived susceptibility to BC and perceived benefit of screening were more likely to be associated with women who frequently attended church.[84] The only intervention study was conducted in Jamaica, where a theory-based educational intervention positively influenced knowledge of BC risk factors, symptoms, and types of screening and increased screening rates in screening-naïve women.[86] The two behavioral studies involving BC cases were conducted in Cuba and Puerto Rico; in Cuba, family history of BC was perceived as a risk factor, but the concept of genetic risk had little meaning[83]; in Puerto Rico, patients with BC had low physical activity, despite access to exercise equipment and facilities.[87]

Barriers to early detection and BC treatment. Seven Caribbean studies yielded eight publications

related to barriers to early detection and treatment.[89-96] Lack of knowledge of signs and symptoms was highlighted in Haiti,[91] and low frequency of breast self-examination, infrequent clinical breast examinations, and limited access to mammography were reported in Trinidad.[95] Health care cost was seen as a barrier to treatment in Haiti[92] and a barrier to screening in Trinidad.[95] In Trinidad, knowledge of family history as a risk factor for BC was common (76.8%), but knowledge of other risk factors was limited.[96] In contrast, in Barbados and Grenada, university students identified multiple BC risk factors, such as genetics, stress, smoking, and diet.[89] Similarly, among BC survivors in Guadeloupe and Martinique, stress, genetic causes, and poor diet were the most frequently cited risk factors.[90] In Puerto Rico, two studies respectively reported that underserved women diagnosed with BC were treated comparably to other patients[93] and that referral by a physician was an important factor related to mammogram compliance.[94]

Genetic risk factors and molecular biomarkers. Examinations of genetic and molecular biomarkers among Caribbean women were limited in comparison with US and European populations.[97-103] *BRCA1/2* mutations were the only genetic risk factors evaluated, with the highest prevalence reported in the Bahamas (approximately 27%).[97,99] A Bahamian study showed that genetic testing of unaffected family members of patients with BC with *BRCA1/2* mutations might be more effective if investigators use the proband as an intermediary to communicate with them.[98] In addition, the only molecular biomarker investigated in outcomes of patients with BC was reported from Cuba, where a strong expression of interleukin-10 in tumors was associated with tumor markers of poor prognosis.[101]

Cost analysis. The only Caribbean study on cost was a cost analysis of labor market productivity loss in Puerto Rico as a result of premature mortality from cancer. The study showed that death resulting from BC was included among cancer-related mortality causes that contributed the most to productivity loss.[104]

DISCUSSION

Our literature review includes 92 publications of BC burden and research in native Caribbean women from 35 Caribbean nations over a span of 43 years and underlines the lack of precise field data as well as the limited research scope. The countries with the most research publications were countries with long-standing cancer registries and local scientific teams.

Most publications focused on describing cancer trends and clinicopathologic features (Fig 3), which were in line with GLOBOCAN estimates,[2] placing BC as one of the top cancer sites for incidence and mortality among Caribbean women. However, several factors contribute to the weaknesses of these publications, such as the limited number of cancer registries with high-quality data and the rare focus on the impact of social and environmental factors on epidemiologic trends.[2,106]

Moreover, availability of cancer screening programs and access to these programs play key roles in BC trends. Access to cancer screening programs varies not only according to an individual's geographic residence but also among countries. A recent review of Caribbean cancer screening programs revealed that for 12 countries that have BC screening services available, mammography is not available in the public sector for more than half of them.[107] It is then plausible that Caribbean women with private insurance and those with higher socioeconomic status may have better access to mammography. Furthermore, although traveling abroad to other countries for BC screening is unlikely, for those who can afford it, traveling abroad to other Caribbean countries (eg, Trinidad, Martinique, or Puerto Rico), the United States, the United Kingdom, or France for confirmation of a BC diagnosis or for treatment may be an option. All these factors may influence epidemiologic trends in BC. Therefore, BC incidence reported in Caribbean publications may have been underreported and subject to ascertainment bias caused by variability in data quality, completeness, socioeconomic status, BC screening access, and guidelines.

In terms of clinicopathologic status, few Caribbean studies described late stage at diagnosis, and a majority reported on ER-positive and/or PR-positive BC, with triple-negative BC averaging approximately 15% of all cases.[53,61] As previously mentioned, these reports of cinicopathologic characteristics may have been influenced by limited access to and uptake of BC screening in the region. Furthermore, the availability of or access to HRS testing in each country may also have had an impact. Immunohistochemistry

(IHC) staining for BC receptors is part of the standard care in a few Caribbean countries. For others, IHC is not performed routinely except in the private sector, and for patients in Martinique and Guadeloupe, IHC is performed primarily in mainland France. Resolution of indeterminate HER2 results usually requires additional testing via in situ hybridization, and in these instances, samples are typically sent to the United States for testing. Therefore, some Caribbean countries may not experience the prognostic benefit of hormone receptor profiling, and although Caribbean publications report differences in the prevalence of ER and PR status among countries, these data may not necessarily reflect true biologic differences among Caribbean populations. These limitations should also be considered when reviewing published data from the Caribbean.

Although HRS and more advanced cancer stages are linked to poorer survival, as described by the few Caribbean studies on the subject,[53,61,77] there are still multiple issues pertaining to cancer outcome and survival that have yet to be fully examined. Survival studies have almost exclusively been led in Trinidad, and virtually no information exists for other countries. Furthermore, apart from the Dominguez et al[30] study describing disability-adjusted life-years in Cuban women, quality of life of Caribbean BC survivors after diagnosis, during treatment, or after returning to work has rarely been explored. Usual treatment regimens have not been described in detail, nor has access to such regimens. Behavioral factors, which play a major role in compliance with good health practices and screening, are also not well documented, nor is the impact of socioeconomic disparities within and among nations on health outcomes.

Age-specific incidence presented in this review further suggests that research studies are needed in the Caribbean to examine the contribution of hereditary versus sporadic BC. In the limited studies on molecular and genetic factors, mutations in *BRCA1/2* genes were shown to influence early BC onset.[97,103] However, there is an entire panel of highly penetrant (*PALB2*, *TP53*, *CDH1*, and *STK11*) and moderately penetrant germline (*CHEK2*, *BRIP1*, *RAD51*, and *ATM*) pathogenic variants and other genetic markers that are currently being examined in genome-wide association studies in populations other than those of the Caribbean.[108-110] A comprehensive approach toward gene mutation and expression profiling in native Caribbean women must be adopted to characterize specific differences and improve cancer prognosis and outcome.

Key findings from Caribbean publications confirm similarities between the region and other countries, such as the United States. However, these publications also suggest within-region differences, and we have previously described plausible explanations such as differences in ethnic mixes, health care systems and economies, cancer registration, screening use.[110-112] Our review also demonstrates that too little research has been conducted in the Caribbean to provide certified evidence of real or artifactual differences. Our review has highlighted significant research gaps in behavioral, molecular, genetic, and epidemiologic investigations of BC in native Caribbean women.

These disparities among nations, which might be linked to the geographic heterogeneity in BC incidence and mortality in the Caribbean, call for specifically tailored research and cancer control interventions that can only be addressed if the regional research portfolio is expanded to include more large-scale, targeted epidemiologic investigations with diverse research scopes. However, a more diverse research focus also requires adequate expertise and resources (human and infrastructural), which are not always readily available. Only those countries with strong local research teams (university campuses), strong public health policies in terms of cancer control and prevention, and reliable cancer registration and/or screening infrastructures seem able to publish or implement more diverse research studies. This is strongly supported by data shown in Figure 4. In those countries where research gaps exist or that experience challenges in diversifying their research scopes, improved cancer registration, capacity building, resource optimization and sustainability, and collaboration and communication among investigators will be essential in increasing research output and findings.

Today, a regional common unified strategy is necessary to address research needs among nations. Additional solutions lie in developing a strategic plan that includes setting standards for reinforced, sustainable, diverse, and efficient population research. This implies identifying

intra- and intercountry research specialties, needs, and priorities as well as existing tools, resources, stakeholders, and collaborators.

To that end, research consortia, such as the African Caribbean Cancer Consortium,[113] represent a rich network of collaborators (existing and aspiring cancer registries, research and medical teams, governmental and institutional policymakers, and other cancer advocates and research teams at the local, regional, and international levels) and can leverage transdisciplinary expertise as a solution in addressing identified research gaps and promoting more diverse research opportunities in the Caribbean. We will promote research enhancement activities and training and establish research resources (eg, cancer and control cohorts with linked epidemiologic, clinical, and molecular and biomarker data). Regional investigations of BC risk and outcomes as well as tailored strategies for cancer prevention interventions in Caribbean women can be achieved.

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Appendix

The CARICOM (Caribbean Community) countries include English, Dutch, French, and Latin Caribbean nations that are islands, as well as countries on the continents of Central and South America: Anguilla, Antigua and Barbuda, the Bahamas, Barbados, Belize, Bermuda, the British Virgin Islands, the Cayman Islands, Cuba, Dominica, the Dominican Republic, French Guiana, Grenada, Guadeloupe, Guyana, Haiti, Jamaica, Martinique, Montserrat, the Netherlands Antilles (Aruba, Bonaire, Curaçao, Saba, St Eustatius, and the Dutch half of St Martin [Sint Maarten]), Puerto Rico, St Barthélemy, St Kitts and Nevis, St Lucia, the French half of St Martin (Saint-Martin), St Vincent and the Grenadines, Suriname, Trinidad and Tobago, the Turks and Caicos, and the US Virgin Islands.