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Incidence, mortality and receptor status of breast cancer in African Caribbean women: Data from the cancer registry of Guadeloupe

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ABSTRACT

Background: Geographical disparities in breast cancer incidence and outcomes are reported worldwide. Women of African descent show lower incidence, higher mortality rates and earlier age of onset. We analyzed data from the cancer registry of Guadeloupe for the period 2008–2013.
Methods: We describe breast cancer characteristics by molecular subtype, as well as estimated observed and net survival. We used Cox proportional hazard models to determine associations between cancer subtypes and death rate, adjusted for variables of interest.
Results: Overall, 1275 cases were recorded with a mean age at diagnosis of 57(±14) years. World standardized incidence and mortality were respectively 71.9/100,000 and 14.1/100,000 person-years. Age-specific incidence rates were comparable to European and US populations below the age of 45, and higher in Guadeloupean women aged between 45 and 55 years. Overall, 65.1% of patients were hormone receptor (HR)+ and 20.1% were HR-. Triple negative breast cancers (TNBC) accounted for 14% of all cases, and were more frequent in patients under 40 (21.6% vs. 13.4%, $p = 0.02$). Five-year net survival was 84.9% [81.4-88.6]. It was higher for HR+/Her2+ and HR+/Her2- subtypes, and lower for HR-/Her2+ and TNBC patients.
Conclusion: We found high age-specific incidence rates of breast cancer in women aged 45 to 55 years, which warrants further investigation in our population. However, this population of mainly African descent had good overall survival rates, and data according to subtypes are consistent with those reported internationally. These results may suggest that poorer survival in other African descent populations may not be an inherent feature of the disease but may be amenable to improvement.

1. Introduction

Breast cancer ranks first among all cancers in women, and shows geographical disparities in outcomes, incidence and mortality. In 2012, age-standardized incidences rates per 100,000 person-years were highest in Western Europe and North America (96/100000), and lowest in African countries, while the Caribbean region had an intermediate rate (46/100 000) [1]. Breast cancer is the second cause of death in women in more developed regions, and the primary cause of death in less developed regions, but the differences in mortality rates are of lesser magnitude than those observed for incidence over the last decade.

Guadeloupe is a Caribbean archipelago with a population of about 404,000 inhabitants with a mean age of 37 years in 2009. This young country is facing a rapidly accelerating transition from a young towards an ageing population over the coming years. It is commonly acknowledged than over 80% of Guadeloupe's population is of African descent, while Indian descent and Europeans represent approximately 15 and 5 percent of the population respectively. As a French Department, one would expect socio-economic conditions and healthcare delivery to be similar to that of mainland France, yet the demographics of medical services, and the quality of some healthcare facilities do not reach the national standards.

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The French national screening program for breast cancer targets women between 50 years and 74 years old, and was introduced in Guadeloupe in 2004, with a participation rate of 50.9% in 2013 [2]. In a study conducted over the period 1999 and 2006, before the implementation of the population-based cancer registry, Kadhel et al. reported higher expected cases of breast cancer in women between 45 and 54 years old [3]. These findings were consistent with the studies conducted on populations of African ancestry in both US and British studies [4–8].

It is well known that aggressive tumors and high mortality rates are found in young women, before the age of 40 years [8], and many studies report earlier and more aggressive breast cancer in African-American women [9–11]. In the Caribbean, a Trinidadian study also found a higher incidence among African-Caribbean women younger than fifty years [7]. Among the prognostic factors, histological and overall biological characterizations are increasingly important in breast cancer because of their prognostic and predictive value, and their impact on survival. Determination of hormone receptor (HR) status, including estrogen (ER) and progesterone receptor (PR), and human epidermal growth factor receptor 2 (Her2) status has been accepted as a routine procedure in the management of breast cancer. HR positivity is associated with better prognosis [12] and predicts responsiveness to endocrine therapy. Similarly, Her2 positivity is associated with poorer prognosis than Her2 negative tumors [13]. However, detecting overexpression of Her2 enables the selection of patients who will yield the greatest benefit from targeted therapy.

In this context, the aims of this study, performed from a population-based cancer registry, were to describe breast cancer hormonal receptors subtypes and their association with patient and tumor characteristics, and to estimate survival according to cancer subtype, in an Afro-Caribbean population.

2. Methods

We analyzed data from the population-based general cancer registry of Guadeloupe over the period 2008–2013. This registry is member of the French network of Cancer registries (Francim) and of the International Association of Cancer Registries. It routinely records all incident cases of cancer occurring in Guadeloupe since 2008. Potential cases are identified from multiples sources, namely: pathology and hospital discharge records, long-term illness registration by the national health insurance system, and medical files. The data collected include demographic data (date and place of birth, gender, place of residence), tumor characteristics (date of diagnosis, tumor size, histological type, staging and hormonal markers) and first treatment (date and type of treatment). We could not assess ethnicity, since current French legislation does not allow the recording of ethnic origin. Population data for each year of incidence were obtained from the French National Institute of Statistics and Economic Studies (INSEE) [14]. Data regarding deaths from breast cancer for patients residing in Guadeloupe were obtained from the French epidemiological center on medical causes of death from the French National Institute of Health and Medical Research (CépiDc, Inserm: http://www.cepidc.inserm.fr/site4/). This institute is responsible for developing annual national statistics on the medical causes of death. For cohort follow-up and with the authorization of the French National authority for the protection of privacy and personal data (CNIL), data regarding the vital status of an individual are provided by the CépiDc.

We calculated age-specific incidence rates for the year 2012 to compare them with Globocan's data in different populations. Age-standardized incidence and mortality rates per 100,000 person-years [95% confidence intervals], were calculated over the period 2008–2013 using the direct method and the World standard population as proposed by Segi[15] and modified by Doll et al. [16]

We categorized patients according to hormone receptors status and Her2 gene expression. Luminal A or B classification could not be used because of missing data for KI67 status for the earliest years of the registry. Patients positive for both estrogen receptors (ER) and progesterone receptors (PR) were coded as hormone receptors positive (HR+) and were coded HR- when both receptors were negative. We considered four main groups of patients: HR+/HER2+, HR+/HER2-, HR-/HER2+ and triple negative breast cancer (TNBC). Patients not classified within these four groups (missing or discordant data) were considered as unknown. Because of missing data for TNM, we used the simplified cancer staging (localized/local spread, regional spread, metastatic/non resectable) from the European Network Cancer Registries (ENCR) [17].This condensed staging is recommended by the ENCR when T, and/or N, and/or M have not been explicitly recorded in the clinical/pathological records for some cancer sites (breast, colon, rectal and cervical cancer). Cancer registries are invited to attempt to score extent of disease according to this condensed TNM scheme. For breast cancer, the conventional values of T that correspond to the ENCR "Localized" stage include T1 to T3, while T4 corresponds to the ENCR "Advanced" stage.

Tumor grading was classified with the modified Scarff and Bloom-Richardson (MSBR) grading system from pathology report (grades from 1 to 3). We also considered first line treatment, which is routinely recorded by the registry, as main variables. Missing data for tumor size, cancer staging, MSBR grade and first treatment were considered as an unknown group for the analyses.

Quantitative variables are reported as mean (standard deviation) and qualitative variables as number (percent). Descriptive analyses were performed according to breast cancer subtype using Anova or median test for quantitative variables and Pearson's Chi-square test for qualitative variables. Kaplan-Meier survival curves were estimated and mean overall survival time in months after diagnosis was compared with the logrank test for the main variables of interest, i.e. age groups, cancer subtype, cancer staging and first therapy. Net survival was estimated with the unbiased Pohar-Perme estimator method using expected mortality rates derived from the observed mortality rates available by sex, annual age, year of death and department of residence as recommended by Roche et al. for cancer registry data [18].

The endpoint date was set to December 31, 2015 which was the last update for patients' vital status. Patients lost to follow-up and not identified by CepiDc were censored at the date of their last visit (hospitalization or medical consultation recorded).

We examined the distribution of clinical characteristics by subtype of hormone receptors and Her2 status, and used Cox's proportional hazards model to determine hazard ratios with adjustment for age, cancer stage and first course of treatment. The assumption of proportional hazards for the Cox model was tested with Schoenfeld residuals. Hazard ratios for death are presented with the associated 95% Confidence interval (CI). All analyses were performed using Stata statistical software release 14.0 (Stata Corp LP, College Station, TX, USA) and a p value of 0.05 was considered statistically significant.

3. Results

From January 2008 to December 2013, 1275 women with histologically confirmed invasive breast carcinoma were recorded by the cancer registry. The mean age at diagnosis was 57 ± 14 years. Among the overall population, 33.3% of patients were diagnosed with breast cancer before the age of 50 years and 9.1% were under 40.

The standardized incidence and mortality rates of breast cancer were respectively 71.9/100 000 and 14.10/100 000 person-years. An increase of 3.1% in the incidence rate was observed between 2008 and 2013, whereas the mortality rate increased by only 0.3% over the same period.

The age-specific incidence rates of breast cancer were comparable to those from European and US populations in patients younger than 45 years of age and higher for Guadeloupean women aged between 45 and 55 years old. The age-specific incidence rate was twice the estimated rate for the Caribbean and Africa (Fig. 1).

Table 1 presents the characteristics of the patients at diagnosis according to cancer subtype. Regional extension was found in 26% of the cases and 4% of patients had metastatic cancer at diagnosis. Overall, 65.1% patients were HR+ and 20.1% were HR-. Triple positive patients (HR+ with over expression of Her2) represented 23.5% of cases, whereas TNBC accounted for 14% of all cases. TNBC was significantly higher in patients under 40 compared to patients over 40 (21.6% vs. 13.4%, $p = 0.02$).

At the cut-off date of December 2015, 227 deaths were notified. Higher rates were found within the TNBC (26.7%) and HR-/Her2+ (21.6%) subtypes compared to the HR+/Her2+ (16.7%) and HR+/Her2- (15.5%) subtypes. Five-year net survival was 84.9% [81.4–88.6] for the overall population. It was similar for HR+/Her2+ and HR+/Her2- subtypes, respectively 82.3% [77.0–89.3] and 84.5% [79.9–89.3]. It was 76.9% [65.5–90.3] for HR-/Her2+ and 71.9% [64.0–80.8] for TNBC subtypes (Fig. 2).

Mean survival time differed significantly between cancer subtypes: it was 42.7 months for HR+/Her2-, 44.9 months for

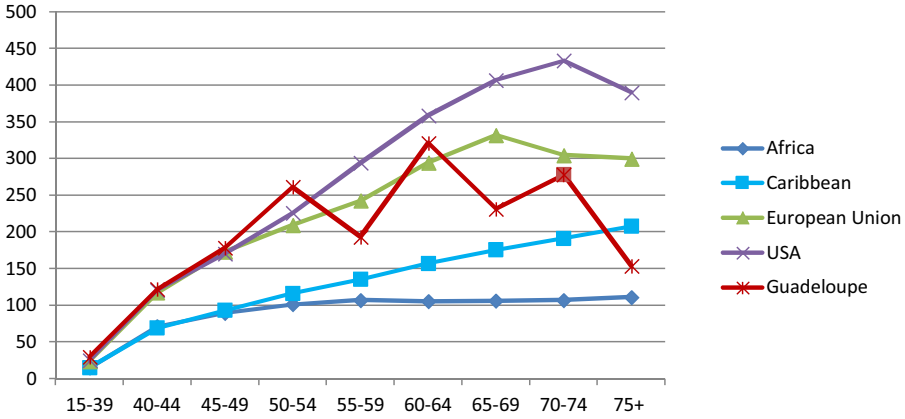

Fig. 1. Age-specific incidence rates of female breast cancer in Guadeloupe (cancer registry 2012) and different populations (globocan 2012: http://globocan.iarc.fr).

Table 1
Patient characteristics at diagnosis according to invasive breast cancer subtypes, Guadeloupe Cancer Registry: 2008–2013.

		Breast cancer subtypes n (%)					
	Number of cases N = 1275	**HR+/Her2-** N = 534 (41.9)	**HR+/Her2+** N = 299 (23.5)	**HR-/Her2+** N = 74 (5.8)	**TNBC** N = 180 (14.1)	**Unknown** N = 188 (14.7)	p
Mean age, years (SD)	57.3 (13.9)	58.7(13.9)	55.9 (14.2)	55.1 (10.8)	56.1 (14.1)	56.9 (14.7)	0.02
Age groups							
<40	116 (9.10)	29 (9.7)	42 (7.9)	3 (4.05)	25 (13.9)	17 (9.0)	0.03
40–49	308 (24.2)	86 (28.7)	112 (21.0)	22 (29.7)	39 (21.7)	49 (26.1)	
>=50	851 (66.7)	184 (61.5)	380 (71.2)	49 (66.2)	116 (64.4)	122 (64.9)	
Length of follow-up (months)	41 (26.9)	42.1 (26.3)	44.6 (26.4)	38.3 (25.5)	41.8 (26.6)	32.2 (28.5)	$<10^{-4}$
SBR grading							
Grade 1	222 (17.4)	136 (25.5)	50 (16.7)	2 (2.7)	9 (5.0)	25 (13.3)	$<10^{-4}$
Grade 2	585 (45.9)	277 (51.9)	163 (54.5)	33 (44.6)	53 (29.4)	59 (31.4)	
Grade 3	307 (24.1)	85 (15.9)	68 (22.7)	32 (43.2)	104 (57.8)	18 (9.6)	
Missing data	161 (12.6)	36 (6.7)	18 (6.1)	7 (9.5)	14 (7.8)	86 (45.7)	
ENCR Condensed Staging							
Localized/local spread*	660 (51.8)	279 (52.2)	166 (55.5)	38 (51.3)	108 (60.0)	69 (36.7)	$<10^{-3}$
Regional§	332 (26.0)	165 (30.9)	77 (25.7)	27 (36.5)	39 (21.7)	24 (12.8)	
Extended‡	47 (3.7)	16 (3.0)	11 (3.7)	2 (2.7)	7 (3.9)	11 (5.8)	
Unknown†	236 (18.5)	74 (13.9)	45 (15.1)	7 (9.5)	26 (14.4)	84 (44.7)	
Morphology							
Duct carcinoma	1059 (83.1)	441 (82.6)	262 (87.6)	69 (93.2)	156 (86.7)	131 (69.7)	$<10^{-4}$
Lobular carcinoma	68 (5.3)	42 (7.9)	15 (5.0)	0	2 (1.1)	9 (4.8)	
Other carcinoma	148 (11.6)	51 (9.5)	22 (7.4)	5 (6.8)	22 (12.2)	48 (25.5)	
First line therapy							
Surgery	941 (73.8)	430 (80.5)	233 (77.9)	58 (78.4)	138 (76.7)	82 (43.6)	$<10^{-3}$
Radio/Chemotherapy	107 (8.4)	33 (6.2)	27 (9.0)	8 (10.8)	19 (10.6)	20 (10.6)	
Unknown	227 (17.8)	71 (13.3)	39 (13.1)	8 (10.8)	23 (12.8)	86 (45.8)	

HR, hormone receptor; TNBC, triple-negative breast cancer; SD, standard deviation; SBR, Scarff-Bloom Richardson; ENCR, European Network of Cancer Registries; *Localized (TL/N0/M0)/Local spread (TA/N0/M0); § Regional spread (anyT/N+/M0); ‡ Extended; Metastatic (any T/any N/M +) or Non-resectable; †TX/NX/MX.

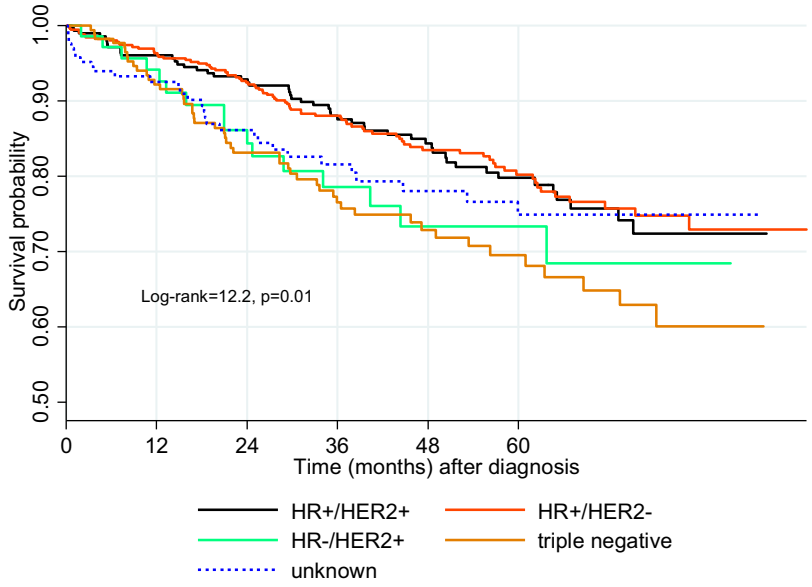

Fig. 2. Kaplan-Meier overall survival after breast cancer diagnosis in women according to cancer subtype. Guadeloupe cancer registry 2008–2013.

Table 2
Cox proportional Hazard ratio (HR [95% CI]) of death after breast cancer according to cancer subtypes in Guadeloupian's women over the years 2008–2013.

	No. of cases	No. of death	Crude HR [95%CI]	Model 1 [95%CI]	Model 2 [95%CI]
Cancer subtypes					
HR+/Her2- (ref)	531	83 (15.5)	1	1	1
HR+/Her2+	297	50 (16.7)	1.03 [0.72–1.46]	1.11 [0.78–1.57]	0.99 [0.69–1.41]
HR-/Her2+	73	16 (21.6)	1.54 [0.90–2.63]	1.76 [1.03–3.01]	1.62 [0.95–2.77]
TNBC	178	48 (26.7)	1.74 [1.22–2.49]	1.96 [1.38–2.81]	1.93 [1.34–2.77]
Unknown	184	30 (16.3)	1.33 [0.87–2.02]	1.40 [0.92–2.12]	0.98 [0.64-]

TNBC: triple negative breast cancer; **HR**: Hazard Ratio: **Model 1**: Adjusted for age only; **Model 2**: Adjusted for age, cancer staging and first course treatment.

HR+/Her2+, 38.8 months for HR-/Her2+ and 42.3 months for TNBC ($p = 0.01$).

Table 2 displays the crude and adjusted hazard ratios for death after diagnosis, taking the HR+/Her2- subtypes as reference. The adjusted HR for death was higher (HR = 1.93 [1.34-2.77], $p < 10^{-3}$) for TNBC patients in model 2 (adjusted for age, cancer stage and first treatment). It was higher but non-significant for the HR-/Her2 + subtype in model 2 (HR = 1.62 [0.95-2.77], $p = 0.07$). The hazard ratio of death did not differ for HR+/Her2+ and HR+/Her2- subtypes.

4. Discussion

This is the first study conducted from the population-based cancer registry of Guadeloupe, and we report a higher incidence of breast cancer in our population than in most other Caribbean populations, but lower rates compared to both European industrialized countries and North America. We observed higher age-specific incidence rates for patients between 45 and 55 compared to European and US populations. We found the same distribution of subtypes as those describe internationally in more than 90% of cases and a frequency of TNBC patients that was lower than in other black populations, but similar for patients under 40 years of age. Our population also had good overall survival rates, with lower survival observed for the TNBC and HR-/Her2+ subtypes.

The increasing incidence of breast cancer is closing the gap with developed countries. Few registry-based data are available in the Caribbean and among those available, the Barbados National Cancer Registry reported a breast cancer incidence of 68.5 [57.3-81.3] per 100 000 person-years in the year 2008 [19],which is close to the rate observed in Guadeloupe over our six-year study period. For two other Caribbean countries, Cuba and Trinidad and Tobago (TT), estimated incidence was lower, at respectively 50.4 per 100 000 person-years for Cuba and 56.9 for TT [1].

The increases in both incidence and mortality observed in our population could be related to major changes in lifestyle and dietary habits in recent decades. A transition from a rural lifestyle to a westernized way of life occurred in Guadeloupe over a fifty-year period and by 2008, 98% of the population lived in an urban area. These major changes in dietary habits therefore resulted in a high prevalence of overweight, obesity and chronic diseases such as hypertension and type 2 diabetes. A link between obesity and cancer risk has been widely reported, and confirmed in a meta-analysis performed by Wang et al. [20]. Although a strong association between body mass index (BMI) and breast cancer incidence has been documented, the strength of this association differed between ethnic groups and no data on populations of African descent are available.

Along with lifestyle, environmental factors such as exposure to both professional and domestic pollutants have been incriminated in the increasing incidence of cancer worldwide, but no formal association has been found for breast cancer [21–23]. The French West Indies departments of Guadeloupe and Martinique show similar patterns in cancer incidence and are both characterized by the widespread use of pesticides, organochlorine and particularly

chlordecone (Kepone), in banana plantations from 1973 to 1993. Multigner et al. reported the findings of epidemiological studies on chlordecone as an endocrine-disrupting chemical. Although a potential relationship with hormone-dependent cancer, mainly prostate cancer, was considered, no association has been investigated for breast cancer [24].

In our population, the proportion of women diagnosed with an invasive breast cancer before the age of 50 reached 33%, and patients under the age of 40 –an early onset that is classically linked to hereditary factors – accounted for 9.1% the cases. This latter result is higher than that observed in developed countries (5 to 7%) [25] and comparable to the data from the Surveillance, Epidemiology and End Results (SEER) program, which reported a rate of 10% for African-American women compared to 5% for white patients [8]. In African women, data from two population-based cancer registries in Mali and Gambia found rates over 20% [26], and this was partially linked to the age distribution of the populations. Younger age at diagnosis of breast cancer is usually associated with molecular profiles of poor prognosis, particularly the TNBC subtype. Black women have been reported in several studies to have the highest rates of TNBC cancer, in different populations. These rates vary from 19.3% in the SEER database [27,28] to 27% in a Nigerian population [29]. A study by Lund et al. found rates reaching up to 46% [10]. Data for the Caribbean region cannot be fully assessed due to a paucity of studies.

These age distribution of breast cancer and mortality data for young women have led professionals to advocate earlier implementation of the mass screening program in Guadeloupe. From a general population perspective, this proposal remains controversial in many countries [30,31]. Nevertheless, the high incidence of breast cancer in women aged under 50 in our population argues in favor of considering early mammography screening, despite recognized concerns, as underlined by Johnson et al. in the U.S.A. for African-American women [8].

The TNBC subtype has been associated with younger age, more advanced stage at diagnosis, poorly differentiated histology, lower socioeconomic status and poorer survival [32]. Our results show that this subtype is less common in our population than in other black populations, but is similar if we consider women under the age of 40. In the age group of 40–49 years old, the TNBC rate was 12.7% and shows no difference with patients over the age of 50. These lower rates may be due to ethnic diversity, since our population is composed predominantly of people of African descent, but also includes people of Indian and European descent, with various degrees of interbreeding.

Cancer subtype was found to be a predictor of survival, with lower survival for TNBC and HR-/Her2+ subtypes, and comparable or higher survival for HR+/Her2- and HR+/Her2 + subtypes. These results are similar to those of the SEER database, where cancer-related mortality for black women diagnosed with TNBC and HR-/Her2+ subtypes was significantly higher compared with women diagnosed with other breast cancer subtypes [28].

After adjustment for age, cancer staging and first therapy, TNBC patients had a 1.93-foldhigher risk of death compared to those in the HR+/Her2- group, whereas the risk of death for the HR-/Her2+ subtype was higher but without reaching statistical significance. The association between HR- subtypes and survival is well known, and has been reported in several studies. According to Colzani et al., the influence of HR status on death resulting from breast cancer decreases over time and is no longer significant 5 years after diagnosis [33]. Longer follow-up would be required to test this hypothesis in our study.

In a review article, Danforth proposed a model with both biological and non-biological factors to explain the difference between Caucasian and African American women for 4 categories of disparities i.e. age at onset, stage of presentation, histological characteristics and survival. The association of the *Msp1*polymorphism in the *CYP1A1* gene, an enhanced expression of cyclin E associated with larger ER- tumors, and the loss of critical tumor suppressor genes, including p53, RASSF1A, RARβ, and HIN-l [34] were identified as biological factors for age at onset, whereas less breastfeeding, higher parity and elevated waist to hip ratio as an indicator of adiposity, accounted for non-biological factors. The biological pathway has yet to be explored in our population, but among the non-biological factors, the increasing prevalence of overweight and obesity is becoming a major public health concern, particularly in women, of whom 31.5% were overweight and 27% obese [35]. Regarding overall survival, Danforth showed that even after adjustment for the major prognostic indicators for breast cancer (age, stage, histology, ER-negative and TNBC, access to health care, comorbidity, treatment, and socioeconomic factors) the higher mortality rate for African American remained only partially explained.

One third of our patients had a regional and/or extended disease at diagnosis. The overall net survival for the period 2008–2013 was 84.9%. It was 88% in mainland France for the period 2005–2010 [36]. In Guadeloupe, free access to healthcare is available through the French universal social welfare system and most patients underwent surgery and/or radiotherapy as first course of treatment. Contrary to some oncology specialties, which require transfer of patients to mainland France for treatment, medical and surgical coverage for breast cancer is adequate on site in Guadeloupe. Yet, some patients still travel to mainland France to undergo first line therapy. These patients are usually from a higher socioeconomic background, but unfortunately, we were unable to study survival specifically according to this factor. Nevertheless, follow-up data and vital status are collected for all patients by the registry from different sources (medical records, health insurance schemes and the national mortality database with identifiable records) both in Guadeloupe, and whenever the follow-up is performed in mainland France. The estimate of observed survival is therefore accurate. Despite the high incidence of breast cancer in young women in our population, the overall net survival differed little compared to mainland France, consistent with the existence of good access to healthcare for women with breast cancer in Guadeloupe. However, we observed lower survival for patients with the HR- cancer subtype, whatever the Her2 status, with the lowest survival observed among TNBC patients.

The main limitations of our study were the lack of data on ethnicity and socioeconomic status, which are not currently recorded in the registry. Another bias could be the rate of available data for cancer subtypes and lack of data for KI67. We were therefore unable to perform molecular luminal classification. In our study, missing data for cancer subtype represented 14.7% of cases compared to 11.7% in the SEER program study. As reported by McShane et al. [37], missing data for tumor marker prognostic studies could lead to bias if associated with patient outcome or tumor size. Nevertheless, our data were population-based and covered the whole population of Guadeloupe and we furthermore report similar results to those of the SEER program for this Caribbean population of women with specific patterns of breast cancer presentation, incidence and survival.

5. Conclusion

Breast cancer in Guadeloupe shows high age-specific incidence rates in women aged between 45 and 55 years, and this warrants further study to assess the combined impact of biological, non-biological and environmental risk factors in the onset of early breast cancer in our population. Nevertheless, this population of African descent has survival rates by subtype that are consistent with those reported internationally. This good overall survival may

suggest that the poorer survival reported in other populations of African descent may not be an inherent feature of the disease, but may be linked to factors amenable to improvement, such as access to care.

Authorship contribution statement

J. Deloumeaux: conception and design, analysis and interpretation of data, draft of the article.

B. Bhakkan: acquisition of data and analyses, final approval of the version to be published

S. Gaumond: acquisition of data, interpretation of data, draft of the article, final approval of the version to be published

Nsome Manip M'Ebobisse, W. Lafrance, Pierre Lancelot, D. Vacque, A. Diedhiou: acquisition of data, final approval of the version to be published

Y. Negesse: acquisition of data, revision of the article, final approval of the version to be published

P. Kadhel: acquisition and interpretation of the data. Revision of the article and final approval of the version to be published.

Conflicts of interest

None.

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