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Ancestry and self-reported race in Brazilian breast cancer women

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SUMMARY

OBJECTIVE: This study aimed to evaluate the association between self-reported race/color and ancestry in Brazilian patients with breast cancer.

METHODS: This was an observational, transversal, epidemiological study, evaluating race and ancestry in 1,127 patients with breast cancer. For genetic ancestry, a 46-AIM-INDEL panel was used. The ancestral profile was evaluated with the Structure v.2.3.3 software. Descriptive statistics were performed. To assess differences between race and ancestry, an analysis of variance with Bonferoni adjustment was used.

RESULTS: The race distribution was 77.7% white, 17.6% brown, 4.1% black, 0.4% yellow, and 0.3% cafuse. The African ancestry proportion was significantly ($p<0.001$) more evident in black [0.63±0.21 (0.17–0.96)], followed by brown [0.25±0.16 (0.02–0.70)], and less frequent in white skin color. The European ancestry proportion was significantly ($p<0.001$) higher in white [0.72±0.17 (0.02–0.97)], followed by brown [0.57±0.19 (0.12–0.92)], yellow [0.27±0.31 (0.12–0.620], and black [0.24±0.19 (0.02–0.72)]. The Asiatic ancestry proportion is significantly ($p<0.001$) higher in yellow [0.48±0.51 (0.04–0.93)]. The Amerindian ancestry proportion frequency was the least frequent in all groups, and cafuse patients did not express differences between all race groups. The brown race group presented differences in African and European ancestry.

CONCLUSION: Although we found many similarities between white European ancestry, black African ancestry, and yellow Asian ancestry, there is great miscegenation between patients. Although they can be labeled as having one race, they do present many ancestral genes that would allow their inclusion in another race group.

KEYWORDS: Breast neoplasms. Epidemiology. Genetic variation. Pathology, molecular.

INTRODUCTION

The human species is considered to have been built over time, occurring at a time when there was a single continent. There were two main theories: one with a specific group of Hominids from Africa and a parallel evolution theory with multiple groups with admixture. Furthermore, our ancient human relatives spread around the globe, co-existing and admixing with other kinds of humans, affecting their DNA distribution. On the European/Asian continent, there were racial separations, i.e., the black race on the African continent, the white race in the North, and the yellow race in the East. The ancient DNA (aDNA) shows a history of humans rich in admixture between modern humans[1-3].

The relationship between ancestry and diseases is complex, involving age of disease onset, its relationship with reproductive capacity, treatment, and mortality rate. Also, external factors influence the main type of population mortality. From the 19th century until the middle of the 20th century, infectious diseases were the main determinants of mortality. The development of medicine and healthcare has led to further aging of the population, making cardiovascular diseases and cancer important factors associated with mortality.

The evolution of clinical and genomic knowledge has allowed us to better understand diseases, identifying subgroups of patients at greater risk for cancer development and specific molecular cancer subtypes[4]. Askenasi descendants are associated with elevated risk of BRCA mutation, breast cancer, and triple-negative tumors[5]. Black race was also associated with triple-negative tumors[6].

Also, the association between race and cancer is somewhat generic, as it involves family groups in which dietary, cultural, income, and education factors are present, influencing diseases, cancer, and the stage of cancer at diagnosis[3,7,8]. The development of ancestry markers has led to a better understanding of these factors, facilitating a better understanding of the relationship among race, ancestry, and patterns associated with neoplasia, i.e., molecular subtypes or cancer in young patients.

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The Brazilian population, due to its origin, is highly mixed, with great variation in the different regions with regard to race and ancestry[6,9]. Evaluating breast cancer, a TP53 mutation was observed in the southern and southeastern regions of Brazil[10]. A previous study evaluated the relationship among age, geographical region, and ancestry and the molecular subtypes of breast cancer[6,11]. Here, negative subtype was reported to be more frequent in white women, whereas triple-negative subtype was more frequent in nonwhite women[12]. Although there is a relationship between ancestry and self-reported race, they do not represent the same condition, justifying a study evaluating these two conditions in breast cancer patients. The objective of this study was to evaluate the self-referred color in relation to genetic ancestry in patients with breast cancer in Brazil.

METHODS

The evaluation of ancestry and Brazilian breast cancer patients was previously reported[11]. Now, we performed a subgroup analysis related to self-referred race/color (SRRC). This study was approved by the local ethics committee under number 1136/2016.

In summary, this was an observational, cross-sectional, epidemiological study. From 1,312 patients in the Biobank, the molecular subtype was identified in 1,282 patients, and DNA extraction was possible in 1,194 patients. Due to the databank and DNA recovery, we used DNA from 21 formalin-fixed paraffin-embedded and 1,194 buff coat samples. The final databank included 1,215 patients. Although DNA was extracted from 1,215 patients, the assessment of genetic ancestry was possible only in 1,127 patients.

We evaluated patients who were diagnosed between April 2000 and June 2018. The main inclusion criteria for the study were as follows: (1) invasive breast carcinoma; (2) female sex; (3) molecular subtype; (4) self-referred ethnicity; (5) born in one of five Brazilian regions; (6) DNA extraction; and (7) the presence of fragments of DNA ≥230 bp, a size that allowed us to evaluate ancestry.

Each patient described its SRRC as defined by Instituto Brasileiro de Geografia e Estatística (IBGE)[13]. We considered five groups of ethnicity/color: white ("branca"), black ("preta"), yellow ("amarela"), brown ("parda"), and indigenous ("indígena"). Briefly, brown ethnicity represents mixed color (white and black). Yellow was considered to refer to an individual who self-declared as being of Japanese, Chinese, or Korean origin, all representing Asian origin. The term Cafuzo represents ancestry admixture of the African with the Indigenous, and based on IBGE information, Cafuzo[13] is considered brown color. Due to its indigenous origin, we considered Cafuzo to have indigenous ancestry.

DNA provided by the Barretos Cancer Hospital Biobank was extracted to evaluate genetic ancestry. For genetic ancestry, a 46-AIM-INDEL panel was used, and the PCR products were subjected to capillary electrophoresis.

Four types of ancestry were considered: European, African, Amerindian, or Asian. The genetic ancestry of the patients was determined using ancestry-informative markers (AIMs), as previously reported[14-17]. Briefly, 46 small insertion-deletion (INDEL) polymorphisms were ascertained to maximize the divergence between four major human population groups: European (EUR), African (AFR), Asian (ASN), and Amerindian (AME). These markers were selected due to their high allele frequency divergence between different ancestral or geographically distant populations, including more than 1,000 individuals from 40 reference populations from the Human Genome Diversity Project (HGDP)-Centre d/Etude du Polymorphisme (CEPH) plus individuals from Angola, Portugal, Taiwan, and indigenous Brazil, which allowed us to establish the ancestral proportions in high admixture individuals and populations, such as the Brazilian population[18,19]. Ancestral profiles were evaluated using the Structure v.2.3.3 software[11].

We performed descriptive statistics [mean±standard deviation (minimum–maximum)] of ancestry contribution in different SRRCs (Table 1), expressed in Figure 1.

Analysis of variance (ANOVA) (Table 1) and Bonferroni's adjustment test (Table 2) were used to assess differences among groups. $p<0.05$ was considered significantly different. IBM SPSS® for Mac® version 20 was used for statistical analyses. STROBE checklist was used in this project[11].

RESULTS

A total of 1,127 patients were evaluated. SRRC was distributed as follows: 77.7% (876) white, 17.6% (198) brown, 4.1% (46) black, 0.4% (4) yellow, and 0.3% (3) cafuse. Evaluating the influence of ancestry in relation to SRRC, we observed (Table 1 and Figure 1) that European ancestry was observed more frequently among women who self-referred as white, brown, and cafuso; African ancestry was more frequent among women who self-referred as black and brown; Asian ancestry was more frequent among women who self-referred as yellow; and Amerindian ancestry was more frequent among women who self-referred as brown.

Genetically, the African ancestry proportion was significantly ($p<0.001$) more evident among women who self-referred as black [0.63±0.21 (0.17–0.96)], followed by brown [0.25±0.16 (0.02–0.70)], and less frequently white. The European ancestry proportion was significantly ($p<0.001$) higher among

Table 1. Percentage of self-referred color in different ancestry.

Ancestry	Mean	Standard deviation	Median	CI (5–95%)	CI (25–75%)	Minimum–maximum	ANOVA p-value
African							
Black	0.63	0.21	0.65	0.57–0.70	0.46–0.85	0.17–0.96	<0.001
Brown	0.25	0.16	0.23	0.23–0.27	0.12–0.37	0.02–0.70	
Yellow	0.15	0.17	0.15	0.01–0.31	0.01–0.31	0.01–0.32	
White	0.11	0.12	0.07	0.11–0.12	0.03–0.17	0.01–0.75	
Cafuse	0.02	0.01	0.02	0.01–0.02	0.01–0.02	0.01–0.03	
European							
Cafuse	0.89	0.06	0.88	0.84–0.88	0.84–0.88	0.84–0.95	<0.001
White	0.72	0.17	0.80	0.74–0.77	0.67–0.88	0.02–0.97	
Brown	0.57	0.19	0.60	0.55–0.60	0.44–0.73	0.12–0.92	
Yellow	0.27	0.31	0.24	0.01–0.58	0.01–0.58	0.12–0.62	
Black	0.24	0.19	0.19	0.18–0.30	0.06–0.36	0.02–0.72	
Asiatic							
Yellow	0.48	0.51	0.49	0.04–0.93	0.04–0.93	0.04–0.93	<0.001
Brown	0.07	0.08	0.05	0.06–0.09	0.03–0.09	0.01–0.86	
Black	0.07	0.06	0.05	0.05–0.09	0.03–0.09	0.01–0.27	
White	0.06	0.10	0.04	0.06–0.07	0.03–0.06	0.01–0.94	
Cafuse	0.05	0.03	0.05	0.02–0.05	0.02–0.05	0.02–0.08	
Amerindian							
Brown	0.10	0.10	0.07	0.84–0.11	0.03–0.08	0.01–0.62	<0.001
Yellow	0.08	0.07	0.05	0.04–0.15	0.04–0.15	0.04–0.18	
White	0.07	0.07	0.04	0.06–0.07	0.03–0.08	0.01–0.56	
Black	0.05	0.04	0.05	0.41–0.65	0.03–0.06	0.01–0.19	
Cafuse	0.04	0.02	0.05	0.03–0.05	0.02–0.05	0.02–0.05	

ANOVA evaluating group differences. CI: confidence interval.

women who self-referred as white [0.72±0.17 (0.02–0.97)], followed by brown [0.57±0.19 (0.12–0.92)], yellow [0.27±0.31 (0.12–0.620)], and black [0.24±0.19 (0.02–0.72)]. The Asian ancestry proportion was significantly (p<0.001) higher among women who self-referred as yellow, with few differences among the other groups. Finally, the Amerindian ancestry proportion frequency was the least frequent among all racial groups, and cafuso individuals did not self-refer as any racial group. Women who self-referred as brown presented differences in African and European ancestry.

DISCUSSION

In the variation in the human genome, there are short tandem repeat sequences and single-nucleotide polymorphisms (SNPs), but there are also sequences of variations in lineage markers and structural variations. In the analysis of human ancestry, genetic polymorphism is a factor of fundamental importance. AIMs represent a genomic sequence. In forensic medicine[20], SNPs are more frequently assessed, but small insertion-deletion (INDEL) polymorphisms are also examined; in the present study, INDELs were used to evaluate ancestry and have been described in previous studies related to the general Brazilian population[9] and cancer[11,15,21].

In the molecular era, it is important to have single, reproductive references using inexpensive classifications. INDEL evaluation needs technology and is associated with representative costs. The same condition occurs in molecular classification of breast cancer, in which immunohistochemistry simplifies breast subtype classification for clinical use[22,23]. SRRC has an association with ancestry, but they are not the same condition, and this study reported this condition in breast cancer patients.

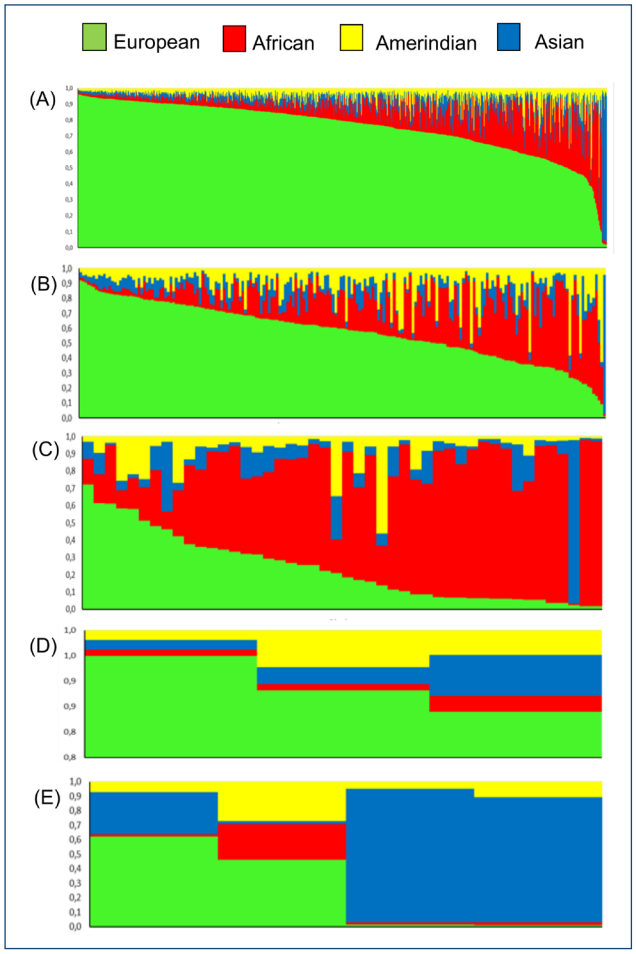

Figure 1. Representation of genetic admixture between ancestry groups in relation to self-reported race/color. (A) White; (B) brown; (C) black; (D) Amerindian; and (E) Asian. Chart line: horizontal: individuals; vertical: genetic ancestry (%).

Table 2. ANOVA with Bonferroni adjustment for correction evaluating multiple comparisons between ancestry and race/color.

Ancestry	White	Brown	Black	Yellow	Cafuse
African					
White	–	<0.001	<0.001	0.966	0.728
Brown	<0.001	–	<0.001	0.628	0.222
Black	<0.001	<0.001	–	<0.001	<0.001
Yellow	0.966	0.628	<0.001	–	0.648
Cafuse	0.728	0.022	<0.001	0.648	–
European					
White	–	<0.001	<0.001	<0.001	0.655
Brown	<0.001	–	<0.001	0.007	0.018
Black	<0.001	<0.001	–	0.993	<0.001
Yellow	<0.001	0.007	0.993	–	<0.001
Cafuse	0.665	0.018	<0.001	<0.001	–
Asiatic					
White	–	0.647	0.986	<0.001	0.999
Brown	0.647	–	1.000	<0.001	0.993
Black	0.986	1.000	–	<0.001	0.996
Yellow	<0.001	<0.001	<0.001	–	<0.001
Cafuse	0.999	0.993	0.996	<0.001	–
Amerindian					
White	–	<0.001	0.770	0.997	0.966
Brown	<0.001	–	0.002	0.984	0.632
Black	0.770	0.002	–	0.965	0.997
Yellow	0.997	0.984	0.965	–	0.954
Cafuse	0.966	0.632	0.997	0.954	–

In Brazil, according to the IBGE, there are four main national races/skin colors. In IBGE surveys, race is self-reported by respondents. The 2022 National Household Sample Survey (PNAD)[24] indicated that the Brazilian population is divided into white (42.8%), brown (45.3%), black (10.6%), and others. In this study, personal ethnicity was self-reported. Miscegenation leads to biogeographic ancestry[25], determining a range of changes and differences in physical structure, such as pigmentation of the skin, hair, and eyes; height; hair type; and nasal and lip formation. Skin color is a difference that is simplistic and subject to potential bias. Thus, using SRRC, we sought to evaluate the relationship between it and ancestry in a subgroup of patients with breast cancer.

The patients used in this study were identified through a database of women with breast cancer, with race being secondary information in the initial study[11]. This study reports the characteristics of population, ancestry variables (reported as continuous or categorical), and main associations about ancestry, geographical region, and molecular subtype. More information can be obtained by evaluating the other article[11] and supplementary file[11], which represent 10 tables and 6 figures. In this article, we performed a subgroup analysis evaluating exclusively the relationship between ancestry and self-reported color in Brazilian women with breast cancer. We repeated some information in the Methods section, but as the objective was different, we took care not to perform plagiarism and opted to show exclusively information associated with the objective of this publication. Repeated information is allowed only in the Methods section and is not considered plagiarism.

We observed that ancestry and race represent different conditions and a great admixture in Brazilian women. Self-reported black patients have high African genetic ancestry (0.63±0.21 SD) and low European genetic ancestry

(0.24±0.19 SD). Self-reported white patients have high European genetic ancestry (0.72±0.17 SD) and low European genetic ancestry (0.11±0.12 SD). Self-reported brown patients have intermediary differences with high European genetic ancestry (0.57±0.19 SD) and intermediary African genetic ancestry (0.25±0.16 SD).

The context of race and the onset of cancer involves many dimensions because the onset of cancer is influenced not only by genetic factors but also by the environment and cultural and dietary habits[8]. Likewise, staging at diagnosis is influenced by factors related to the health system and the availability of individual or public resources, schooling and education regarding the need to perform exams regularly, and attitude toward undergoing exams or seeking health professionals, factors that are associated with advanced staging in more vulnerable populations and that are accentuated in historically disadvantaged races[7]. The relationship between racial disparities in social and historical contexts should increasingly be discussed to better understand the role of racial hierarchy in access to and dependence on public health[26]. The discussion about race is of fundamental importance, as it is associated with prejudices and attitudes related to racial subgroups[27,28]. To minimize some historical differences, in Brazil, the Quota Law[29] was created to determine inclusion in higher education and in public service exams, helping racial subgroups, mainly black, mixed races, and indigenous people.

Evaluating breast cancer in the United States, there is discussion about racial/ethnic disparities, incidence, and mortality rates linked to hereditary factors, risk factors, treatment, and health disparities[30]. The same occurs in Brazil, where differences in mortality may indicate inequities in access to diagnosis and treatment[31], but other pathological factors may be associated[6]. To improve this discussion, we also observed a large percentage of admixture in all races. Based on the data presented here, there are interesting contexts that can be considered in clinical practice. Our data were obtained from patients with breast cancer from the five Brazilian regions, yielding an SRRC distribution of 77.9% white, 17.4% mixed race, 4.1% black, 0.3% yellow, and 0.2% cafuso, percentages that are different from those obtained by the PNAD. In our data, there is potential bias as two regions are numerically underrepresented, reflecting the representativeness bias of the institutional Biobank. We initially sought to increase the sample from these regions by inviting other professors from these regions who could contribute patients, but the response was negative. Despite these limitations, this study investigated SRRC race and ancestry using a convenience sample.

Evaluating the results related to ancestry, something apparently obvious was numerically proven. Regardless of the SRRC, there was significant miscegenation among the groups and among all races. Evaluating European ancestry, a greater proportion of this ancestry was observed among women who self-referred as white, significantly different from that observed among women who self-referred as brown, black, and yellow, and in this sample, cafusos were predominantly of European ancestry. When assessing African ancestry, a high frequency was observed among women who self-referred as black, but a difference was observed among all groups. Asian ancestry was more frequent among women who self-referred as yellow, with a difference among all groups. The frequency of Amerindian ancestry was similar among race groups, with the exception of women who self-referred as yellow.

The mixed race is intermediate between the white and black races. The mixed race had a high rate of European and African ancestry, with equivalent ancestry percentages among women who self-referred as white and black. When evaluating the graphs and Table 1, although 50% percentiles do not overlap, there are women of high African ancestry and low European ancestry with ancestry percentages similar to those for black women; likewise, they present high European ancestry and similarities with African ancestry only in percentiles above 50%. This can be explained by the phenotype, which raises questions about the use of self-reported color for this race, where these individuals can be considered white and/or black depending on skin tone, which may influence results related to race and which may be influenced by the type of evaluator and the place where the individual lives.

Among black women, there was high African ancestry but not 100%; in this group, there is a considerable frequency of European ancestry and a small frequency of yellow and Amerindian races. Women considered to be black have high European miscegenation. Similar to white women, they presented a moderate rate of African miscegenation. The line between color and race is very thin, which should make any derogatory racial discussion unfeasible[27], especially in Brazil, where there is high miscegenation.

As limitations of the study, there was an unequal distribution of participants from all geographical regions in Brazil, and only female patients with breast cancer were included in the study. In ideal conditions, both sexes would be included, with equal distribution among all regions. A convenience sample was used in this study, and therefore future studies with more comprehensive samples are needed. This is one of the first studies to address ancestry and race/color in patients with breast cancer in Brazil and can thus serve as a basis for future comparisons.

CONCLUSION

We observed that there is great miscegenation between patients, and although they can be labeled as having one color, they do present many ancestral genes that would allow their inclusion in another race group. Care should be taken when evaluating race/color, as its conditions do not represent the same ancestry.

AUTHORS' CONTRIBUTIONS

RACV: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. **DS'A:** Data curation, Formal Analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **ACL:** Data curation, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **RMR:** Conceptualization, Writing – original draft, Writing – review & editing.

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