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Research article

Assessment of breast density in women from different regions of Brazil

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ABSTRACT

In many countries, there is an interest in determining the location of the women with the highest breast density. This investigation is important for optimize screening for breast cancer for women with dense breasts as other imaging modalities since 2D mammography is not very efficient on this type of breast. The objective of this study was to evaluate the variations in breast density in Brazilian women of different regions of Brazil. The mammographic images were taken from four regions of Brazil. The images, in the cranial caudal (CC) projection, were separated into intervals of compressed breast thickness (CBT) and patient age and were analysed by the software VolparaDensity, where volumetric breast density (VBD) calculations were performed. For each interval, null hypothesis tests for the mean difference between the VBD from the four regions of Brazil were performed. The paired tests indicated that there was a significant difference in the VBD of the women in the different regions of Brazil, with variations from 11.05% to 36.73%. Higher VBD was observed for women living in the Southeast region, followed by the Midwest, Northeast, and North regions. The Brazilian IBGE data show that the most urbanised region in Brazil is the Southeast, which coincides with the second highest rate of breast cancer in Brazil, according to the Brazilian National Cancer Institute (INCA). It is also known that breast cancer is strongly related to breast density; therefore, the results of this work support the data presented by federal agencies demonstrating that women living in the most urbanised region of Brazil (e.g., Southeast) present the highest breast density.

1. Introduction

Breast cancer is the most prevalent cancer in women worldwide. In 2018, 2.1 million new cases were recorded (Bray et al. 2018; Ferlay et al. 2018). In developed countries, a decrease in breast cancer mortality is observed due to the massive implementation of screening tests (Thana et al. 2020; Hu et al. 2019). Currently, mammography is still the most widely used screening test for the early detection of cancer, especially for women in age groups where the risk of developing breast cancer is high (Almeida et al., 2017). Unfortunately, in Brazil, a decrease in mortality caused by breast cancer has not yet been achieved; therefore, an increase in disease detection is followed by an increase in the death rate (INCA 2020).

The mammary density represents the percentage of glandular tissue in the breast, and it is a risk factor for the development of breast cancer (Boyd et al. 2011; Ko et al. 2014; Manning et al. 2016; McCormack et al. 2006). This is related to the linear attenuation coefficient proximity between glandular tissue and carcinoma, causing possible masking in the mammographic findings. Thus, in very dense breasts, the cancer detection rate with mammographic screening is not as effective. Some authors have suggested that alternative imaging tests should be used for dense breasts, such as ultrasound or digital breast tomosynthesis (DBT), since these are not as affected by the amount of glandular tissue (Boyd et al. 2007; Ko et al. 2014; Vilaverde et al. 2016). The glandular tissue proportion varies according to the breast size and patient age (Kotre 2011). Moreover, some works have shown that the ethnicity of the women and their geographical location are also factors relevant to breast density, which are associated with socio-economic conditions and lifestyle (Aitken et al. 2010; Moore et al. 2020; Perry et al. 2008; Van der Waal et al. 2015; Viel and Rymzhanova 2012; Zulfiqar et al. 2011).

Therefore, knowledge of breast density is fundamental for better quality breast cancer screening. Moreover, high density breasts are associated with an increase in the mean glandular dose (MGD) (Yamamuro et al. 2018). In many states in the United States of America (USA),

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the policy of presenting the risk associated with screening mammography in patients with high breast density is already used. In 2017, the Ministry of Health, Labor and Welfare of Japan also implemented a policy of investigating breast density and informing the population of practices for improving screening exams (Yamamuro et al. 2018). In addition to Japan and the USA, other countries, such as Malaysia and the Netherlands, have also carried out breast density surveys reinforcing the importance of these analyses to encourage individualised screening programs (Van der Waal et al. 2015a; Zulfiqar et al. 2011).

In Brazil, there are still no national breast density surveys to support more individualised breast screening analyses. Moreover, Brazil is a country with a continental extension (8.516 million km^2), reflecting significant socio-economic and ethnic diversity. Thus, it is extremely important to investigate the relationship between breast density and its regionality. This data analysis can be implemented in a national database to encourage an advance in breast screening policies in Brazil, currently in the country, the guidelines for breast cancer screening use only mammography as a strategy (Migowski et al., 2018). Moreover, this study may contribute to international debates regarding the weighting of breast density in screening programs for breast cancer. Therefore, the present work aimed to evaluate the volumetric breast density (VBD) between different regions of Brazil and to evaluate if there is any difference among these regions. The breast density of women from the Midwest, Northeast, North, and Southeast was evaluated. Statistical tools were used to quantify the differences among the regions.

2. Methodology

From 2016 to 2019, mammographic images of 3,328 women from four regions in Brazil were collected in Digital Imaging and Communications in Medicine (DICOM) format. The breast mammographic images were performed in a cranial caudal (CC) view. The VBD values were estimated from the clinical images using Volpara Data Manager Software version 1.1.109. The compressed breast thickness (CBT) and patient age were obtained from the DICOM header. In the data analysis for each patient, the VBD and CBT values were calculated as the mean values for left and right breasts.

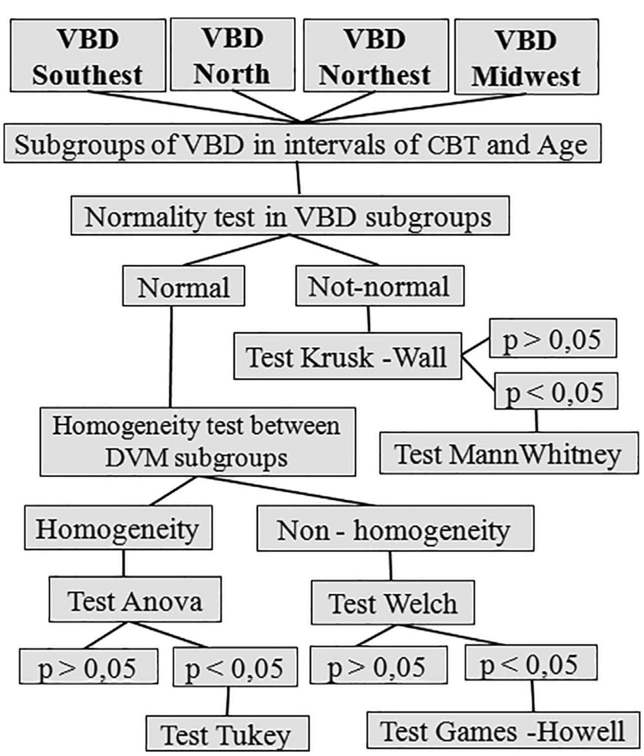

Figure 1. Graphic scheme of the used methodology.

Figure 1 shows a schematic diagram of the methodology used in this work. Initially, the VBD of each region was divided into intervals of CBT and age of the patient, thus forming four subgroups of VBD in each of the intervals. The intervals used for the variables were the following: CBT <40, $40 \leq$ CBT <50, $50 \leq$ CBT <60, $60 \leq$ CBT <70, $70 \leq$ CBT <80, $40 \leq$ age <50, $50 \leq$ age <60, $60 \leq$ age <70, and age ≥ 70.

The Statistical Package for the Social Sciences (SPSS) was used to perform the statistical analysis. For each subgroup of VBD, we checked whether the sample followed a normal distribution. The Shapiro-Wilk test was performed for subgroup cases with $n < 30$. In cases where the four subgroups of VBD within a certain interval of CBT or the patient's age had a normal distribution, the Levene test was used to verify the existence of homogeneity.

For the same interval of CBT or age of the patient, the null hypothesis test for the mean difference of the VBD from different regions was analysed. For each interval of patient CBT or age, when the VBD of all regions resulted in a normal and homogeneous distribution, ANOVA with a post-hoc Tukey test (Field 2011) was used. For cases where the VBD from the four regions had a normal but non-homogeneous distribution, the Welch test with post-hoc Games-Howell test (Ruxton and Beauchamp 2008) was performed. Finally, the Kruskal-Wallis test with the Mann-Whitney (Ruxton and Beauchamp 2008) test was used for cases where the VBD from one or more regions did not present a normal distribution.

In the intervals where the ANOVA, Welch and Kruskal-Wallis tests resulted in a $p < 0.05$, indicating that there was a significant difference in the breast density of the four samples, paired analyses (Tukey, Games-Howell and Mann-Whitney) were performed between the VBD. These analyses were executed to check where the significant difference is in each two samples, since the ANOVA, Welch and Kruskal-Wallis tests do not perform analyses pair by pair.

The collection of images for this study was approved by the Ethics Committee of the Ezequiel Dias Foundation (FUNED) according to CAAE protocol 25993919.5.0000.9507.

3. Results

From the mean value (left and right breasts) of the 3,328 patient images, we obtained 1,664 values of VBD, CBT, and age from patient.

Figure 2 shows the evaluated patient percentage from all regions of Brazil as a function of age. The patient age in the sample ranged between 40 and 87 years, with a mean age of 54.69 ± 11.55 years. Figure 3 shows the percentage of patients evaluated as a function of CBT. The CBT in the sample ranged between 19.51 and 79 mm, resulting in a mean CBT of

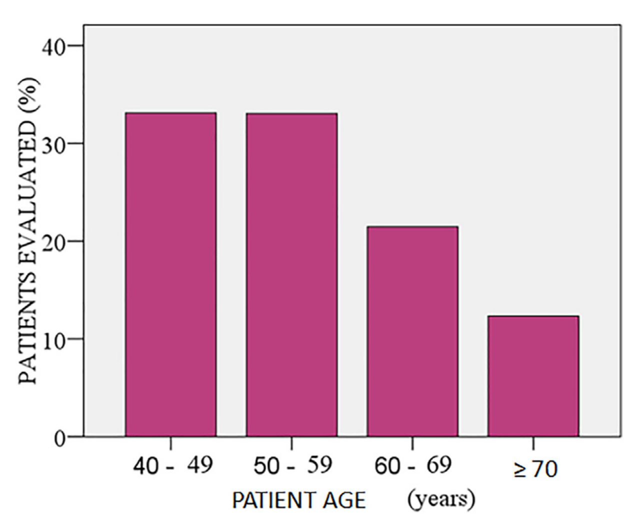

Figure 2. Percentage of patients evaluated as a function of age.

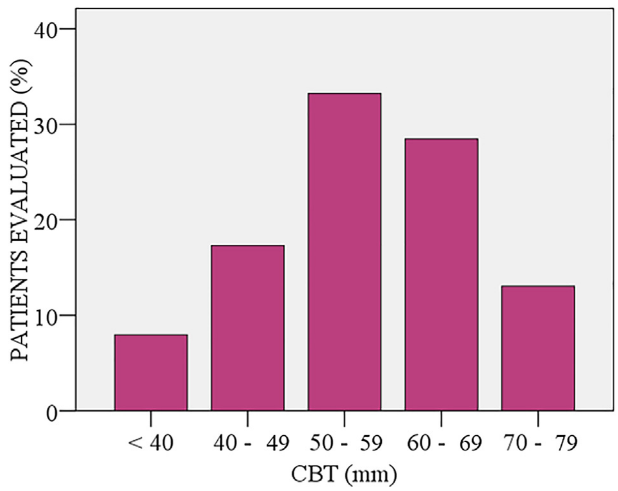

Figure 3. Percentage of patients evaluated as a function of CBT.

57.96 ± 12.19 mm. Finally, Figure 4 shows the percentage of patients as a function of VBD, which ranged from 1.91% to 35.18%, with a mean VBD of 9.40 ± 6.13%.

3.1. Statistical analysis

3.1.1. Hypothesis test: normality of the samples

According to the central limit theorem (Field 2011), samples with $n > 30$ were treated as a normal distribution. For the Shapiro-Wilk test, when the test resulted in a p of >0.05, it was considered a normal distribution, and for a p of <0.05, a non-normal distribution was accepted.

In the case of subgroups of VBD divided into CBT intervals, all samples from the Midwest, North, and Southeast regions and samples from the Northeast region in the CBT intervals of CBT <40, $50 \leq$ CBT <60, $60 \leq$ CBT <70, and $70 \leq$ CBT <80 could be treated having a normal distribution within the analyses proposed in this study ($n > 30$ or $p > 0.05$). Only the subgroup $40 \leq$ CBT <50 in the Northeast region did not present a normal distribution ($p < 0.05$).

In the case of VBD samples divided into patient age ranges, one of the subgroups of the Midwest region (AGE ≥ 70) and one of the Northeast regions (AGE ≥ 70) presented non-normal distribution ($p < 0.05$). The rest of the samples were treated as normal distributions ($n > 30$ or $p > 0.05$).

3.1.2. Hypothesis test: homogeneity between samples

Followed by the normality analysis, the homogeneity among the samples was verified for the VBD cases that presented a normal distribution. Therefore, the VBD homogeneity ($p > 0.05$) was found for two intervals: CBT <40 and $40 \leq$ AGE <50. All other cases presented a p of <0.05, indicating non-homogeneity among the VBD samples.

3.1.3. Hypothesis test: difference in volumetric breast density (VBD) in women from different regions

For CBT <40 and $40 \leq$ AGE <50, the VBD samples had normal distribution, and homogeneity among VBD samples from different regions was seen. Therefore, in these samples the ANOVA test was performed. The intervals $50 \leq$ CBT <60, $60 \leq$ CBT <70, $70 \leq$ CBT <80, $50 \leq$ AGE <60, and $60 \leq$ AGE <70 had normal but non-homogeneous distribution among the VBDs from different regions. Therefore, the Welch test was executed. Moreover, the VBD samples of $40 \leq$ CBT <50 and AGE ≥ 70 had non-normal distribution; therefore, the Kruskal-Wallis test was performed.

The VBDs from all regions for $50 \leq$ CBT <60 and $70 \leq$ CBT< 80 ranges did not present significant statistical differences, which are the intervals whose hypothesis tests for mean difference resulted in a p of >0.05. Figures 5 and 6 show the mean of the VBDs and their respective standard deviations for all analysed regions in the $50 \leq$ CBT <60 and $70 \leq$ CBT <80 intervals, respectively. In these figures, it is possible to note that the mean VBD of at least one particular region is in the range of the standard deviation of the VBD of the other regions, indicating that there is no significant difference between the VBD of women from different regions.

All other intervals of CBT and patient age presented a p of <0.05, showing that a significant statistical difference was obtained. Therefore, a paired analysis (region per region) was performed in these cases. Through these tests, the regions that had a statistically significant difference were identified. Tables 1 and 2 show the p from Tukey, Games-Howell and Mann-Witney tests for samples that presented VBDs with: normal/homogeneous, normal/non-homogeneous and non-normal distributions, respectively.

Table 1 shows the results from the paired analyses among VBD from regions on each CBT intervals, it found a significant statistical difference ($p < 0.05$) between the breast density of women from North and Southeast Brazil with CBT <40 and $40 \leq$ CBT <50, women from Midwest and North Brazil ($40 \leq$ CBT <50), and women from Midwest and Southeast Brazil ($60 \leq$ CBT <70).

For cases where the CBT was <40, a maximum percentage difference of 23.29% among the VBDs from the North (11.39 ± 2.49%) and Southeast (14.85 ± 1.85%) was observed. For $40 \leq$ CBT <50, the

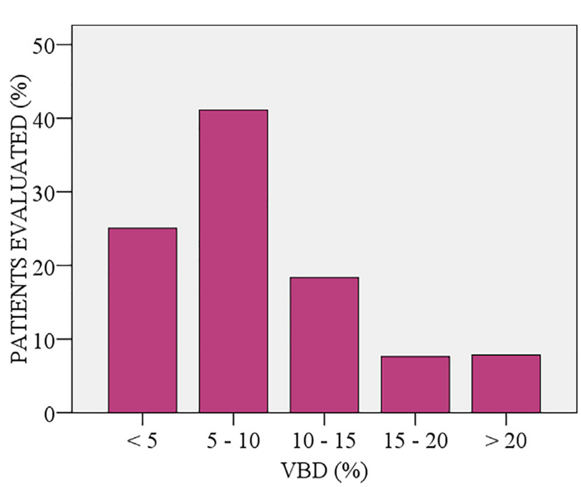

Figure 4. Percentage of patients evaluated as a function of VBD.

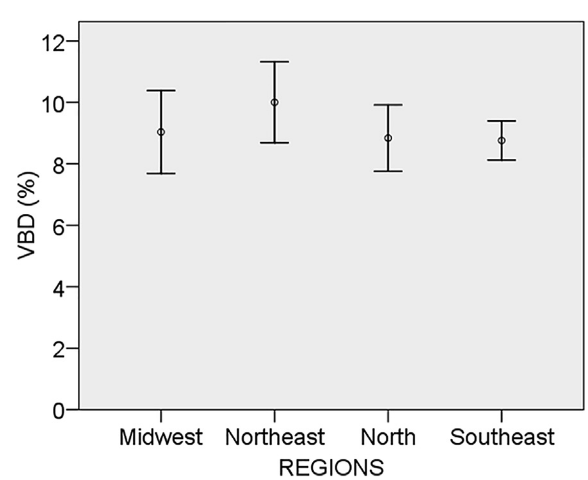

Figure 5. Mean VBD and standard deviation in $50 \leq$ CBT <60 interval for each region.

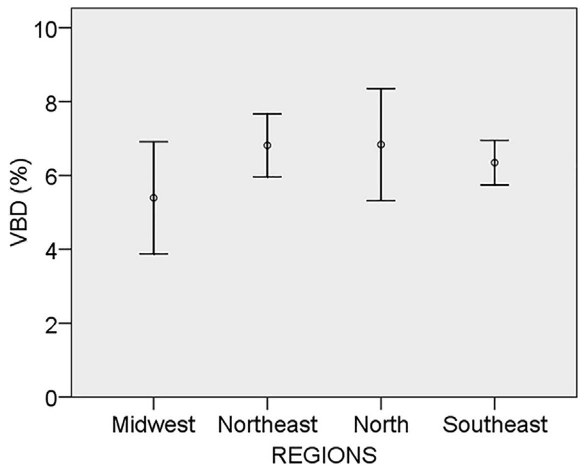

Figure 6. Mean VBD and standard deviation in 70 ≤ CBT <80 interval for each region.

maximum difference was 25.62% among the Midwest (13.70 ± 2.52%) and North (10.19 ± 1.35%), followed by 17.68% between the North (10.19 ± 1.35%) and Southeast (12.02 ± 1.02%). For 60 ≤ CBT <70, the percentage difference was 15.52% for the VBD among women from the Midwest (7.02 ± 0.99%) and Southeast (8.31 ± 0.48%).

Table 2 shows the results from the paired analyses among VBD from regions on each age intervals. The regions that presented p of <0.05, indicating a significant statistical difference between VBD values, were the Midwest and North (40 ≤ age <50), Northeast and Southeast (50 ≤ age <60, 60 ≤ age <70 age ≥70), North and Southeast (50 ≤ age <60, 60 ≤ age <70, age ≥70), and Midwest and Southeast (60 ≤ age <70, age ≥70).

The women from the Midwest (11.22% ± 1.01%) and North (9.98% ± 0.67%) regions presented a VBD percentage difference of 11.05% for the 40 ≤ age <50 interval. For the 50 ≤ age <60 interval, the highest variation was 19.06% among the Northeast (7.13 ± 0.83%) and Southeast (8.81 ± 0.67%), followed by 17.13% for the North (7.30 ± 0.76%) and Southeast. For the range of 60 ≤ age <70, the maximum difference was 32.48% for women from the Midwest (5.28 ± 1.25%) and Southeast (7.82 ± 0.81%), followed by 26.98% for the Northeast (5.71 ± 0.73%) and Southeast (7.82 ± 0.81%) and 25.70% for the North (5.81 ± 0.70%) and Southeast (7.82 ± 0.81%). For the age ≥70 interval, the highest variation was 36.73% among women from the Midwest (4.22 ± 0.88%) and Southeast (6.67 ± 0.54%) regions, followed by 29.83% between the North (4.68 ± 0.92%) and Southeast and 22.03% between the Northeast (5.20 ± 0.76%) and Southeast.

4. Discussion

In Figure 2, we show that 54% of the patients are in the age range of 50–69 years. For this range, the Health Ministry (HM) of Brazil recommends screening mammography every two years (INCA 2020). Thirty-three percent of patients in the range of 40 ≤ age <50 are related to women from high-risk groups, such as those with a family history of early breast cancer. In these cases, the HM recommends screening mammography beginning at 35 years (INCA 2020). The 13% of women over 70 years of age that went through a mammography screening are those who at some point in their life had lumps in the breasts or those who never underwent the screening and only had it performed when they were elderly (INCA 2020).

In Figure 3, the highest percentage of CBTs (59.25%) is between 50 and 70 mm Figure 4 shows that the mean VBD of Brazilian women is 9.40 ± 6.13%, which is close to the VBD of Dutch women (7.25%), as described by Van der Waal et al. (2015a). The four volumetric density ranges of the breast: VBD1 (0–4.5%); VBD2 (4.5–7.5%); VBD3 (7.5–15.5%) and VBD4 (>15.5%) corresponds to the BIRADS-A, BIRADS-B, BIRADS-C and BIRADS-D classifications, respectively (Van der Waal et al., 2015b). Therefore, the Brazilian women analysed in this study are mostly classified as BIRADS-B (30%) and BIRADS-C (35%), which correspond to breasts with scattered and heterogeneously density, in that order.

For the normality analyses, from the 36 subgroups of VBD analysed in this study, only three presented non-normal distribution due to their small sample size (n < 30) (Ghasemi and Zahediasl 2012). The non-homogeneity (p < 0.05) prevailing in the VBD samples is related to the large sample size and the large differences among the n values from sample to sample (Field 2011).

Of the nine analysed intervals, no significant differences were found for the VBD of women in the four regions for two of the intervals. In the other seven, the paired tests were performed. For these samples, the percent variation of the mean VBD between women from different regions that presented a p of <0.05 was 11.05%–36.73%. Table 1 shows

Table 1. The p-value for the paired tests of VBD, separated in CBT intervals, from images of women from the Midwest, Northeast, North and Southeast regions and the statistic value for the null hypothesis tests for the mean difference.

CBT intervals	Regions		p	F/X^2 Statistic
CBT <40	Midwest	Northeast	p > 0.05	ANOVA [F (3,144) = 3,083; p < 0,05]
		North	p > 0.05	
		Southeast	p > 0.05	
	Northeast	North	p > 0.05	
		Southeast	p > 0.05	
	North	Southeast	p < 0.05	
40 ≤ CBT <50	Midwest	Northeast	p > 0.05	Kruskal – Wallis [X^2 (3) = 9,974; p < 0,05]
		North	p < 0.05	
		Southeast	p > 0.05	
	Northeast	North	p > 0.05	
		Southeast	p > 0.05	
	North	Southeast	p < 0.05	
60 ≤ CBT <70	Midwest	Northeast	p > 0.05	Welch [F (3,165) = 3,912; p < 0,05)
		North	p > 0.05	
		Southeast	p < 0.05	
	Northeast	North	p > 0.05	
		Southeast	p > 0.05	
	North	Southeast	p > 0.05	

Table 2. The p-value for the paired tests of VBD, separated in age intervals, from images of women from the Midwest, Northeast, North and Southeast regions and the statistic value for the null hypothesis tests for the mean difference.

Age Intervals	Regions		p	F/X^2 Statistic
$40 \leq$ age <50	Midwest	Northeast	$p > 0.05$	ANOVA [F (3,455) = 3,292; p < 0,05]
		North	$p < 0.05$	
		Southeast	$p > 0.05$	
	Northeast	North	$p > 0.05$	
		Southeast	$p > 0.05$	
	North	Southeast	$p > 0.05$	
$50 \leq$ age <60	Midwest	Northeast	$p > 0.05$	Welch [F (3,219) = 5,441; p < 0,05]
		North	$p > 0.05$	
		Southeast	$p > 0.05$	
	Northeast	North	$p > 0.05$	
		Southeast	$p < 0.05$	
	North	Southeast	$p < 0.05$	
$60 \leq$ age <70	Midwest	Northeast	$p > 0.05$	Welch [F (3,118) = 9,833; p < 0,05]
		North	$p > 0.05$	
		Southeast	$p < 0.05$	
	Northeast	North	$p > 0.05$	
		Southeast	$p < 0.05$	
	North	Southeast	$p < 0.05$	
age ≥ 70	Midwest	Northeast	$p > 0.05$	Kruskal – Wallis [X^2 (3) = 33,076; p < 0,05]
		North	$p > 0.05$	
		Southeast	$p < 0.05$	
	Northeast	North	$p > 0.05$	
		Southeast	$p < 0.05$	
	North	Southeast	$p < 0.05$	

the results from the paired tests of the VBD from the four regions of Brazil, per interval of CBT, resulting in 18 analyses, from which only 22% presented a significant difference between the regions. The paired tests of the VBDs of the 4 regions, per age interval (Table 2), resulted in 24 analyses, from which 37% presented significant statistical difference since the p were below 0.05.

From these statistical analyses, it was possible to verify that for different intervals of CBT and age, higher breast density was found among women from the Southeast, followed by the Midwest, North, and Northeast. Therefore, the results of this study demonstrate that the highest breast density is presented by women who live in more urbanised regions of Brazil. According to the Brazilian Institute of Geography and Statistics (IBGE) estimative, the highest rates of urbanisation in Brazil are in the states of São Paulo and Rio de Janeiro (Southeast region), followed by the Federal District and Goiás (Midwest) and, finally, the states of Maranhão, Piauí, Sergipe, and Pará (Northeast and North regions) (IBGE 2016). This trend was also observed in other studies, in which the authors observed that women residing in highly urbanised cities in the Netherlands (Van der Waal et al. 2015a), England and Wales (Aitken et al. 2010), France (Viel and Rymzhanova 2012), and the USA (Perry et al. 2008) presented high breast densities. Another important aspect observed here is that the regions in which women presented the higher VBD coincide with the highest rates of breast cancer predicted for 2020 to 2022 (INCA 2020).

5. Conclusions

Through the null hypothesis for the mean difference of VBD and using the parameters CBT and patient age, the present study demonstrated that women living in more urbanized regions of Brazil (Southeast followed by the Midwest) have higher breast densities. Although a statistically significant difference was found in a low percentage of matched analyses between the MVD of women from different regions, this inclination can be seen. In addition, this work consists of the first national statistical analysis of the breast density of Brazilian women.

Another important aspect observed here is that the regions in which women presented the higher VBD coincide with the highest rates of breast cancer predicted for 2020 to 2022 in accordance to the Brazilian National Cancer Institute (INCA) (INCA 2020).

Based on the experience of other countries, such as the USA and Japan (Yamamuro et al. 2018), who successfully implemented the breast density analyses to improve the quality and safety of breast screening, we also believe that the breast density of each woman should be considered to improve the breast cancer screening programs in Brazil.

The next steps in this work will consist of increasing the representative sample of each region and including the South region in the analyses. In addition, to verify which qualitative factors contribute to a higher breast density in women living in more urbanized regions.

Declarations

Author contribution statement

Camila Engler: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Lucas Paixão and Luiza Freire de Souza: Analyzed and interpreted the data; Wrote the paper.

Margarita Chevalier: Contributed reagents, materials, analysis tools or data.

Maria do Socorro Nogueira: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

The authors are unable or have chosen not to specify which data has been used.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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