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Benign Breast Disease and Associated Factors in Women Attending in A Public Hospital

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Abstract **- The aim of this study was to present the main features of women with benign breast disease (BBD) and the factors associated with these diseases. Our study was a case-control, masked and hospital-based study. Sociodemographic, clinical and gynecological, as well as obstetrical, anthropometric and lifestyle data were collected from the BBD-diagnosed women and controls. Most participants were diagnosed with fibroadenoma. The three protective factors against the development of BBD included parity, late menarche and breastfeeding. In general, these major protective effects are connected to the endogenous hormone levels and main reproductive events, which are more difficult factors to control. The type of benign breast disease, age of diagnosis, degree of education and woman's age seem to contribute to this relationship.**

Index Terms **- benign breast disease, breast cancer, risk factors, Brazilian women**

I. INTRODUCTION

Benign breast disease (BBD) includes the heterogeneous group of lesions with a variety of histological subtypes and occurs more frequently than breast cancer (BC). The etiology has been attributed to hormone level changes during the life of women and to the reproductive cycles, in particular, which contributes to the differentiation in breast structure and cellularity [1, 2]. Therefore, recognizing benign breast lesions becomes crucial to facilitate selecting the most suitable treatment plan for each type [3].

At present, the main challenge it to gather data on the epidemiology of BBD, as a standardized histologic classification system commonly available to the scientific community is absent, and realistic estimates of the prevalence of this condition in the general population are lacking [4].

Cohort studies, however, demonstrated a higher risk of breast cancer development in women who had benign breast disease [5, 6]. From a recent meta-analysis multiethnic, BBD appeared to be the common factor that raised the risk of BC by approximately 1.17 for non-proliferative disease, 1.76 for disease unspecified and 3.93 for unspecified atypical proliferative disease without atypia, 2.07 for benign breast hyperplasia [4]. Further, in African women with proliferative disease atypia a three-fold increased risk of subsequent development of breast cancer was observed compared with those who had non-proliferative disease [7].

Pankratz and co-workers, therefore, developed a model which could predict the likelihood of BC developing in women, right at the time of benign biopsy. Based on the recognized histological features, as well as the patients' demographic and clinical characteristics, this model could well be a significant step in individualized risk prediction of the BC in women BBD [8].

Some studies suggested that on average, the time from the initial diagnosis of BBD to breast cancer diagnosis was between 6.4 and 10.7 years [4, 5, 7]. As the risk of recurrence lies in the women population with BBD, special attention must be paid to the reaction of these women to the diagnosis, because the treatment directly influences their quality of life [9].

Clinical evaluation, therefore, becomes critical to the exclusion of malignancy, and the clinical management must necessarily be differentiated, based mostly on patient age. Young women (< 35 years) with BBD, do not always opt for nodule excision. The size, location and the patient desire to undergo the procedure must be considered. In consenting patients, fine-needle aspiration has been found to be the most suitable procedure. At present, for patients over 35 years, the treatment is based on the triple diagnosis, as clinical, imaging and histological, with surgical indication. This is justified as the incidence of BC tends to progressively increase with age [3].

Breast cancer has been recognized as a public health problem, because of its repercussions on the social, health / morbidity, psychological and economic factors in society [10]. In the breast disease process, the psychosocial impact is evident by high anxiety levels and or depression and patient concern regarding body image and sexuality [9]. Another major concern is the high cost, whether direct (outpatient, hospital, drugs) or indirect (absenteeism, early retirement, loss of productivity) [10]. Thus, there is an urgent need for early detection and diagnosis, followed by correct treatment of patients at risk, in order to reduce the complications and increase survival.

This article describes the main characteristics of women with BBD, given assistance in a public hospital. Besides, the

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BBD-related factors have been identified compared with the control group.

II. MATERIAL AND METHODS

This is a case-control, masked and hospital-based study, conducted on the women attending in the Mastology or Gynecology Service of Motherhood Odete Valadares, Hospital Foundation of Minas Gerais (FHEMIG) of Belo Horizonte, Minas Gerais, Brazil, in 2006 [11, 12].

Women undergoing routine tests, breast or gynecologic surgery at the hospital were invited to participate in the study by signing the Term of Free and Clear consent form. The study was approved by the National Committee for Research Ethics, in the advice number 1889/2005, and was conducted according to Declaration of Helsinki.

All patients with a confirmed diagnosis of benign breast disease by pathological examination were included in this study; those excluded were patients below 20 years, those diagnosed prior with breast cancer or benign breast disease and those lacking complete data, like patients with incomplete questionnaires, absence of the pathological examination results, and lack of recent mammography (maximum of two years prior to the interview date).

The volunteers were categorized into two groups: group benign breast disease (GBBD), composed of women with a histopathologic diagnosis of non-proliferative breast tissue changes or other benign proliferative breast diseases and the group control (GC) which included women who had undergone a recent mammogram with Class I or II disease according to the BI-RADS classification criteria of the Brazilian Society of Mastology. The final sample thus involved 338 women.

We utilized a previously validated questionnaire for the population study [13]. Patient identification, including data sociodemographic, clinical and gynecological data and anthropometric and lifestyle characteristics was collected.

Weight was measured on an electronic scale Tanita® - Tanita Body Fat Monitor Scale (Model TBF 531®, Tanina Corporation of America, Illinois, USA), with maximum capacity of 150 kg and sensitivity of 100 g. The height was recorded with a vertical anthropometer (Alturaexata®), having a rigid rod with a scale bilaterally showing 35 to 213 cm in 1 mm divisions. These measurements were performed according to the standard recommendations by Jelliffe [14] and Frisancho [15]. Body mass index (BMI) was then calculated using the formula: weight (kg) / height (m^2) and overweight was defined as BMI > 25.0 kg / m^2 [16].

The following cutoffs were considered risk factors: age of menarche less than 12 years; first pregnancy after 30 years; first mammogram indicated before of 40 years [10].

The description of the population was initially done based on the type of benign breast disease and the age of diagnosis. The descriptive analysis of general characteristics was presented based on the relative frequency distributions. Evaluation of the factors related to the BBD was performed using binary logistic regression. The results are shown as *odds ratios* (OR) and confidence intervals of 95% (CI 95%) for crude and adjusted models by age and education. The significance level was set at 5%. The data were analyzed using SPSS for Windows (SPSS INC. Chicago, IL. USA), version 20.0.

III. RESULTS

Depending on the difficulty of the standardized histological classification for BBD, a survey of the clinical and histological characteristics was proposed, as seen in Table 1. We reviewed the literature according to the findings found in this study from the analysis of the pathologist from our staff. We have also prepared illustrative images of different types of benign breast lesions of the women in this study (Figure 1 and 2).

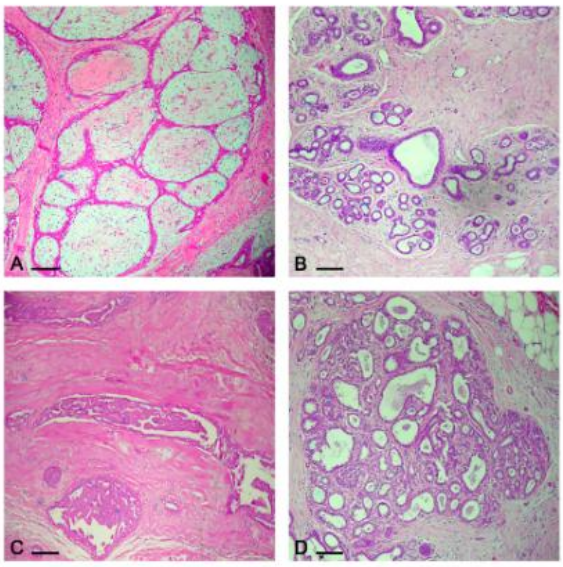

Fig 1 Illustrative images of different types of benign breast lesions in women. A: Fibroadenomas; B: Fibrocystic changes; C: Ductal hyperplasia; D: Adenosis. Scale bars: 50 µm

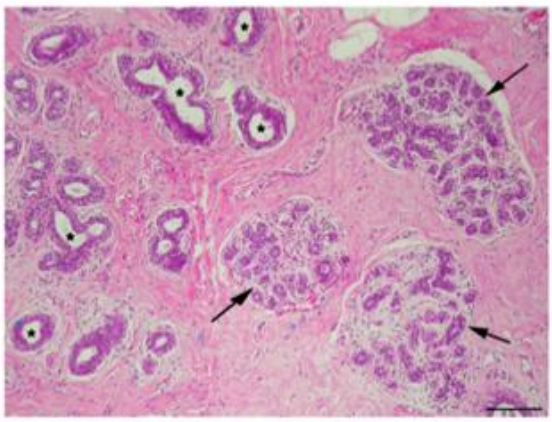

Fig 2 Photomicrograph showing the mammary lobules transition region of normal tissue for the hyperplastic. On the left side the usual ductal hyperplasia (*) on the right side and normal tissue. The arrows indicate the normal tissue. Scale bars: 50 µm

The study included 338 women undergoing breast cancer treatment at a referral hospital. Among these, 159 (47.1%) had benign breast disease (GBBD) and 179 (52.9%) were controls (GC). Most of the women with BBD were diagnosed with fibroadenoma (43.9%). Regarding the age of diagnosis, younger women (39.4 ± 12.9 years) showed fibroadenoma, while the older ones (52.7 ± 14.8 years) had atypical hyperplasia (Table 2).

Table 1 Main clinical and histopathological features of benign breast lesions [17], [18]

Pathological diagnosis:	Characteristics: Clinics	Histopathological
Fibroadenomas	- Small nodule (up to 3 cm), single; - Hard consistency and elastic; - Mobile on palpation; - Painless; - Slow growth;	- Lobed surface, well delimited; - Hyperplasia of lobules normal;
Fibrocystic breast changes	- Variable size palpable mass; - Margins generally ill-defined;	Alone or combined presence: - stromal fibrosis; - apocrine metaplasia; - adenosis;
Proliferative disease without atypia	- Irregular growth; - No evident cell borders;	- Cells proliferate in addition 3 to 4 layers above the basement membrane, tending to distend and fill the ducts involved; - Cell orientation can be in snails, arches and bridges; - Ductal hyperplasia of usual type;
Benign phyllodes tumor	- Unilateral mass (low 4 cm); - Mobile on palpation; - Painless;	- Margins are not so defined, with lobulated border; - Standard "cloverleaf"; - Mesenchymal component is hypercellular, mainly around the glandular structures; - Minimal or absent cell atypia;
Atypical ductal hyperplasia	- Small lesions (menor 2mm); - Hard consistency; - Nonpalpable; - Asymptomatic;	- Intraductal proliferation of monomorphic cells, with regular distribution; - Homogeneous cell proliferation; - Formation of micropapilas; - Hyperchromasia may be present; - Hiperplasia ductal atípica;
Atypical lobular hyperplasia	- Nonpalpable; - Asymptomatic;	- Multifocal and bilateral distribution; - The cells may extend through the ducts.

Table 2 Percentage of different histological subtypes of benign breast disease according to the mean age of diagnosis (n=157)

Type of benign breast disease:	n (%)	Age at diagnosis Dean (SD)
Fibrocystic breast changes	19 (12.1)	47.7 ± 11.9
Fibroadenomas	69 (43.9)	39.4 ± 12.9
Other breast lesions nonproliferative	37 (23.5)	46.7 ± 12.0
Proliferative lesions without atypia	24 (15.2)	49.50 ± 11.2
Benign phyllodes tumor	4 (2.5)	44.5 ± 6.4
Atypical hyperplasia	4 (2.5)	52.7 ± 14.8

Women between 40 and 59 years old and with low degree of education (< 5 years) were more likely to have BBD. However, no relationship of the disease with marital status, occupation, smoking, alcohol consumption or physical activity was noted (Table 3).

In the sample were observed crude associations between breastfeeding, nulliparity, age at menarche, overweight, the first mammography age and BBD. After adjustment for age and education, only age at first mammogram did not remain associated (Table 4).

Table 3 Factors sociodemographic, behavioral and benign breast disease

Variables	Groups GBBD (n=159) [n (%)]	GC (n=179) [n (%)]	OR (95% CI)
Age (years)			
20 - 39	48 (30.1)	29 (16.2)	1
40 - 59	94 (59.2)	126 (70.4)	2.337 (1.078 – 5.065)
≥ 60	17 (10.7)	24 (13.4)	1.053 (0.536 – 2.071)
Marital status			
Married	87 (54.7)	91 (51.2)	1
Separate / Divorced	16 (10.0)	33 (18.5)	1.593 (0.735 – 3.454)
Single	44 (27.7)	34 (19.1)	0.808 (0.318 – 2.052)
Widow	12 (7.6)	20 (11.2)	2.157 (0.927 – 5.017)
Education (years)			
< 5	26 (16.3)	47 (26,2)	1
≥ 5	133 (83.7)	132 (73,8)	0.549 (0.321 – 0.939)
Occupation			
Retired	11 (6.9)	14 (7.8)	1
Education service	8 (5.1)	1 (0.6)	0.157 (0.016 – 1.548)
Health Service	8 (5.1)	7 (3.9)	0.229 (0.021 – 2.456)
Social service	51 (32.0)	52 (29.2)	0.196 (0.022 – 1.738)
Domestic Service	81 (50.9)	104 (58.5)	0.148 (0.017 – 1.289)
Smoking			
Current	21 (19.9)	28 (16.0)	0.615 (0.201 – 1.887)
Former	6 (5.6)	13 (7.4)	0.792 (0.422 – 1.488)
Never	79 (74.5)	133 (76.6)	1
Alcohol Consumption			
No	87 (82.8)	151 (85.8)	1
Yes	18 (17.2)	25 (14.2)	1.250 (0.645 – 2.420)
Physical activity			
No	134 (84.3)	154 (86.5)	1
Yes	25 (15.7)	24 (13.5)	0.835 (0.455 – 1,531)

GBBD: group benign breast disease; GC: group control; BMI: body mass index; OR: odds ratio; CI: confidence interval.

IV. DISCUSSION

Most of the biopsies showed non-proliferative lesions (79.8%), including fibrocystic changes of the breast, fibroadenoma, and other non-proliferative breast lesions. About 17.7% of the biopsies revealed proliferative lesions without atypia (proliferative lesions without atypia, benign phyllodes tumor) and 2.5% had atypical hyperplasia (Table 2). Our results are concurrent with those of other studies which also found the same profile of benign breast lesions, showing greater occurrence of non-proliferative lesions and lower frequency of proliferative with atypia [5-7].

Noteworthy is also the breast lesions that occur in most cases are benign. Thus, fibroadenoma, considered a non-proliferative lesion, is the commonest among the benign tumors in female breast, and the most frequent in women of reproductive age, particularly in the thirddecade of life [17]. Indeed, our results corroborate with the description given above, in that fibroadenoma was diagnosed early in women, in their third decade of life.

In this study, the mean age of the women diagnosed with BBD at the time of the first breast biopsy was 42.2 ± 12.8 years. Other studies reported the average age being slightly higher, at 48.6 years for African women [7], and 46.6 years for women included in a multiethnic meta-analysis [4].

A few studies also indicated that women having a previous history of benign breast disease had a higher risk of developing breast cancer, in particular those with proliferative breast disease, over those with nonproliferative type [4, 7]. Hartmann and co-workers highlighted the risk factors for breast cancer after the diagnosis of benign breast disease, which include the histologic classification of a benign breast tissue lesion and having a family history of breast cancer [5].

Table 4 Characteristics clinical, gynecological, obstetric and anthropometric with benign breast disease

	Total			
	GBBD	GC	OR (95% CI) Crude	OR (95% CI) Ajusted
Nulliparity				
Yes	40	17	1	1
No	117	160	0.311 (0.168-0.575)	0.397 (0.205-0.767)
Menarche				
< 12 years	42	27	1	1
≥ 12 years	122	149	0.483 (0.281-0.831)	0.542 (0.311-0.946)
Menopause				
No	100	104	1	1
Yes	57	73	0.812 (0.522-1.263)	1.264 (0.736-2.170)
Age of first full pregnancy				
< 30 years	147	101	1	1
≥ 30 years	13	17	1.909 (0.888-4.106)	1.957 (0.900-4.256)
Age of first MMG				
≤ 40 years	106	100	1	1
> 40 years	51	77	0.625 (0.400-0.977)	0.789 (0.471-1.324)
Breastfeeding				
No	58	27	1	1
Yes	99	149	0.305 (0.181-0.514)	0.361 (0.208-0.628)
Stillbirth				
No	140	154	1	1
Yes	12	23	0.574 (0.275-1.196)	0.671 (0.317-1.418)
Abortion				
No	100	115	1	1
Yes	53	62	0.983 (0.624-1.548)	1.199 (0.742-1.937)
Use of oral contraceptives				
No	52	61	1	1
Yes	105	114	1.080 (0.685-1.703)	1.048 (0.655-1.675)
Hormone replacement therapy				
No	136	145	1	1
Yes	19	29	0.699 (0.374-1.304)	0.825 (0.436-1.563)
Overweight (BMI)				
No	83	62	1	1
Yes	74	117	0.480 (0.309-0.746)	0.540 (0.343-0.849)

GBBD: group benign breast disease; GC: group control; MMG: mammography; OR: odds ratio;
CI: confidence interval. Adjusted for age and education.

It is now concluded that the precursors involved in breast cancer development may already exist in benign breast disease. This finding arises from the observation that breast cancer occurred in the same breast, particularly in those women with earlier diagnosis of proliferative disease with atypia [5].

In this study, after adjusting for covariates, the birth of at least one child acted as a protective factor against the development of BBD, as were late menarche and breastfeeding. Women with benign breast disease were then tested to identify the reproductive factors, hormonal and lifestyle aspects connected with the risk of breast cancer development in the future. In light of this finding, patients with the first live birth before 25 years of age and three or more pregnancies had an OR value of 0.49 for breast cancer, implying a protective effect of early age at first pregnancy and higher parity [19].

The literature reports age of menarche lower than 12 years as a risk factor for breast cancer, probably due to the prolonged exposure of the breast epithelium to estrogen and progesterone induced by the early onset of the regular menstrual cycles and ovulation. Our results emphasize that delayed menarche decreases the length of exposure time to the endogenous sex hormones, thereby protecting the women of this study, against the development of BBD, because the age of menarche is a chronological index of the initiation of ovarian activity [20].

Estrogen and progesterone ovarian govern the processes of both epithelial cell proliferation in the breast tissue, as well as the rise of hormones like prolactin and IGF-1. During adolescence and adulthood, these may be the major factors that determine the risk of developing breast cancer by increasing those cells which trigger the promotion of carcinogenesis and tumor growth [21].

Two likely mechanisms have been suggested to show that mammary carcinogenesis is linked with estrogen production. The first is dependent on the estrogen receptor, which mediates the stimulation of the cell proliferation in the breast, increasing the mutation rate. Finally, the mechanism, independent of the estrogen receptor-mediated genotoxic metabolites of estrogen, results in more DNA mutations. If either of these pathways or both are active, the mutations will accumulate over time, and thus induce neoplastic transformation [22].

Further, breastfeeding is definitely a protective mechanism, because it is during this time that the amenorrhea induced by the lactating mammary cells are exposed to the effect of the sex hormones for a lesser time span, as they decrease at this period. Another mechanism proposed is that the cells which has suffered DNA damage got eliminated, via strong exfoliation through the breast tissue and epithelial cell apoptosis [23].

Pregnancy also offers protection which is mediated by breast tissue differentiation. The pregnancy-related epigenetic changes in mammalian cells lower their susceptibility to tumor formation, because gestation triggers a local reprogramming and some possibly unsuitable genes are muted, like the ones connected with cell proliferation [24].

Thus, age at menarche, age of first pregnancy, and breastfeeding appear to have no bearing on fibrocystic breast disease or fibroadenoma [25]. In contrast, another study reported that breast tissue density alone was associated with benign proliferative breast disease, showing around twice the risk (OR = 1.91). However, all other possible epidemiological risk factors that were evaluated are not associated, including lifestyle, socioeconomic and anthropometric factors, as well as the reproductive and menstrual history [26].

In this study, the overweight was significantly associated with a lower risk of developing BBD in both models, crude and adjusted for age and education. At present, there is a gap in knowledge regarding the BMI and the BBD. However, recent research showed an inverse relationship between BMI and the benign pathologies evaluated, i.e. the patients with increasing BMI had a lower incidence of BBD [27].

V. CONCLUSIONS

It is a well accepted fact that the BBD is very common, although the incidence is not well documented in the literature, probably because its importance is underestimate. In light of the results of this study, the mostly protective factors linked with the BBD are related to the concentrations of the endogenous hormone and main reproductive events like menarche and parity, which are the more difficult factors to control. However, breastfeeding should be encouraged, as it contributes to a lowering of the incidence of BBD and possibly in the subsequent development of breast cancer in the future.

Therefore, further studies in this field are warranted to raise our awareness of the behavior of benign breast disease in this population. This will enable the identification of the high-risk women who could benefit from heightened vigilance and, ultimately, clear diagnosis and early treatment.

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