# Breast Cancer in Men: Clinical and Pathological Analysis of 817 Cases

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## Abstract

The objective of the current study was to describe breast cancer cases in men according to age, stage, and histology, calculating risks compared to women. It is a retrospective cross-sectional study of all breast cancer cases of the Hospital Cancer Registry of São Paulo state, Brazil, 2000–2015. Variables were age, sex, stage, and histology. Absolute numbers and proportions, Mann–Whitney test and prevalence ratio with 95% confidence interval were used.

The study included 93,737 cases, of which 817 were males. The mean age at diagnosis was 60.3 years in men and 56.2 years in women (p < .001). Stage II was the most common in both sexes (33.9% in men and 36.5% in women). Men had a higher frequency of stage III than women (PR 1.18, 95% CI 1.01–1.37). Stage 0 was significantly more common in women (PR 0.69, 95% CI 0.51–0.94). Ductal carcinoma and its variants were the most common histological types in both sexes (88.7% in men and 89.0% in women). Men had a higher frequency of rarer histological types such as papillary (PR 2.17, 95% CI 1.36–3.44) and sarcomas (PR 4.10, 95% CI 1.86–9.01). In conclusion, in men, breast cancer diagnosis occurred in more advanced ages and stages. Invasive ductal carcinoma was the primary histological type observed, although rarer types were more frequent.

## **Keywords**

Breast neoplasms male, men's health, neoplasm staging, rare diseases

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Breast cancer has the highest incidence and mortality rates in the female population worldwide. The World Health Organization estimates that around 1.7 million new cases and 522,000 deaths occur every year (Ferlay, 2013). Only 1% of total breast cancer cases occur in the male gender (National Cancer Institute - b). Once rare, breast cancer in men is poorly understood.

Risk factors for the development of breast cancer in men are age, family history, diseases associated with hyperestrogenism, such as cirrhosis and Klinefelter's syndrome, radiation exposure, hormone replacement with estrogens, black race, and obesity. The most critical risk factor is a positive family history of breast cancer: risk increases by twofold if the history is positive for first-degree relatives and five times if there are other affected first-degree relatives (Sanguinetti et al., 2016).

The familial factor is related to mutations in several genes: the *BRCA2* and *BRCA1* genes (Hereditary Breast

and Ovary Syndrome), the *TP-53* gene (Li–Fraumeni Syndrome), the *MLH1*, *MSH2*, *MHH6*, or *PMS2* genes (Lynch Syndrome) and *PALB2* genes. In women, the mutation in the *BRCA1* gene is the most common, whereas, in men, it is the mutation in *BRCA2*. In men, *BRCA2* mutations are responsible for 60–76% of families at high risk for breast cancer, whereas *BRCA1* mutations are involved in only 10–16% of cases (Ding et al., 2011; Sanguinetti et al., 2016). Breast cancer in men shows more positivity for estrogen receptors and more negativity for overexpression of HER-2 (human epidermal growth

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The male patient himself usually notes the first clinical sign of breast cancer. The most common presentation is the appearance of a nodule or nipple retraction. Breast discharge, palpable axillary adenopathy, and skin ulceration may also occur. The most common and highly prevalent differential diagnosis is with gynecomastia (Giordano, 2018). Symptoms are usually noted later by men than women. On average, diagnosis occurs at around 67 years old (Giordano, 2018). Clinical presentation varies in men and women. Men have more localized tumors, but more lymph node involvement and higher chances of metastasis at diagnosis. Axillary involvement is the main predictor of local recurrence and risk of metastasis and is present in approximately 50% of cases of male breast cancer (Giordano et al., 2004). Stage at diagnosis in men tends to be more advanced (Greif et al., 2012). Survival rates and prognosis between men and women are similar when comparing patients with the same clinical stage and tumor characteristics (hormone receptors, axillary involvement, tumor size, and histology) (Bender et al., 2017). Survival in men is lower than in women when compared to earlystage disease without lymph node involvement, suggesting that there are differences between gender in the pathogenesis and biology of the neoplasia (Nahleh et al., 2007). There are few data in the literature on differences in prognosis related to the histological type.

The most common histological type in both sexes is invasive ductal carcinoma, occurring in about 80% of cases. In women, the second most prevalent type is lobular carcinoma (11.8%), which may be rare in men (Fentiman, 2009). Men have a high positivity rate of estrogen and progesterone receptors (Cardoso et al., 2018).

Breast cancer in men is poorly understood. Although rare, its incidence has increased by 26% in the last 25 years (Sanguinetti et al., 2016). Few studies address this issue, and usually, they have small numbers, which makes it challenging to analyze epidemiologically (Cardoso et al., 2018; Giordano et al., 2004; Greif et al., 2012; Sanguinetti et al., 2016). This study aimed to describe the distribution of breast cancer cases in men according to age, stage at diagnosis, and histological type in a highly populated urban sample in Brazil, as well as to calculate the risk of having this diagnosis compared to women.

## **Materials and Methods**

It was a retrospective cross-sectional study with secondary data analysis from the Hospital Cancer Registry of the Oncocentro Foundation of São Paulo (HCR-FOSP), from 2000 to 2015 (Brasil, Fundação Oncocentro do Estado de São Paulo, 2018). The HCR-FOSP contains the registry of all female and male cases admitted for cancer treatment in hospitals in São Paulo state, the most populous in Brazil. São Paulo corresponds to 22% of the Brazilian population. The sample consisted of all cases of breast cancer registered in the HCR-FOSP in the period, a total of 93,737 cases. Public and private hospitals are obligated to report cancer cases to the HCR-FOSP to obtain the license to treat cancer patients. The number of cases registered each year was consistent with the population growth.

The variables available were age, sex, clinical stage, and histological type. Cases were grouped in the following age groups: less than 40 years, 40–49 years, 50–59 years, 60–69 years, and over 70 years. Stages were grouped according to the classification of the American Joint Committee (AJCC) (American Joint Committee Breast Cancer, 2017). Histological types were classified according to the International Classification of Diseases for Oncology (ICD-O). Some rare types have been grouped (e.g., sarcomas). All 817 cases in men and 92,920 cases in women registered in the period were included. The stage was not reported in 30 cases in men (3.7%) and 2,190 cases in women (2.4%).

Distribution of cases was shown in absolute numbers and proportions. Mann–Whitney test was used to compare the numerical variables between sexes. For risk assessment, the prevalence ratio with a 95% confidence interval (CI) was used, with a significance level adopted for the statistical tests of 5% (p < .05).

The Ethics Committee of the *(blinded for review)*. The Committee waived the need for consent.

## Results

The study included 93,737 cases of breast cancer in the period, of which 817 (0.87%) were male and 92,920 (99.13%) were female. The mean age at diagnosis was 60.3 years for men and 56.2 years for women (p < .001). Figure 1 presents the distribution of cases according to the analyzed age group.

Table 1 presents the prevalence of stage cancer at diagnosis. Stage was not available in 2,220 cases (2.4%) and was not included in this analysis. Stage II was the most common in both sexes: 266 cases (33.9%) in men and 33,105 cases (36.5%) in women. Men had a higher frequency of stage III and IV than women (PR 1.18, 95% CI 1.01–1.37 and PR 1.35, 95% CI 1.09–1.68, respectively). Stage 0 was significantly more common in women (PR 0.69, 95% CI 0.51–0.94).

In Table 2, the distribution of cases is presented according to stage and age group in men and women. It is observed that stage II was the most frequent in all age groups in both sexes, except in the group of 60–69 years in men when stage III was the most frequent one.

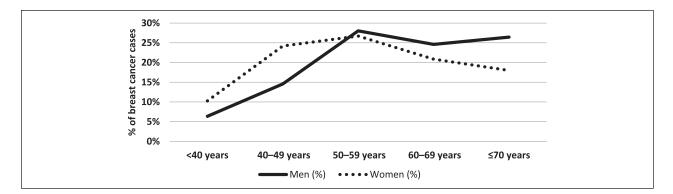


Figure 1. Distribution of breast cancer cases by age and sex in 93,737 cases in São Paulo, Brazil, 2000–2015.

Table I. Pr	revalence of Breast	Cancer Cases	by Stage and Sex in	São Paulo, Brazil, 2000–2015.
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Stage	Men n (%)	Women n (%)	Total	Prevalence ratio	95% confidence interval
0	42 (5.36)	6,904 (7.61)	6,946	0.69	0.51-0.94
I	157 (20.03)	19,257 (21.22)	19,414	0.93	0.78-1.11
11	266 (33.93)	33,105 (36.49)	33,371	0.89	0.77-1.04
111	229 (29.21)	23,554 (25.96)	23,783	1.18	1.01-1.37
IV	90 (11.48)	7,910 (8.72)	8,000	1.35	1.09-1.68
Total	784 (100)	9,0730 (100)	91,514		

Table 2. Distribution of Breast Cancer Cases by Age, Sex, and Stage in São Paulo, Brazil, 2000–2015.

Stage		<40 years n (%)	40–49 years n (%)	50–9 years n (%)	60–69 years n (%)	≥70 years n (%)
0	Men	4 (8.2)	12 (10.3)	13 (5.8)	8 (4.2)	5 (2.4)
	Women	457 (5.0)	1,999 (9.1)	2,085 (8.6)	1,469 (7.8)	894 (5.5)
l	Men	10 (20.4)	23 (19.8)	48 (21.4)	43 (22.6)	33 (16.1)
	Women	1,253 (13.6)	4,250 (19.3)	5,430 (22.4)	4,720 (24.9)	3,604 (22.1)
I	Men	16 (32.7)	45 (38.8)	76 (33.9)	56 (29.5)	73 (35.6)
	Women	3,485 (37.7)	8,155 (37.1)	8,749 (36.0)	6,797 (35.9)	5,919 (36.4)
11	Men	15 (30.6)	20 (17.2)	60 (26.8)	66 (34.7)	68 (33.2)
	Women	3,081 (33.3)	5,933 (27.0)	6,038 (24.9)	4,355 (23.0)	4,147 (25.5)
V	Men	4 (8.2)	16 (13.8)	27 (12.1)	17 (9.0)	26 (12.7)
	Women	965 (10.4)	1,634 (7.4)	1,973 (8.1)	1,620 (8.5)	1,718 (10.6)
Total	Men	49 (100)	116 (100)	224 (100)	190 (100)	205 (100)
	Women	9,241 (100)	21,971 (100)	24,275 (100)	18,961 (100)	16,282 (100)

Table 3 presents the histological types observed as a function of sex. Ductal carcinoma and its variants were the most common histological types for both genders, corresponding to 88.7% of cases in men and 89.0% of cases in women. In men, *in situ* carcinomas and their variants were detected in 6.4% of cases, while in women, the invasive lobular type was the second most common, representing 5.8% of cases.

The higher frequency of *in situ* carcinoma and its variants in men (PR 1.54, 95% CI 1.16-2.03) was

mainly determined by the higher prevalence of *in situ* intraductal tumors (RP 1.73, 95% CI 1.29–2.33). They also had a higher frequency of more rare histological types such as papillary (PR 2.17, 95% CI 1.36–3.44) and sarcomas (PR 4.10, 95% CI 1.86–9.01), as well as very rare histological types, here classified as other (PR 1.85, 95% CI 0.99–3.43) and poorly defined histology as undifferentiated carcinoma (PR 26.37, 95% CI 18.88–36.82). In women, a higher frequency of invasive ductal carcinoma (PR 0.67, 95% CI 0.57–0.79) and

	Men	Women	Prevalence ratio (95%
Histological types	n (%)	n (%)	confidence interval)
Carcinoma in situ types	52 (6.36%)	3,920 (4.22%)	1.54 (1.16–2.03)
Papillary non invasive	0 (0%)	206 (0.22%)	0.28 (0.02-4.41)
Intraductal (in situ)	46 (5.63%)	3,072 (3.31%)	1.73 (1.29–2.33)
Lobular (in situ)	4 (0.49%)	539 (0.58%)	0.84 (0.32-2.25)
Paget disease	2(0.24%)	103 (0.11%)	2.19 (0.55–8.65)
Ductal types	725 (88.74%)	82,656 (88.95%)	0.98 (0.79-1.21)
Ductal invasive	643 (78.70%)	78,676 (84.67%)	0.67 (0.57-0.79)
Inflammatory	5 (0.61%)	302 (0.33%)	1.87 (0.78-4.48)
Medulary	5 (0.61%)	372 (0.40%)	1.52 (0.64–3.65)
Mucinous	11 (1.35%)	1,109 (1.19%)	1.13 (0.62–2.04)
Papillary	18 (2.20%)	947 (1.02%)	2.17 (1.36–3.44)
Tubular	5 (0.61%)	329 (0.35%)	1.72 (0.72-4.12)
Undifferentiated carcinoma	28 (3.43%)	98 (0.11%)	26.37 (18.88–36.82)
Metaplastic	0 (0.00%)	208 (0.22%)	0.27 (0.02-4.37)
Other	10 (1.22%)	615 (0.66%)	1.85 (0.99–3.43)
Lobular invasive	22 (2.69%)	5,410 (5.82%)	0.45 (0.29–0.69)
Linfomas	I (0.12%)	87 (0.09%)	1.30 (0.19–9.17)
Sarcomas	6 (0.73%)	163 (0.18%)	4.10 (1.86–9.01)
Phyllodes	0 (0.00%)	290 (0.31%)	0.20 (0.01–3.14)
Others*	(1.35%)	394 (0.42%)	3.15 (1.75–5.66)
Total	817 (100.00%)	92,920 (100.00%)	

 Table 3. Histology Types of Breast Cancer Cases by Sex in 93,737 Cases in São Paulo, Brazil, 2000–2015.

\*Others: Neoplasia, NOS, carcinofibroma, compound carcinoid, cutaneous appendage carcinoma, sclerosing sweat ductal gland carcinoma, squamous cell carcinoma, fusocellular carcinoma, lifoepithelial carcinoma, aggressive fibromatosis, melanoma, transitional cell neoplasia, germ cell neoplasia, and Mullerian mixed tumor.

invasive lobular carcinoma (PR 0.45, 95% CI 0.29–0.69) was observed.

## Discussion

In this assessment of secondary data on male breast cancer, it was observed that cases in men were rare (<1%) and occurred in more advanced ages and stages than in women. Although cases in men were more advanced, a higher frequency of carcinomas *in situ* and their variants was observed. Rare histology types such as papillary, sarcomas, and others were also more frequent in men.

In this study, the mean age at diagnosis was 60.3 years old in men and 56.2 years old in women. Another sample of cases in Brazil found an average age in men of 59.6 years from 2000 to 2009 (Thuler & Bergmann, 2015). The mean age observed in women in this study was similar to what is seen by other authors that used similar data (Renna Junior & Silva, 2018). In the United States, the average age in women observed from 2011 to 2015 was 62 years old (National Cancer Institute -a), in Mexico from 2004 to 2006, it was 56 years old (Mexico. Secretaria de Salud, 2011), and in Colombia, from 2008 to 2012, it was 58 years old (Murillo et al., 2016).

In men, breast cancer is commonly associated with a poor prognosis, probably due to the usual delay in detecting the disease, mainly due to the lack of knowledge about this disease among men. While stage II was the most common in both sexes, men had a higher frequency of stage III and IV than women. The literature points to the diagnosis of more advanced stages in men, probably reflecting differences in access and prevention policies (Fentiman, 2009; Giordano et al., 2004; Greif et al., 2012; Thuler, 2015).

The worst prognosis has been attributed to the delay in diagnosis and the increase in age (Giordano, 2018). It is possible that the older age found in male is due to the delay in diagnosis, but is more likely that the difference between can be attributed to the hormonal exposition in women until menopause. The behavioral difference between the female and male tumors can also be explained mainly by the anatomical difference between both sexes. In men, the breast tissue is very close to the skin, whose lymphatic drainage is attached to the subareolar and axillary plexus. In contrast, in female breasts, the subareolar plexus plays a prominent role in lymphatic drainage, although major lymphatic drainage occurs within the breast, rather than occurring on the surface, close to the skin. For this reason, it can be justified why, when comparing similar clinical stages between men and women, the 5-year survival rate is lower in the male population (Giordano et al., 2004). Interestingly, a retrospective cohort study in Brazil found no significant difference in prognosis but could found differences in clinical and sociodemographic characteristics (Bender et al., 2017).

The histological types most frequently observed in both sexes were the ductal types, especially the invasive ductal, in agreement with the literature data (Fentiman, 2009; Thuler & Bergmann, 2015). The second most common type in women was the lobular type, which did not happen in men, probably because male breast shows little lobular differentiation, consisting mainly of ducts and fibrous tissue (Giordano, 2018).

The literature states that only 10% of men with breast cancer have carcinoma *in situ*, and when they do, the most common *in situ* subtype is ductal carcinoma, which rarely manifests as a palpable mass (Anderson & Devesa, 2005). In this sample, this was the second most frequent histological type in men, probably due to a lower proportion of invasive lobular carcinomas, which are the most common in women. The increased risk of having carcinoma *in situ* in men should not represent a more straightforward diagnosis of these tumors in this gender, but a proportional increase in nonductal types.

This study had the benefit of a large sample of cases from a middle-high income state in Brazil. The HCR-FOSP data are of a high quality due to the completeness of the information. The study, however, found some limitations, such as the scarcity of data in the literature. Although the São Paulo state is the most populous in Brazil, this study evaluates only about a quarter of the Brazilian population. Because it is a hospital record data, it is not possible to use it to calculate incidence. The estimated number of breast cancer cases in São Paulo state in 2018 was around 16,000 women per year (Brasil, Instituto Nacional de Câncer, 2017). In this study, the sample was 93,737 cases, which may correspond to less than half of the estimated number of cases for the state in the period. The cases not recorded at the HCR-FOSP possible were under registered by the hospitals or were treated at small private clinics. As a rare disease, it is more likely that male cases were well represented in this sample, following the tendency to refer rare and complex cases to tertiary or university hospitals with good notification practices.

It is not known which cases were diagnosed through screening, and there was no characterization of men's high-risk families. Other variables were not available, hampering analyses on prognosis and survival.

Studies claim that initiatives of programs aimed at educating the male population about breast cancer, especially among those at highest risk for developing the disease. Patients with a previous history of breast cancer or other types, especially prostate cancer, or family history of breast cancer, should be considered candidates for screening, but the literature does not yet define when the onset and frequency of cancer prevention are recommended. The National Comprehensive Cancer Network (NCCN) states that men with BRCA mutation should be candidates for breast self-exam training in addition to being screened annually from age 35 onward (Daly et al., 2010). High clinical suspicion and availability of access to diagnosis and treatment can contribute to early diagnosis and improvements in prognosis.

## Conclusions

In conclusion, breast cancer was much less common in men than in women, and the diagnosis occurred in more advanced ages and stages. Invasive ductal carcinoma was the primary histological type observed, although rarer types were more frequent.

#### **Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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