RESEARCH ARTICLE

Men Have a Higher Incidence of Seroma after Breast Cancer Surgery

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Abstract

Background and Objectives: Male breast cancer (MBC) is rare. While surgical treatment may result in several complications in women, little is known about how it affects men. The objective of this study was to compare the incidence of postoperative wound complications between men and women after breast cancer surgery. **Methods:** This cohort study included all male patients enrolled for breast cancer surgical treatment at the Brazilian National Cancer Institute, between 1999 and 2013. Each was matched with three female breast cancer patients. Parameters analyzed were necrosis, seroma and infection. Odds ratios (OR) were generated and statistical significance was considered at $p<0.05$. **Results:** We included in this study 71 men and 213 women with an average age of 63.5 (±12.0). The incidences of complications in men and women were: necrosis, 32.8% and 37.8% (p=0.477); seroma, 80.6% and 59.4% (p=0.003); and surgical site infection, 14.8% and 18.2% (p=0.54). After adjustment, men had a 3 times greater risk of developing seroma compared to women (OR=3.0; IC95%=1.4-6.4; p=0.004). No statistically significant differences was detected in the incidences of wound infection and necrosis. **Conclusion:** Men have a greater risk of developing seroma after surgery for breast cancer than women, whereas infection and necrosis occur at similar frequencies in both genders.

Keywords: Breast neoplasms- male breast cancer- surgical wound infection- seroma- necrosis

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Introduction

Breast cancer is a serious public health issue. Male breast cancer is rare, representing 0.6% of all breast cancer cases and 1% of male neoplasias (Bourhafor, et al., 2011). Data from Population-Based Cancer Registries between 1988 and 2012 indicate that from the 138,754 breast cancer cases registered in Brazil, 1391 (1.0%) affected males (Brasil, 2015a). Data from the Brazilian Mortality Information System indicate that from the 14,388 deaths caused by breast cancer in 2013, 181 (1.2%) affected males (Brasil, 2015b).

Several studies have reported differences between incidence patterns for male breast cancer in men (MBC) and women regarding the age at diagnosis, histological types, expression of hormone receptors, clinical presentation and prognosis (Sousa et al., 2013; Ruddy and Winer, 2013). Because breast cancer is rare in men and information from clinical trials involving men is lacking, treatment of MBC still relies on extrapolating knowledge from breast cancer in women (Bender et al., 2014).

Surgical treatment in women may lead to several complications, such as infection and necrosis of the postoperative wound, seroma, adhesion and scar dehiscence, limitation of shoulder range of motion, axillary web syndrome, pain, paresthesia, muscle weakness and lymphedema (Bevilacqua et al., 2012; Bergmann et al., 2012; Fabro et al., 2012). A recent systematic literature review failed to find studies on complications of oncological treatments for MBC (Bender et al., 2014).

The goal of this study was to compare the incidence of postoperative wound complications between men and women after breast cancer surgery..

Materials and Methods

A cohort study was performed with all male patients submitted to breast cancer surgical treatment (with axillary lymphadenectomy and/or sentinel lymph node biopsy), diagnosed and treated at the National Cancer Institute (INCA), in Rio de Janeiro, Brazil, between 1 January 1999 and 31 December 2013. From the 20,208 new breast cancer cases identified during this period, 98 (0.5%) affected males. For analysis, each male patient was matched with three female breast cancer patients . Matching was based on age at diagnosis (±3 years), year of diagnosis, and clinical stage. Women for each stratum were selected via random electronically generated numbers. Patients submitted to neo-adjuvant or adjuvant oncological treatments in other institutions were excluded.

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The variables collected were: socio-demographic variables (age, race/color of the skin [white x non white], schooling [years of study], marital status, alcohol and tobacco consumption [consumer, ex-consumer, non consumer]); clinical variables (comorbidities); tumor variables (histological type, histological grade, tumor size, lymph node involvement [number of positive lymph nodes], clinical staging, expression of the Human epidermal growth factor receptor-2 [HER-2], expression of the estrogen hormone receptor [ER], expression of the progesterone hormone receptor [PR]); and treatment variables (type of surgery [mastectomy x conservative surgery x exclusive axillary lymphadenectomy], type of axillary approach [lymphadenectomy x sentinel lymph node biopsy x none], performance of radiotherapy, chemotherapy or hormone therapy).

The following outcomes were considered: postoperative necrosis, seroma and surgical site infection (SSI) occurring up to 2 months after the breast cancer surgical treatment. Necrosis was considered as de-vascularized lesion in the scar margin of the surgical wound accompanied by tissue decomposition with a liquefactive or coagulative appearance. Seroma was considered as the accumulation of liquid (>50ml) in the subcutaneous tissue, usually formed by plasma and/or lymph. SSI was considered as infection occurring up to thirty days after surgery, involving skin and subcutaneous tissue or deep soft tissues, associated to at least one of the following events: purulent drainage, with or without laboratory confirmation; fever (≥38°C) accompanied by one or more infection signs or symptoms (pain, edema, redness or localized heat); the incision was deliberately opened by a surgeon to manage the infection, unless the culture was negative; diagnosis of superficial or deep infection of the postoperative wound by the surgeon or assistant physician with an indication for use of an antimicrobial agent.

A descriptive analysis of the study's population was built based on measures of central tendency and dispersion for continuous variables, and frequency distribution for categorical variables. Odds Ratio (OR) was used to evaluate the association between outcomes and gender. A multiple logistic regression using the Stepwise Forward method was performed when the association was significant ($p<0.05$), and the adjustment variables were identified as those having $p<0.20$ in the univariate analysis (potential confounders). The variables with statistical significance ($p<0.05$) and/or clinical significance were kept in the model. The SPSS (Statistical Package for the Social Sciences) program, version 20.0, was used to perform the statistical analyses of this study. The Ethics Committee for Research of INCA approved this project (CAAE 12107913.3.0000.5274).

Results

We included in the study 71 men and 213 women with an average age of 63.5 (±12.0). Regarding socio-demographic and clinical characteristics, having a companion ($p<0.001$), being alcoholic ($p<0.001$) and smoking ($p<0.001$) were more frequently reported by men than women at the time of diagnosis (Table 1).

Regarding tumor characteristics, no statistically significant differences in histological grades, tumor size and lymph node involvement were detected between men and women. At the time of diagnosis, the disease was in advanced stages for more than half of the patients (58.6%) (≥IIB). As for expression of hormone receptors, men presented a higher frequency of ER ($p=0.001$) and PR ($p=0.002$) positive tumors. While HER-2 expression was not detected in man, 18.8% of women were HER-2 positive ($p=0.002$) (Table 2).

Regarding the treatments performed, statistically significant differences between men and women were found for indication for radical mastectomy, neo-adjuvant chemotherapy and adjuvant radiotherapy (Table 3).

Table 4 describes the incidence of postoperative wound complications. While 32.8% of men developed necrosis, 14.8% had SSI and 80.6% developed a seroma. Concerning women, 37.8% developed necrosis, 18.2% had

Table 1. Distribution of Socio-Demographic and Clinical Characteristics According to Gender

Variables	Male N=71* N (%)	Female N=213* N (%)	p value
Race/Skin color			
White	33 (54.1)	103 (52.0)	0.884
Non white	28 (45.9)	95 (48.0)	
Marital status			
Without a companion	16 (23.5)	119 (57.8)	**<0.001**
With a companion	52 (76.5)	87 (42.2)	
Years of study			
0 to 7	32 (49.2)	118 (58.7)	0.197
8 or more	33 (50.8)	83 (41.3)	
Alcohol consumption			
Consumer	19 (30.6)	43 (22.2)	**<0.001**
Ex-consumer	11 (17.7)	3 (1.5)	
Non consumer	32 (51.6)	148 (76.3)	
Tobacco consumption			
Consumer	12 (18.8)	26 (12.9)	**<0.001**
Ex-consumer	22 (34.4)	27 (13.4)	
Non consumer	30 (46.9)	148 (73.6)	
Arterial hypertension			
Yes	37 (52.1)	136 (63.8)	0.092
No	34 (47.9)	77 (36.2)	
Diabetes			
Yes	15 (21.1)	39 (18.3)	0.603
No	56 (78.9)	174 (81.7)	
Heart diseases			
Yes	6 (8.5)	26 (12.2)	0.516
No	65 (91.5)	187 (87.8)	
Liver diseases			
Yes	0	5 (2.3)	0.336
No	71 (100.0)	208 (97.7)	

*, Differences in the frequency of variables are due to missing information; Column percentages are presented; Statistically significant differences are highlighted in bold.

Table 2. Distribution of Tumor Characteristics According to Gender

Variables	Male N=71* N (%)	Female N=213* N (%)	p value
Histological type			
Invasive Ductal Carcinoma	55 (77.5)	176 (82.6)	**0.002**
Papillary Carcinoma	9 (12.7)	5 (2.3)	
Others	7 (9.9)	32 (15.0)	
Histological Grade			
High grade (grade III)	18 (29.5)	74 (43.0)	0.069
Low grade (grades I and II)	43 (70.5)	98 (57.0)	
Tumor size			
< 2 cm	34 (47.9)	84 (39.6)	0.081
2 – 5 cm	22 (31.0)	97 (45.8)	
> 5 cm	15 (21.1)	31 (14.6)	
Clinical staging			
< 2B	29 (41.4)	87 (41.4)	1
≥ 2B	41 (58.6)	123 (58.6)	
Lymph node involvement			
Negative	32 (46.4)	111 (53.9)	0.745
1-4 positive lymph nodes	21 (30.4)	48 (23.3)	
> 4 positive lymph nodes	16 (23.2)	47 (22.8)	
Estrogen receptor			
Positive	61 (88.4)	142 (68.9)	**0.001**
Negative	8 (11.6)	64 (31.1)	
Progesterone Receptor			
Positive	50 (75.8)	111 (54.1)	**0.002**
Negative	16 (24.2)	94 (45.9)	
HER-2			
Positive	0	15 (18.8)	**0.002**
Negative	23 (82.1)	63 (78.8)	
Undetermined	5 (17.9)	2 (2.5)	

*, Differences in the frequency of variables are due to missing information; Column percentages are presented; Statistically significant differences are highlighted in bold

Table 3. Distribution of Treatment Characteristics According to Gender

Variables	Male N=71* N (%)	Female N=213* N (%)	p value
Type of surgery			
Radical mastectomy	70 (98.6)	162 (76.1)	**<0.001**
Conservative surgery	1 (1.4)	51 (23.9)	
Type of axillary approach			
Lymphadenectomy	64 (90.1)	170 (79.8)	0.104
Sentinel lymph node biopsy	5 (7.0)	37 (17.4)	
No	2 (2.8)	6 (2.8)	
Neo-adjuvant chemotherapy			
Yes	12 (16.9)	64 (30.0)	**0.030**
No	59 (83.1)	149 (70.0)	
Neo-adjuvant radiotherapy			
Yes	2 (2.8)	7 (3.3)	0.845
No	69 (97.2)	206 (96.7)	
Neo-adjuvant hormone therapy			
Yes	3 (4.2)	7 (3.3)	0.71
No	68 (95.8)	206 (96.7)	
Adjuvant chemotherapy			
Yes	32 (45.1)	82 (38.5)	0.328
No	39 (54.9)	131 (61.5)	
Adjuvant radiotherapy			
Yes	31 (43.7)	128 (60.1)	**0.019**
No	40 (56.3)	85 (39.9)	
Adjuvant hormone therapy			
Yes	50 (70.4)	137 (64.3)	0.348
No	21 (29.6)	76 (35.7)	
Palliative chemotherapy			
Yes	10 (14.1)	19 (9.6)	0.295
No	61 (85.9)	179 (90.4)	
Palliative radiotherapy			
Yes	9 (12.7)	21 (10.6)	0.635
No	62 (87.3)	177 (89.4)	
Palliative hormone therapy			
Yes	4 (5.6)	22 (11.1)	0.18
No	67 (94.4)	176 (88.9)	

*, Differences in the frequency of variables are due to missing information; Column percentages are presented; Statistically significant differences are highlighted in bold.

SSI and 59.4% developed a seroma. Men had a greater risk of developing seroma than women after adjusting for axillary approach and diabetes (crude OR= 2.9; IC95% 1.4-5.7 p=0,003; adjusted OR=3.0; IC95% 1.4-6.4 p=0.004). No statistically significant differences were detected for SSI and necrosis incidence between men and women (Table 4).

Discussion

The present study identified differences in socio-demographic (marital status, alcohol and tobacco consumption), clinical (type of surgery, neo-adjuvant chemotherapy and adjuvant radiotherapy) and tumor characteristics (histological type; ER, PR and HER-2 positivity) between gender.

Male breast cancer is considered to be biologically different from that in females (Shaaban et al., 2012). Nevertheless, because male breast cancer is rare (98 male cases and 20,110 female cases were registered in this study; a 1:205 ratio), and given that fewer studies involve male subjects, knowledge is typically extrapolated from female breast cancer data (Thuler and Bergmann, 2015). Male diagnosis is typically performed in advanced stages. Consequently, men are submitted to more aggressive treatments and show poorer clinical responses (Thuler

Table 4. Risk of Postoperative Wound Complications in Men with Breast Cancer

Complications	Male	Female	Crude			Adjusted		
	N (%)*	N (%)*	OR	95% CI	p value	OR	95% CI	p value
Necrosis								
Yes	20 (32.8)	73 (37.8)	1.3	0,7-2.3	0.48	-	-	-
No	41 (67.2)	120 (62.2)						
Surgical Site infection								
Yes	9 (14.8)	34 (18.2)	0.8	0.4-1.7	0.54	-	-	-
No	52 (85.2)	153 (81.8)						
Seroma								
Yes	50 (80.6)	114 (59.4)	2.9	1.4-5.7	**0.003**	3.0	1.4-6.4	**0.004**
No	12 (19.4)	78 (40.6)						

OR, Odds Ratio; CI, Confidence interval; *Column percentages are presented; Statistically significant differences are highlighted in bold.

and Bergmann, 2015; Yoney et al., 2009).

This study included all male breast cancer cases submitted to surgery, in one single institution, for 14 years. From those, 58.6% were in advances stages of the disease (≥IIB) at the time of diagnosis. In a recent study that included 59,317 women with surgical and non-surgical breast cancer treated between 2000 and 2009 in 239 Brazilian cancer centers, 53.5% were reported to be in advanced stages of the disease (≥IIB) at the time of diagnosis (Abrahão et al., 2015). However, the present study included only patients submitted to surgery, therefore excluding men who were at more advanced stages of the disease, without surgical indication.

The demographic and clinical patient profile was similar to studies performed in other countries: men with breast cancer were typically white, married and with a low level of schooling (Generlich et al., 2011; Ahmed et al., 2012; Shah et al, 2012; Xingyu et al., 2013;). The most frequent histological type described for men was invasive ductal carcinoma, representing 77.5% of all cases. This is lower than the percentage described in studies performed in the United States (83.0%) (Shin et al., 2014), in Morocco (96%) (Bourhafor, et al., 2011), in Egypt (94.5%) (El-Beshbeshi and Abo-Elnaga, 2012), and from a multicenter study in Brazil (83.7%) (Thuler and Bergmann, 2015).

An analysis of 13,457 male breast cancer cases registered in the "National Cancer Data Base" between 1998 and 2007 in the United States showed that 88.3% of cases were estrogen receptor (ER)-positive and 76.8% were Progesterone receptor (PR)-positive (Greif et al., 2012). Similar percentages were found in this study, where 88.4% and 75.8% of male breast cancer was ER and PR positive, respectively. Tural et al., (2013) reported lower values in 2013, in a study involving 99 men in Turkey (65% and 68% were ER and PR positive, respectively).

There is practically no information available in the literature for postoperative complications of male breast cancer. Elshafiey et al., (2011) performed a study involving 32 men with breast cancer in 2011, 25 of which were submitted to surgical treatment. The most frequent complications observed were seroma (36%), dehiscence (12%) and SSI (4%). The study presented here found much higher values: 80.6% of cases had seroma, 32.8% developed necrosis and 14.8% SSI.

The complications developed by women submitted to breast cancer surgical treatment included seroma in 59.4% of patients, tissue necrosis in 37.8% and SSI in 18.2%. These percentages are much higher than those previously described by others. Analysis of data from the National Surgical Quality Improvement Program of the American College of Surgeons, based on 44,533 patients, concluded that the percentage of SSI varied between 1.8 and 2.0% and dehiscence varied between 0.65 and 0.28%, depending on whether neo-adjuvant chemotherapy was or was not used (Decker et al., 2012). A study including 354 Nigerian women performed by Ogundiran et al., (2013) found the following postoperative complications: seroma (6.0%), SSI (4.4%) and skin necrosis (1.7%). Another study performed in Italy with 490 women, reported that seroma (4.8%) and SSI (3.8%) were the most common complications for breast cancer surgery (Rocco et al., 2013). A study by Chirappapha et al., (2014) involving 124 mastectomies performed in women at the European Institute of Oncology in Milan reported that 8.1% developed postoperative wound necrosis, 5.6% had bruising and 2.4% developed infection.

A recent systematic literature review by Bender et al. failed to find studies that compared the incidence of postoperative wound complications in men and women following surgery for breast cancer treatment (Bender et al., 2014). In this study men showed a greater risk of developing a seroma than women, even after adjusting for axillary surgery and diabetes. Other complications (tissue necrosis and postoperative wound infection) occurred at similar frequencies in men and women. This can be partially explained by the type of work men undertake, which requires using more muscle strength than women in the majority of times (Diéguez, 2010).

The main limitation of this study was sample size, given the low frequency of male breast cancer. Furthermore, as the data were collected retrospectively and based on information available in hospital records, a measurement bias underestimating the incidence of complications may have been introduced, given that health professionals not always register events and may use different criteria for defining the outcomes. However, it is hoped that complications registering was not different

between men and women.

As underlined by Greif et al., (2012) specific differences should be analyzed considering the disparities between men and women – in the ways in which breast cancers are detected and regarding comorbidities in both genders – and considering the deficiencies in data collection and presentation reporting.

This is the first study to report data concerning the incidence of postoperative complications following surgical treatment in MBC. The results of this study may therefore contribute significantly to the design of strategies for controlling postoperative wound complications.

In conclusion, after comparing the incidence of postoperative wound complications between men and women with breast cancer, we found that men have a greater risk of developing seroma. No differences in the other complications analyzed could be detected between gender.

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Conflict of interest

No competing financial interests exist.

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