

Hospital incidence and medical costs of female breast cancer in Spain: a retrospective multicenter study

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Abstract

Background: Breast cancer is the most prevalent cancer type in women worldwide, causing the greatest number of cancer-related deaths. This study aimed to evaluate the use of healthcare resources associated with female breast cancer in Spain, to analyze trends in hospitalization and death rates, and the related direct medical costs.

Methods: A retrospective multicenter study was designed analyzing records of hospital and ambulatory visits of women diagnosed with breast cancer in Spanish hospitals between 1 January 2005 and 31 December 2018.

Results: In total, 353,080 admission files were reviewed, mainly inpatient hospital admissions, corresponding to 299,585 individual patients. Median patient age was 59 years, 12.7% of admissions registered the presence of metastatic tumors and 15.7% registered unspecified secondary tumors. Mean in-hospital death rate was 3.0% for patients without a metastatic disease and 10.5% in patients with a metastatic disease, decreasing significantly over the study period. Total age-adjusted hospitalization rate increased between 2005 and 2011, and decreased after 2012. Mean direct medical cost was €3824 per outpatient visit, €3995 per hospital admission up to 3 days and €5001 per hospital admission over 3 days. Admission cost increased in patients with a metastatic disease and in those deceased during the hospitalization.

Conclusions: This study supports previous findings regarding the relative increase in breast cancer incidence that could be attributed to the intensive screening, along with the reduction in the death rate. Mean direct medical cost in this study varied greatly with length of stay, presence of metastatic tumors and disease fatality.

Keywords: breast cancer; mortality; incidence; healthcare cost; Spain.

Introduction

Breast cancer is the third most common malignancy worldwide, with 2 million incident cases in 2017, and the most common cancer type in women [1]. Breast cancer represents a substantial burden for healthcare systems worldwide that derives from its elevated prevalence and the associated medical needs. At the European level, breast cancer is estimated to reach the €6 billion annually in healthcare costs, a burden that may increase if predictions prove correct [2].

In Spain, breast malignancies are the third most common cancer, with 32,953 new cases in 2020, while data indicates that its 5-year prevalence in women (36.2%) has surpassed any other cancer type [3]. Additionally, breast cancer incidence in Spain displayed an increasing trend between 1985 and 2012, which was associated with the major occurrence of risk factors (environmental, lifestyle and behavioral exposures) and a major diagnostic pressure [4].

Prognosis is generally favorable when diagnosed in its early stages; additionally, the generalization of mammography and ultrasound screenings have been associated with a reduction in mortality [5].

Spain has a National healthcare system that guarantees free access, funded by taxes. Free, universal screening programs in Spain began between 1990 and 1999, varying among different regions, and covered the complete population in 2005 [6]. Currently, all women between 50 and 69 years of age in Spain are invited to participate in the program [7]. In parallel, treatments have been modified and improved: a multimodal therapeutic approach is now used to treat malignant breast neoplasms [8]. This novel approach includes surgery, radiation, molecular therapy and chemotherapy, complemented with the early identification of tumor characteristics and stage, which allows the application of a suitable, personalized treatment [9]. Altogether, with the improvement of screening and

treatment protocols, breast cancer mortality has decreased substantially over the past three decades at the national level; however, several studies predict a gradual deceleration of this trend as a consequence of the rapidly aging population [9,10]. Female breast cancer was the fifth leading cause of cancer mortality worldwide in 2020 [11].

This study aimed to assess the use of medical resources in hospital and ambulatory settings of women with breast cancer in Spain, to analyze trends in hospitalization and death rates, and to measure the associated medical costs, providing a basis for budget allocation decisions in the National Healthcare System.

Methods

Study setting

Records of inpatient and outpatient (ambulatory) visits to hospitals and specialized care centers in Spain registered between 1 Jan 2005 and 31 Dec 2018 were analyzed in a retrospective multicenter study. Healthcare records were extracted from a Spanish National discharge database, which includes a representative sample of discharge records from Spanish hospitals, covering 90% of hospitals across Spanish regions. Data was codified at the hospital level by means of the International Statistical Classification of Diseases and Related Health Problems, 9th version (ICD-9) prior to 2016 and 10th version (ICD-10) after the year 2016 [12,13]. The database is validated internally and subjected to periodic audits; in this process, errors and unreliable data are eliminated.

Data extraction

Records of visits in which a malignant neoplasm of the female breast was registered as the primary diagnosis were petitioned using the corresponding ICD-9 and ICD-10 codes: 174 and C50, respectively. All the parameters identifying healthcare centers or medical history were re-coded within the healthcare centers to maintain records anonymized, in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

This research did not involve human participants and there was no access to identifying information; in this context the Spanish legislation does not require patient consent and ethics committee approval [14].

Study variables

The database registers both inpatient and outpatient visits with the term “admission”, discernible by the length of stay. The variables obtained and included in the analysis were: patients’ age, date of admission, type of admission, date of discharge, type of discharge (including death), primary diagnosis, up to 20 secondary diagnoses registered during the admission, medical procedures and admission costs. Admission costs were not available for the year 2018 at the time of the study.

Data analysis

Patient characteristics were analyzed per subgroups considering: patients admitted through urgent admissions, patients diagnosed with metastatic tumors and patients deceased during the admission. Data from three departments (oncology, obstetrics and gynecology and surgery services), and that from outpatient visits and inpatient admissions (under and over 3 days), were considered separately for the analysis of costs.

Age-adjusted hospitalization rate was measured as the annual number of women admitted with breast cancer within the population. In-hospital death rate was calculated as the annual number of deaths within the group of patients registered with breast cancer in the database. Direct medical costs were calculated based on the admission costs registered in the database; these are assigned according to the standardized average expenses of admissions and medical procedures determined by the Spanish Ministry of Health (include all expenses related to the admission: examination, medication, surgery, diet, costs associated to personnel, medical equipment and resources).

Normality was tested with the Kolmogorov-Smirnov test. Frequencies and percentages are presented for dichotomous variables and mean or median and interquartile range (IQR) were calculated for continuous variables. Two-tailed non-parametric independent t-test (Mann-Whitney U test) or one-way analysis of variance (Kruskal-Wallis test) were used as appropriate and two-sample Z tests were used to test for differences in sample proportions, with a $p < 0.05$ considered statistically significant.

Statistical analyses were performed using Microsoft Excel© Professional Plus 2010 (Microsoft Corporation, Redmond, WA, USA) and StataSE 12 for Windows (StataCorp LP, 2011. Stata Statistical Software: Release 12. College Station, TX, USA).

Results

The 353,080 admission files obtained corresponded to 299,585 individual patients. Median patients' age was 59 years, and remained stable over the study period. Mean Charlson comorbidity index (CCI) was 4.1 in the study population, whereas mean CCI was 9.0 in patients with a metastatic disease.

Most of the analyzed files corresponded to inpatient admissions (>99%), with a mean length of hospital stay (LOHS) of 4.6 days (median=3; IQR=4) (Table 1). LOHS decreased significantly over the study period ($p < 0.001$), from 6.4 days on average in 2005 to 3.6 days in 2018. LOHS was extended in patients with a metastatic disease, with a mean of 6.1 days ($p < 0.001$ vs. patients without metastatic disease), and in those with a CCI over 4, with a mean of 5.8 days ($p < 0.001$ vs. patients with $CCI \leq 4$). LOHS also increased significantly with patients age (≤ 59 years vs. > 59 years; $p < 0.001$). Only 10.5% of admissions were urgent admissions, a percentage that remained stable over the study period.

Metastatic malignant neoplasms were registered in 12.7% of admissions and unspecified secondary tumors were found in 15.7% of admissions, mainly in the lymph nodes,

followed by the respiratory and digestive systems. The portion of patients that were diagnosed with a metastatic tumor increased significantly over the study period ($p<0.001$), tripling the number of cases between 2009 and 2010. General comorbidities, namely hypertension, hyperlipidemia and diabetes, were registered in 23.4%, 10.2% and 8.7% of admissions, respectively. Tobacco use disorder was registered in 5.2% of all admissions.

Tumor location was specified in only 56.5% of admissions. Of these, 36.6% were found in the upper-outer quadrant of the breast, 30.8% were overlapping tumors and tumors of ectopic site or midline of the breast, 11.2% were found in the upper-inner quadrant of the breast, 7.7% in the lower-inner quadrant, 6.3% in the upper-outer quadrant, while other locations represented less than 10% of tumors.

In-hospital death rate was 4.1% over the study period; 3.0% in patients with a non-metastatic disease and 10.5% in patients with a metastatic disease. Death rate decreased significantly over the study period (4.3% to 3.5%; $p<0.001$) (Figure 1A). An abrupt decrease was registered between the year 2009 and 2010 in the death rate of patients diagnosed with a metastatic disease partly due to the increase in the total number of patients that were diagnosed with a metastatic tumor.

Age-adjusted hospitalization rate, as registered in hospitals and other specialized care centers, was 9.0 per 10,000 women in 2018. Hospitalization rate increased steadily between 2005 and 2011 (8.7 to 10.92 per 10,000; $p<0.001$), while a decreasing trend was registered between 2012 and 2018 (10.92 to 9.01 per 10,000; $p<0.001$) (Figure 1B).

Medical procedures registered during the admission were analyzed separately outpatient visits and inpatient admissions (Table 2). Outpatient visits registered mainly diagnostic procedures and the administration of chemotherapy, whereas inpatient admissions were principally associated with biopsies and tumor excision procedures.

Mean direct medical cost of ambulatory care was €3824 per admission, while mean cost for inpatient care increased with length of stay from €3995 in admissions up to 3 days to €5001 in admissions over 3 days (Table 3). Mean admission cost was higher in patients diagnosed with metastatic tumors ($p < 0.001$ vs. patients without metastasis) and in patients deceased during the admission ($p < 0.001$ vs. non-deceased patients).

The mean annual cost associated to breast cancer increased significantly between 2005 and 2008 ($p < 0.001$), decreasing between 2011 and 2014 ($p < 0.001$) and stabilizing after 2014 (Figure 2).

Discussion

This study provides a close examination of the recent trends and use of healthcare resources associated with female breast cancer in Spain since 2005. Breast cancer is highly prevalent in Spain, with an incidence rate that has generally increased over the past decades [4]. The hospitalization rate estimated in this study raised between 2005 and 2011, while it decreased between 2011 and 2018. The initial increase in the hospitalization rate is similar to that observed in the breast cancer incidence rate in Spain [15]. This trend could be partially associated to the generalization of cancer screening programs in the country, established in 2005 and the increasing participation in such programs over the past decade [7]. Breast cancer screening is also assumed to contribute to the reduction of the mortality rate; the Spanish Medical Oncologist Society informed of a mortality rate of breast cancer of the 6.6% the year 2020, considering both men and women [3]. In this study, in-hospital death rate for female breast cancer decreased significantly over the study period. An abrupt decrease on the death rate was registered between 2009 and 2010 in patients with a metastatic disease, which was associated to the significant increase of metastatic cases registered in that period. The year 2010 a new ICD codification manual was distributed in Spain revising the codification system used

in the country [16]; it is possible that the registered increase in the number of metastatic patients corresponds to the correct codification of cases that were not previously registered.

Patients included in this study displayed a mean Charlson comorbidity index of 4.1. Yet, further evaluations will be required to analyze the presence of co-existing comorbid conditions in patients with breast cancer. Previous studies have identified highly prevalent conditions in women diagnosed with breast cancer, including ischemic heart disease, heart failure, depression, diabetes, osteoporosis and hypothyroidism, conditions that were not dominant in this population [17,18].

Most of the hospital and ambulatory admissions analyzed in this study were into surgery services, while the surgical excision of breast or lymphatic tissue was also registered in obstetrics and gynecology services. Currently, the interpretation and validity of these results must take into account the effects of the COVID-19 pandemic; data suggests a reduction in surgery indications and consultations during the COVID-19 emergency, with severe delays in diagnosis [19,20]. Further research will be required to evaluate the real impact of the pandemic in females with breast cancer in Spain.

The infusion or injection of chemotherapy appeared underrepresented in this study. Additionally, treatment varies greatly with the absence or presence of the molecular markers for estrogen or progesterone receptors and for the human epidermal growth factor 2, and according to stage [21]; however, treatment analyses herein could not be more specific due to the lack of codes identifying tumor stage and pathophysiology.

Mean direct medical cost in this study was €3824 for ambulatory visits, €3995 for inpatient admissions up to 3 days and €5001 for inpatient admissions of more than 3 days. In the United States, the total annual healthcare expenditure in patients with breast cancer was €12,840 (\$14,912), with higher total annual costs dedicated to ambulatory care than

to inpatient hospital care [22]. One study developed in Belgium estimated health care costs summing €23,768 per patient over a 6-year period [23]. This same study indicated that direct health care cost accounted for 11% of total costs, when considering indirect costs and productivity losses. In Spain, labor productivity losses of female breast cancer were €2,137 million in total over a ten-year period, which should be taken into account for the evaluation of the total burden of this malignancy in the country [24].

In terms of direct medical costs, this study revealed significant differences among patient groups and admission regimens. As aforementioned, more extended hospital stays were associated with higher admission costs. Similarly, the treatment cost of patients diagnosed with metastatic tumors was higher in all settings, as well as the treatment cost of patients deceased during the admission. These results support previous findings on the importance of early detection and treatment of breast malignant neoplasms from an economic perspective; indeed, breast cancer screening programs proved to be cost-effective in the Basque Country [25]. An additional study evaluating medical costs of breast cancer in the Basque Country, determined a mean cost per diagnosis of €1119, and unit costs of €3028-4072 for surgery, €227 for a radiotherapy session and €244-1653 for a chemotherapy session [26].

Finally, the fluctuations registered in admission costs could be associated to distinct factors, including the implementation of more efficient and specific molecular treatments [27]. On the contrary, the reduction in admission costs found between 2011 and 2014 is presumably associated with the effects of the economic crisis in Spain, when healthcare expenses were considerably reduced [28].

The results of this study may be limited by several factors. The database did not include codes identifying tumor molecular markers or disease stage, which restricted the analysis of management and cost. Further research will be required to explore the treatment,

outcomes and costs of the different tumor types based on histology and biomarkers. Additionally, the admissions included in the study were a sample and do not cover all of the admissions corresponding to a single patient, with the majority of outpatient admissions being left out; thus, the underrepresentation of admissions for the infusion of chemotherapy and possibly other outpatient procedures. The database contains a representative sample of files obtained from 90% of hospitals in Spain, ambulatory care files are slowly being introduced in the database, yet remain a very small percentage. This factor must also be considered when interpreting patients' overall condition, with the potential bias towards more advanced or severe cases. In terms of costs, the lack of outpatient data is a major limitation in the calculation of outpatient visit costs, further studies will be required to evaluate all outpatient medical costs associated to female breast cancer. Finally, the possibility of overdiagnosis was not considered in this study and should be further explored.

Conclusions

This study supports previous findings regarding the relative increase in breast cancer incidence that could be attributed to the intensive screening, along with the reduction in death rate. Mean direct medical cost per admission in this study was highly dependent on length of stay and patient condition, identified as per the diagnosis of metastatic tumors. Future budget allocation decisions should take into account changes in patient profile and costs associated to hospital care in patients with breast cancer.

Declarations

Ethics approval and consent to participate

This study did not include human participants nor any identifiable patient information. In this context, ethics committee approval and consent were not required for this study, in accordance to Spanish legislation.

Data Availability Statement

The data that support the findings of this study is available from the Spanish Ministry of Health via the Unit of Health Care Information and Statistics (Spanish Institute of Health Information) for researchers who meet the criteria for access to confidential data at <https://www.mscbs.gob.es/estadEstudios/sanidadDatos/home.htm>

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Author contributions

Josep Darbà: analysis and interpretation of the burden associated to female breast cancer in Spain, major contribution in the intellectual content revision. Alicia Marsà: interpretation of the statistical data, major contributor in writing the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

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Tables

Table 1 Admission files included in the study and principal comorbid conditions registered upon admission.

	Total	Non-metastatic disease	Metastatic disease
Total admissions, N	353,080	308,274	44,806
Outpatient admissions, %	0.5	0.5	0.1
Inpatient admissions ≤ 3 days, %	73.9	56.2	43.4
Inpatient admissions > 3 days, %	25.6	43.3	56.5
Mean length of stay (median, IQR)	4.6 (3,4)	4.4 (3,3)	6.1 (4,5)
Median age, years (IQR)	59 (21)	59 (21)	59 (24)
Charlson comorbidity index (CCI)	4.1	3.3	9.0
Metastatic malignant neoplasms, %	12.7	-	-
In-hospital death rate, %	4.1	0.9	12.2
<i>Comorbid conditions:</i>	-	-	-
Essential hypertension, %	23.4	23.2	25.0
Hyperlipidemia and hypercholesterolemia, %	10.2	10.1	12.2
Diabetes mellitus, %	8.7	8.7	9.9
Breast dysplasia, lump or deformity, %	6.2	6.1	7.4
Thyroid disorders, %	5.7	5.5	6.9
Tobacco use disorder, %	5.2	5.1	6.0
Cardiac dysrhythmias, %	3.0	2.9	4.0
Pleurisy, %	1.1	0.8	3.3
Acute or chronic respiratory failure, %	1.1	0.9	2.9

Table 2 Procedures registered in more than 5% of admissions in outpatient and inpatient care.

Medical procedures	Non-metastatic disease	Metastatic disease
<i>Outpatient care</i>	(N=1445)	(N=313)
Injection or infusion of chemotherapy	13.6	36.8
Diagnostic X-ray	13.6	25.6
Physiotherapy, rehabilitation	9.6	13.6
Microscopic examination of sample	4.4	13.6
Electrocardiogram	5.2	12.8
<i>Inpatient care ≤ 3 days</i>	(N=173,383)	(N=19,427)
Excision or destruction of breast tissue	67.4	54.5
Simple or radical excision of lymphatic structure	55.5	68.4
Other biopsy (excluding breast)	23.2	17.8
Diagnostic X-ray	16.3	21.4
Breast biopsy	10.5	6.3
Radioisotope scan and function study	10.7	11.8
Other operations on the breast[§]	7.1	8.8
Injection or infusion of chemotherapy	5.1	13.4
Other repair and plastic operations on breast[¶]	4.0	7.3
<i>Inpatient care > 3 days</i>	(N=133,446)	(N=25,066)
Mastectomy	49.6	44.0
Simple or radical excision of lymphatic structure	48.1	49.7
Excision or destruction of breast tissue	34.7	25.1
Diagnostic X-ray	28.9	66.0
Other biopsy (excluding breast)	16.8	18.4
Breast biopsy	10.0	9.2
Other operations on the breast[§]	8.2	7.3
Injection or infusion of chemotherapy	6.8	17.3
Radioisotope scan and function study	7.3	11.5
Microscopic examination of sample	6.2	19.4
Antibiotic injection	5.0	8.3

[§]Namely aspiration of breast, insertion or removal of breast tissue expander and removal of implant of breast. [¶]Principally pedicle graft to breast and muscle flap graft to breast.

Table 3 Mean direct medical cost per group and admission type.

	All admissions	Outpatient care	Inpatient care, ≤ 3 days	Inpatient care, > 3 days
Mean admission cost	€4458	€3824	€3995	€5001
Urgent admissions	€4690	€4880	€4117	€4985
Scheduled admissions	€4431	€3265	€3986	€5004
<i>Per medical service</i>	-	-	-	-
Oncology services	€4724	€4552	€4342	€4869
Obstetrics and gynecology services	€4395	€3199	€3901	€4946
Surgery services	€4425	€3038	€4029	€5049
<i>Per patient group</i>	-	-	-	-
Non-metastatic disease	€4414	€3553	€3963	€4978
Metastatic disease	€4785	€4891	€4308	€5131
Deceased patients	€5376	€5116	€5186	€5469

Figures

Figure 1 A) In-hospital death rate of female breast cancer and B) hospitalization rate in Spain (2005-2018).

Figure 2 Mean annual direct medical cost of hospital and ambulatory care of females with breast cancer in Spain (2005-2017).