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Healthcare use and costs in early breast cancer: a patient-level data analysis according to stage and breast cancer subtype

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ABSTRACT

Background The cost of breast cancer care rises with higher stage at diagnosis; however, there are no real-world data regarding the cost of care according to breast cancer subtypes. This study aimed to estimate direct medical costs for early breast cancer care in the first 3 years after diagnosis according to subtype and stage, using patient-level data.

Methods Women with newly diagnosed stage I–III breast cancer, admitted in 2012 to a Portuguese cancer centre were prospectively followed within the NEON-BC cohort. The use of health resources was obtained from each patient's clinical and administrative records and costs were computed. Tumours were classified into the classic subtypes (hormone receptor-positive (HR+)/HER2–; HER2-positive (HER2+); triple-negative breast cancer (TNBC)) and surrogate intrinsic subtypes (luminal A-like; luminal B-like; HER2 enriched; basal like).

Results A total of 703 patients were included: 48.9% had stage I, 35.8% stage II and 15.2% stage III breast cancer; 76.4% had HR+/HER2–, 15.9% HER2+ and 7.7% TNBC. Median cost of care was €9215/patient in stage I, €13 019/patient in stage II and €15 011/patient in stage III and €10 540/patient in HR+/HER2–, €11 224/patient in TNBC and €41 513/patient in HER2+ breast cancer. Systemic therapy accounted for 69.2% of the cost of care among patients with HER2+, 12.0% among HR+/HER2– and 7.5% among TNBC patients. Similar differences were observed across surrogate intrinsic subtypes.

Conclusions The cost of early breast cancer care was mainly driven by the tumour subtype and, to a lesser extent, by stage. The median cost of care was fourfold higher among patients with HER2+ tumours compared with those with HR+/HER2– and TNBC. These data provide information for the economic evaluation of innovative treatments for early breast cancer and highlight the weight that targeted systemic therapy might have in the overall cost of care among patients with early breast cancer.

INTRODUCTION

In developed countries, breast cancer is the most incident cancer and its standardised mortality rates have been decreasing over the last decades.[1] This decline has been attributed to both an increasing frequency of

Key questions

What is already known about this subject?
► Breast cancer comprises different tumour subtypes, associated with specific treatment strategies, yet there are no real-world data regarding cost of care according to each of these subtypes. This knowledge is paramount to the economic evaluation of innovative therapies, to provide evidence for reimbursement schemes and to substantiate healthcare policies.

What does this study add?
► We estimated direct medical costs for early breast cancer care in the first 3 years after diagnosis according to subtype and stage, using patient-level data. We have seen that the median cost of care was fourfold higher among patients with HER2+ tumours compared with those with hormone receptor-positive/HER2-negative and triple-negative breast cancer. This difference was mainly attributed to adjuvant treatment with trastuzumab.

How might this impact on clinical practice?
► We demonstrate that the cost of early breast cancer care was mainly driven by tumour subtype. Clinicians and stakeholders must be aware of the weight that targeted systemic therapies may have in the overall cost of care and, given the recent approval of many drugs for the treatment of early breast cancer, that this predominance will probably increase in the future.

early diagnosis and access to more efficient and targeted systemic treatments, besides improved radiotherapy and surgery.[2] At the same time, the cost of each patient's cancer care increased, due to new treatments, but also to the development of new technologies, such as imaging.[3]

There are several studies estimating the cost of breast cancer care according to stage, showing that it increases from stages 0 to IV.[4] Nevertheless, it is widely recognised that

breast cancer is a group of molecularly distinct neoplasms,[5] thus, drug regimens are now tailored not only to stage, but also to the tumour molecular subtype.[6] This may have also led to rising costs, due to an increased use of targeted drugs, such as anti-HER2 treatments (eg, trastuzumab).[7] Although health resource use may be expected to differ according to tumour subtype, there are other factors, such as number of affected lymph nodes, histological grade and medical history, that affect treatment decisions.[6] Hence, the individual cost of cancer care can differ between patients with tumours of the same subtype, even within the same hospital. Nonetheless, there are no real-world data regarding cost of early breast cancer treatment according to the different tumour subtypes. This information is paramount to economic evaluations of innovative therapies, to provide evidence for reimbursement schemes and to substantiate healthcare policies. This is particularly important as the sustainability of healthcare systems is now being debated, and especially of cancer care.[8]

In the European Union, in 2009, breast cancer represented the second highest economic cost (€15.0 billion, 12% of overall cancer costs) and accounted for the highest cancer-related healthcare costs (€6.7 billion; 13% of all cancer-related healthcare costs).[9] In the USA, estimates of lifetime per-patient costs of breast cancer in 2009 ranged from US$20 000 to US$100 000,[10] corresponding to 43%–212% of the US gross domestic product per capita at that time. Data from low-income and middle-income countries is scarcer, but some economic studies have also shown an increased cost of breast cancer care with rising stage.[11–14]

Therefore, the aim of the present study was to estimate all direct medical costs regarding diagnosis and treatment of patients with early breast cancer for the first 3 years after diagnosis according to tumour subtype and stage, using patient-level data.

METHODS
Setting
The Portuguese Institute of Oncology of Porto (IPO-Porto) is the largest cancer-dedicated hospital in Portugal, admitting patients from any part of the country, but especially from the Northern region.[15] IPO-Porto admits over 1000 new breast cancer cases/year in its Breast Clinic and covers the entire breast cancer continuum, from diagnosis to treatment (surgery, radiotherapy, systemic therapy and supportive care) and follow-up. All patients are discussed at a multidisciplinary tumour board and treatment is usually decided according to the European Society for Medical Oncology guidelines.[16] After concluding surgery, radiotherapy and/or chemotherapy, patients with early breast cancer enter a follow-up phase, in which they have a medical consultation every 3 months until the end of the third year of follow-up and then every 6 months.

Study design and participants
Patients with newly diagnosed breast cancer, admitted to the Breast Clinic of IPO-Porto in 2012 were included in the "NEON-BC - Neuro-oncological complications of breast cancer" prospective observational cohort.[17–20] Patients were eligible if they were 18 years or older, with histologically confirmed breast cancer, proposed for surgery and expected to be followed at IPO-Porto. In 2012, participants were excluded if they had a previous primary cancer treated with chemotherapy and/or axillary/thoracic radiotherapy; received breast surgery outside IPO-Porto; had a Montreal Cognitive Assessment score below 17 (or below 16 for women over 65 years old); were illiterate had a major psychiatric illness (eg, bipolar disorder, schizophrenia, among others); or due to other reasons (eg, previous breast surgery for benign conditions). However, at the third and fifth year of follow-up, 272 patients initially excluded from the cohort due to the above-mentioned reasons were invited to join the study and thus 240 additional patients were included (online supplemental figure 1). Women with stage 0 (*in situ* carcinoma) or stage IV breast cancer, and those without tumour biomarkers' assessment were excluded from the present analysis.

Data collection
Patients' sociodemographic characteristics were collected through face-to-face interviews using a structured questionnaire. Tumour characteristics, including stage, grade and biomarkers' assessment were retrieved from clinical records. The occurrence of a previous primary cancer was collected through face-to-face interviews and from clinical records.

Staging was defined by the AJCC TNM seventh edition classification.[21] Histological grade was classified from grade 1 (well differentiated) to grade 3 (poorly differentiated).[22] Expression of hormone receptors (HR; oestrogen receptor (ER) and progesterone receptor (PgR)), overexpression/amplification of HER2 and Ki67 score were assessed by immunohistochemistry on the primary tumour, as described in the literature.[23–25] When the immunohistochemistry score was 2+ (HER2-equivocal), fluorescence *in situ* hybridisation was performed. HRs were considered positive when their expression was ≥1%. Tumours were grouped according to the 'classic' classification into HR-positive/HER2-negative (HR+/HER2−); HER2-positive (HER2+); and triple-negative breast cancer (TNBC; HR-negative/HER2-negative). Tumours were also classified into surrogate intrinsic subtypes, using the 2011 St. Gallen Consensus guidelines: luminal A-like (ER-positive/PgR-positive/HER2-negative and Ki67 <15% (or grade 1, in cases in which Ki67 was not available)); luminal B-like (ER-positive, HER2-negative and either PgR positivity <20% or Ki67 ≥15% (or grade 3); or ER-positive and HER2-positive); HER2 enriched (HR-negative/HER2-positive); and basal like (HR-negative/HER2-negative).[26]

Healthcare use during the first 3 years following breast cancer diagnosis was obtained from clinical and administrative records of each participant, namely: surgery (ie, breast and axillary); systemic treatment (ie, chemotherapy, hormone therapy and targeted therapy); radiation (ie, external radiotherapy and brachytherapy); appointments (ie, medical outpatient visits and nursing, psychology and social services appointments); hospitalisations; imaging; and laboratory and pathology examinations (including genetic testing). As IPO-Porto is a dedicated cancer centre, all patients' healthcare use within the hospital was considered to be related with their breast cancer diagnosis. This information was used to compute the cost of each component of treatment and follow-up for each patient. The unit cost of drugs were provided by the Management and Planning Service of IPO-Porto and all other costs were retrieved from the 2015 Price Tables of the Portuguese National Health Service (NHS).[27] When patients received breast cancer surgery, chemotherapy or targeted therapy before being admitted at IPO-Porto, the cost of those procedures was imputed based on the median cost of the same procedures at IPO-Porto. All costs were reported in euros at constant 2015 prices.

Information on relapse, diagnosis of a second primary cancer or death by any cause during the first 3 years after diagnosis was obtained from clinical records. Costs related to disease relapse or to a second primary cancer were integrated in this analysis.

Statistical analysis

Patients' characteristics are presented as counts and proportions for all categorical variables, and median and percentiles 25 and 75 (P25–P75) for continuous variables. For statistical analysis, patients were stratified by classic tumour subtype. Adjusted ORs (aORs) and 95% CIs were computed using multinomial logistic regression to quantify the association between tumour subtype and healthcare use and costs from diagnosis to the third year of follow-up (dependent variable). Models were adjusted for age (continuous variable), education (≤4, 5–9, ≥10 years) and stage (I, II, III). Additionally, analyses were performed according to the surrogate intrinsic subtypes. The median cost of overall cancer care per patient according to stage (I vs II vs III) was also assessed. All analyses were performed using STATA V.15 (StataCorp). All tests were two sided and a p<0.05 was considered significant.

RESULTS
Patients' characteristics

Among the 703 patients, 48.9% presented with stage I, 35.8% with stage II and 15.2% with stage III; 76.4% had a HR+/HER2- tumour, 15.9% presented with HER2+ and 7.7% with TNBC (online supplemental figure 1, table 1). Patients with TNBC were younger, and patients with HER2+ and TNBC tumours were more frequently diagnosed at a later stage — proportion of patients with stage III: 20.5% and 20.4% among HER2+ and TNBC, respectively, vs 13.6% among HR+/HER2−. Other

sociodemographic characteristics were similar among the three subgroups, as well as history of a previous cancer diagnosis. During the first 3 years of follow-up, there were 18 patients (out of 617; 2.9%) with disease relapse, 12 (out of 656; 1.8%) with a second primary cancer and 12 (out of 703; 1.7%) patients had died.

Healthcare use

When adjusting for age, education and stage at diagnosis, there were no differences in the type of breast or axillary surgery across the three classic subtype subgroups (table 2). Patients with HER2+ (aOR 27.09; 95% CI 9.79 to 74.98) and TNBC (aOR 2.74; 95% CI 1.08 to 6.97) were more likely to receive chemotherapy, compared with patients with HR+/HER2− tumours. Almost all patients with HR+/HER2− tumours received hormone therapy (99.8%) and 93.8% of HER2+ patients received targeted systemic therapy (trastuzumab). Overall, 74.1% of patients received adjuvant radiotherapy, with no significant differences between subgroups.

Healthcare costs

The median (P25–P75) overall cost of care per patient during the first 3 years after diagnosis was €11 516 (€7890–€16 376). The median cost of care was €9215 (€7268–€13 117)/patient for stage I, €13 019 (€10 075–€19 194)/patient for stage II and €15 011 (€11 469–€22 530)/patient for stage III (figure 1).

The median (P25–P75) overall cost was €10 540 (€7480–€13 611)/patient among HR+/HER2€, €11 224 (€9158–€14 645)/patient among TNBC and €41 513 (€36 011–€47 015)/patient among patients with HER2+ tumours (figure 1, table 3). The discrepancy between patients with HER2+ vs HR+/HER2− and TNBC was mainly driven by the cost of trastuzumab (median €25 006/patient). There was also a higher cost associated with chemotherapy and day hospital use among patients with HER2+ (median of €386 and €2164/patient, respectively) and TNBC (€398 and €590/patient) compared with those with HR+/HER2− tumours (€98 and €394/patient). HER2+ patients also had a higher cost associated with surgeries, appointments, imaging and other medical expenses than the HR+/HER2− subgroup. Patients with TNBC had a significantly higher cost associated with other medical expenses than HR+/HER2− patients. Overall, expenses associated with systemic therapy constituted 69.2% of the median cost of care of HER2+ patients, while they contributed to 12.0% and 7.5% among HR+/HER2− and TNBC patients, respectively (figure 2). In the HR+/HER2− and TNBC subgroups, surgery accounted for around 25% of the total cost, similar to radiotherapy (20% of total cost).

The cost of care by year after cancer diagnosis dropped abruptly from the first to the second and third years for patients with HR+/HER2− and TNBC (figure 1). However, among patients with HER2+ tumours, the cost was €9347/patient during the second year due to adjuvant trastuzumab treatment.

Table 1 Sociodemographic and clinical characteristics of patients at baseline, according to classic breast cancer subtypes*

	HR+/HER2− (N=537)	HER2+ (N=112)		TNBC (N=54)	
	N (%)	N (%)	P value†	N (%)	P value‡
Age, years					
<50	165 (30.7)	43 (38.4)		26 (48.1)	
50–64	228 (42.5)	46 (41.1)		19 (35.2)	
≥65	144 (26.8)	23 (20.5)	0.206	9 (16.7)	**0.028**
Education, years					
≤4	243 (48.3)	39 (37.9)		23 (46.0)	
5–9	124 (24.7)	32 (31.1)		16 (32.0)	
≥10	136 (27.0)	32 (31.1)	0.144	11 (22.0)	0.483
Net monthly income before diagnosis, euros					
≤500	282 (57.1)	49 (49.0)		27 (54.0)	
>500	212 (42.9)	51 (51.0)	0.138	23 (46.0)	0.675
Marital status					
Married or cohabitating	362 (72.0)	74 (72.8)		35 (70.0)	
Other§	141 (28.0)	28 (27.2)	0.861	15 (30.0)	0.768
Employment					
Employed	239 (47.5)	51 (49.5)		31 (62.0)	
Other¶	264 (52.5)	52 (50.5)	0.711	19 (38.0)	0.051
Place of residence					
Porto Metropolitan Area	181 (36.3)	39 (38.2)		22 (44.0)	
Outside Porto Metropolitan Area	318 (63.7)	63 (61.8)	0.708	28 (56.0)	0.281
Breast cancer stage					
I	283 (52.7)	43 (38.4)		18 (33.3)	
II	181 (33.7)	46 (41.1)		25 (46.3)	
III	73 (13.6)	23 (20.5)	**0.016**	11 (20.4)	**0.024**
Previous primary cancer diagnosis (including breast cancer)	48 (9.8)	5 (5.1)	0.134	3 (6.0)	0.384

The total may not add to 703 due to missing data. May not sum to 100% due to rounding.
*Classic subtypes were defined according to the assessment of the oestrogen receptor, the progesterone receptor and HER2 status on the surgical specimen (preferably) or on the biopsy core specimen (when the surgical specimen's pathology report was unavailable).
HR+/HER2−: oestrogen receptor and/or progesterone receptor positive and HER2-negative (a score of 0 or 1+ in immunohistochemistry, or a score of 2+ with a non-amplified fluorescence *in situ* hybridzsation (FISH) test result); HER2+: HER2-positive (a score of 3+ in immunohistochemistry or a score of 2 with an amplified FISH test result), regardless of the oestrogen and progesterone receptor status; TNBC: oestrogen receptor negative, progesterone receptor negative and HER2-negative.
†HER2+ vs HR+/HER2−. Values in bold correspond to statisticallysignificant differences.
‡TNBC vs HR+/HER2−. Values in bold correspond to statisticallysignificant differences.
§Other marital status includes: single, widowed and divorced women.
¶Other employment includes: unpaid family workers, unemployed, housewives, retired and sick leave.
HR, hormone receptors; TNBC, triple negative breast cancer.

When combining the cost of care per subtype and stage, although patients with stage II and III had a higher median cost of care/patient versus those with stage I, these differences were small within each subtype—among HR+/HER2− patients, the cost ranged from €8498/patient (stage I) to €13 332/patient (stage III); in the HER2+ subgroup, it ranged from €38 216/patient (stage I) to €41 564/patient (stage III). Likewise, among patients with TNBC, the median cost was €9566/patient in stage I and €14 645/patient in stage III (online supplemental figure 2).

Surrogate intrinsic subtypes analyses

When categorising tumours according to the surrogate intrinsic subtypes classification, there were 87 patients with HR+/HER2− tumours, for whom it was not possible to discriminate between luminal A-like and luminal B-like, due to absence of information regarding PgR, Ki67 and/or histological grade. Among the 616 patients with available surrogate intrinsic subtype information, 33.1% had luminal A-like tumours, 52.9% had luminal B-like tumours (of which 246 were HER2− and 80 HER2+), 5.2% had HER2-enriched and 8.8%

Table 2 Association between breast cancer classic subtype and healthcare use in the first 3 years following a breast cancer diagnosis in 2012

	HR+/HER2− (N=537)	HER2+ (N=112)			TNBC (N=54)		
	N (%)	N (%)	aOR (95% CI)*	aOR (95% CI)†	N (%)	aOR (95% CI)*	aOR (95% CI)†
Surgery							
Breast surgery‡							
Total mastectomy (vs breast-conserving surgery)	241 (51.2)	59 (62.1)	1.66 (1.04 to 2.67)	1.41 (0.85 to 2.35)	25 (51.0)	1.18 (0.64 to 2.18)	0.84 (0.43 to 1.64)
Axillary surgery§							
Axillary dissection (vs none or sentinel lymph node biopsy)	154 (33.3)	45 (48.4)	1.74 (1.08 to 2.78)	1.32 (0.67 to 2.61)	19 (39.6)	1.30 (0.69 to 2.44)	0.51 (0.21 to 1.24)
Other surgeries/interventions (≥4 vs <4)¶	181 (33.7)	85 (75.9)	6.40 (3.83 to 10.69)	6.60 (3.81 to 11.43)	34 (63.0)	3.01 (1.60 to 5.67)	2.43 (1.24 to 4.74)
Systemic therapy							
Any chemotherapy (yes vs no)	286 (53.3)	105 (93.8)	17.58 (6.87 to 44.97)	27.09 (9.79 to 74.98)	44 (81.5)	3.70 (1.64 to 8.36)	2.74 (1.08 to 6.97)
Timing of chemotherapy							
Adjuvant (vs neoadjuvant)	260 (91.9)	91 (89.2)	0.70 (0.32 to 1.56)	0.56 (0.22 to 1.41)	38 (86.4)	0.53 (0.20 to 1.41)	0.49 (0.16 to 1.52)
Chemotherapy scheme							
Anthracycline-based (yes vs no)**	283 (99.0)	99 (94.3)	0.21 (0.05 to 0.90)	0.18 (0.04 to 0.82)	43 (97.7)	0.48 (0.05 to 4.95)	0.50 (0.05 to 5.45)
Hormone therapy (yes vs no)††	536 (99.8)	80 (71.4)	--	--	0 (0.0)	--	--
Targeted therapy (yes vs no)‡‡	0 (0.0)	105 (93.8)	--	--	0 (0.0)	--	--
Other treatments							
Radiotherapy (yes vs no)	395 (73.2)	82 (73.2)	0.85 (0.52 to 1.40)	0.72 (0.43 to 1.22)	44 (81.5)	1.47 (0.68 to 3.16)	1.19 (0.54 to 2.65)
Brachytherapy (yes vs no)§§	110 (27.8)	14 (17.1)	0.58 (0.31 to 1.08)	0.71 (0.37 to 1.36)	8 (18.2)	0.52 (0.22 to 1.22)	0.67 (0.27 to 1.61)
Other healthcare use¶¶							
Appointments (≥55 vs <55)***	132 (24.6)	45 (40.2)	1.77 (1.12 to 2.80)	1.55 (0.96 to 2.52)	19 (35.2)	1.54 (0.81 to 2.90)	1.27 (0.65 to 2.46)
Hospitalisations (≥2 vs <2)†††	209 (38.9)	43 (38.4)	0.93 (0.60.1.45)	0.97 (0.62 to 1.51)	19 (35.2)	0.86 (0.46 to 1.57)	0.90 (0.49 to 1.66)
Genetic testing (yes vs no)‡‡‡	63 (11.7)	12 (10.7)	0.60 (0.29 to 1.27)	0.63 (0.27 to 1.34)	9 (16.7)	0.90 (0.37 to 2.23)	0.94 (0.38 to 2.34)

Continued

	HR+/HER2− (N=537)			HER2+ (N=112)			TNBC (N=54)		
	N (%)	aOR (95% CI)*	aOR (95% CI)†	N (%)	aOR (95% CI)*	aOR (95% CI)†	N (%)	aOR (95% CI)*	aOR (95% CI)†

Table 2 Continued

The total may not add to 703 due to missing data. May not sum to 100% due to rounding.

*Adjusted for age (continuous) and education (≤4, 5–9, ≥10 years).

†Further adjusted for stage (I–III).

‡Patients who had breast-conserving surgery followed by total mastectomy are included in the total mastectomy group. Information regarding the type of breast surgery is not available for 84 patients who underwent surgery outside IPO-Porto.

§Patients who had sentinel lymph node biopsy followed by axillary lymph node dissection are included in the axillary dissection group. One patient did not receive any type of axillary surgery (included in the HR+/HER2− subgroup). Information regarding the type of axillary surgery is not available for 84 patients who underwent surgery outside IPO-Porto.

¶Other surgeries/interventions include breast reconstruction surgeries, central venous catheter placement/removal and other ambulatory surgeries/interventions. The cut-off used was determined as percentile 75 of the number of other surgeries/interventions among the HR+/HER2− subgroup.

**Anthracycline-based chemotherapy includes: AC regimen: four or six cycles of concomitant doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2); FEC regimen: six cycles of concomitant 5-FU (500 mg/m^2), epirubicin (100 mg/m^2) and cyclophosphamide (500 mg/m^2); AC–T regimen: four cycles of concomitant doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2), followed by four cycles of docetaxel (100 mg/m^2); AC–paclitaxel regimen: four cycles of concomitant doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2), followed by four cycles of paclitaxel (80 mg/m^2); FEC–D regimen: three cycles of concomitant 5-FU (500 mg/m^2), epirubicin (100 mg/m^2) and cyclophosphamide (500 mg/m^2), followed by three cycles of docetaxel (100 mg/m^2).

††Among HR+/HER2−: 71 patients (13.2%) only received tamoxifen; 116 (21.6%) only received aromatase inhibitors; 104 (19.4%) received both tamoxifen and aromatase inhibitors; 90 (16.8%) received tamoxifen and/or aromatase inhibitors, plus goserelin (for ovarian function suppression during adjuvant treatment) or fulvestrant (for relapsed disease); 155 (28.9%) unknown. Among HER2+: 9 (11.2%) only received tamoxifen; 24 (30.0%) only received aromatase inhibitors; 10 (12.5%) received both tamoxifen and aromatase inhibitors; 18 (22.5%) received tamoxifen and/or aromatase inhibitors, plus goserelin (for ovarian function suppression during adjuvant treatment) or fulvestrant (for relapsed disease); 19 (23.8%) unknown.

‡‡Targeted therapy includes trastuzumab. Seven patients with HER2+ breast cancer did not receive trastuzumab due to: age >80 years (n=2), cardiovascular disease (n=3), T1a tumour (n=1), refusal (n=1).

§§Among those who received radiotherapy (n=521).

¶¶Does not include the number of laboratory and pathology tests, and imaging examinations, for which only the total cost per patient was available (included in table 3).

***Appointments: number of outpatient visits (surgery, medical oncology and radiation oncology, among others), and nursing, psychology and social services appointments. The cut-off used was determined as percentile 75 of the number of appointments among the HR+/HER2− subgroup.

††††The cut-off used was determined as percentile 75 of the number of hospitalisations among the HR+/HER2− subgroup.

‡‡‡Genetic testing includes: BRCA1 mutations and BRCA2 mutations (hereditary breast and ovarian cancer syndrome); deletions in MLH1 (hereditary nonpolyposis colon cancer); and TP53 mutations (Li-Fraumeni syndrome).

aOR, adjusted OR; HR, hormone receptors; IPO-Porto, Portuguese Institute of Oncology of Porto; TNBC, triple negative breast cancer.
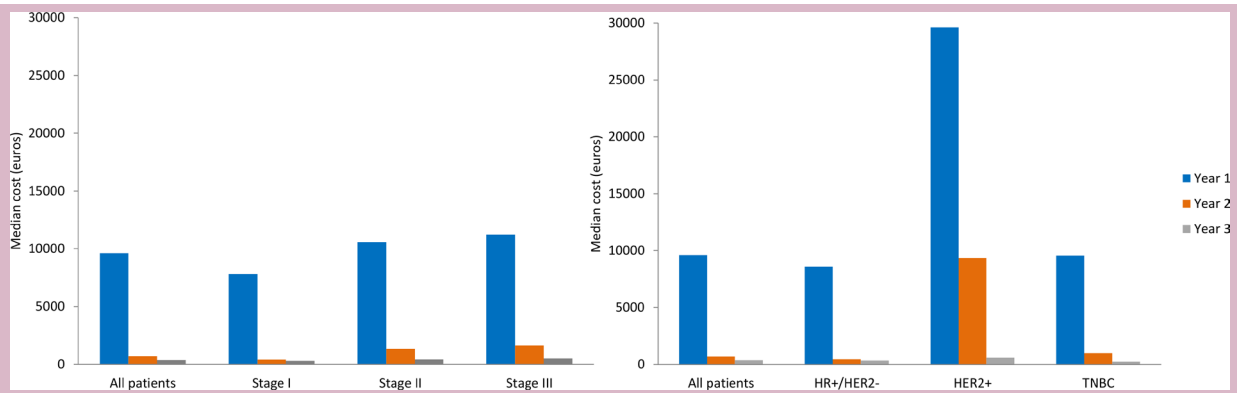
Figure 1 Median cost per year (1–3) for all patients and by stage (left) and classic subtype (right). HR: hormone receptor; TNBC: triple-negative breast cancer.

had basal-like tumours. Patients with luminal B-like, HER2-enriched and basal-like tumours were diagnosed at a more advanced stage compared with luminal A-like patients (online supplemental table 1). Only 16.2% of luminal A-like patients received chemotherapy vs 76.4% of luminal B-like, 100% of HER2-enriched and 81.5% of basal-like patients (online supplemental table 2). Patients with luminal A-like tumours also had a lower number of appointments than the other subgroups.

The median overall cost of care during the first 3 years after diagnosis was €8232 (€6391–€10 931)/patient among luminal A-like, €12 493 (€8723–€22 237)/patient among luminal B-like, €38 297 (€34 510–€42 529)/patient among HER2-enriched and €11 224 (€9158–€14 645)/patient among the basal-like subgroup (online supplemental table 3 and online supplemental figure 3). Similar to that described for classic subtypes above, the higher treatment cost among patients with HER2-enriched tumours was mainly driven by the cost of trastuzumab. Among luminal B-like patients, 73 (22.4%) also received trastuzumab (as they had HER2+ tumours), which also partly explains the higher median cost of care of luminal B-like vs luminal A-like patients. The other reason is the higher spending related to chemotherapy and day hospital use among luminal B-like (median of €255 and €590/patient) vs luminal A-like patients (median of €0/patient, as 84.0% did not receive chemotherapy). Overall, systemic therapy accounted for 9.0% of the total median cost of care of luminal A-like patients, while it accounted for 45.6% among luminal B-like and 69.6% among HER2-enriched patients (online supplemental figure 4). Among patients with HER2-enriched tumours, treatment cost was stable across the different stages at diagnosis, due to the fact that they all received trastuzumab. Conversely, there was an increase in treatment cost from stage I to stage III among patients with the other three subtypes, especially among the luminal A-like subgroup (online supplemental figure 5).

DISCUSSION

To the best of our knowledge, this is the first study to estimate all direct medical costs among patients with early breast cancer according to tumour subtype. We found that the median overall cost of care during the first 3 years after breast cancer diagnosis was fourfold higher among patients with HER2+ tumours than HR+/HER2− or TNBC patients, and that this was primarily driven by the cost of adjuvant trastuzumab treatment. This cost relates not only to the trastuzumab price itself, but also to all other expenditures related to its administration and toxicity monitoring, that is, daily hospital use, appointments and medical tests (including cardiac imaging).

We have also shown that, among patients with HR+/HER2− and TNBC, the cost of breast cancer care was mainly driven by surgery and radiotherapy rather than by systemic therapy (chemotherapy and/or hormone therapy). Similar results were observed when comparing cost of care according to patients' surrogate intrinsic subtype.

Additionally, we found that there is an increase in the total median cost of care from stage I (€9215/patient) to stage III (€15 011/patient). This is in line with a previous study from Portugal, conducted at IPO-Lisbon (a similar, dedicated cancer centre) in 2014, assessing costs within the first 2 years after breast cancer diagnosis. The authors estimated the mean cost to be €6094/patient in stage I, €9785/patient in stage II and €11 893/patient in stage III.[28] These figures are similar to those reported in other European countries with an NHS, such as Italy,[29] France[30] and the UK.[31]

Yet interestingly, the cost discrepancies by stage are negligible when compared with the differences observed according to breast cancer subtypes. This is primarily explained by the fact that, in breast cancer, the intensity and type of treatment is driven not only by stage, but mostly by biology: most patients with TNBC and HER2+ tumours have indication to receive chemotherapy and anti-HER2 therapy (in the case of HER2+). Likewise, all patients with HR+ tumours should receive hormone therapy, regardless of stage.[16] Concerning locoregional therapy, most

Table 3 Association between breast cancer classic subtype and healthcare costs, in euros, in the first 3 years following a breast cancer diagnosis in 2012

	HR+/HER2− (N=537)			HER2+ (N=112)			TNBC (N=54)		
	N (%)	aOR (95% CI)*	aOR (95% CI)†	N (%)	aOR (95% CI)*	aOR (95% CI)†	N (%)	aOR (95% CI)*	aOR (95% CI)†
Surgery‡§									
Surgeries, euros									
Median (P25–P75)	2522.01 (1434.07–2880.94)			2684.49 (2511.01–3939.67)			2522.01 (2094.72–3654.94)		
≤1800¶	179 (33.3)			10 (8.9)			9 (16.7)		
1801–2700	208 (38.7)			58 (51.8)	6.31 (2.77 to 14.40)	5.88 (2.53 to 13.64)	25 (46.3)	2.20 (0.93 to 5.23)	1.65 (0.68 to 4.02)
>2700	150 (27.9)			44 (39.3)	6.28 (2.70 to 14.63)	6.02 (2.55 to 14.19)	20 (37.0)	2.63 (1.09 to 6.37)	2.09 (0.85 to 5.14)
Systemic therapy									
Chemotherapy§**, euros									
Median (P25–P75)	98.35 (0.00–389.44)			385.96 (265.92–412.82)			397.58 (269.14–533.39)		
None (0)¶	251 (46.7)			7 (6.3)			10 (18.5)		
≤400	164 (30.5)			65 (58.0)	18.74 (7.22 to 48.66)	27.65 (9.95 to 76.80)	17 (31.5)	2.66 (1.08 to 6.53)	2.16 (0.80 to 5.81)
>400	122 (22.7)			40 (35.7)	15.68 (5.84 to 42.06)	23.83 (8.06 to 70.52)	27 (50.0)	5.27 (2.20 to 12.64)	4.07 (1.47 to 11.29)
Hormone therapy§, euros									
Median (P25–P75)	101.71 (73.27–120.79)			78.41 (0.00–112.51)			0.00 (0.00–0.00)		
≤80¶	177 (33.0)			58 (51.8)			54 (100.00)		
81–110	161 (30.0)			22 (19.6)	0.43 (0.24 to 0.76)	0.41 (0.23 to 0.73)	0 (0.0)	--	--
>110	199 (37.1)			32 (28.6)	0.52 (0.32 to 0.85)	0.52 (0.32 to 0.87)	0 (0.0)	--	--
Targeted therapy§††, euros									
Median (P25–P75)	0.00 (0.00–0.00)			25 005.56 (21 353.67–29 808.79)			0.00 (0.00–0.00)		
None (0)¶	537 (100.0)			7 (6.3)			54 (100.00)		
≤26000	0 (0.0)			53 (47.3)	--	--	0 (0.0)	--	--
>26000	0 (0.0)			52 (46.4)	--	--	0 (0.0)	--	--
Day hospital§‡‡, euros									

Continued

Table 3 Continued

	HR+/HER2− (N=537)			HER2+ (N=112)			TNBC (N=54)		
	N (%)	aOR (95% CI)*	aOR (95% CI)†	N (%)	aOR (95% CI)*	aOR (95% CI)†	N (%)	aOR (95% CI)*	aOR (95% CI)†
Median (P25–P75)	393.52 (0.00–590.28)			2164.36 (2164.36–2262.74)			590.28 (590.28–590.28)		
None (0)¶	228 (42.5)			4 (3.6)			10 (18.5)		
≤600	193 (35.9)			2 (1.8)	0.49 (0.05 to 4.52)	0.72 (0.07 to 7.07)	35 (64.8)	3.70 (1.63 to 8.40)	2.60 (1.01 to 6.69)
>600	116 (21.6)			106 (94.6)	246.48 (69.64 to 872.35)	485.71 (123.60 to 1908.67)	9 (16.7)	0.85 (0.27 to 2.72)	0.56 (0.16 to 2.03)
Radiotherapy§§§, euros									
Median (P25–P75)	2627.35 (0.00–3240.43)			2615.60 (0.00–3273.33)			2649.30 (2569.82–3401.36)		
None (0)¶	149 (27.7)			30 (26.8)			10 (18.5)		
≤2675	192 (35.8)			44 (39.3)	1.01 (0.58 to 1.75)	0.77 (0.42 to 1.40)	22 (40.7)	1.62 (0.70 to 3.74)	1.11 (0.45 to 2.72)
>2675	196 (36.5)			38 (33.9)	0.81 (0.46 to 1.43)	0.76 (0.43 to 1.35)	22 (40.7)	1.53 (0.66 to 3.52)	1.37 (0.58 to 3.21)
Other healthcare use									
Appointments§, euros									
Median (P25–P75)	1139.00 (909.00–1495.00)			1370.00 (1127.00–1785.50)			1374.50 (1084.00–1676.00)		
≤1000¶	189 (35.2)			15 (13.4)			11 (20.4)		
1001–1350	174 (32.4)			39 (34.8)	2.63 (1.33 to 5.23)	2.53 (1.26 to 5.07)	15 (27.8)	1.48 (0.60 to 3.67)	1.24 (0.50 to 3.11)
>13500	174 (32.4)			58 (51.8)	3.89 (1.98 to 7.63)	3.50 (1.74 to 7.06)	28 (51.9)	2.92 (1.25 to 6.83)	2.22 (0.92 to 5.34)
Hospitalisation§, euros									
Median (P25–P75)	1694.78 (1434.07–2346.70)			1694.78 (1434.07–3391.17)			1694.78 (1434.07–3000.90)		
≤1450¶	179 (33.3)			36 (32.1)			21 (38.9)		
1451–1800	194 (36.1)			30 (26.8)	0.82 (0.47 to 1.41)	0.65 (0.36 to 1.16)	17 (31.5)	0.78 (0.38 to 1.57)	0.54 (0.26 to 1.16)
>1800	164 (30.5)			46 (41.1)	1.36 (0.81 to 2.27)	1.14 (0.67 to 1.93)	16 (29.6)	0.82 (0.40 to 1.67)	0.62 (0.29 to 1.31)
Genetic testing§, euros									
Median (P25–P75)	0.00 (0.00–0.00)			0.00 (0.00–0.00)			0.00 (0.00–0.00)		

Continued

Table 3 Continued

	HR+/HER2− (N=537)	HER2+ (N=112)			TNBC (N=54)		
	N (%)	N (%)	aOR (95% CI)*	aOR (95% CI)†	N (%)	aOR (95% CI)*	aOR (95% CI)†
None (0)¶	474 (88.3)	100 (89.3)			45 (83.3)		
≤550	19 (3.5)	4 (3.6)	0.58 (0.18 to 1.90)	0.58 (0.18 to 1.90)	2 (3.7)	0.64 (0.13 to 3.09)	0.63 (0.13 to 3.05)
>550	44 (8.2)	8 (7.1)	0.61 (0.26 to 1.43)	0.65 (0.27 to 1.56)	7 (13.0)	1.03 (0.38 to 2.78)	1.11 (0.40 to 3.04)
Other medical expenses§¶‖, euros							
Median (P25–P75)	623.84 (268.50–1119.00)	1121.48 (747.39–1806.18)			883.83 (579.64–1217.50)		
≤350¶	180 (33.5)	2 (1.8)			6 (11.1)		
351–900	176 (32.8)	40 (35.7)	37.46 (5.08 to 276.41)	43.10 (5.78 to 321.52)	21 (38.9)	3.54 (1.28 to 9.77)	2.93 (1.02 to 8.42)
>900	181 (33.7)	70 (62.5)	60.09 (8.23 to 438.59)	73.12 (9.74 to 549.08)	27 (50.0)	4.82 (1.80 to 12.89)	3.50 (1.18 to 10.37)
Imaging§, euros							
Median (P25–P75)	560.00 (347.80–874.22)	1348.91 (1043.57–1714.80)			821.91 (456.59–1099.03)		
≤450¶	192 (35.8)	5 (4.5)			12 (22.2)		
451–750	165 (30.7)	7 (6.3)	2.05 (0.59 to 7.20)	2.60 (0.73 to 9.29)	14 (25.9)	2.04 (0.82 to 5.10)	1.57 (0.60 to 4.07)
>750	180 (33.5)	100 (89.3)	24.94 (8.82 to 70.53)	36.32 (12.08 to 109.21)	28 (51.9)	3.25 (1.38 to 7.68)	2.16 (0.84 to 5.58)
Total cost§, euros							
Median (P25–P75)	10539.5 (7480.38–13610.61)	41513.47 (36010.75–47015.02)			11224.27 (9157.58–14644.81)		
≤8250¶	179 (33.3)	3 (2.7)			9 (16.7)		
8251–12250	179 (33.3)	2 (1.8)	1.18 (0.16 to 8.55)	1.63 (0.22 to 12.12)	25 (46.3)	3.13 (1.24 to 7.89)	2.34 (0.91 to 6.03)
>12250	179 (33.3)	107 (95.5)	63.70 (14.88 to 272.80)	103.91 (22.62 to 477.38)	20 (37.0)	2.35 (0.87 to 6.30)	1.41 (0.50 to 4.01)

Continued

Table 3 Continued

	HR+/HER2− (N=537)			HER2+ (N=112)			TNBC (N=54)		
	N (%)	aOR (95% CI)*	aOR (95% CI)†	N (%)	aOR (95% CI)*	aOR (95% CI)†	N (%)	aOR (95% CI)*	aOR (95% CI)†

The total may not add to 703 due to missing data. May not sum to 100% due to rounding.

For items: surgeries, hormone therapy, appointments, hospitalisation, other medical expenses, imaging and total cost, the cut-offs used to define each category were determined as percentiles 33 and 66 of the respective cost among the HR+/HER2− subgroup. For items: chemotherapy, targeted therapy, day hospital, radiotherapy and genetic testing, categories were defined as none (0) and the median cost among the HR+/HER2− subgroup (among those who received the respective item) was used as the cut-off to define the other two categories.

*Adjusted for age (continuous) and education (≤4, 5–9, ≥10 years).

†Further adjusted for stage (I–III).

‡All surgeries/interventions, including breast surgeries and axillary surgeries. Imputed surgery cost for 87 patients who underwent surgery outside IPO-Porto.

§Dependent variable in the multinomial logistic regression model.

¶Category being used as the reference in the multinomial logistic regression model.

**Imputed chemotherapy cost for three patients who received chemotherapy outside IPO-Porto.

††Imputed targeted therapy cost for one patient who received targeted therapy outside IPO-Porto.

‡‡Day hospital sessions include the administration of intravenous, subcutaneous and/or intramuscular therapy (ie, chemotherapy, trastuzumab, goserelin and fulvestrant).

§§The cost of brachytherapy for the seven patients who only received brachytherapy (and no external radiotherapy) is included in hospitalisation costs and not in radiotherapy costs.

¶¶Other medical expenses include laboratory and pathology tests, and blood transfusions.

aOR, adjusted OR; HR, hormone receptors; IPO-Porto, Portuguese Institute of Oncology of Porto; TNBC, triple negative breast cancer.

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patients with smaller tumours receive breast-conserving surgery, and subsequently, radiotherapy; while patients with more advanced tumours may undergo mastectomy, but likely receive radiotherapy afterwards as well. Therefore, the cost of locoregional therapy may not change dramatically according to stage. Similarly, as there are no guidelines defending a differential timing of follow-up by stage, we did not expect to see differences in follow-up intensity according to stage.[16] Conversely, breast cancer subtype determines the type of adjuvant systemic therapy that the patient receives, which may lead to an increased number of appointments, in order to monitor toxicity to chemotherapy, trastuzumab and/or hormone therapy.

This study has the advantage of having used the micro-costing method, in which resources and associated unit costs were directly measured at the patient level, making estimates much more reliable. Additionally, unlike previous studies,[28–31] we have also reported the quantities of resources used separately from costs, allowing for a more detailed assessment of healthcare use.

Many studies assessing the cost of breast cancer care have compared costs of breast cancer cases to control groups (without breast cancer), in order to calculate breast cancer-attributable treatment costs, as a way to avoid overestimations.[4] Since IPO-Porto is a dedicated cancer centre, we did not need to perform these estimations, as healthcare use among patients in this study can all be virtually attributed to their breast cancer care, making our estimates much more accurate. Moreover, we also included the costs associated with the treatment of patients who have a disease relapse, increasing the generalisation of our findings to the real-world clinical setting.

We only assessed direct medical costs attributable to IPO-Porto and the Portuguese NHS, and did not take into account out-of-pocket expenses paid by patients. However, in Portugal, as in other European NHS,[28–31] almost all direct medical costs related to cancer care are covered by the public health system, thus out-of-pocket expenses are small. Yet, some direct costs related to breast cancer care such as physiotherapy (usually received in the community setting) were also not included in the analysis. Indirect costs, such as loss of productivity, have been shown to account for more than half of the total costs associated with breast cancer;[9] however, these were not included in this analysis, which may have underestimated the cost associated with some procedures, such as surgery or chemotherapy.

This study also has the limitation of being a single-centre study, which may impair the generalisation of the results. Nonetheless, IPO-Porto is a large hospital, receiving patients from any part of the country, with different sociodemographic backgrounds and it includes patients presenting with the entire spectrum of breast cancer in terms of stage and subtypes. Moreover, this also presents advantages: there was no lost to follow-up and we were able to obtain detailed patient-level data, which allowed for understanding the main factors behind the cost of care.
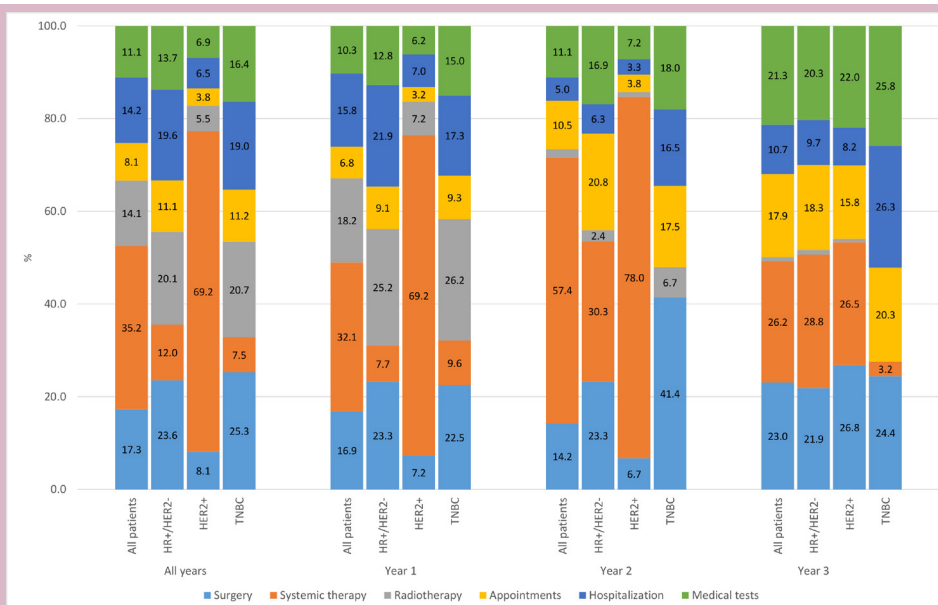
Figure 2 Proportion of the median cost attributed to surgery, systemic therapy, radiotherapy, appointments, Hospitalisation and medical tests among all patients, by year after breast cancer diagnosis (all years; years 1–3) and by classic subtype. 'Systemic therapy' includes chemotherapy, targeted therapy, hormone therapy and day hospital use. 'Medical tests' includes laboratory and pathology tests, blood transfusions, imaging and genetic testing. When the proportion of the median cost of a certain item was ≤2% of the overall cost, the respective label was deleted from the figure. HR: hormone receptor; TNBC: triple-negative breast cancer.

From 2012 until now, there have been major advances in loco-regional and in systemic therapy for early breast cancer.[3] The cost of radiotherapy may have decreased due to the adoption of hypofractionated regimens and of accelerated partial-breast irradiation (to selected patients), which decreases the number of radiotherapy sessions needed and, therefore, reduces both direct and indirect costs.[32 33]

Among patients with HER2+ breast cancer, the introduction of trastuzumab biosimilar drugs and of a subcutaneous trastuzumab formulation lowered the price of this adjuvant therapy.[34 35] Additionally, the Persephone trial showed that 6-month therapy with trastuzumab is non-inferior to the standard 12-month regimen.[36] Nonetheless, the 6-month regimen has not been widely adopted, due to the negative results of other non-inferiority trials and due to concerns regarding its efficacy among higher-risk groups.[37] Hence, 12 months of adjuvant trastuzumab continues to be considered the standard-of-care in developed countries.[16] On the other hand, since 2013, three more anti-HER2 drugs were approved in the (neo)adjuvant setting: pertuzumab, neratinib and T-DM1.[16] As an example, in our cohort, 60% of patients with HER2+ tumours had stage II/III and would currently be proposed to neoadjuvant chemotherapy plus trastuzumab/pertuzumab. As four cycles of pertuzumab have a direct cost of €13 978,[38] this means that the overall median cost per patient could have increased by 20% among this subgroup. However, these drugs also decrease the likelihood of disease relapse, thus potentially reducing expenditures related to the treatment of breast cancer recurrence.

On the other hand, around half of the patients with HR+/HER2− tumours in our cohort received chemotherapy. Nowadays, a part of these patients could have their tumours tested with a genomic signature (eg, PAM50, oncotype, Mammaprint)[16] in order to avoid chemotherapy, which would decrease both direct and indirect costs. However, after the publication of the SOFT/TEXT trials,[39] many premenopausal women with HR+ tumours started receiving adjuvant tamoxifen or exemestane plus ovarian suppression for 5 years, which have potentially increased the cost of their treatment. Therefore, patients' menopausal status should be taken into account in future analyses of the cost of breast cancer care. In addition, there are large ongoing randomised clinical trials, testing two to 3 years of adjuvant treatment with CDK4/6 inhibitors in patients with HR+/HER2− breast cancer (monarchE; NATALEE, NCT03701334), which may significantly increase the cost of treatment for this subgroup of patients. For example, the total cost of 2 years of therapy with abemaciclib (tested in the monarchE trial[40]) is almost €100 000/patient, only considering the cost of the drug and not taking into account all the other direct (laboratory tests, medical appointments, etc) and indirect expenses associated with the treatment. Likewise, in early TNBC, treatment costs may significantly escalate in the future due to the possible introduction of new immunotherapy drugs[41] or poly-ADP ribose polymerase (PARP) inhibitors (OlympiA trial, NCT02032823).

Therefore, due to the increase in the number of available systemic therapy options, namely of targeted drugs, there is a growing concern regarding the 'financial toxicity' of treating breast cancer due to the escalation of costs. This concern exists not only in the metastatic setting, but increasingly in the early setting as well.[42 43] The European Society for Medical Oncology developed the 'Magnitude of Clinical Benefit Scale', which aims to objectively evaluate the clinical benefit of each approved systemic drug, taking into account the drug's survival benefit, associated toxicity and impact on quality of life.[44] These evaluations, coupled with real-life cost assessments such as the one presented in this study, may help inform stakeholders on reimbursement options for the many drugs that are currently being tested and regarding other cancer care policies.

CONCLUSION

In this patient-level data analysis, the cost of early breast cancer care within the first 3 years following diagnosis was mainly driven by the breast cancer subtype and, to a lesser extent, by stage at diagnosis. Among patients with HER2+ breast cancer, the median overall cost of care was fourfold higher compared with those with HR+/HER2− and TNBC, and this difference was mostly related to the cost of systemic therapy, including trastuzumab. These data provide important information for the design of future economic studies, including the evaluation of innovative drugs, as it accurately quantified the use and cost associated with each of the different components of early breast cancer care. Moreover, these findings highlight the preponderance that targeted systemic therapy might have in the overall cost of care for patients with early breast cancer.

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REFERENCES

1 Bray F, Ferlay J, Soerjomataram I, *et al*. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424.
2 Autier P, Boniol M, La Vecchia C, *et al*. Disparities in breast cancer mortality trends between 30 European countries: retrospective trend analysis of who mortality database. *BMJ* 2010;341:c3620.
3 Harbeck N, Penault-Llorca F, Cortes J, *et al*. Breast cancer. *Nat Rev Dis Primers* 2019;5:1–31.
4 Sun L, Legood R, Dos-Santos-Silva I, *et al*. Global treatment costs of breast cancer by stage: a systematic review. *PLoS One* 2018;13:e0207993.
5 Sotiriou C, Pusztai L. Gene-Expression signatures in breast cancer. *N Engl J Med* 2009;360:790–800.

6   Burstein HJ, Curigliano G, Loibl S, *et al*. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen international consensus guidelines for the primary therapy of early breast cancer 2019. *Ann Oncol* 2019;30:1541–57.

7   Seferina SC, Ramaekers BLT, de Boer M, *et al*. Cost and cost-effectiveness of adjuvant trastuzumab in the real world setting: a study of the Southeast Netherlands breast cancer Consortium. *Oncotarget* 2017;8:79223–33.

8   Kerr DJ, Jani A, Gray SM. Strategies for sustainable cancer care. *Am Soc Clin Oncol Educ Book* 2016;35:e11–15.

9   Luengo-Fernandez R, Leal J, Gray A, *et al*. Economic burden of cancer across the European Union: a population-based cost analysis. *Lancet Oncol* 2013;14:1165–74.

10 Campbell JD, Ramsey SD. The costs of treating breast cancer in the US. *Pharmacoeconomics* 2009;27:199–209.

11 Hoang Lan N, Laohasiriwong W, Stewart JF, *et al*. Cost of treatment for breast cancer in central Vietnam. *Glob Health Action* 2013;6:18872.

12 Meneses-García A, Ramírez T, Ruiz-Godoy L, *et al*. Costs of breast cancer treatment prior to the introduction of Immune-based therapy in Mexico. *Rev Med Inst Mex Seguro Soc* 2012;50:19–24.

13 Davari M, Yazdanpanah F, Aslani A, *et al*. The direct medical costs of breast cancer in Iran: analyzing the patient's level data from a cancer specific hospital in Isfahan. *Int J Prev Med* 2013;4:748–54.

14 Tekin RN, Saygılı M. Determining breast cancer treatment costs using the top down cost approach. *Eur J Breast Health* 2019;15:242–8.

15 Breast Clinic. IPO-PORTO. Available: https://www.ipoporto.pt/en/clinica/mama/ [Accessed 18 Oct 2019].

16 Cardoso F, Kyriakides S, Ohno S, *et al*. Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up†. *Ann Oncol* 2019;30:1194–220.

17 Pereira S, Fontes F, Sonin T, *et al*. Neurological complications of breast cancer: study protocol of a prospective cohort study. *BMJ Open* 2014;4:e006301.

18 Nouws S, Brandão M, Fontes F, *et al*. Factors associated with time to breast cancer diagnosis and treatment in unscreened women in Portugal. *Women Health* 2019;59:1–14.

19 Morais S, Costa AR, Lopes-Conceicao L, *et al*. Treatment and other healthcare use of breast cancer patients with a previous cancer diagnosis. *Anticancer Res* 2020;40:1041–8.

20 Lopes-Conceição L, Brandão M, Araújo N, *et al*. Quality of life trajectories during the first three years after diagnosis of breast cancer: the NEON-BC study. *J Public Health* 2019;22. doi:10.1093/pubmed/fdz159. [Epub ahead of print: 27 Dec 2019].

21 Edge S, Byrd D, Compton C, *et al*. *Ajcc cancer staging manual*. 7th ed. New York: Springer, 2010.

22 Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology* 1991;19:403–10.

23 Wolff AC, Hammond MEH, Schwartz JN, *et al*. American Society of clinical Oncology/College of American pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol* 2007;25:118–45.

24 Hammond MEH, Hayes DF, Dowsett M, *et al*. American Society of clinical Oncology/College of American pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol* 2010;28:2784–95.

25 Dowsett M, Nielsen TO, A'Hern R, A'Hern R, *et al*. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in breast cancer Working group. *J Natl Cancer Inst* 2011;103:1656–64.

26 Goldhirsch A, Wood WC, Coates AS, *et al*. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol* 2011;22:1736–47.

27 Portaria 234/2015, 2015-08-07. Diário Repúb. Eletrónico, 2015. Available: https://dre.pt/web/guest/pesquisa/-/search/69968713/details/maximized [Accessed 2 Feb 2020].

28 Harfouche A, Silva S, Faria J, *et al*. [Breast Cancer: Value-Based Healthcare, Costs and Financing]. *Acta Med Port* 2017;30:762–8.

29 Capri S, Russo A. Cost of breast cancer based on real-world data: a cancer registry study in Italy. *BMC Health Serv Res* 2017;17:84.

30 Laas E, Vataire A-L, Aballea S, *et al*. Evaluation of the costs and resource use associated with adjuvant chemotherapy for breast cancer in France. *J Med Econ* 2012;15:1167–75.

31 Wolstenholme JL, Smith SJ, Whynes DK. The costs of treating breast cancer in the United Kingdom: implications for screening. *Int J Technol Assess Health Care* 1998;14:277–89.

32 Smith BD, Bellon JR, Blitzblau R, *et al*. Radiation therapy for the whole breast: Executive summary of an American Society for radiation oncology (ASTRO) evidence-based guideline. *Pract Radiat Oncol* 2018;8:145–52.

33 Correa C, Harris EE, Leonardi MC, *et al*. Accelerated partial breast irradiation: Executive summary for the update of an ASTRO evidence-based consensus statement. *Pract Radiat Oncol* 2017;7:73–9.

34 Barbier L, Declerck P, Simoens S, *et al*. The arrival of biosimilar monoclonal antibodies in oncology: clinical studies for trastuzumab biosimilars. *Br J Cancer* 2019;121:199–210.

35 Hedayati E, Fracheboud L, Srikant V, *et al*. Economic benefits of subcutaneous trastuzumab administration: a single institutional study from Karolinska university hospital in Sweden. *PLoS One* 2019;14:e0211783.

36 Earl HM, Hiller L, Vallier A-L, *et al*. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (Persephone): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial. *Lancet* 2019;393:2599–612.

37 Pondé N, Gelber RD, Piccart M. Persephone: are we ready to de-escalate adjuvant trastuzumab for HER2-positive breast cancer? *NPJ Breast Cancer* 2019;5:1–4.

38 Borges A, Pereira R, Redondo P, *et al*. PCN204 COST-ESTIMATE of adding neoadjuvant pertuzumab for the treatment of HER2+ breast cancer in an institution in Portugal. *Value Health* 2019;22:S475.

39 Francis PA, Pagani O, Fleming GF, *et al*. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N Engl J Med* 2018;379:122–37.

40 Johnston SRD, Harbeck N, Hegg R, *et al*. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2–, node-positive, high-risk, early breast cancer (monarchE). *Journal of Clinical Oncology* 2020:JCO.20.02514.

41 Schmid P, Cortes J, Pusztai L, *et al*. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med* 2020;382:810–21.

42 Semin JN, Palm D, Smith LM, *et al*. Understanding breast cancer survivors' financial burden and distress after financial assistance. *Support Care Cancer* 2020;28:4241–8.

43 Chino F, Peppercorn JM, Rushing C, *et al*. Out-Of-Pocket costs, financial distress, and underinsurance in cancer care. *JAMA Oncol* 2017;3:1582–4.

44 Cherny NI, Sullivan R, Dafni U, *et al*. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for medical oncology magnitude of clinical benefit scale (ESMO-MCBS). *Ann Oncol* 2015;26:1547–73.