Net Costs of Breast Cancer in Colombia: A Cost-of-Illness Study Based on Administrative Claims Databases

Gabriel Fernando Torres (gftorresa@unal.edu.co)
Universidad Nacional de Colombia
Brigitte Alejandra Alarcón
Pfizer (Colombia)
Juan Manuel Reyes-Sanchez
Pfizer (Colombia)
Natalia Castaño-Gamboa
Pfizer (Colombia)
Giancarlo Buitrago
Universidad Nacional de Colombia

Research Article

Keywords: breast cancer, cost-of-illness study, net costs

Posted Date: October 11th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3416926/v1

Additional Declarations: Competing interest reported. Alarcon A, Castano N and Reyes JM are paid employees of Pfizer (Colombia). Buitrago G has received research contracts through the National University of Colombia from Pfizer, Baxter, Roche, Amgen and Glaxo-Smith-Kline. He also has been sponsored for attendance of academic events by Amgen and Pfizer. Torres G has received research contracts through the National University of Colombia from Pfizer, Roche, Amgen and Glaxo-Smith-Kline. He also has been sponsored for attendance of academic events by Roche.

NET COSTS OF BREAST CANCER IN COLOMBIA: A COST-OF-ILLNESS STUDY BASED ON ADMINISTRATIVE CLAIMS DATABASES

Gabriel Fernando Torres [1]

Brigitte Alejandra Alarcón [2]

Juan Manuel Reyes-Sanchez [2] ORCID: 0000-0003-0806-7173

Natalia Castaño-Gamboa [2] ORCID: 0000-0001-7383-6800

Giancarlo Buitrago [1]

1. Universidad Nacional de Colombia. Address: Carrera 45 # 26-85, Bogotá, Colombia, Zip Code: 111321.

2. Pfizer S.A.S. Address: Av. Suba #95-66, Bogotá, Colombia, Zip Code: 112111

Correspondence to: Gabriel Fernando Torres. Instituto de Investigaciones Clínicas, Universidad Nacional de Colombia, e-mail: gftorresa@unal.edu.co, phone: 573155060023.

ABSTRACT

Background

Breast Cancer (BC) is associated with substantial costs of healthcare; however, real-world data regarding these costs in Colombia is scarce. The contributory regime provides healthcare services to formal workers and their dependents and covers almost half of the population in Colombia. This study aims to describe the net costs of healthcare in women with BC covered by the contributory regime in Colombia in 2019 from the perspective of the Colombian Health System.

Method

The main data source was the Capitation Sufficiency Database, an administrative database that contains patient-level data on consumption of services included in the National Formulary (PBS, in Spanish Plan de Beneficios en Salud). Data on consumption of services not included in the PBS (non-PBS) were calculated using aggregated data from MIPRES database. All direct costs incurred by prevalent cases of BC, from January 1 to December 31, 2019, were included in the analysis. The net costs of the disease were estimated by multiplying the marginal cost and the expected number of cases with BC by region and age group. Marginal costs were defined as the costs of services delivered to patients with BC after subtracting the expected costs of health services due to age, comorbidity burden or region of residence. To calculate these costs, we used Propensity Score Matching in the main analysis. All costs were expressed in 2019 international dollars. Productivity losses, transportation expenses, and caregiving costs were not included.

Results

A total of 46,148 patients with BC were identified. Total net costs were $392.7 million (95% CI $386.4 to $404.9 million) 60% associated with non-PBS services. Marginal costs were $8,507 (95% Confidence Interval $8,305 to $8,708), with substantial variations between regions age groups (from $4,509 for older patients in the Amazonia region to $12,646 for

younger patients in the Pacific region). The costs for PBS services were higher for ambulatory services and for patients who died during 2020.

Conclusions

BC imposes a substantial economic burden for the Colombian Health System with important variations in net costs between regions and age groups. Patients near death and ambulatory services were associated with higher costs of healthcare.

Keywords: breast cancer, cost-of-illness study, net costs.

INTRODUCTION

Breast cancer (BC) is the most common malignancy and one of the leading causes of death among women worldwide (1). According to information published by the Ministry of Health, 6,593 incident cases of BC were diagnosed during 2020 in Colombia, and almost one-third of all these cases were diagnosed at stage III or IV (2). Although incidence rates of BC in high-income countries have usually been higher, incidence rates in low- and middle-income countries (LMICs) have been rising by up to 5% per year (3). This continuous increase in incidence adds up to the high mortality burden associated with BC in patients from LMICs, largely attributed to limited diagnostic and treatment capacity in these settings (4, 5). In addition to the direct effects of the disease on health, BC also increases financial pressures on most health care systems (6, 7). This greater financial burden displaces investments from other programs within health systems.

Cost-of-illness (COI) studies seek to evaluate the economic burden that diseases impose on society in terms of the use of health care resources (8). This information can help estimate the

magnitude of diseases in monetary terms, justify preventive or therapeutic strategies, and provide an economic framework for the evaluation of programs, among other useful applications (9). BC has been the subject of several COI studies (10-16); however, there exists great variability between the estimates from these studies in Colombia. Furthermore, there is no information regarding the net costs associated to BC after adjusting for comorbidities. A failure to adjust for comorbidities increases the risk of double counting due to the attribution of all expenditures to the main diagnosis and is related to the generation of implausible large estimates of attributable costs (17).

Since 1993, Colombia has provided mandatory health insurance to all its citizens through several regimes of affiliation based on a managed care competition system. Formal workers and their dependents are affiliated with the contributory regime and comprise almost 48% of the total country's population. "Despite their regimen of affiliation, all individuals are entitled to receive all health services prescribed by authorized health professionals, included or not, in the National Health Benefit Package (HBP). In theory, the HBP contains all diagnostic, therapeutic and rehabilitation services to which all individuals are entitled to within the Health System, under a cost-effectiveness approach (18). In practice, the Ministry of Health undertakes a yearly updating process which continuously expands the list of services included in the HBP. However, new technologies, as well as off-label uses of some included drugs are, at least temporarily, not included in the HBP. Given the continuous growth of available therapeutic options, the cost of non-HBP services frequently takes a substantial share of the total costs of care in cancer (19). According to data published by the Ministry of Health, almost 90% of non-HBP costs within the health system are related to the delivery of non-HBP drugs (20). Most of these services are provided by health maintenance organizations with mixed public and private ownership, and they are reimbursed by the Ministry of Health through a system of risk-adjusted capitation payments.

This study aims to estimate the net costs of BC in women affiliated with the contributory regime in Colombia in 2019. According to Barlow, net cost is defined as *"the difference between the mean costs for cancer patients and for patients without cancer who are otherwise comparable"(21).* All costs borne by the health system, medications, inpatient and outpatient services, and all diagnostic and surgical procedures, regardless of disease stage or histological classification, are included in this study. Costs not borne by the health system, such as productivity losses, out-of-pocket expenditures, transportation costs or caregiving, are not included.

METHODS

Setting and design

This study uses a retrospective COI approach based on prevalent cases to establish the net costs of BC borne by the contributory regime in 2019. For services included in the HBP (HBP services), net costs are estimated using individual-patient data from existing administrative databases. For services not included in the HBP (non-HBP services), quantities and prices are extracted from aggregated data using the public information system provided by the Ministry of Health (SISPRO from the Spanish *Sistema Integrado de Información de la Protección Social*) and available tariff manuals. Finally, total net costs are calculated as the sum of the costs of HBP and non-HBP services. All costs are transformed to 2019 International US dollars using the Purchasing Power Parity conversion factor for Colombia published by The World Bank (1,343.6 Colombian pesos per international dollar) (22). All analyses are made using Stata MP® 14.0 and Microsoft® Excel® for Microsoft 365 MSO licensed to the National University of Colombia.

Data sources

This study uses data from existing administrative databases within the health system. The main source of data is the Database for the Study of the Sufficiency of the Capitation Unit (UPC from the Spanish *Base de datos para el estudio de la Unidad por Capitación*). The UPC database is used by the Ministry of Health to adjust the capitation payments received by HMOs according to the level of use of HBP services of their affiliates. The available UPC database reports patient-level data on the use of HBP services from approximately 80% of the contributory regime and includes the costs paid by the health system, the diagnosis associated with each service using the International Classification of Diseases (ICD-10), and the 10th revision jointly with the basic demographic characteristics. The UPC database is reported by HMOs to the Ministry of Health, and its data are collected at the point of delivery by health care providers. The process of data cleaning and validation of the UPC database is described in detail by Bolivar et al. (23).

All individuals in the UPC database are identified using an anonymized identification number that allows us to link their data to the Unique Registry of Affiliates (RUAF from the Spanish *Registro Único de Afiliados*) and the Unique Database of Affiliation (BDUA from the Spanish *Base de Datos Única de Afiliación*). RUAF allows health professionals to report data on all births and deaths, and its data are key to estimating, among others, mortality indicators of interest for the Colombian Government. The BDUA contains data from all individuals affiliated with the health system, and its data are essential for all reimbursements made by the Ministry of Health to HMOs. Finally, this study uses aggregated data from the My Prescription Database (MIPRES from the Spanish *Mi Prescripción*) available through SISPRO. MIPRES is a web tool that allows health professionals to report the prescription of non-PBS services, and it supports all claims for non-PBS services made by the HMOs.

Identification of patients

To identify patients with BC affiliated with the contributory regime, this study used the electronic algorithm previously validated by Saldaña et al. (24)

Saldana et al compared the incidence estimates of breast, stomach, and colorectal cancer obtained by several electronic algorithms in the UPC database with the estimates published by a prospective, multicentric, cancer registry in Colombia known as Infocancer. The electronic algorithms that yielded the incidence estimates nearest to the ones published by Infocancer were selected as the recommended algorithms for research within the UPC database.

For BC, the persistence of ICD-10 codes for at least four months and at least one BC-specific procedure (the "specific" algorithm) was selected as the recommended electronic algorithm and was used in this study for the main analysis. To estimate the robustness of these results to changes in the electronic algorithm, we calculated the prevalence estimates and the number of cases detected using the persistence of ICD-10 codes for at least four months without the criteria for BC-specific procedures (the "sensitive" algorithm). The full electronic algorithms used in this study are described in table S1 in the additional file.

All women who fulfilled the specific algorithm at any time from 2015 to 2019 and received at least one health care service during 2019, regardless of the stage of the disease or its histological classification, were included in the main cohort and classified as "exposed". Unexposed individuals were selected among all individuals affiliated with the contributory regime who did not receive any ICD-10 code of BC from 2015 to 2019 and received at least one health care service for any other reason during 2019. Data regarding unexposed individuals without any consumption of health services during 2019 (i.e., non-users), and who did not receive any ICD-10 code of BC from 2015 to 2019, were collected from the corresponding BDUA database.

All costs accrued by exposed and unexposed individuals and borne by the health system, from January 1st to December 31st, 2019, were considered in the analysis. Given that, Colombia provides compulsory insurance coverage for all its citizens and that the UPC database contains data on most individuals affiliated with the Contributory regime, no administrative censorship or losses to follow-up were considered in the cohort.

To explore plausible differences in costs during 2019 between women within the first year of diagnosis of BC or at the end of life, this study identified the subgroups of patients who received their first diagnosis of BC during 2018 or who died during the first semester of 2020 within the main cohort. Given that the available UPC database contains data regarding approximately 80% of the individuals affiliated with the contributory regime, this study will assume that the individuals in the remaining 20% of the contributory regime present a similar distribution of disease conditional prevalence, demographic characteristics, and costs.

Estimation of net costs associated to non-HBP services

To estimate the net costs associated to the delivery of non-HBP services, this study uses data on quantities from the MIPRES database through SISPRO and data on prices from the national tariff manuals (25, 26). Equation 4 summarizes the approach used to calculate the costs of non-HBP services:

$$Cost\ nonHBP = \sum_{region} \sum_{age} \sum_{service} \bar{q}_{ras} \times p_s \times n_{ra} \qquad (1)$$

where $\bar{q}_{iras}$ is the mean number of non-HBP services delivered per patient by region, age group and service, p_s is the price of each service according to the data published by the Ministry of Health in national tariff manuals, and n_{ra} is the expected number of patients per region and age group. To decrease the risks of a misallocation of services to the main disease, this study only considers the costs associated with the delivery of targeted therapies (that includes

183 immunotherapy, hormonal therapy, and standard chemotherapy) in this category. We believe
184 that this is a valid assumption since most non-HBP costs are caused by the delivery of targeted
185 therapies, and these are rarely used for other conditions unrelated to cancer. The full list of
186 included non-HBP therapies is shown in table S2 in the additional file.(20). All estimates are
187 reported with their corresponding 95% confidence intervals (95% CI), assuming a uniform
188 distribution for prices and quantities identified in the MIPRES database as the population
189 parameters.

190 ***Estimation of net costs associated to HBP services***

191 A failure to adjust for comorbidities increases the risk of double counting due to a misallocation
192 of all expenditures to the main diagnosis. To decrease this risk, this study uses an approach
193 based on first estimating the marginal costs of delivering HBP services after adjusting for
194 comorbidities (τ) and then multiplying them by the expected number of individuals (n) per
195 geographical region r and age group a. Equation 1 summarizes this approach:

$$Costs\ HBP = \sum_{region} \sum_{age} \tau_{ra} \times n_{ra} \qquad (2)$$

196 "To estimate τ, this study uses a nearest neighbor propensity score matching (PSM) within a
197 caliper of 1 X 10-3 percentage points without replacement in the main analysis.". PSM allows
198 us to decrease the risk of a misallocation of costs by comparing individuals with and without a
199 given condition, but otherwise, a similar risk of use of resources (19). The methods used to
200 estimate attributable costs in COI studies using PSM have been described previously (27). In
201 summary, propensity scores per individual *i* are defined as the conditional probability of
202 assignment to a particular treatment (*W*=1) versus no treatment (*W*=0) given a vector of
203 observed covariates x_i:

$$e(\mathrm{x}_i) = pr(W_i = 1 | X_i = \mathrm{x}_i) \qquad (3)$$

To estimate the propensity scores, this study uses logistic regression analysis with a binary variable that indicates the disease status as the dependent variable and comorbidities (using the Charlson Comorbidity Index), age, region of residence and employment status (defined as employed or unemployed during the last 12 months) as explanatory variables. Given that data regarding income during the last 12 months is available for approximately 80% of the entire cohort only, we performed a sensitivity analysis to compare our PSM estimates for the full cohort and for the subgroup with available data regarding average income (see table S3 in the additional file). Finally, the marginal cost (τ) is defined as the mean of the expected differences across all the matched pairs. Equation 3 summarizes this approach:

$$\tau_{ra} = \frac{1}{M_{ra}} \sum E[c_{ira} - c'_{ira} \,|e(x)] \qquad (4)$$

where M_{ra} is the number of matched pairs and c_{ira} and c'_{ira} are the costs of delivering health services per individual *i* in the age *a* and region *r* group, with and without BC, respectively.

The quality of the matching was assessed by calculating the remaining differences across the covariates. Standardized differences between individuals with and without BC after matching of greater than 20% were considered unacceptable (see table S4 in the additional file). The robustness of all estimations of marginal costs was tested using ordinary least squares and changes in the identification algorithm. The fitted OLS regression model was:

$$COSTS_i = \beta_0 + \beta_1 BREAST_i + \beta_2 AGE_i + \beta_3 INS_i + \beta_4 REGION_i + \beta_5 JOB_i + \delta \boldsymbol{Z_i} + u_i$$

where $COSTS_i$ represents the costs accrued by the individual i due to the delivery of health services during 2019; $BREAST_i$ represents a dummy variable that can take values of one if the individual is classified with diagnosis of breast cancer, or zero otherwise; AGE represents the age in years, INS is a nominal variable that represents the insurer; $REGION_i$ represents the region where the individual i received most services from 2015 to 2019; JOB_i represents a

dummy variable that can take values of one if the individual i was employed during the last 12 months, or zero otherwise. The vector $\mathbf{Z}_i$ includes all comorbidities defined by the Charlson Comorbidity Index; and u_i represents an idiosyncratic error clustered by individual. The OLS model included all variables available in the dataset to describe baseline sociodemographic and clinical characteristics, therefore no variable selection strategies were used to specify the final model.

All estimates are reported with 95% confidence intervals (95% CIs) using robust standard errors and are reported by category of service and setting. Exploratory estimations of costs are made for the subgroup of patients who received the first diagnosis of BC during 2018 and for the subgroup of those who died during the first semester of 2020.

Estimation of total net costs

Finally, total attributable costs by age group and region are calculated by summing the costs due to the delivery of HBP and non-HBP services as calculated in Equations 1 and 4. All estimates of total attributable costs and their corresponding 95% CI are presented by category, setting of delivery and exploratory subgroups of interest.

RESULTS

Identification of patients with breast cancer in the contributory regime

Using the specific algorithm described by Saldaña et al. (24), this study identified 40,800 women with BC in the UPC database during 2019. Assuming a similar distribution of baseline risks with women with unavailable data, 46,148 women in the contributory regime suffered from BC and used at least one health service during 2019 (see Tables S5 and S6 in the additional file). The age-adjusted prevalence conditional on the use of health services varied

widely across the country, ranging from 3.8 cases per 1,000 women in Amazonia to 5.8 cases per 1,000 women in the Pacific region (see Figure 1). The baseline characteristics of the main study cohort and the prespecified subgroups are described in Table 1. In summary, whereas most women from the main cohort were between 45 and 64 years old and had a Charlson Comorbidity Index (CCI) of I or II (including the cancer diagnosis), most women from the cohort of deceased in 2020 were 65 years old or older and had a CCI of five or more. In contrast, most women from the main cohort and all subgroups lived in Bogotá or the Central region of the country.

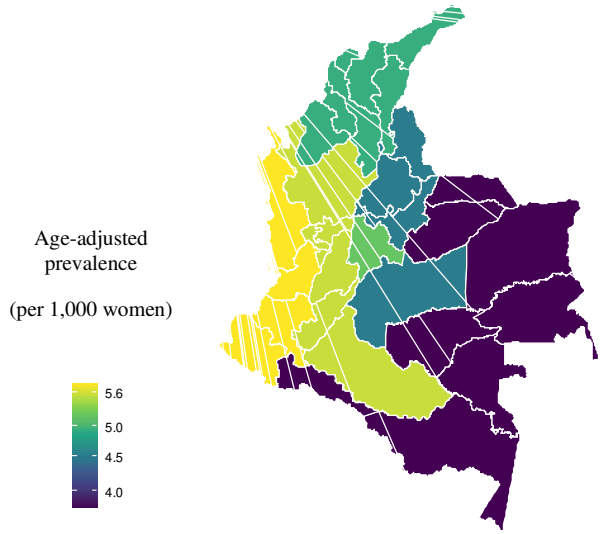


Figure 1. Age-adjusted prevalence of Breast Cancer in the contributory regime by region, conditional to the consumption of at least one health service during 2019

Table 1. Baseline characteristics of the main study cohort

	Main cohort (n=40,800)		Diagnosis in 2018 (n=5,067)		Deceased in 2020 (n=833)	
	n	%	n	%	n	%

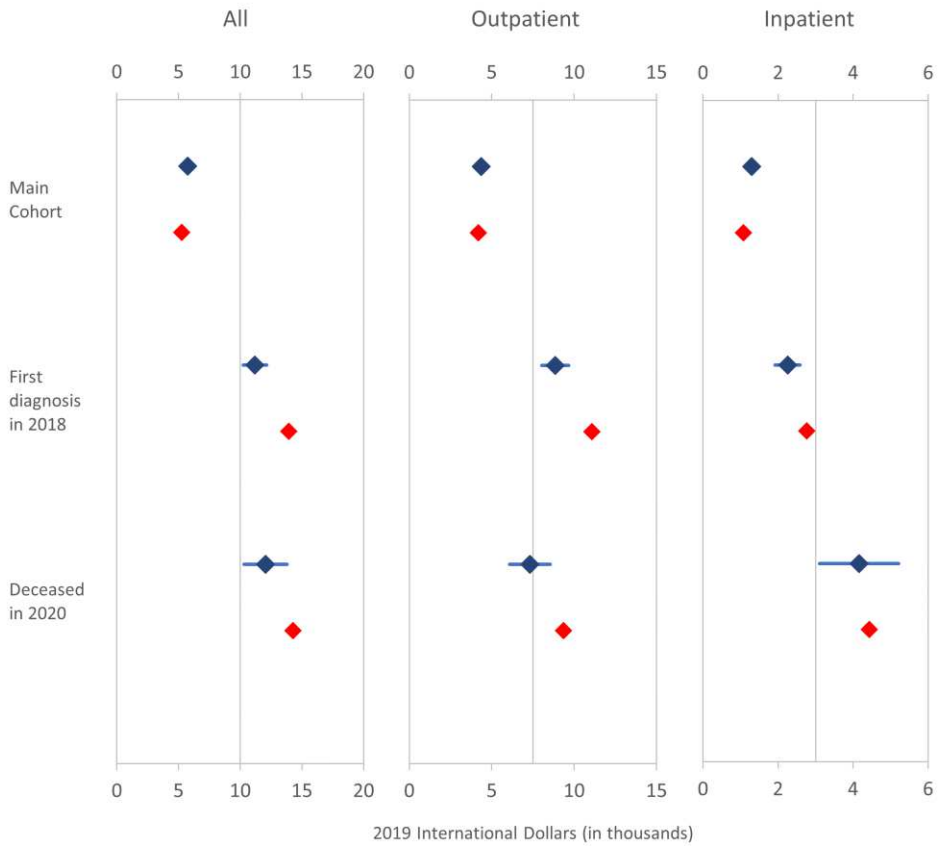
Age (years)						
20 – 44	6,469	15.86	923	18.22	107	12.85
45 – 64	20,804	50.99	2672	52.73	351	42.14
65 or more	13,527	33.15	1472	29.05	375	45.02
Charlson Comorbidity Index						
I – II	19,931	48.85	2943	58.08	226	27.13
III – IV	11,673	28.61	1476	29.13	257	30.85
V or more	9,196	22.54	648	12.79	350	42.02
Presence of ICD-10 codes associated with metastatic disease						
Yes	3,847	9.43	140	2.76	175	21.01
No	36,953	90.57	4,927	97.24	658	78.99
Region of residence						
Atlántica	4,606	11.29	628	12.39	114	13.69
Bogotá	11,994	29.40	1335	26.35	237	28.45
Central	12,316	30.19	1566	30.91	223	26.77
Oriental	5,216	12.78	701	13.83	114	13.69
Orinoquía	226	0.55	35	0.69	3	0.36
Pacífica	6,442	15.79	802	15.83	142	17.05

n: number of cases

Estimation of net costs associated to HBP services

The total net costs associated with the delivery of HBP services in the contributory regime were $243.5 million (95% CI $242.3 to $244.8 million) during 2019. The distribution of these costs across age groups and regions is described in Tables 2, and tables S5 and S6 in the additional file. In brief, the mean attributable cost of delivering HBP services in the contributory regime

268 was $5,277 (95% CI $5,249 to $5,305). These costs were substantially different between
269 regions, age groups and settings of delivery. Regarding regions, mean attributable costs were
270 lower for Bogotá ($4,835, 95% CI $4,786 to $4,884) than for other regions (from $5,037 [95%
271 CI $4,962 to $5,113] in Atlántico to $7,936 [95% CI $7,571 to $8,301] in Orinoquia). Likewise,
272 regarding differences between age groups and settings of delivery, mean attributable costs per
273 patient were lower for women of older ages (from $7,334 to $10,077 in the group of 20 to 44
274 years old to $2,756 to $4,489 in the group of 65 years old or older) and inpatient services (from
275 $1,061 to $1,097 for inpatient services to $4,182.83 to $4,216 for outpatient services). The
276 subgroups of patients with an initial diagnosis during 2018 and those who died during the first
277 semester of 2020 showed higher mean per patient costs of care during 2019 than those in the
278 main cohort. The results of using OLS to estimate the mean attributable costs per patient are
279 shown in Figure 2. No apparent differences were found between the results yielded by both
280 model specifications. Additional information regarding mean attributable costs per patient by
281 category of service is described in table S7 and S8 in the Additional file.



282

283 Figure 2. Marginal costs of delivering services included in the Health Benefit Package in
284 women affiliated with the contributory regime in 2019 by type of model's specification
285 (Propensity Score Matching: blue, Ordinary Least Squares: red)

286

287 ***Estimation of net costs associated to non-HBP services***

288 The total and mean attributable costs per patient due to the delivery of non-HBP services in the
289 contributory regime are listed in Tables 2, and S9 and S10 in the additional file. In summary,
290 the total cost was almost $150 million (95% CI $139.9 to $158.2 million). The mean per patient
291 cost was $3,230 (95% CI $3,030 to $3,427). There were striking differences in these costs
292 between regions, being almost zero in the Orinoquia region and almost $5,000 in the Pacific
293 region. No apparent differences were found between age groups.

294 Table 2. Mean attributable costs per patient in the Contributory Regime during 2019 by region.

	n	Services included in the Health Benefit Package	Services not included in the Health Benefit Package	Total
Atlántica	5,190	5,037.72	3,280.17	8,319.18
		(4,962.03 - 5,113.41)	(2,904.16 - 3,646.38)	(7,930.0 - 8,695.73)
Bogotá	12,887	4,835.78	3,904.43	8,738.14
		(4,786.89 - 4,884.67)	(3,731.39 - 4,073.49)	(8,555.28 - 8,919.13)
Central	13,943	5,263.94	2,400.69	7,663.54
		(5,214.70 - 5,313.18)	(2,252.92 - 2,546.81)	(7,504.09 - 7,819.70)
Oriental	6,032	5,128.65	1,786.20	6,912.83
		(5,043.20 - 5,214.11)	(1,663.04 - 1,905.00)	(6,756.79 - 7,065.41)
Orinoquía	346	7,936.60	15.98	7,952.28
		(7,571.40 - 8,301.80)	(11.26 - 20.73)	(7,590.88 - 8,318.36)
Pacífica	7,752	6,536.16	4,860.81	11,393.14
		(6,357.87 - 6,714.44)	(4,558.42 - 5,152.12)	(11,029.74 - 11,751.18)
All	46,148	5,277.56	3,229.75	8,507.31
		(5,249.85 - 5,305.28)	(3,030.17 - 3,426.80)	(8,305.26 - 8,707.81)

95% Confidence Intervals in parenthesis, n: number of cases by region

Estimation of total attributable costs

The total cost of delivery of health services in patients with BC in the contributory regime in 2019 was $392.7 million (95% CI $386.4 to $404.9 million), with a mean per patient cost of $8,507 (95% CI $8,305 to $8,707). The mean per patient costs ranged from $6,912 in the Oriental region to $11,393 in the Pacific region. In parallel with the findings on costs due to the delivery of HBP services, total attributable costs per patient were consistently lower in women of older ages (from $8,429 to $12,646 in the group of 20 to 44 years old to $4,508 to $9,592 in the group of 65 years old or older).

DISCUSSION

This study estimates the net costs associated to BC in women affiliated with the contributory regime in Colombia in 2019. Total net costs associated to BC and borne by the contributory regime in 2019 ranged from $383.3 to $401.9 million, with mean per patient costs that ranged from $6,912 in the Oriental region to $11,393 in the Pacific region. To the best of our knowledge, this is the first published report that estimates the costs of delivering health services in BC using national data from Colombia, and it is also the first to describe differences in these expenditures across the country.

Several studies have evaluated the economic burden that BC imposes on Latin American health systems. Palacios et al., in a systematic review of the literature, summarized existing evidence regarding the health care costs of patients with BC and their relatives in Latin America and the Caribbean (28). The authors identified 63 studies, 8 of which described the costs of BC in Colombia. Buendia et al., in a cost-effectiveness analysis of trastuzumab for the treatment of early human epidermal growth factor receptor 2-positive (HER2+) BC, estimated the costs of the disease in Colombia in 2012 (13). Using a Markov model, the authors estimated a lifetime cost of $132,361 per patient treated with trastuzumab and of $75,315 per patient on the control treatment. Likewise, using a Markov model, Chicaíza et al. estimated the cost-effectiveness of trastuzumab in the treatment of epidermal growth factor receptor 2-positive (ErbB2+) metastatic BC (14). The authors estimated a 5-year cost per patient that ranged from COP $82,017,207 to COP $105,313,611 ($68,144 and $87,500 in 2012 international dollars), depending on the selected treatment strategy. More recently, Perea et al., in an analysis of the cost-effectiveness of immediate versus delayed breast reconstruction, estimated the health care cost of BC with a time horizon of one year (29). The authors calculated a cost per patient that ranged from $11,060 to $11,165 depending on the type of treatment strategy.

In addition to these model-based estimations, some authors have also used case study methods and an analysis of administrative databases to calculate the costs of BC in Colombia. Gamboa et al., using a case study, estimated the health care costs of BC by clinical stage (11). The costs per year ranged from $10,531 to $30,826 in 2020 international dollars for stages I and IV, respectively (28). Similarly, Moreno et al. evaluated the costs of delivering health care services to patients with BC affiliated with an HMO from 2010 to 2014 (15). The authors estimated a one-year cost per patient ranging from $5,214 to $8,350 depending on the year in the study period. Finally, Franco et al. estimated the costs and resource utilization of health services in patients with advanced HR+/HER2- BC using medical records from 145 patients who initiated first-line treatment from 2012 to 2014 (12). The mean costs per patient ranged from $1,972 to $2,716 by line of treatment.

In contrast to previous studies, this study finds that the mean per patient costs of health services in BC ranged from seven to almost eleven thousand dollars in the contributory regime during 2019. There are several reasons why these results can provide a more accurate estimate of the costs paid by the health system than previous studies. First, the UPC database provides a rich and reliable source of information on the use of health services by individuals. Given that the data are generated at the point of delivery by providers and are key to all claims made by HMOs to the Ministry of Health, we believe that this is an appropriate incentive to avoid an underreporting of health services. Furthermore, as described in detail by Bolivar et al., the UPC database undergoes an extensive process of data cleaning and cross-checking using, among others, the financial reports that HMOs regularly submit to the Ministry of Health and data from RUAF and BDUA (23). This external validation process may serve as an additional auditing tool to identify duplications of reported services or individuals within the database.

A second reason why our results may provide more accurate estimates is that this study includes all services delivered to patients with BC, independent of the type of service and the registered

353 diagnosis. This feature is of great importance since many complications due to the disease or
354 treatment might be registered in administrative databases as “unrelated” to the main diagnosis.
355 In contrast, to decrease the risk of excessively allocating services to the main diagnosis, this
356 study uses econometric methods to isolate the effects of the disease on fitted costs (30).

357 A third reason that further lends support to the accuracy of our results is that the UPC database
358 contains actual data about prices paid by the health system. Given the wide variation in market
359 prices for health services and the extensive bargaining processes that HMOs undertake with
360 individual providers, there may be substantial differences between actual prices paid by the
361 health system and the prices registered in tariff manuals. Using data from UPC allows this
362 study to reduce the reliance of its estimates on unverified assumptions about market prices.

363 Finally, it is well-known that the analysis of healthcare resources poses some significant
364 challenges. These challenges are based on the fact that, among other things, healthcare data
365 often show substantial positive skewness, heavy tales and are often multimodal (e.g. with a
366 mass at zero for non-users) (31). This non-normal distribution is frequently associated with the
367 production of non-informative means. Given that, the mean is the statistic of interest to most
368 policy makers (32), this study calculates the means of 2019 BC healthcare expenditures for two
369 previous pre-specified subgroups: the subgroup of individuals diagnosed during 2018 and the
370 subgroup of individuals who died during the first semester of 2020. We acknowledge that this
371 approach does not allow to make inferences about how mean estimates of costs change during
372 the course of the disease, however, we believe that this information may help policy makers to
373 prioritize health programs for patients with recent diagnosis or who are at the proximity of
374 death

375 One surprising finding of this study is the important differences between the mean per patient
376 costs identified by region. Several differences in the characteristics of demand for health

377 services in BC across the country may help explain this wide variation in costs. A more
378 advanced stage of the disease at diagnosis, especially in regions with low access or utilization
379 of preventive care, may increase the costs of delivering health services in BC (33, 34).
380 Likewise, regions with large segments of their populations with earnings below the poverty
381 line and with low levels of schooling may also present less for HBP and particularly non-HBP
382 services (35).

383 In addition to differences in demand, differences in characteristics of supply may also help
384 explain these large differences in mean per patient costs between regions. The delivery of
385 oncology services in Colombia is highly concentrated in the large urban areas of Bogota,
386 Antioquia and Valle del Cauca (36). Except for Vaupes, in 2018, all departments from the
387 Orinoquia – Amazonia region did not report any registered providers of oncological services.
388 It is highly likely that markets with a higher concentration of providers may exert considerable
389 pressures to decrease prices and therefore lower the mean per patient costs of delivering health
390 services (37).

391 Our study has some weaknesses that must be addressed. The first concerns the use of data
392 regarding the clinical stage to estimate disease severity. The study estimates the impact of the
393 severity of BC on the costs of health services in 2019 by exploring differences in cost estimates
394 for patients who died during the first semester of 2020. The impacts of these advanced stages
395 on the costs of health services are shown in Figure 2. In summary, patients who died during
396 the first semester of 2020 presented an almost three-fold increase in costs compared to patients
397 in the main cohort.

398 Another weakness of this study is that prices were not actually paid by the health system due
399 to the delivery of non-HBP services. Using prices from tariff manuals ignores the fact that the
400 characteristics of health markets may affect the final costs of services. To incorporate this

uncertainty into our estimates, the study used the range of prices identified from tariff manuals to feed 95% confidence intervals for each estimate of costs in non-HBP services.

Another weakness is that unfortunately, we don't have reliable data regarding the population without data in the UPC database. This population is affiliated with insurance companies whose data do not fulfill the minimum standards for quality and completeness required by the Ministry of Health, and therefore, are not available for research purposes (23). This population is, most of the times, affiliated with insurance companies with relatively fewer affiliates, at higher financial risk, and whose affiliates live outside the Andes and Caribe regions (see table S11 in the additional file). Nevertheless, we believe that our approach may provide at least a conservative estimate of the costs of BC in this population. This assumption is based on the fact that, this unfavorable financial conditions is frequently associated with low investments on disease screening and early treatment, and therefore, might result in greater costs due to a higher rate of complications and end-of-life care (38).

Finally, there is no information regarding the histological confirmation of the diagnosis of BC. As mentioned above, to decrease the impact of including patients without the disease (i.e., false-positive cases), the study used the identification algorithm developed by Saldaña et al. (24). According to these authors, BC identification algorithms have a high PPV compared to identification algorithms for other malignancies. Furthermore, the "specific" algorithm developed by Saldaña et al. for the UPC database provides very close estimates of incidence when compared to official registries of cancer in Colombia (39).

CONCLUSIONS

This study estimates net costs associated to BC that were borne by the contributory regime in 2019. It also describes the distribution of these costs across age groups, regions, and settings of delivery of services. These estimates can help in designing public health interventions aimed

425 at promoting the early detection of BC, making informed decisions on the allocation of health
426 resources, and producing essential data for cost-effectiveness analysis of interventions, among
427 others. This study also provides information that will help improve understanding of the
428 financial effects of BC on health systems from LMICs worldwide. Further research is needed
429 to identify the mechanisms that help explain the remarkable differences in mean per patient
430 costs across the country.

431 ## LIST OF ABBREVIATIONS

BC	Breast Cancer
LMICs	low- and middle-income countries
COI	Cost-of-illness studies
HBP	Health Benefit Package
UPC	Database for the Study of the Sufficiency of the Capitation Unit
ICD-10	International Classification of Diseases, 10th revision
RUAF	Unique Registry of Affiliates
BDUA	Unique Database of Affiliation
MIPRES	My Prescription Database
CI	Confidence Interval
PSM	Propensity Score Matching
CCI	Charlson Comorbidity Index
HER2	Human Epidermal Growth Factor Receptor 2
ErbB2	Epidermal Growth Factor Receptor 2

432

DECLARATIONS

Ethics approval and consent to participate:

This study was approved by the Ethics Committee of the Faculty of Medicine of Universidad Nacional de Colombia, Act 008, May 12th, 2022. All datasets used in this study were provided by the Colombian Ministry of Health to Universidad Nacional de Colombia for research purposes and is available under authorization of the Ministry. All data are stored in secure servers at the Faculty of Medicine. All identification data were removed before being delivered to the Instituto de Investigaciones Clínicas. Data from single individuals were identified using an anonymized identifier provided by the Ministry of Health.

Consent for publication

Not applicable

Availability of data

The data that support the findings of this study are available from the Colombian Ministry of Health, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Colombian Ministry of Health.

Competing interests

Alarcon A, Castano N and Reyes JM are paid employees of Pfizer S.A.S. Buitrago G has received research contracts through the National University of Colombia from Pfizer, Baxter, Roche, Amgen and Glaxo-Smith-Kline. He also has been sponsored for attendance of academic events by Amgen and Pfizer. Torres G has received research contracts through the National University of Colombia from Pfizer, Roche, Amgen and Glaxo-Smith-Kline. He also has been sponsored for attendance of academic events by Roche.

Funding

This work was funded by Pfizer S.A.S. All decisions regarding the conceptualization, design, analysis, decision to publish, and preparation of the manuscript were made solely by the authors.

Authors' contributions

GB and GT analyzed the data, GT wrote the first draft of the manuscript and the study protocol. All authors contributed to the design of the study, analysis of the results and read and approved the final manuscript

REFERENCES

1. International Agency for Research on Cancer - World Health Organization. Global Cancer Observatory. 2020 [28/09/2020]; Available from: https://gco.iarc.fr/.

2. Fondo Colombiano de Enfermedades de Alto Costo - Cuenta de Alto Costo (CAC). Situacion del cancer en la poblacion adulta atendida en el SGSSS de Colombia, 2021. Bogota, D.C.2022. Available from: https://cuentadealtocosto.org/site/wp-content/uploads/2022/08/01_agosto_libro_cancer_2021_final.pdf.

3. Anderson BO, Ilbawi AM, El Saghir NS. Breast Cancer in Low and Middle Income Countries (LMICs): A Shifting Tide in Global Health. Breast J. 2015;21(1):111-8.

4. Forouzanfar MH, Foreman KJ, Delossantos AM, Lozano R, Lopez AD, Murray CJL, et al. Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. Lancet. 2011;378(9801):1461-84.

5. Hisham AN, Yip CH. Spectrum of breast cancer in Malaysian women: overview. World J Surg. 2003;27(8):921-3. Epub 2003/06/05.

6. Lao C, Mondal M, Kuper-Hommel M, Campbell I, Cameron MP, Lawrenson R. Breast cancer costs in New Zealand's public health system. N Z Med J. 2021;134(1545):36-46. Epub 2021/11/18.

7. Max W, Sung H-Y, Stark B. The economic burden of breast cancer in California. Breast Cancer Res Treat. 2009;116(1):201-7.

8. Tarricone R. Cost-of-illness analysis. What room in health economics? Health policy (Amsterdam, Netherlands). 2006;77(1):51-63. Epub 2005/09/06.

9. Rice DP. Cost of illness studies: what is good about them? Inj Prev. 2000;6(3):177-9. Epub 2000/09/26.

10. Campbell JD, Ramsey SD. The costs of treating breast cancer in the US: a synthesis of published evidence. Pharmacoeconomics. 2009;27(3):199-209. Epub 2009/04/10.

11. Gamboa Ó, Buitrago LA, Lozano T, Dieleman S, Gamboa C, Guzmán ÉL, et al. Costos directos de la atención del cáncer de mama en Colombia. Rev Colomb Cancerol. 2016;20(2):52-60.

12. Franco S, Lobaton JF, Aruachan S, Montoya ME, Rojas G, Londoño PA, et al. PCN210 Resource Utilization and Cost for Women with Advanced Hr+/Her2- Breast Cancer in Colombian Health Care Settings. Value Health. 2019;22:S476.

13. Buendía JA, Vallejos C, Pichón-Rivière A. An economic evaluation of trastuzumab as adjuvant treatment of early HER2-positive breast cancer patients in Colombia. Biomedica. 2013;33(3):411-7. Epub 2014/03/22.

14. Chicaíza-Becerra L, García-Molina M, Gamboa O, Castañeda-Orjuela C. ErbB2+ metastatic breast cancer treatment after progression on trastuzumab: a cost-effectiveness analysis for a developing country. Rev Salud Publica (Bogota). 2014;16(2):270-80. Epub 2014/11/11.

15. Moreno JA, Muñoz-Galindo IM, Guarin NE, Diaz JA, Arevalo HO. Direct costs of Health care for Breast Cancer, the case of a Health manteinance Organization in Colombia. Value Health. 2015;18(3):A254.

16. Inotai A, Abonyi-Tóth Z, Rokszin G, Vokó Z. Prognosis, Cost, and Occurrence of Colorectal, Lung, Breast, and Prostate Cancer in Hungary. Value Health Reg Issues. 2015;7:1-8. Epub 2015/09/01.

17. Rosen AB, Aizcorbe A, Highfill T, Chernew ME, Liebman E, Ghosh K, et al. Attribution of Health Care Costs to Diseases: Does the Method Matter? Measuring and Modeling Health Care Costs: National Bureau of Economic Research, Inc; 2016. p. 173-210.

515 18. Guerrero R, Gallego AI, Becerril-Montekio V, Vásquez J. [The health system of
516 Colombia]. Salud Publica Mex. 2011;53 Suppl 2:s144-55. Epub 2011/09/09. Sistema de salud
517 de Colombia.

518 19. Torres GF, Amaya JA, Buitrago G. Attributable Costs of Lung Cancer for the
519 Colombian Health System: A Cost-of-Illness Study. Value Health Reg Issues. 2022;30:120-6.
520 Epub 2022/03/29.

521 20. Rojas A, Fernández C, Beltrán L, Díaz I. Cifras financieras del sector salud: recobros
522 al fosyga por tecnologías en salud no incluidas en el plan de beneficios 2009 - 2014. Bogotá:
523 Ministerio de Salud y Protección Social, 2015.

524 21. Barlow WE. Overview of methods to estimate the medical costs of cancer. Med Care.
525 2009;47(7 Suppl 1):S33-6. Epub 2009/06/19.

526 22. The World Bank. PPP conversion factor, GDP (LCU per international $) - Colombia.
527 2019 [20/06/2022]; Available from:
528 https://data.worldbank.org/indicator/PA.NUS.PPP?locations=CO.

529 23. Bolívar Varga MC, Caravalli A, Darío A, Hurtado Cárdenas GE, Torres Ovalle G,
530 Linares Cifuentes JC, et al. Estudio de suficiencia y de los mecanismos de ajuste de riesgo de
531 la unidad de pago por capitación para garantizar el plan obligatorio de salud en el año 2013.
532 Bogotá: Ministerio de Salud y Protección Social; 2014.

533 24. Saldaña Espinel LE, Patiño Benavidez AF, Rozo Agudelo N, Gamboa Garay OA,
534 Paneso Echeverry JE, Bernal Gutierrez M, et al. Estimating breast, stomach, and colorectal

535 cancer incidence in Colombia through administrative database algorithms: A systematic review
536 of literature and real-world data study. J Clin Oncol. 2021;39(15_suppl):e18810-e.

537 25. Ministerio de Salud y de la Protección Social. SISPRO - Sistema Integrado de
538 Información de la Protección Social. 2021 [30/02/2021]; Available from:
539 https://www.sispro.gov.co/Pages/Home.aspx.

540 26. Ministerio de Salud y de la Protección Social. Circular 06 de 2018. 2022 [03/07/2022];
541 Available from: https://www.minsalud.gov.co/salud/MT/Paginas/circular-06-de-2018.aspx.

542 27. Tao B, Pietropaolo M, Atkinson M, Schatz D, Taylor D. Estimating the cost of type 1
543 diabetes in the U.S.: a propensity score matching method. PLoS One. 2010;5(7):e11501. Epub
544 2010/07/17.

545 28. Palacios A, Rojas-Roque C, González L, Bardach A, Ciapponi A, Peckaitis C, et al.
546 Direct Medical Costs, Productivity Loss Costs and Out-Of-Pocket Expenditures in Women
547 with Breast Cancer in Latin America and the Caribbean: A Systematic Review.
548 Pharmacoeconomics. 2021;39(5):485-502. Epub 2021/03/31.

549 29. Perea AH, Rosselli D. Immediate versus delayed breast reconstruction in breast cancer
550 patients in Colombia: A costutility analysis. Biomedica. 2018;38(3):363-78. Epub 2018/10/20.

551 30. Rizzo JA, Chen J, Gunnarsson CL, Naim A, Lofland JH. Adjusting for comorbidities
552 in cost of illness studies. J Med Econ. 2015;18(1):12-28. Epub 2014/09/26.

553 31. Mihaylova B, Briggs A, O'Hagan A, Thompson SG. Review of statistical methods for
554 analysing healthcare resources and costs. Health Econ. 2011;20(8):897-916. Epub 2010/08/28.

555 32. Arrow KJ, Lind RC. Uncertainty and the Evaluation of Public Investment Decisions.
556 Am Econ Rev. 1970;60(3):364-78.

557 33. Lao C, Mondal M, Kuper-Hommel M, Campbell I, Lawrenson R. What affects the
558 public healthcare costs of breast cancer in New Zealand? Asia Pac J Clin Oncol. 2022. Epub
559 2022/09/18.

560 34. Mohar A, Bargalló E, Ramírez MT, Lara F, Beltrán-Ortega A. [Available resources for
561 the treatment of breast cancer in Mexico]. Salud Publica Mex. 2009;51 Suppl 2:s263-9. Epub
562 2010/01/09. Recursos disponibles para el tratamiento del cáncer de mama en México.

563 35. OECD. OECD Reviews of Health Systems: Colombia 20162015.

564 36. Murcia E, Aguilera J, Wiesner C, Pardo C. Oncology services supply in Colombia.
565 Colombia Médica. 2018;49:89-96.

566 37. Statements of Antitrust Enforcement Policy in Health Care. In: U.S. Department of
567 Justice and the Federal Trade Commission, editor. Washington, D.C. 1996.

568 38. Fonseca Salguero MA, Martinez Peñuela DA. Caracterización de peticiones, quejas y
569 reclamos del SGSSS en Colombia en 2014-2019: retos y perspectivas.

570 39. Cáncer de Mama. Instituto Nacional de Cancerología - Ministerio de Salud y de
571 Protección Social; 2022 [cited 08/11/2020]; Available from:
572 https://www.cancer.gov.co/conozca-sobre-cancer-1/informacion-sobre-cancer-para-
573 pacientes/tipos-cancer/cancer-mama.
574

ADDITIONAL FILES

Name: Additional_file.docx.

Title: Supplementary Data.

Description: This file contains additional information regarding cost estimates by region, age group and category of costs. It also includes additional information regarding sensitivity analysis and balance of variables before and after matching.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile.docx