The European Journal of Health Economics (2020) 21:451–464
https://doi.org/10.1007/s10198-019-01148-w

ORIGINAL PAPER

# Healthcare costs associated with breast cancer in Germany: a claims data analysis

**Kristine Kreis[1] · Marika Plöthner[1] · Torben Schmidt[1] · Richard Seufert[2] · Katharina Schreeb[3] · Veronika Jahndel[3] · Sylke Maas[3] · Alexander Kuhlmann[1] · Jan Zeidler[1] · Anja Schramm[2]**

Received: 17 April 2019 / Accepted: 12 December 2019 / Published online: 2 January 2020


## Abstract

**Purpose** This study estimates the healthcare costs associated with breast cancer (BC) for different treatment phases (initial, intermediate, terminal) in Germany from the payer's perspective.

**Methods** The analysis uses claims data from the AOK Bayern covering 2011–2014 for continuously insured BC patients identified through inpatient and outpatient diagnoses. We calculate the healthcare costs attributable to BC using a control group design comparing the target population to a 1:2 matched control group adjusted for age, gender, and comorbidities. For incident and prevalent BC cases, we calculate age-standardized phase-specific incremental costs stratified by cost domain.

**Results** The initial, intermediate, and terminal phases comprise 3841, 28,315, and 1767 BC cases, respectively. BC-related incremental costs follow a u-shaped curve, with costs highest near diagnosis and death, and lower in between. With average costs of €33,237 per incident and €28,211 per prevalent case in the remaining 11 months before death, the highest BC-related incremental healthcare costs can be found in the terminal phase. In the initial phase, there were mean incremental costs of €21,455 the first 11 months after diagnosis. In the intermediate phase, incremental costs totaled €2851 per incident and €2387 per prevalent case per year. Healthcare costs decreased with age in most phases. The cost drivers depend on the treatment phase, with cytostatic drugs and inpatient treatment showing the highest economic impact in most phases.

**Conclusion** The study concludes that BC care costs impose a relevant economic burden on statutory health insurance and vary substantially depending on the treatment phase.

**Keywords** Breast cancer · Disease cost · Claims data · Joinpoint · Germany

**JEL Classification** I10 · I13 · I14

## Introduction

Breast cancer (BC) is the world's second most common type of cancer and the most frequent in women. It represents 12% of all new cancer cases and 25% of all cancers in women [1].

✉ Kristine Kreis
kjk@cherh.de

[1] Center for Health Economics Research Hannover (CHERH), Gottfried Wilhelm Leibniz Universität Hannover, Otto-Brenner-Straße 7, 30159 Hannover, Germany

[2] AOK Bayern, Die Gesundheitskasse, DLZ Versorgungsmanagement, Bruderwöhrdstr. 9, 93055 Regensburg, Germany

[3] BioNTech AG, An der Goldgrube 12, 55131 Mainz, Germany

In 2014, the age-standardized rate of incidence for women was 114.6 per 100,000 people in Germany, representing 69,220 new BC cases. Between 1980 and 2004, the incidence rate increased by about 50% [2]. Moreover, 559,900 German women (10-year prevalence) were living with a BC diagnosis in 2014, and 17,670 of them died from the disease. However, the relative 5-year survival rate increased from 69% in 1980 to 81% in 2004 [3]. This improvement resulted from better treatment options (e.g., higher radiation doses [4]), new drug interventions [5], and earlier diagnoses (e.g., through mammography screening [6]).

The treatment and prognosis of BC are influenced by factors such as age, cancer stage, and tumor characteristics (status of estrogen receptor, progesterone receptor, human epidermal growth receptor 2, and the histologic grade) [7]. The disease stage (diseases stage 0–IV) influences

disease-specific costs [8], which range from $60,637 (stage 0) to $134,682 (stage IV) per patient in the initial 12 months postdiagnosis. In the European Union, cancer incurred €126 billion of costs in 2009, €15 billion of which were attributable to BC. Accounting for 12% of total cancer costs, BC represents the second highest economic cancer burden [9]. Germany's costs of illness (COI) for BC were estimated at around 2169 million euros in 2015 [10]. Germany has Europe's highest BC healthcare costs per person [9].

Cost analyses are important for political decision making concerning prioritization and allocation [11]. Economic studies on BC cost patterns [12] include few analyses of BC-attributable health expenditures in Germany [13, 14]. Only two studies have reported the COI of BC using claims data from a statutory health insurance (SHI) in Germany [14, 15] of which one was only published as a poster abstract [15]. The second study is based on highly aggregated data sets referring to the year 1999 and covering inpatient spending, medication costs and sickness benefits, thus neglecting further cost domains (i.e., outpatient care, remedies/medical aids, rehabilitation). Moreover, stratification by cost category did not take place [14]. Claims data from SHIs are well suited for cost analyses, since they are routinely collected for billing and reimbursement. However, a detailed analysis of overall direct disease-related costs that identifies the cost-driving factors is required, because the extant studies differ substantially in their cost-calculation methods and cost domains considered.

Moreover, unlike US data [16], the German data have not been analyzed for cost patterns through a clinically meaningful phase-of-care approach in relation to diagnosis and death. The phases used by US studies are commonly divided into initial, intermediate and terminal care, and phase duration can be determined theoretically or empirically. This approach takes into account that costs may differ strongly across phases according to the need for treatment and healthcare costs are expected to be highest near diagnosis and death [16]. This is the first study that estimates the BC-attributable health expenditures in Germany according to empirically determined treatment phases.

## Methods

### Data source and study population

AOK Bayern provided data on all services reimbursed. Its sickness fund covered almost 4.3 million insured individuals in 2011 [17]. The analysis includes costs for inpatient and outpatient care, medication/cytostatic drugs, remedies and medical aids, rehabilitation, sick leave, and travel expenses. Patient identification was based on the ICD-10-GM system with ICD codes C50.0 to C50.9. Inclusion in the study population required documentation for at least one inpatient diagnosis or secured outpatient BC diagnosis in 2012. For exclusive identification by outpatient diagnosis, a second secured outpatient diagnosis was required within the following three quarters (i.e., occurring in 2013). We used 2011 to differentiate between incident and prevalent cases. Patients were defined as "incident" if no C50 diagnosis (outpatient/inpatient) was documented in 2011. All sample patients had to be continuously insured from 2011 to 2014 or until death (whichever came first). Male patients and patients under 18 were excluded, as both groups require special treatment.

### Study design

We calculated BC-attributable costs using a control group design with pairwise direct matching. We compared BC patients to a 1:2 matched control group adjusted for gender, age and comorbidities. Using the Elixhauser comorbidity score [18], we calculated comorbidities for both the intervention and control groups in 2011 on the basis of at least one inpatient/secured outpatient diagnosis. To avoid overadjustment, BC diagnosis was excluded in the count. For matching, we used the nearest neighbor approach, allowing for a caliper of 5 years/points. The control sample consisted of females continuously insured by AOK Bayern from 2011 to 2014 without a BC diagnosis. Replacement of control group members was only allowed once.

Follow-up started for BC cases identified by hospitalization from the beginning of the month of the inpatient diagnosis. In German claims data, outpatient diagnoses are reported on a quarterly basis. Thus, within the quarter of each BC diagnosis, we defined the beginning of the month in which the first service date (according to the Uniform Valuation Scheme [EBM]) was documented as the approximate date of the index event. Follow-up ended in the latest 2 years following the index event or in the month of death, whichever came first. We ensured that all BC cases classified as "non-deceased" had not died within 6 months following the end of the observation. For controls, we considered follow-up periods analogously to the BC cases.

Following US studies [16, 19–25], we divided the time after BC diagnosis into clinically relevant treatment phases: (1) initial phase, comprising the primary course of therapy (e.g., surgery, chemotherapy, radiation); (2) intermediate phase, including active surveillance and ongoing medication to prevent recurrence (e.g., hormone blockade) or treatment complications derived from the initial course of therapy; and (3) terminal phase, comprising (palliative) services provided in the last months before death. Lacking a scientific consensus on the duration of BC treatment phases, we first calculated the monthly BC-attributable costs and examined the average cost patterns from diagnosis to death. Using Trend Analysis Software from the National Cancer

Institute [26], we applied joinpoint regression [22, 27] to determine the length of the initial and terminal phase by assessing the points at which statistically significant changes occur in the cost slope. According to joinpoint regression analysis, there must be at least 12–16 data points (months) to receive two joinpoints. As the observation period's maximum was 24 months and BC cases showed different characteristics (e.g., incident vs. prevalent, alive vs. deceased), not all individuals underwent all phases of care. Therefore, to determine the length of the initial phase, we examined average cost patterns of newly diagnosed BC cases that were observable for 18–24 months. Similarly, definition of terminal phase length was based on prevalent BC cases that had died during the observation period and were observable for 18–24 months preceding death.

After determination of phase care length, individuals were assigned to phases of care. Following the literature [22, 24], the observation period for BC cases who died was first assigned to the terminal phase of care. Any remaining time under observation, and all follow-up time for BC survivors, was then transferred to the initial treatment phase, and the most recent was assigned to the intermediate phase. In the initial and terminal phases, patients were excluded if they were not observable for the period determined by the joinpoint regression analysis. To be included in the intermediate phase, BC cases had to be observable for at least 12 months (costs are on an annual basis).

### Calculation and presentation of healthcare costs

Copayments and out-of-pocket payments were not considered because costs were analyzed from the SHI perspective. Healthcare costs in euro were extracted from the database for both BC cases and controls. For each inpatient/rehabilitation stay and sick leave period, costs were divided by the length of stay/duration and calculated according to the start and end of each phase. Unfortunately, only annual outpatient care costs were available. To obtain monthly values, outpatient care costs were divided by the months under observation. To provide a better overview, the costs of cytostatic drugs and any remaining medication are reported separately. These medication costs include only prescriptions for outpatient care. The costs of drugs administered during inpatient episodes are part of total inpatient costs.

By comparing the cost differences between BC cases and controls, we could calculate the BC-attributable costs differentiated according to care phase. To adjust for age differences between SHIs, we standardized costs according to the 5-year age structure of compulsory insured women in Germany for 2011 using data from the Federal Ministry of Health [17]. As the cases were few, we aggregated the costs of BC cases younger than 45 (initial and intermediate phase) and younger than 50 (terminal phase) before standardization.

Sensitivity analyses were also conducted, calculating standardized healthcare costs by treatment type for the initial and terminal phase of care. Patient allocation to treatment types was based on clinical knowledge defining codes for surgery, radiotherapy and chemotherapy (see Appendix 1). Inclusion required at least one healthcare service. Data management and statistical analyses were performed with SAS 9.4.

## Results

### Study population

The inclusion criteria produced 36,033 BC patients (see Fig. 1). Of these, 32,058 were matched to 64,116 controls (1:2) and followed for a maximum of 2 years. After the matching, no significant differences were observed between BC cases and the controls concerning gender, age, or comorbidity score (see Table 1). Overall, 13% of BC cases were identified as incident, and 6% died within the follow-up period.

Through the joinpoint regression analysis, the initial treatment phase was defined as the month of diagnosis and the following 10 months. The terminal phase comprised the last 11 months of life, and the intermediate phase comprised all months between the initial and terminal phases. In the initial and terminal phase, the joinpoint regression analysis identified the points at which BC-related costs decreased

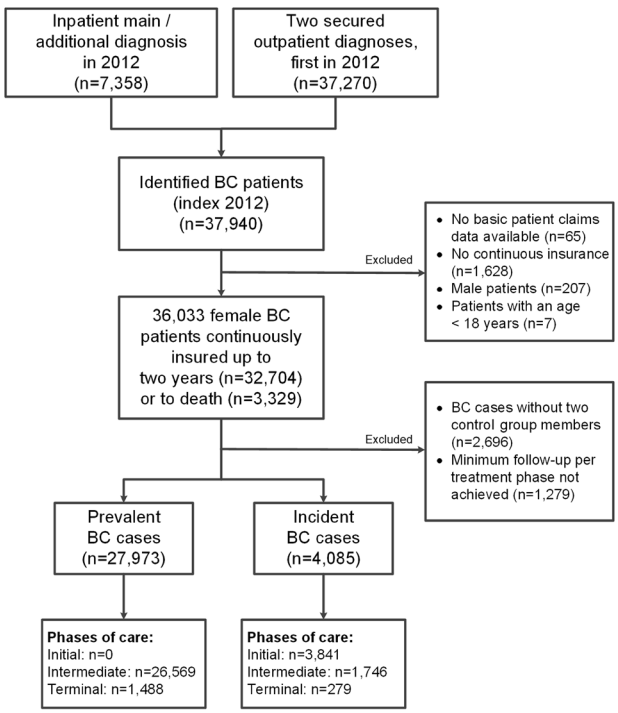


**Fig. 1** Cohort selection

**Table 1** Demographic characteristics after matching

| Group | Gender: female | | Age | | Elixhauser comorbidity score | | *n* |
|---|---|---|---|---|---|---|---|
| | % | $p^a$ | Mean [SD] | $p^b$ | Mean [SD] | $p^b$ | |
| BC cases | 100 | 1 | 67.12 [12.17] | 0.99 | 5.93 [8.67] | 0.99 | 32058 |
| Controls | 100 | | 67.13 [12.16] | | 5.93 [8.67] | | 64116 |

*SD* standard deviation

[a]Chi-square test

[b]U test following Mann and Whitney

significantly. BC cases were included in one (94%) or two (6%) phases of care. Survivors were followed for 23 months on average (SD = 1) and deceased individuals 17 months (SD = 4) on average.

Concerning demographic characteristics, Table 2 shows that age at phase onset averaged around 67 in the initial phase, 67 (incident cases) versus 68 years (prevalent cases) in the intermediate phase, and 77 (incident cases) versus 76 years (prevalent cases) in the terminal phase. The mean Elixhauser score was 4 points for BC cases in the initial phase, 4 (incident cases) versus 6 (prevalent cases) points in the intermediate phase and was highest for individuals assigned to the terminal phase (7 versus 13 points). Within each phase, prevalent cases had a significantly higher comorbidity score than incident individuals ($p < 0.001$; Mann–Whitney *U* test).

### Healthcare costs

The highest incremental BC costs are in the terminal phase, followed by the initial and intermediate phases. Tables 3 and 4 show the age-standardized healthcare costs in euro per cost component within each treatment phase for incident and prevalent patients.

As Table 3 shows, in the first 11 months following diagnosis, the average BC-related incremental costs totaled €21,455 per patient. At €11,220 per patient, cytostatic drugs represent more than half (52%) of initial phase costs, followed by inpatient care (23%), outpatient care (11%), and sick leave payments (8%). All remaining cost compounds are of minor importance. Subgroup analyses revealed that total initial phase costs varied substantially by treatment type (see appendix 2). Incremental costs totaled €60,000 in patients treated with surgery, radiotherapy and chemotherapy, whereas incremental costs of those treated with surgery alone (€7874) or surgery and radiotherapy (€11,210) were much lower.

In the intermediate phase, there were €2851 mean BC-related incremental costs for incident and €2387 for prevalent patients per year. For incident BC cases, almost a third of the costs is attributable to outpatient care. Cytostatic drugs, inpatient care, and sick leave payments each accounted for 15–20% of incremental BC-related costs. In contrast, accounting for over half of incremental costs in prevalent cases, the highest cost drivers are cytostatic drugs, followed by outpatient care (18%), inpatient care (14%), and remedies/medical aids (9%). In both incident and prevalent cases, all remaining medication, rehabilitation, and travel expenses have limited effects on incremental costs.

In the terminal phase (11 months before death), mean BC-related incremental costs totaled €33,237 in incident and €28,211 in prevalent cases. In both incident and prevalent cases, nearly half of the costs were attributable to inpatient care, followed by cytostatic drug treatment (accounting for 29–34%). Differentiating phase costs by treatment type, subgroup analyses showed that total terminal care costs ranged between €11,608 in patients without active therapy (no claim for surgery, radiotherapy and chemotherapy) and €52,651 in those treated with radiotherapy and chemotherapy (see Appendix 3).

Several studies suggest that BC costs differ substantially by age [13, 14]. Given the unstandardized costs stratified by 5-year age groups (see Appendices 4 and 5), incremental BC-related costs in the initial phase decreased substantially by age, with €56,169 in patients aged 30–34 compared to €4530 in patients aged 85 or older. Though not apparent in all 5-year age groups, this general trend is also evident in the intermediate and terminal phases.

## Discussion

Cancer costs are typically first reported at the initial diagnosis, for a specific event like recurrence, or generally (for cancer survivors) in a specific year. However, costs may change over time when measured longitudinally starting from initial cancer diagnosis to long-term survival or death. In the US, phase-specific approaches are often used to analyze cancer cost patterns [16, 25]. This study used claims data on real-life treatment to estimate the costs of BC care for Germany according to clinically relevant treatment phases. Using definitions of treatment phases according to joinpoint regression analysis, our study suggests that incremental BC-related costs differ substantially by care phase. Standardized

**Table 2** Baseline characteristics of BC cases

| Phase | Age (at phase onset) | | | | | Elixhauser comorbidity score | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | [SD] | Median | Min | Max | Mean | [SD] | Median | Min | Max | *n* |
| Initial | | | | | | | | | | | |
| Incident | 66.78 | [13.15] | 68 | 21 | 101 | 3.99 | [7.31] | 1 | − 11 | 49 | 3841 |
| Intermediate | | | | | | | | | | | |
| Incident | 67.03 | [13.12] | 69 | 21 | 102 | 3.84 | [7.29] | 0 | − 10 | 49 | 1746 |
| Prevalent | 67.81 | [11.83] | 69 | 19 | 107 | 5.81 | [8.57] | 3 | − 14 | 58 | 26569 |
| Terminal | | | | | | | | | | | |
| Incident | 76.97 | [13.35] | 80 | 23 | 100 | 7.15 | [8.42] | 6 | − 7 | 39 | 279 |
| Prevalent | 76.49 | [11.75] | 78 | 37 | 100 | 13.35 | [10.16] | 12 | − 7 | 49 | 1488 |

*SD* standard deviation

**Table 3** Age-standardized healthcare costs of incident BC cases in Germany (in €, mean [standard deviation])

| Cost sector | Initial phase (11 months) | | | | | | Intermediate phase (12 months) | | | | | | Terminal phase (11 months) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BC cases | | Controls | | Increment | | BC cases | | Controls | | Increment | | BC cases | | Controls | | Increment | |
| Medication (sum) | 12043 | [24100] | 495 | [1723] | 11548 | [24227] | 1186 | [7070] | 491 | [1516] | 695 | [7237] | 11971 | [22320] | 690 | [3915] | 11281 | [22696] |
| Cytostatic drugs | 11224 | [23676] | 4 | [165] | 11220 | [23679] | 577 | [6769] | 0 | | 577 | [6769] | 9805 | [21863] | 0 | | 9805 | [21863] |
| Other medication | 819 | [2021] | 491 | [1702] | 328 | [2637] | 609 | [1848] | 491 | [1516] | 118 | [2383] | 2166 | [3529] | 690 | [3915] | 1476 | [5389] |
| Remedies/medical aids | 525 | [1090] | 231 | [578] | 295 | [1220] | 573 | [1144] | 289 | [767] | 283 | [1368] | 1247 | [1685] | 279 | [837] | 969 | [1817] |
| Outpatient care | 3119 | [2541] | 765 | [615] | 2353 | [2626] | 1736 | [1620] | 850 | [642] | 886 | [1761] | 3528 | [3065] | 853 | [751] | 2675 | [3186] |
| Inpatient care | 6141 | [7111] | 1160 | [4254] | 4982 | [8303] | 1864 | [4515] | 1383 | [4493] | 482 | [6376] | 16513 | [14745] | 1024 | [2810] | 15488 | [15125] |
| Rehabilitation | 178 | [734] | 81 | [513] | 97 | [882] | 118 | [627] | 94 | [578] | 24 | [850] | 357 | [1355] | 91 | [497] | 266 | [1448] |
| Sick leave payments[a] | 1862 | [4421] | 126 | [1051] | 1736 | [4483] | 560 | [2094] | 111 | [885] | 448 | [2224] | 1643 | [4033] | 61 | [525] | 1581 | [3909] |
| Travel expenses | 508 | [860] | 64 | [332] | 444 | [923] | 112 | [392] | 80 | [398] | 32 | [555] | 1031 | [1241] | 55 | [205] | 976 | [1266] |
| Sum | 24377 | [29560] | 2922 | [5686] | 21455 | [30297] | 6149 | [10186] | 3298 | [5889] | 2851 | [11823] | 36289 | [30060] | 3052 | [6372] | 33237 | [31236] |

[a]If an illness lasts longer than 6 weeks, the employee will receive sick leave payments from the health insurance covering 70% of the gross salary for up to 78 weeks

**Table 4** Age-standardized healthcare costs of prevalent BC cases in Germany (in €, mean [standard deviation])

| Cost sector | Intermediate phase (12 months) | | | | | | Terminal phase (11 months) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BC cases | | Controls | | Increment | | BC cases | | Controls | | Increment | |
| Medication (sum) | 1890 | [10128] | 568 | [1642] | 1322 | [10229] | 12,003 | [23427] | 643 | [1982] | 11360 | [23427] |
| Cytostatic drugs | 1220 | [9654] | 7 | [284] | 1213 | [9657] | 9698 | [22836] | 6 | [359] | 9692 | [22840] |
| Other medication | 670 | [1857] | 561 | [1610] | 109 | [2427] | 2306 | [3460] | 638 | [1943] | 1668 | [3959] |
| Remedies/medical aids | 511 | [890] | 305 | [856] | 206 | [1208] | 1238 | [1542] | 416 | [1187] | 822 | [1931] |
| Outpatient care | 1295 | [1191] | 871 | [716] | 424 | [1376] | 2876 | [2557] | 872 | [710] | 2005 | [2683] |
| Inpatient care | 1684 | [4539] | 1353 | [3556] | 330 | [5711] | 14,914 | [15460] | 1885 | [5466] | 13029 | [16567] |
| Rehabilitation | 95 | [469] | 92 | [449] | 3 | [638] | 202 | [906] | 98 | [547] | 103 | [1056] |
| Sick leave payments[a] | 214 | [1166] | 141 | [936] | 73 | [1479] | 298 | [1532] | 139 | [1339] | 158 | [1978] |
| Travel expenses | 105 | [368] | 77 | [324] | 27 | [481] | 834 | [1078] | 99 | [435] | 735 | [1151] |
| Sum | 5794 | [12561] | 3407 | [5201] | 2387 | [13443] | 32,365 | [30141] | 4153 | [7752] | 28211 | [30612] |

[a]If an illness lasts longer than 6 weeks, the employee will receive sick leave payments from the health insurance covering 70% of the gross salary for up to 78 weeks

BC-attributable costs were highest in the terminal phase (11 remaining months before death), averaging around €33,237 in incident cases and €28,211 in prevalent case. Initial care costs in the 11 months after diagnosis totaled €21,455. Costs of €2,851 for incident and €2,387 for prevalent cases were incurred each year in the intermediate phase. Average costs in the intermediate phase are significantly lower ($p < 0.001$; Wilcoxon rank sum test) than for the initial and terminal phase. Consistent with US BC studies, the costs follow a u-shaped curve, with costs highest near diagnosis and death, and lower in between. Comparing absolute costs with US data would be challenging due to differences in treatment structures and reimbursement schemes as well as methodological inconsistencies (e.g., in data sources, study populations, matching criteria, and phase selection methods).

European studies that have not applied a data-driven phase-of-care approach have also found that the economic burden of BC is highest in the periods following diagnosis and near death [13]. With standardized costs of €21,455 per person for the first 11 months after diagnosis, initial care costs in our study are much higher than are those in other studies. Based on German claims data, Damm et al. [15] reported that BC-attributable costs averaged around €4,300 per person in the 1st year after diagnosis. The 12-month costs of initial care have been reported to total around €8553 for Sweden (converted from SEK to € with an average 2005 exchange rate of 9.2822 SEK/€) [28]) and €7982 for Belgium [29]. However, studies differ in their data sources and cost-calculation methods, as well as in the cost domains examined, leading to an underestimation of costs. Moreover, BC healthcare costs per case [30]/per person in the EU [9] are generally found to be more than two to three times higher in Germany than in Belgium or Sweden.

For the intermediate phase, annual direct BC-related healthcare costs were estimated at €2851 for incident and €2387 for prevalent cases. While Broekx et al. [29] reported much lower costs for the 2nd year following diagnosis (€1317 per patient for Belgium), our results are in line with Lidgren et al.'s [28] finding that annual direct costs for the 2nd and following years after initial BC diagnosis /recurrence totaled €2359 (converted from SEK to € with an average 2005 exchange rate of 9.2822 SEK/€). Moreover, our results indicate that incident cases result in a significant ($p < 0.001$; Mann–Whitney $U$ test) average cost impact of about €460 per year compared to prevalent cases. Given the proximity in time to the primary diagnosis, active surveillance and therapy for complications resulting from the initial course of therapy might be paramount. In prevalent cases, more than half of the costs are attributable to cytostatic drugs, indicating that our sample might include BC cases experiencing recurrent events. Although BC costs are generally higher near diagnosis and death, intermediate phase costs will become increasingly economically important, even if patients remain recurrence-free, as BC is showing increasing survival rates. Further examination of whether intermediate care costs will decline after initial diagnosis, as reported by Broekx et al. [29], is required.

Few studies have examined mortality costs. In the 11-month terminal phase of care, direct BC-related healthcare costs averaged €33,237 in incident cases and €28,211 in prevalent cases. The only German study that calculated BC costs in the terminal phase found, by applying the propensity score method and adjusting for age and comorbidities, incremental direct healthcare costs of €10,950 in the last year before death [15]. However, unlike our analysis, this study did not include all cost domains from the perspective of the SHI and performed one-to-one matching to balance patient characteristics between cases and controls. The choice of comparison cohort can strongly impact the net costs of cancer [31], but the scientific literature displays

no broad consensus on the choice of comparison group in cancer cost estimation. As healthcare costs vary strongly, depending on comorbidities and resource consumption, one-to-two matching may lead to more robustness in estimation.

Concerning direct costs, most studies report inpatient care [13, 15, 32] or both inpatient care and drugs [9] as the greatest cost drivers in BC. Our results suggest that the cost-driving factors depend on the care phase. In the initial phase, cytostatic drug costs were the main driver, whereas in the terminal phase inpatient treatment was paramount. The impact of cytostatic drugs in the intermediate phase was greater for prevalent (51%) than for incident (20%) patients. Inpatient care costs contributed to 23% of costs in the initial phase and 14–17% in the intermediate phase. The differences in the economic relevance of inpatient care and medication might reflect the fact that cytostatic drug costs represent only outpatient prescriptions and that chemotherapy might also be administered during an inpatient episode and thus be included in inpatient costs.

Consistent with previous German studies [13, 14], we found that direct BC-attributable costs decreased with age, particularly in the initial treatment phase (see Appendix 4 and 5). Older women might have a lower chance of receiving aggressive treatment due to comorbidities or lower expected long-term benefits, or because they reject chemotherapy. Similar to Gruber et al. [14], we found that, while 97% of healthcare costs were BC-attributable in 25–29-year-old women, the share decreased to 56% in women over 85. In the intermediate phase, the share decreased from 77 to 23% in incident and from 71 to 15% in prevalent cases. Younger women might be more likely to take time off from work after diagnosis and, as they receive more aggressive treatment, may also experience more lasting effects from the initial therapy. Hence, if BC could be detected earlier or even prevented, especially among young women, the overall cost burden could be reduced.

This study is limited by the nature of its data source. First, as claims data are routinely collected for billing and reimbursement, they do not include information on clinical parameters, thus preventing cost stratification by cancer stage or tumor type. However, we differentiated between incident and prevalent patients as well as different treatment types. As patient allocation to treatment cohorts (subgroup analyses) was based exclusively on services reimbursed by SHI and some services/drugs are not indication-specific (e.g., methotrexate), some patients might not have been (adequately) captured. However, consulting a clinical expert, we developed an algorithm using a wide range of different classification systems. Moreover, with regard to the differentiation of incident and prevalent cases, using a lookback period of 1 year might overestimate incident BC cases. Nevertheless, when performing sensitivity analyses identifying BC cases in 2013 ($n = 37{,}824$) and extending the lookback period from 1 to 2 years, we found a small decrease in the percentage of incident patients from 13.5% (1 year) to 12.0% (2 years).

Second, claims data lack information on cause of death. Hence, BC cases assigned to the terminal phase might have died from causes other than BC. Third, as only annual (calendar year) outpatient care cost data were available, monthly costs might not have been assigned adequately to the care phases. However, in the 12-month intermediate phase, more than 80% of the individuals started their phase in the first quarter of 2012, covering almost the full calendar year. Fourth, sick leave payments include exclusively SHI costs. German law requires that an employee will only receive sick leave payments from the health insurance (covering 70% of the gross salary for up to 78 weeks) if an illness lasts longer than 6 weeks. During the first 6 weeks of sickness, the employer has to pay 100% of the salary. Fifth, we used data from one regional sickness fund. As the composition of health insurances differs (e.g., in terms of age, gender and social status [33, 34]) our results' generalizability might be limited. The median age at diagnosis and death was about 3 and 5 years, respectively, above the median age reported in registry data [3], because the AOK Bayern included a higher proportion of insured women 70 or older and a lower proportion of insured women 30–70 relative to all statutory insured women in Germany in 2011 [17]. To address this issue and generalize costs, we standardized them according to gender and the 5-year age structure of the German health insurance population. We thus calculated BC-related incremental costs under real-life conditions, including all cost domains that might be relevant from the SHI perspective. Ours is the first study to calculate direct BC costs for Germany using an incidence-based phase-of-care approach.

## Conclusion

The economic burden of BC represents a major challenge for the SHI. This study indicates that BC healthcare costs depend on treatment phase, with higher costs near diagnosis and death and lower costs in between. The greatest economic burden occurs in the first 11 months following diagnosis and the last 11 months before death, depends heavily on patient age, with cytostatic drugs and inpatient care accounting for three quarters of total costs. Although intermediate phase costs are lower than those in phases near diagnosis and death, they remain substantial. Future studies should stratify German BC care costs according to cancer stage and tumor characteristic by linking claims data with clinical information.

**Funding** This study was supported by the Federal Ministry of Education and Research (Grant number 13GW0078B).

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants performed by any of the authors.

## Appendix 1

See Table5

**Table 5** Claims defining treatment typesin BC patients

| Code | System | Name/description |
|---|---|---|
| Chemotherapy[a] | | |
| 9999092 | PZN | Cytostatic drugs (parental preparations) |
| L01XA01 | ATC | Cisplatin |
| L01DB01 | ATC | Doxorubicin |
| L01DB03 | ATC | Epirubicin |
| L01DB07 | ATC | Mitoxantrone |
| L01AA09 | ATC | Bendamustine |
| L01XC07 | ATC | Bevacizumab |
| L01BC06 | ATC | Capecitabine |
| L01AA01 | ATC | Cyclophosphamide |
| L01XX41 | ATC | Eribulin |
| L01BC02 | ATC | Fluorouracil |
| L01BC52 | ATC | Fluorouracil, combinations |
| L01BC05 | ATC | Gemcitabine |
| L01XA02 | ATC | Carboplatin |
| L01CD01 | ATC | Paclitaxel |
| L01CD03 | ATC | Paclitaxel poliglumex |
| L01CD02 | ATC | Docetaxel |
| L01CA04 | ATC | Vinorelbine |
| L01AA06 | ATC | Ifosfamide |
| L01BA01 | ATC | Methotrexate |
| L01DC03 | ATC | Mitomycin |
| L01XX17 | ATC | Topotecan |
| L01DC04 | ATC | Ixabepilone |
| L01CA03 | ATC | Vindesine |
| 8–54 | OPS | Cytostatic chemotherapy, immunotherapy and antiretroviral therapy |
| Surgery[a] | | |
| 5–87 | OPS | Excision and resection of breast |
| 5–88 | OPS | Other mammary operations |
| 5–40 | OPS | Lymphatic tissue operation |
| J01Z | DRG | Tissue transplantation with microvascular anastomisation in case of malignant neoplasms of skin, subcutis and breast |
| J06Z | DRG | Mastectomy with prosthesis implantation and plastic surgery in case of malignant neoplasms |
| J07A | DRG | Minor interventions of the breast with axillary excision of lymphatic nodes or extremely severe or severe complication or comorbidity in case of malignant neoplasms, with intervention on both sides |
| J07B | DRG | Minor interventions of the breast with axillary excision of lymphatic nodes or extremely severe or severe complication or comorbidity in case of malignant neoplasms, without intervention on both sides |
| J08C | DRG | Skin graft or debridement without complex procedure, with specific intervention on the skin, subcutis and breast, with extremely severe complication or comorbidity |
| J10A | DRG | Plastic surgery of skin, subcutis and breast in case of malignant neoplasms |
| J14A | DRG | Plastic reconstruction of the breast in case of BNB with complex reconstruction or mastectomy on both sides in case of BNB or radiotherapy with oper. proc. in case of diseases and disorders of the skin, subcutis and breast, with prosthesis implantation on both sides or skin expander implantation |
| J14B | DRG | Plastic reconstruction of the breast in case of malignant neoplasms without complex reconstruction |

**Table 5** (continued)

| Code | System | Name/description |
|---|---|---|
| J16A | DRG | Mastectomy on both sides in case of malignant neoplasms |
| J23Z | DRG | Major interventions on the breast in case of malignant neoplasms without complex intervention, without specific intervention on female reproductive organs in case of malignant neoplasms |
| J25Z | DRG | Minor interventions on the breast in case of malignant neoplasms without or extremely severe or severe complication or comorbidity |
| J26Z | DRG | Plastic reconstruction of the breast with complex skin graft or major intervention on the breast in case of malignant neoplasms with complex intervention or specific intervention on female reproductive organs in case of malignant neoplasms |
| J62A | DRG | Malignant neoplasms of the breast, more than 1 day of hospitalization, with extremely severe complication or comorbidity |
| J62B | DRG | Malignant neoplasms of the breast, 1 day of hospitalization or extremely severe complication or comorbidity |
| Radiotherapy[a] | | |
| 8–52 | OPS | Radiotherapy |
| 8–530 | OPS | Therapy with open radionuclides |
| 25211 | EBM | Radiotherapy: flat fee in case of malignant neoplasms |
| 25310 | EBM | Soft X-ray or orthovoltage therapy |
| 25320, 25321, 25322, 25323 | EBM | High-voltage therapy |
| 25330, 25331, 25333 | EBM | Bracytherapy |
| 40840, 40841 | EBM | Lump sum for individual adjustments in case of radiotherapy (e.g. positioning aids) |

*PZN* pharmaceutical registration number, *ATC* anatomical therapeutic chemical classification, *OPS* classification for the encoding of operations, procedures and general medical measures, *DRG* diagnosis-related groups, *EBM* catalogue of the Uniform Value Scale

[a]Inclusion required at least one healthcare service

## Appendix 2

See Fig. 2

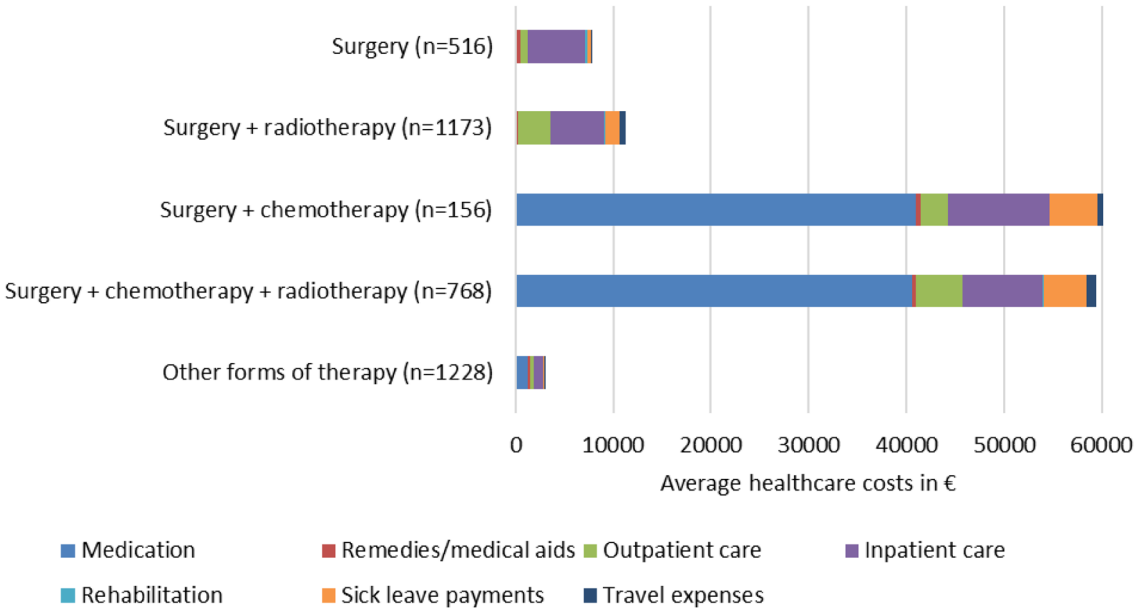


**Fig. 2** Age-standardized incremental healthcare costs of BC cases in the initial phase by treatment type (in €, mean). As cases were few we aggregated BC cases with radiotherapy ($n=68$) or chemotherapy ($n=33$) or radiotherapy + chemotherapy ($n=17$) or no active therapy ($n=1110$) to "other forms of therapy". The group "no active therapy" includes all BC cases without any claim for surgery, radiotherapy and chemotherapy

## Appendix 3

See Fig. 3

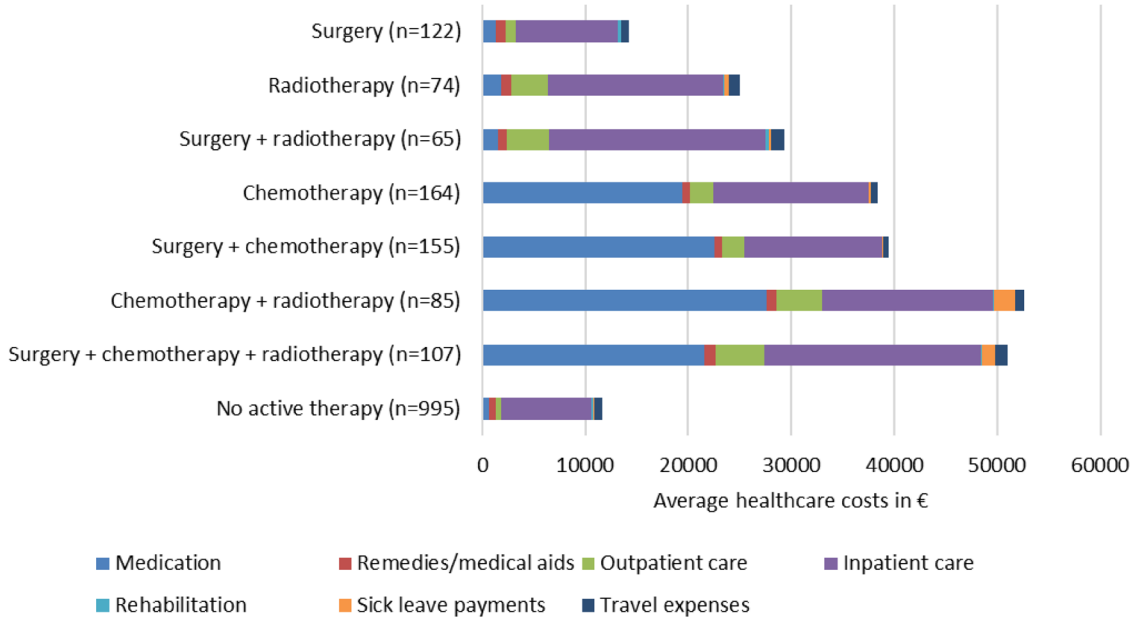


**Fig. 3** Age-standardized incremental healthcare costs of BC cases in the terminal phase by treatment type (in €, mean). The group "no active therapy" includes all BC cases without any claim for surgery, radiotherapy and chemotherapy

## Appendix 4

See Table 6

**Table 6** Unstandardized healthcare costs of incident BC cases (*n*) in Germany by age group (in €, mean [standard deviation])

| Age | Initial phase (11 months) | | | | | | | Intermediate phase (12 months) | | | | | | | Terminal phase (11 months) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n[a] | BC cases | | controls | | Increment | | n[a] | BC cases | | controls | | Increment | | n[a] | BC cases | | controls | | Increment | |
| < 20 | | | | | | | | | | | | | | | | | | | | | |
| 20–24 | 6 | 12380 | [27084] | 2275 | [4778] | 10106 | [22876] | 2 | 1645 | [1930] | 687 | [454] | 959 | [1247] | 1 | 14315 | | 362 | [256] | 13954 | [256] |
| 25–29 | 13 | 55784 | [48537] | 1512 | [2256] | 54273 | [46892] | 8 | 8765 | [8657] | 1995 | [2234] | 6769 | [9236] | | | | | | | |
| 30–34 | 26 | 58166 | [55411] | 1997 | [4147] | 56169 | [54360] | 15 | 6201 | [5657] | 1245 | [1308] | 4956 | [5974] | 3 | 39466 | [16105] | 4482 | [6279] | 34984 | [17635] |
| 35–39 | 58 | 47073 | [34753] | 1554 | [1723] | 45520 | [34727] | 24 | 8030 | [6232] | 2209 | [3773] | 5821 | [7011] | 1 | 46219 | | 6244 | [7550] | 39975 | [7550] |
| 40–44 | 125 | 42923 | [39533] | 2373 | [4518] | 40550 | [39680] | 61 | 6316 | [10138] | 2645 | [4715] | 3671 | [11048] | 4 | 70818 | [9948] | 1864 | [1632] | 68954 | [9184] |
| 45–49 | 262 | 37070 | [34548] | 2258 | [4319] | 34812 | [34483] | 127 | 6641 | [7734] | 2489 | [5257] | 4152 | [9183] | 6 | 73724 | [35729] | 1744 | [1965] | 71980 | [34894] |
| 50–54 | 350 | 32299 | [32725] | 2587 | [5766] | 29711 | [33316] | 162 | 7381 | [14994] | 2607 | [4789] | 4774 | [15765] | 11 | 39262 | [19836] | 1818 | [2368] | 37444 | [19665] |
| 55–59 | 364 | 29207 | [33346] | 2988 | [5562] | 26218 | [34108] | 168 | 5262 | [7208] | 2523 | [3930] | 2739 | [8250] | 13 | 53116 | [36986] | 3115 | [5605] | 50000 | [37103] |
| 60–64 | 485 | 23409 | [28398] | 2599 | [4218] | 20810 | [28804] | 231 | 6592 | [16187] | 3012 | [5452] | 3580 | [17148] | 15 | 48134 | [42877] | 4425 | [14797] | 43709 | [45887] |
| 65–69 | 446 | 18389 | [21133] | 3288 | [9093] | 15101 | [23064] | 209 | 4976 | [8811] | 3706 | [6976] | 1270 | [11346] | 18 | 32434 | [21911] | 2406 | [3084] | 30028 | [22561] |
| 70–74 | 604 | 17213 | [18705] | 2873 | [5520] | 14340 | [19341] | 266 | 5990 | [9313] | 3542 | [5937] | 2448 | [11065] | 31 | 29079 | [17431] | 3769 | [4485] | 25310 | [17602] |
| 75–79 | 524 | 13049 | [12921] | 3856 | [5854] | 9193 | [14387] | 233 | 5494 | [7853] | 3824 | [5837] | 1669 | [9766] | 40 | 25067 | [23894] | 2938 | [5432] | 22129 | [24596] |
| 80–84 | 333 | 10551 | [9669] | 3624 | [5908] | 6927 | [11083] | 150 | 6686 | [9263] | 5464 | [9768] | 1222 | [13818] | 55 | 17776 | [16291] | 3335 | [4398] | 14442 | [17385] |
| > 84 | 245 | 8020 | [9320] | 3490 | [4581] | 4530 | [10518] | 90 | 5590 | [5758] | 4315 | [5035] | 1275 | [7410] | 81 | 10214 | [6666] | 3355 | [4256] | 6860 | [7712] |

[a]number of BC cases

## Appendix 5

See Table 7

**Table 7** Unstandardized healthcare costs of prevalent BC cases (*n*) in Germany by age group (in €, mean [standard deviation])

| Age | Intermediate phase (12 months) | | | | | | | Terminal phase (11 months) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n[a] | BC cases | | controls | | Increment | | n[a] | BC cases | | controls | | Increment | |
| < 20 | 1 | 2815 | | 2093 | [1592] | 722 | [1592] | | | | | | | |
| 20–24 | 7 | 9269 | [15984] | 1592 | [1311] | 7677 | [14712] | | | | | | | |
| 25–29 | 28 | 6941 | [13800] | 2040 | [3346] | 4901 | [14559] | | | | | | | |
| 30–34 | 90 | 12790 | [24404] | 2489 | [3457] | 10301 | [24508] | | | | | | | |
| 35–39 | 199 | 9607 | [22449] | 2730 | [5458] | 6877 | [23196] | 7 | 84436 | [39194] | 4111 | [6556] | 80324 | [39268] |
| 40–44 | 663 | 7825 | [20122] | 2861 | [5240] | 4965 | [20461] | 10 | 37061 | [17529] | 3586 | [5505] | 33475 | [17772] |
| 45–49 | 1295 | 6738 | [19038] | 2708 | [4935] | 4030 | [19654] | 33 | 37403 | [23323] | 5678 | [13748] | 31725 | [26243] |
| 50–54 | 2248 | 5472 | [10925] | 3131 | [5922] | 2341 | [12145] | 46 | 57206 | [42144] | 4070 | [8522] | 53135 | [39679] |
| 55–59 | 2686 | 5178 | [11441] | 3320 | [5319] | 1858 | [12304] | 74 | 42479 | [36820] | 4457 | [7580] | 38022 | [37378] |
| 60–64 | 3304 | 5094 | [10517] | 3045 | [4815] | 2049 | [11482] | 101 | 30722 | [18845] | 3470 | [8066] | 27253 | [21178] |
| 65–69 | 3609 | 5416 | [11111] | 3383 | [5403] | 2033 | [11937] | 120 | 32262 | [27941] | 4289 | [8731] | 27974 | [29468] |
| 70–74 | 5202 | 5296 | [8752] | 3634 | [4891] | 1662 | [9836] | 219 | 25412 | [19748] | 3608 | [4901] | 21804 | [20670] |
| 75–79 | 3636 | 5571 | [8364] | 4116 | [5607] | 1455 | [9886] | 250 | 21973 | [20860] | 4417 | [5872] | 17556 | [21411] |
| 80–84 | 2191 | 5330 | [6456] | 4265 | [4900] | 1065 | [7977] | 273 | 15843 | [12530] | 4183 | [5494] | 11661 | [13530] |
| > 84 | 1410 | 4928 | [5123] | 4166 | [4600] | 763 | [6722] | 355 | 10745 | [9087] | 3714 | [4781] | 7031 | [10069] |

[a] number of BC cases

## References


1. Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D.M., Forman, D., Bray, F.: Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN. Int. J. Cancer **136**, E359–E386 (2015)
2. Kaatsch P, Spix C, Katalinic A, Hentschel S, Luttmann S, Stegmaier C, Caspritz S, Christ M, Ernst A, Folkerts J, Hansmann J, Klein S, Kranzhöfer K, Kunz B, Manegold K, Penzkofer A, Treml K, Weg-Remers S, Wittenberg K, Baras N, Barnes B, Bertz J, Buttmann-Schweiger N, Dahm S, Fiebig J, Franke M, Haberland J, Kraywinkel K, Wienecke A, Wolf U (2015) Contributions on federal health monitoring: cancer in Germany 2011/2012 [German]. Berlin: Robert Koch-Institut. [Gesundheitsberichterstattung für Deutschland]
3. Robert Koch-Institut (2017) Cancer in Germany 2013/2014 [German]: RKI-Bib1 (Robert Koch-Institut)
4. Bartelink, H., Horiot, J.-C., Poortmans, P.M., Struikmans, H., van den Bogaert, W., Fourquet, A., Jager, J.J., Hoogenraad, W.J., Oei, S.B., Wárlám-Rodenhuis, C.C., Pierart, M., Collette, L.: Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881–10882 trial. J. Clin. Oncol. **25**, 3259–3265 (2007)
5. Davis, C., Naci, H., Gurpinar, E., Poplavska, E., Pinto, A., Aggarwal, A.: Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009–13. BMJ **359**, j4530 (2017). **(Clinical research ed.)**
6. Kaplan, H.G., Malmgren, J.A., Atwood, M.K., Calip, G.S.: Effect of treatment and mammography detection on breast cancer survival over time: 1990–2007. Cancer **121**, 2553–2561 (2015)
7. Hamm, C., El-Masri, M., Poliquin, G., Poliquin, V., Mathews, J., Kanjeekal, S., Alam, Y., Kulkarni, S., Elfiki, T.: A single-centre chart review exploring the adjusted association between breast cancer phenotype and prognosis. Curr. Oncol. **18**, 191–196 (2011)
8. Blumen, H., Fitch, K., Polkus, V.: Comparison of treatment costs for breast cancer, by tumor stage and type of service. Am. Health Drug Benefits **9**, 23–32 (2106)
9. Luengo-Fernandez, R., Leal, J., Gray, A., Sullivan, R.: Economic burden of cancer across the European Union: a population-based cost analysis. Lancet Oncol. **14**, 1165–1174 (2013)
10. Cost of illness: Germany, Years, Disease diagnoses (ICD-10) (2015) [https://www-genesis.destatis.de/genesis/online/logon?sequenz=tabelleErgebnis&selectionname=23631-0001&sachmerkmal=ICD10Y&sachschluessel=ICD10-C00-C97,ICD10-C00-C14,ICD10-C15-C26,ICD10-C16,ICD10-C18,ICD10-C20,ICD10-C25,ICD10-C30-C39,ICD10-C33-C34,ICD10C43-C44,ICD10-C50,ICD10-C51-C58,ICD10-C53,ICD10-C60-C63,ICD10-C61,ICD10-C64-C68,ICD10-C67,ICD10-C81-C96,ICD10-C91-C95,]. Accessed 09 Apr 2018
11. Stollenwerk, B., Welchowski, T., Vogl, M., Stock, S.: Cost-of-illness studies based on massive data: a prevalence-based, top-down regression approach. Eur. J. Health Econ **17**, 235–244 (2106)
12. Radice, D., Redaelli, A.: Breast cancer management: quality-of-life and cost considerations. PharmacoEconomics **21**, 383–396 (2003)
13. Damm, O., Hodek, J.-M., Greiner, W.: Methodological standards for cost-of-illness studies using breast cancer, prostate cancer and colon cancer as an example [German]. Zeitschrift für Evidenz, Fortbildung und Qualität im Gesundheitswesen **103**, 305–316 (2009)
14. Gruber, E.V., Stock, S., Stollenwerk, B.: Breast cancer attributable costs in Germany: a top-down approach based on sickness funds data. PLoS ONE **7**, e51312 (2012)

15. Damm, O., Leppert, F., Greiner, W.: PCN47 Cost-of-Illness of common cancer types - results of a health insurance claims data analysis. Value Health **15**, A417 (2012)
16. Yabroff, K.R., Lund, J., Kepka, D., Mariotto, A.: Economic burden of cancer in the United States: estimates, projections, and future research. Cancer Epidem Biomark. Prev. **20**, 2006–2014 (2011)
17. Member statistics KM6 (Statutory health insurance: Insured persons) (2018) [https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/Statistiken/GKV/Mitglieder_Versicherte/KM6_2011.xls]. Accessed 22 June 2018
18. Van Walraven, C., Austin, P.C., Jennings, A., Quan, H., Forster, A.J.: A modification of the elixhauser comorbidity measures into a point system for hospital death using administrative data. Med. Care **47**, 626–633 (2009)
19. Riley, G.F., Potosky, A.L., Lubitz, J.D., Kessler, L.G.: Medicare payments from diagnosis to death for elderly cancer patients by stage at diagnosis. Med. Care **33**, 828–841 (1995)
20. Taplin, S.H., Barlow, W., Urban, N., Mandelson, M.T., Timlin, D.J., Ichikawa, L., Nefcy, P.: Stage, age, comorbidity, and direct costs of colon, prostate, and breast cancer care. J. Natl. Cancer Inst. **87**, 417–426 (1995)
21. Fireman, B.H., Quesenberry, C.P., Somkin, C.P., Jacobson, A.S., Baer, D., West, D., Potosky, A.L., Brown, M.L.: Cost of care for cancer in a health maintenance organization. Health Care Financ. R **18**, 51–76 (1997)
22. Brown, M.L., Riley, G.F., Schussler, N., Etzioni, R.: Estimating health care costs related to cancer treatment from SEER-Medicare data. Med. Care **40**(IV), 104–117 (2002)
23. Warren, J.L., Brown, M.L., Fay, M.P., Schussler, N., Potosky, A.L., Riley, G.F.: Costs of treatment for elderly women with early-stage breast cancer in fee-for-service settings. J. Clin. Oncol. **20**, 307–316 (2002)
24. Yabroff, K.R., Lamont, E.B., Mariotto, A., Warren, J.L., Topor, M., Meekins, A., Brown, M.L.: Cost of care for elderly cancer patients in the United States. J. Natl. Cancer I **100**, 630–641 (2008)
25. Barlow, W.E.: Overview of methods to estimate the medical costs of cancer. Med. Care **47**, S33–S36 (2009)
26. Joinpoint Regression Program, Version 4.6.0.0 (2018) Statistical methodology and applications branch, Surveillance Research Program [https://surveillance.cancer.gov/joinpoint/]. Accessed 11 June 2018
27. Kim, H.J., Fay, M.P., Feuer, E.J., Midthune, D.N.: Permutation tests for joinpoint regression with applications to cancer rates. Stat. Med. **19**, 335–351 (2000)
28. Lidgren, M., Wilking, N., Jönsson, B., Rehnberg, C.: Resource use and costs associated with different states of breast cancer. Int. J. Technol. Assess. Health Care **23**, 223–231 (2007)
29. Broekx, S., Den Hond, E., Torfs, R., Remacle, A., Mertens, R., D'Hooghe, T., Neven, P., Christiaens, M.-R., Simoens, S.: The costs of breast cancer prior to and following diagnosis. Eur. J. Health Econ. **12**, 311–317 (2011)
30. A review of breast cancer care and outcomes in 18 countries in Europe, Asia, and Latin America (2009) [https://www.comparatorreports.se/A_review_of_breast_cancer_care_and_outcomes_26Oct2009.pdf]. Accessed 18 July 2018
31. Chen, A.B., Li, L., Cronin, A.M., Brooks, G.A., Kavanagh, B.D., Schrag, D.: Estimating costs of care attributable to cancer: does the choice of comparison group matter? Health Serv. Res. **53**, 3227–3244 (2017)
32. Wai, E.S., Trevisan, C.H., Taylor, S.C.M., Mates, D., Jackson, J.S., Olivotto, I.A.: Health system costs of metastatic breast cancer. Breast Cancer Res. Tr **65**, 233–240 (2001)
33. Hoffmann, F., Icks, A.: Structural differences between health insurance funds and their impact on health services research: results from the Bertelsmann Health-Care Monitor [German]. Gesundheitswesen [Bundesverband der Arzte des Offentlichen Gesundheitsdienstes (Germany)] **74**, 291–297 (2012)
34. Jaunzeme, J., Eberhard, S., Geyer, S.: How "representative" are SHI (statutory health insurance) data? Demographic and social differences and similarities between an SHI-insured population, the population of Lower Saxony, and that of the Federal Republic of Germany using the example of the AOK in Lower Saxony [German]. Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz **56**, 454–474 (2013)