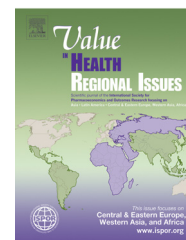




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Prognosis, Cost, and Occurrence of Colorectal, Lung, Breast, and Prostate Cancer in Hungary

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ABSTRACT

Background: There is an increasing social debate on expenditures on the care of patients with malignant diseases, especially in Central Eastern European countries with limited health resources. **Objectives:** The aim of this research was to estimate the epidemiological and quality measures and resource use indicators in Hungary in four malignant conditions (breast, colorectal, lung, and prostate cancer) from the National Health Insurance Fund (NHIF) database. **Methods:** Survival and cost analyses were performed on the NHIF database. Patient records containing the *International Classification of Diseases (ICD)* codes C50 (breast cancer), C18–C20 (colorectal cancer), C33–C34 (lung cancer), and C61 (prostate cancer) were considered eligible. Inclusion criteria were at least two consecutive ICD codes between 2000 and 2012, with a minimum of 30-day difference, or one ICD code, followed by patient death within 60 days. A total of 428,860 social insurance numbers met inclusion criteria. **Results:** The number of new cases was 6381 for breast cancer, 8457 for colorectal cancer, 8902

for lung cancer, and 3419 for prostate cancer. The probability of 5-year overall survival from the first diagnosis was 75.2%, 41.3%, 17.1%, and 62.1%, respectively. Median time from first diagnosis to treatment initiation was less than 1 month in all conditions except for lung cancer. The annual cost of treatment was €2585, €3165, €4157, and €2834, respectively. Cost figures were compared with hemophilia as benchmark (€8284). **Conclusions:** The results indicated that the database of the Hungarian NHIF is suitable for real-world data analysis in the field of oncology and can support long-term evidence-based policymaking.

Keywords: breast cancer, colorectal cancer, cost, evidence-based policymaking, hemophilia, lung cancer, mortality, new cases, payer's database, prostate cancer, survival, time to treatment.

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Introduction

Malignant diseases represent considerable clinical, economical, and humanistic burden in middle- and higher-income countries [1–3]. There is an increasing social debate on the money spent on the care of patients with malignant diseases [4], especially considering some high-priced treatments with marginal health gain [5]. This is especially true for Central Eastern Europe, with even more limited health care resources compared with Western countries [6]. Countries of the region, though, are generally associated with poorer health status than are countries of Western Europe and North America [7,8], indicating a higher need for appropriate decisions in prioritizing among interventions and disease areas [9]. Estimating the clinical burden via epidemiologic indicators, evaluation of quality indicators of treatment, and monitoring effectiveness and cost of care are therefore becoming increasingly important in the region. Burden of disease studies are suitable to support evidence-based decision making by identifying unmet need and disease areas for public health care

investment [10–12]. In Hungary, data to estimate these indicators are routinely collected in the database of the National Health Insurance Fund (NHIF) [13].

The aim of this research was to estimate the epidemiological (occurrence and mortality) and quality (survival and time from diagnosis to treatment) measures and resource use (annual health care cost of patient) indicators in Hungary in four malignant conditions (colorectal cancer, lung cancer, breast cancer, and prostate cancer) from the payer's database.

Methods

The analyses were performed on the NHIF database. Inpatient or outpatient care patient records containing the following *International Classification of Diseases (ICD)* [14] codes (main or supplementary diagnosis) were considered eligible for the study: C18–C20 (colorectal cancer), C33–C34 (lung cancer), C50 (breast cancer), and C61 (prostate cancer). Patient records were included

Conflict of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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in the study from January 1, 2000, to December 31, 2012, in which there were

1. at least two consecutive ICD codes from those listed above, with a minimum of 30-day difference between their establishment, or
2. one of these ICD codes, and the patient died within 60 days.

Multiple different cancer codes (except for colon + rectum) were excluded from the study.

The period 2000 to 2003 was considered as a run-in period in the estimation of the number of new cases. Because in this period patients who had their diagnosis established before 2000 might have received care, their inclusion into this period might have resulted in an overestimation of the number of new cases. Therefore, we estimated it only between 2004 and 2011 annually. The reason for omitting 2012 from the calculation was that because two occasions of care with the same ICD code were required over a 30-day interval for inclusion in the study, and patients receiving care first at the end of 2012 and then at the beginning of 2013 would not have been included in the calculation of the number of new cases for 2012, it would have resulted in an underestimation.

Two separate survival analyses were performed by applying the Kaplan-Meier method in newly diagnosed patients. In the first analysis, death from any cause was considered as an outcome, whereas in the second analysis, time to the occurrence of the combined outcome of being either treated or dead was considered. To estimate the time from diagnosis to treatment, patients were considered as treated patients who had radiotherapy/chemotherapy (L01 and partially L02 ATC)/surgery with the same ICD code as the diagnosis. Epidemiological and quality measures were compared with the data of the Hungarian Central Statistical Office, the National Cancer Registry, and international references from the medical literature.

In cost analyses, the following categories were considered: outpatient cost (including some forms of radiotherapy), inpatient cost (surgery, chemotherapies from the NHIF manual, other high-price drugs, radiotherapy, "hotel costs"), sick allowance, cost of

reimbursed drugs, drug co-payment, cost of computed tomography (CT)/magnetic resonance imaging (MRI), cost of high-price medical devices, diagnostics, and interventions (e.g., positron emission tomography [PET]/CT), and cost of high-price drugs. High-price drugs were considered at 80% price to compensate for the effects of the expected rebate from manufacturers toward the NHIF.

Costs were segmented into disease- and non-disease-associated costs. Disease-associated costs included drug cost (with the same ICD code on the prescription as in the patient's diagnosis—available from 2007), inpatient cost (coded with the same ICD code as the diagnosis), outpatient cost (coded with the same ICD code as the diagnosis), CT/MRI, and high-price medical devices (e.g., PET CT) and interventions (coded with the same ICD code as the diagnosis). However, non-disease-associated cost reflected similar categories, but coded with ICD codes other than those for the diagnosed condition. Sick allowance was also calculated. In Hungary, inpatient services are financed by the diagnosis related group (DRG) system and outpatient services are financed via German points. Unit costs of DRG (150,000 HUF in 2011) and German point (1.5 HUF in 2011) were multiplied by the actual values of each service utilization documented in the NHIF database and aggregated in this analysis. Cost figures of the study are presented at constant 279.21 HUF/1 euro (€) (2011 average exchange rate); longitudinal cost figures did not consider inflation (nominal values).

To compare the cost figures of this study, hemophilia, another serious condition with high impact on patient's quality of life and payer's health care budget, was selected. Patient records containing D66–D68 ICD codes from January 1, 2008, to December 31, 2012, were considered eligible. At least two occurrences of these ICD codes with a minimum of 30-day gap were required for inclusion in the study. In addition, the screening syntax involved those patients who were prescribed factor products for hemophilia. The following cost categories were considered for patients with hemophilia: outpatient cost, inpatient cost, drug cost, CT/MRI, high-price medical devices, diagnostics, and interventions (e.g., PET CT), and cost of high-price drugs (at 80%).

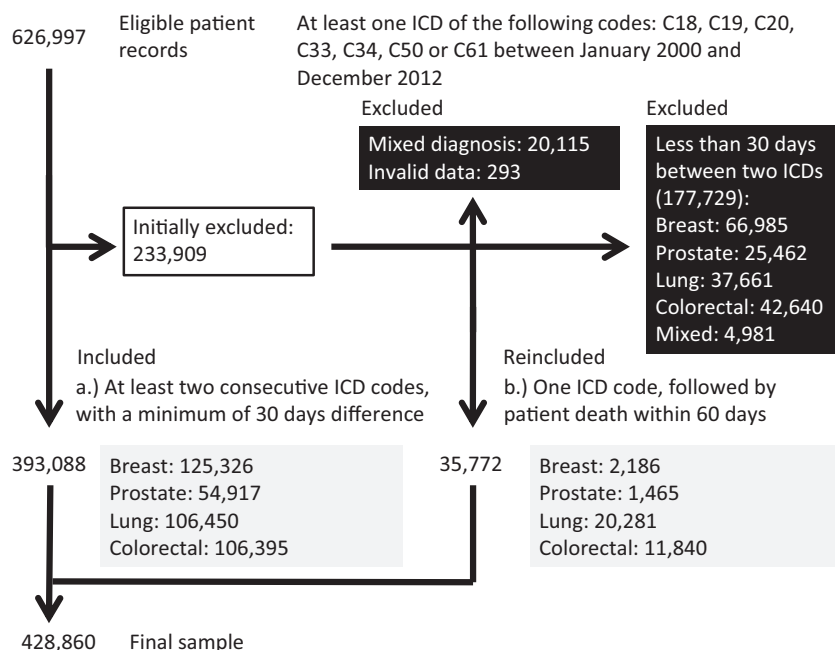


Fig. 1 – Patient flow. ICD, International Classification of Diseases.

Results

The patient flow is described in Fig. 1. Of the 626,997 eligible patient records (at least one ICD code of the following: C18, C19, C20, C33, C34, C50, or C61, between January 1, 2000, and December 31, 2012), 233,909 were initially excluded, but 35,772 of these were reincluded in the sample because the patients died within 60 days (reasons for exclusion: mixed diagnosis, 20,115; invalid data, 293; <30-day difference between the two ICD codes, 177,729). The final sample contained 428,860 records (colorectal cancer 106,395 + 11,840, lung cancer 106,450 + 20,281, breast cancer 125,326 + 2,186, and prostate cancer 54,917 + 1,465).

The epidemiological measures (number of new cases [for 2004–2011] and deaths [for 2011]) from this study and from the National Cancer Registry and mortality statistics are summarized in Table 1.

In 2011 (last complete study year), according to our analysis, there were 6381 new breast cancer, 8457 new colorectal cancer, 8902 new lung cancer, and 3419 new prostate cancer cases in Hungary. The numbers of patients who suffered from these diseases and died were 3741, 6282, 8317, and 2412, respectively.

Tables 2 and 3 indicate the quality indicators of the treatment (probability of 5-year overall survival [OS] [%] and time from diagnosis to treatment) together with benchmark results from the literature. Data suggest that breast and prostate cancers were associated with the highest probability of 5-year OS (75.2% and 62.1%, respectively) whereas the prognosis of colorectal and lung cancers was poor (probability of 5-year OS 41.3% and 17.1%, respectively) (Table 2). The median time from diagnosis to treatment was less than 1 month in all conditions (breast cancer 29 days, colorectal cancer 23 days, and prostate cancer 21 days) except for lung cancer (50 days) (Table 3).

Table 1 – Number of new cases (2004–2011) and deaths (2011).

Type of cancer	New cases								Newly diagnosed cases (National Cancer Registry) (2011)	No. of deaths in patients with malignant condition (2011)	Cause of death statistics (CSO) (2011)
	2004	2005	2006	2007	2008	2009	2010	2011			
Breast cancer (C50)	7 869	7 838	6 775	6 216	6 465	6 342	6 439	6381	7,329	3741	2138
Colorectal cancer (C18–C20)	8 179	8 318	8 058	7 843	8 357	8 340	8 231	8457	10,658 (C18–C21)	6282 (C18–C20)	5054 (C18–C21)
Lung cancer (C33–C34)	9 157	9 149	9 058	8 764	8 971	8 988	8 747	8902	11,706 (C34)	8317	8533
Prostate cancer (C61)	4 105	3 897	3 463	3 114	3 268	3 497	3 584	3419	4,368	2412	1198

CSO, Central Statistical Office.

Table 2 – 5-y survival probability.

Type of cancer	Reference studies (country, year of publication)						
	Present study	National Cancer Registry (Tusnády et al., 2008), Hungary [16]	Agüero et al., 2012, Spain [17]	Deleuran et al., 2013, Denmark [18]	DeSantis et al., 2014, USA [21]	Marcos-Gragera et al., 2012, Spain [19]	Nguyen-Nielsen et al., 2013, Denmark [20]
Time frame	2004–2012 (OS)	2002–2005 (OS)	2003–2007 (OS; specific survival)	2009–2011 (OS)	2003–2009 (cause-specific survival)	2000–2003 (OS)	2009–2011 (OS)
Breast cancer (C50)	75.2%	72%–73%			88.6%		
Colorectal cancer (C18–C20)	41.3%	30%–40%	48.6%/ 60.4%				
Lung cancer (C33–C34)	17.1%	10%–20%		13%			
Prostate cancer (C61)	62.1%	52%–60%				67.4%	65%

OS, overall survival.

Table 3 – Median time to treatment from first suspicion, visit, and establishing the diagnosis (d).

Type of cancer	From diagnosis to treatment				From symptom onset to treatment			From first visit to treatment
	Present study	Macià et al., 2013, Spain [23]	Hansen et al., 2011, Denmark [22]	Esteva et al., 2013, Spain [24]	Lagenbach et al., 2010, Germany [25]	Yaman et al., 2009, Turkey [26]	Diaconescu et al., 2011, Canada [27]	
Time period	2004–2012	1992–2006	2004–2005	2006–2009	2005–2008	2004–2006	2005–2007	2003
Breast cancer (C50)	29	42	12					
Colorectal cancer (C18–C20)	23	21	14	22	Colon: 110 Rectum: 174			
Lung cancer (C33–C34)	50	25	23			57	62	94
Prostate cancer (C61)	21	102	9					

Figure 2 shows the percentage of treated patients and risk of death from any cause among patients with a first diagnosis of the malignant condition as a function of time by disease. Among patients with breast cancer, at 1 month, 47% of the patients received no treatment, 51.6% (52.3% among those who were alive) were treated, and the 1-month risk of death was 1.4%. In patients with a first diagnosis of prostate cancer, these figures were 40.5%, 58% (58.9%), and 1.5%, respectively. The 1-month risk of death in patients with the first diagnosis of colorectal cancer was 7.7%, and 37.7% of them were untreated, while 54.6% received treatment (59.2% of those who were alive were treated) within the first month. These indicators were worse in patients with lung cancer: the 1-month risk of death was 13.9%, and 56.1% of them received no treatment in the first month, while 30.0% of the patients were treated (34.8% of those who were alive).

Table 4 presents the detailed longitudinal cost structure of patients for 2005, 2008, and 2011 (last complete study year) paid by the NHIF. In 2011, the annual cost of the NHIF for an average patient was €3165 (in colorectal cancer), €2585 (in breast cancer), €2834 (in prostate cancer), and €4157 (in lung cancer), respectively. Disease-associated costs were higher in all malignancies than non-disease-associated costs (colorectal cancer €1920 vs. €1151, breast cancer €1550 vs. €949, prostate cancer €1582 vs. €1222, and lung cancer €2544 vs. €1462, respectively) in 2011. Overall costs were highest in 2008 except for lung cancer and were higher in 2011 than in 2005 in all conditions except for prostate cancer. The number of treated patients was 41,967 (in colorectal cancer), 64,801 (in breast cancer), 24,472 (in prostate cancer), and 20,550 (in lung cancer) in 2011, respectively. By multiplying the number of treated patients with the annual cost of NHIF per patient, the overall NHIF expenditure on the four malignancies was calculated. In 2011, the NHIF expenditure for patients with one of the four conditions reached €132.82 million (in colorectal cancer), €167.51 million (in breast cancer), €69.35 million (in prostate cancer), and €85.42 million (in lung cancer), respectively. The annual cost of patients with hemophilia was applied as benchmark. Within the €8284 annual cost, in 2011, the highest amount was the cost of hemophilia factor products (€7207), followed by drug costs (€531), and costs of inpatient (€336) and outpatient (€124) care.

Discussion

According to our results, lung cancer was associated with the poorest prognosis among the observed four malignant conditions. Moreover, quality indicators were the worse in lung cancer, while this condition was associated with the highest annual cost.

The method used for participant selection had some limitations in this study. Patients were included on the basis of first occurrence of the respective ICD codes in their health service utilization files. This does not necessarily imply that patients had a definitive diagnosis. To reduce the chance that patients who had diagnostic workup toward the studied malignancies but actually did not have these diseases would be included, two occasions of health service utilization were required with the same ICD code with at least 30 days between the two occasions, or if the patients died within 60 days. Although it increased the specificity of the selection, the possibility remained that some patients might have been included in the study without a relevant condition (false-positive patients). However, patients with end-stage disease, who died more than 60 days after the first service use without contacting the health service again, after a month, were not included. The number of these persons is likely to be very small.

The external validity of data presented in this study was assessed by comparing the results with relevant Hungarian

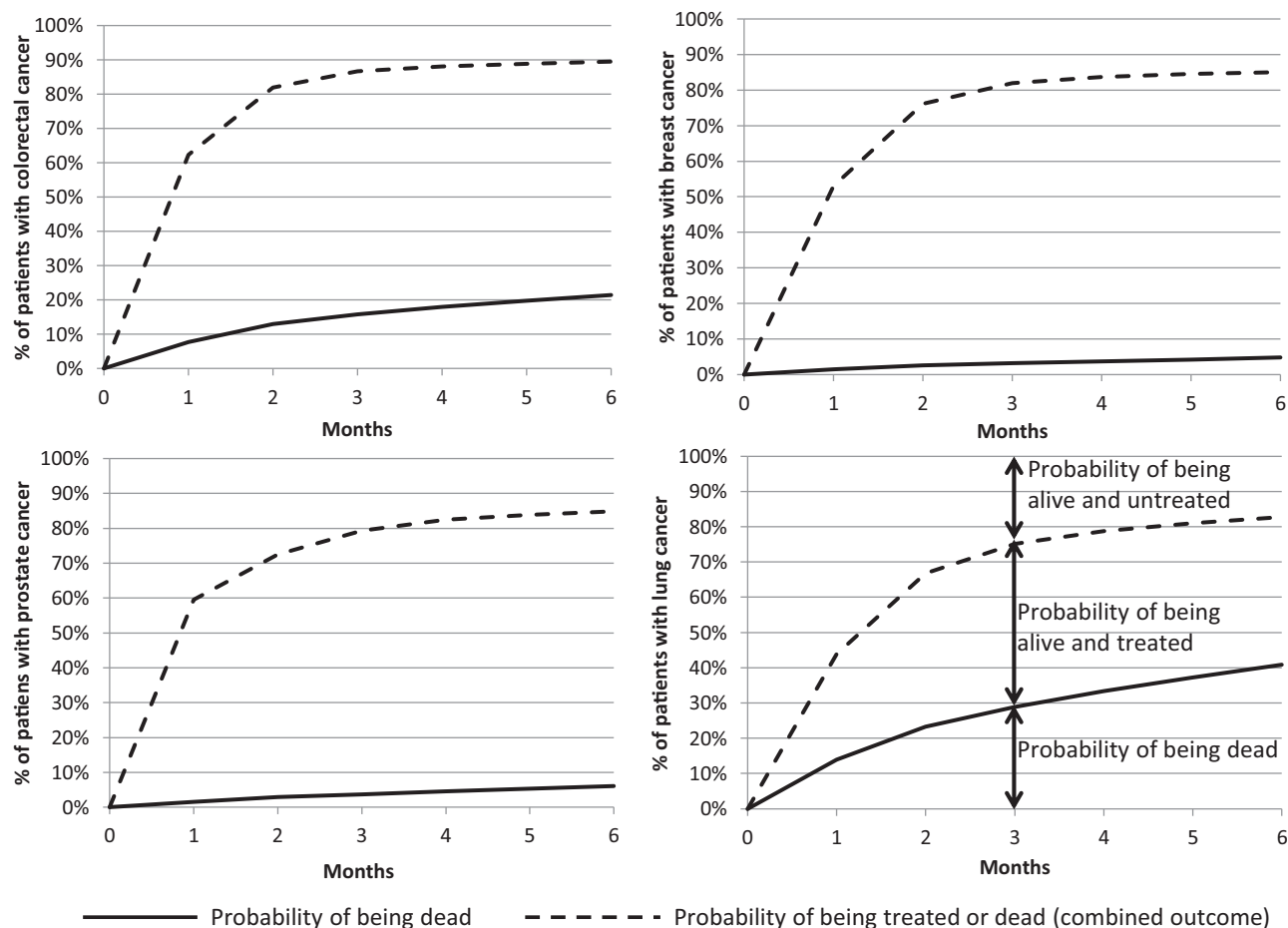


Fig. 2 – Overall survival analyses of the four malignant conditions (death from any causes).

databases (Hungarian Central Statistical Office and National Cancer Registry) and with published references of the medical literature. The number of new cases reported in this study was lower than that reported by the Hungarian Central Statistical Office on the basis of the National Cancer Registry for 2011. This provides evidence that our estimate is conservative. Our selection procedure described above was specific but not very sensitive (Table 1). Regarding colorectal cancer, the difference is partly because the C21 ICD code was not included among the selection criteria of our analysis, although it is included in the official colorectal cancer statistics. The number of new cases reported by Boncz et al. [15] in colorectal cancer (4677 males and 4085 females in 2001) using the NHIF database is similar to our results. Longitudinal trends in the number of new cases from 2004 to 2011 should be interpreted with care because the run-in screening period to exclude prevalent cases was 7 years longer in 2011 than in 2004, indicating a false decreasing trend.

The number of deaths of patients receiving care for the studied malignancies was higher than the mortality due to these cancers reported by the Hungarian Central Statistical Office. It is consistent with the expectations because not all patients with cancer die of cancer. The difference was the smallest in case of lung cancer, indicating that this type of cancer has the poorest prognosis of the four studied malignancies.

Compared with the National Cancer Registry [16], this study provides a good estimate for probability of 5-year OS (Table 2), and it is also in concordance with other data published in the medical literature [17–21]. The 5-year OS probability of breast

cancer and especially colorectal cancer appears to be somewhat worse than some international references. Direct comparison of the OS probabilities requires caution because no information was available about relevant patient characteristics that may have affected survival.

Timely access to appropriate treatment is critical in oncology, especially in conditions with rapid progression such as colorectal or lung cancer. Significant delays in treatment initiation may result in progression of the disease, and therefore may be considered as a cause of wasting scarce resources. According to Table 3, there is still room to improve the timeliness of lung cancer treatment initiation (median 50 days), while the time lag between the first care marked with a relevant ICD code and the initiation of treatment can be considered fair for the three other conditions. Still, treatment delay indicators reported by Hansen et al. [22] have been better in all four conditions in Denmark than in Hungary. In that study, similarly to our results, lung cancer was associated with the highest median treatment delay among the four malignant conditions with 23 days. Macià et al. [23] have reported data from Spain with better median values for lung cancer but worse indicators for the treatment of breast and prostate cancers compared with Hungary. Median data reported by Esteva et al. [24] in colorectal cancer have been similar to our results. Further figures are also available for colorectal cancer [25] and lung cancer [26–28] in the literature; however, these studies report median data on treatment delay from first suspicion/visit/symptom onset instead of first diagnosis; therefore, they result in higher delays.

Table 4 – Average cost (€) of National Health Insurance Fund per patient with the four malignancies in 2005, 2008, and 2011.

Cost (€)	Breast cancer			Colorectal cancer			Lung cancer			Prostate cancer		
	2005	2008	2011	2005	2008	2011	2005	2008	2011	2005	2008	2011
Disease-related cost												
Drug reimbursement	0	756	450	0	85	82	0	422	560	0	422	1156
Drug co-payment	0	15	9	0	6	5	0	17	14	0	17	15
Inpatient cost	572	820	650	1354	2062	1392	1486	1802	1457	1486	1802	335
Outpatient cost	66	77	70	35	49	41	37	54	51	38	52	56
CT	15	23	24	31	51	47	45	55	49	45	55	20
High-price medical devices and interventions	4	23	29	33	55	63	36	68	83	36	68	0
High-price drugs (at 80%)	0	195	317	0	0	289	0	0	330	0	0	0
Total disease-related cost	658	1908	1550	1453	2308	1920	1603	2417	2544	1605	2416	1582
Non-disease-related cost												
Drug reimbursement	1045	368	440	630	417	446	630	538	683	630	538	498
Drug co-payment	79	89	93	88	98	103	70	83	92	70	83	134
Inpatient cost	268	277	284	476	441	438	471	509	502	471	509	452
Outpatient cost	100	98	97	94	94	95	78	88	94	76	89	96
CT	23	24	23	48	49	43	58	65	58	58	65	20
High-price medical devices and interventions	6	10	12	23	19	27	24	33	32	24	33	22
High-price drugs (at 80%)	0	0	0	0	0	0	0	0	0	0	0	0
Total non-disease-related cost	1521	867	949	1359	1119	1151	1329	1316	1462	1328	1317	1222
Sick allowance	112	126	86	120	130	94	205	211	151	205	211	29
Total cost	2292	2901	2585	2932	3556	3165	3137	3944	4157	3137	3944	2834

CT, computed tomography.

To facilitate weighing the cost of care of a patient with cancer, we compared it with the cost of care of a patient with hemophilia. We selected hemophilia because it is a similarly severe disease, and it strongly affects the quality of life of patients and their caregivers. Furthermore, the budget impact of the care of patients with hemophilia has recently been a topic of public debate on health care costs, just like the cost of care of patients with malignancies. As compared with the data given in Table 4, the annual NHIF cost of a patient with hemophilia was twice as much as of a patient suffering from lung cancer, the condition associated with the highest annual cost among the observed four malignancies in 2011.

According to the report of Boncz et al. [15], in 2001, €38.871 million was spent on colorectal cancer treatment of 40,057 outpatients and 10,187 inpatients, indicating an annual per capita cost of €774, which is less than a quarter of our estimate 10 years later. Direct comparison of cost data reported in this study with previous Hungarian reports, however, is difficult because many potentially relevant articles reported aggregated data on the entire budget for each condition without indicating the number of treated patients [29–31]. The NHIF spent in total €4347 million on curative and preventive health care, drug reimbursement, and sick allowance in 2011 [32]. According to our analyses, NHIF expenditures on patients with the four malignancies reached a share of 3.06% (in colorectal cancer), 3.85% (in breast cancer), 1.6% (in prostate cancer), and 1.96% (in lung cancer) in 2011, respectively.

The real drug cost of the payer is less than the data we presented because of the additional contributions of pharmaceutical companies. There is an obligatory contribution after reimbursed products sold in pharmacies, amounting to 20% of the reimbursement amount calculated on ex-manufacturers' price level, and an additional 10% tax for those innovative drugs with a history of at least 6 years of reimbursement and without reimbursed generic alternative in Hungary. New innovative drugs can be involved into the reimbursement system only with a risk-sharing scheme including price volume agreement. Manufacturers may also offer free drugs for hospitals. Also, in many countries, sick allowance is not within the responsibility of the health care system; therefore, in conclusion, because of these factors, our figures may overestimate the real costs compared with international references.

However, in the past 5 years, the government provided extra financing for hospitals to settle their cost overrun, which is not included in the activity-based financing (e.g., in DRGs or fee-for-service ambulatory payments); therefore, our figures may underestimate the real costs. These factors also limit the comparability of our findings with international references.

Strengths and Weaknesses of the Study

This analysis is based on a payer's database that contains records that have financial consequences for the payer; therefore, it may have limitations to capture all the relevant costs for a condition. In addition, financial incentives for health care providers might have caused biases in the reporting. Unfortunately, the NHIF provides only aggregate results to protect privacy of personal data, which prevented us from conducting multiple regression analysis. Without data on disease population characteristics, such as age and case-mix, comparability and interpretability of our results with other published references is limited. Further research in the future could address the suitability of the NHIF database to provide more detailed data on patients, procedures, interventions, and outcomes such as disease-specific survival in specific disease groups. Linking health service utilization data with the data of the National Cancer Registry would provide valuable additional opportunities for more detailed analyses.

Policy Implications of the Study

In addition to clinical trials, complementary evidence is needed to evaluate the effectiveness of reimbursed treatments and care in oncology. The NHIF database is suitable for estimating epidemiological and quality measures and resource use indicators. These types of analyses can support long-term evidence-based policymaking by evaluating the outcomes of health investment decisions in oncology. Real-world evidence can also increase the validity of value propositions of new medicines in the Central Eastern Europe region.

Conclusions

This article summarized some epidemiological and quality measures and economic indicators of the care of patients with colorectal cancer, lung cancer, breast cancer, and prostate cancer on the basis of NHIF data in Hungary. The 5-year survival estimates of this study were in accordance with the National Cancer Registry data and further international references. The time spent from establishing the diagnosis to treatment was fair in all conditions, except for lung cancer. Disease-associated costs were higher than non-disease-associated costs in all malignant conditions. The annual per capita costs of care of patients with the studied malignancies were less than half of the annual costs of a patient with hemophilia. The results indicated that the database of the Hungarian NHIF is suitable for real-world data analysis in the field of oncology.

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