


BMJ Open Economic burden of cancers in Taiwan: a direct and indirect cost estimate for 2007–2017

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ABSTRACT

Objective Cancers result in significant economic burdens on patients, health sectors and society. Reliable burden estimates will help guide resource allocation. This study aimed to perform a nationwide cost analysis of the direct and indirect costs of the top ten most costly cancers, and acute coronary syndrome (ACS), as a comparison, in Taiwan.

Setting A population-based cohort study.

Participants In total, 545 221 patients with newly diagnosed cancer (lung cancer, female breast cancer, colorectal cancer, liver cancer, oral cancer, leukaemia, prostate cancer, non-Hodgkin's lymphoma, gastric cancer and oesophageal cancer) and 170 879 patients with ACS between 2007 and 2014 were identified.

Primary and secondary outcome measures Direct medical costs were calculated from claims recorded in the National Health Insurance Research Database. Indirect costs, comprising morbidity-associated and mortality-associated productivity losses, were estimated from public life expectancy, average wage and employment data. The costs incurred in the 3 years after diagnosis were assessed. As a comparison, the cost of ACS was also estimated using the same study frame. A cost driver analysis was conducted to identify factors impacting cancer costs.

Results The cancers with the highest mean direct medical costs and total costs were leukaemia (US\$28 464) and oesophageal cancer (US\$81 775), respectively. Indirect costs accounted for over 50% of the total economic burden of most cancers, except for prostate cancer and female breast cancer. The costs of ACS were lower than those of most cancers. From the cost driver analysis, older age at diagnosis significantly ($p<0.05$) decreased the total cost of cancer; in contrast, male, tumour metastasis, comorbidities and treatment in medical centres increased the costs.

Conclusions This study demonstrates the comprehensive economic burden of the top 10 most costly cancers in Taiwan. These results are valuable for optimising healthcare resource allocation.

INTRODUCTION

Much attention has been paid to cancer as a major threat to public health. As the second leading cause of death worldwide, cancer led to approximately 9.6 million deaths in 2018.^{1,2}

Strengths and limitations of this study

- The major strength of this study was the evaluation from a broader societal perspective of both the direct medical and indirect costs of cancers, using the most recent nationwide data for representing the current status.
- The inclusion of high-expenditure but low-prevalence haematologic cancers, such as leukaemia and non-Hodgkin's lymphoma, was more appropriate for the theme of cost analyses.
- The lack of data on out-of-pocket costs due to the natural restriction of National Health Insurance Research Database may lead to an underestimation of direct medical costs.
- The study population was limited to adult patients (age ≥ 20 years old), which requires future studies focusing on the economic burdens of cancers in children (age < 20 years old), especially in cancers associated with younger ages.

Nearly one in six global deaths is due to cancer. In addition, a substantial economic burden on both patients and society is imposed by cancer. The estimated total annual economic cost of cancer in 2010 was approximately 1.16 trillion US\$, which was more than 2% of the total global gross domestic product.³ In Taiwan, cancer also results in a large economic burden on the National Health Insurance (NHI) system. According to the annual statistical reports from the NHI Administration, the estimated total medical expenditures for treating cancers were 3.1 billion US\$ in 2017, and the medication costs accounted for up to 38% of the total medical expenditures, which was approximately 1.2 billion US\$.⁴ This trend seems unstoppable due to an increasing number of new cases of cancer and therapeutic advancements in oncology.^{5,6}

Precise estimates of economic burdens are thus essential to help prioritise and allocate resources efficiently. However, the available quantification of economic burdens has several limitations. First, the estimation

of costs is largely limited to direct medical costs from a payer's perspective^{7–10} without taking into account indirect costs such as morbidity (ie, productivity loss) and mortality (ie, premature death) costs attributable to cancer from a societal perspective. This approach may underestimate the economic burden of cancers and may make justification of the value of innovative oncology treatment difficult. Second, most existing studies were limited to one single type of cancer^{10–12} or a certain stage of one single type of cancer,¹³ which makes comprehensive comparisons between different cancers impossible. Third, very few studies¹⁴ have compared the economic burdens of cancers with other diseases, such as cardiovascular disease. However, these data are critical for allocating public resources. In other words, we need such data to know whether to prioritise our resources for cancer or other diseases, especially under the pressure of restricted resources faced by most countries. Fourth, public statistics and previous studies have provided national-level data for the economic burdens of different cancers, but the cost drivers behind the different cancers are usually unknown.

To address these limitations, this study aimed to estimate the economic burdens, including direct and indirect costs, of the top 10 high-expenditure cancers (lung cancer, colorectal cancer, female breast cancer, liver cancer, oral cancer, prostate cancer, gastric cancer and oesophageal cancers, and haematologic cancer such as non-Hodgkin's lymphoma (NHL) and leukaemia) in Taiwan.⁴ The economic burden of an acute coronary syndrome (ACS), the second leading cause of death in Taiwan, was also estimated for comparisons. In addition, cost driver analyses were conducted to identify factors impacting the economic burdens of cancers.

METHODS

Data sources

The study cohort was identified by the Taiwan Cancer Registry Database (TCRD), which contains data of all patients with newly diagnosed malignant cancers since 1979.^{15 16} Essential information such as date of diagnosis, grade, cancer site and histological results are documented in the TCRD. In this study, data after duplicate checks and quality controls in the period of 2007–2014 were extracted to identify the incident cancer cases.

To acquire detailed information on medical utilisation, we also linked the data to Taiwan's National Health Insurance Research Database (NHIRD), which contains both the outpatient and inpatient medical claims of 23 million individuals within the Registry for Beneficiaries of Taiwan's National Health Insurance.^{17 18} The NHIRD represents more than 99% of the entire population in Taiwan through the single-payer National Health Insurance programme and comprises information on baseline demographics, disease diagnoses, procedures, prescriptions and related medical expenditures.¹⁷ All administrative claims data during the period from January 2007 to December 2017 were analysed.

Study cohort

Our study cohort consisted of patients with diagnoses of either a cancer of interest or ACS. For the cancers of interest, patients aged 20 years or older with newly diagnosed cancer between 1 January 2007 and 31 December 2014 included in the TCRD were identified. International Classification of Disease for Oncology, Third Edition (ICD-O-3) codes were used to determine diagnoses of the following cancers: lung cancer (C33–C34), female breast cancer (C50), colorectal cancer (C18–C21), liver cancer (C22), oral cancer (C00–C06, C09–C10, C12–C14), prostate cancer (C61), gastric cancer (C16), oesophageal cancer (C15), leukaemia (M-980–M-999) and NHL (M-967–M-972). For ACS, we identified adult patients who were hospitalised from 1 January 2007 to 31 December 2014 with ACS (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code: 410, 411.1, 411.8 and 413) as the primary diagnosis via hospitalisation claims in the NHIRD.

Direct medical and indirect costs

The comprehensive economic burdens of diseases assessed in this study included direct medical costs and indirect costs, which were estimated at the individual level. Direct medical costs were defined as all expenditures related to the treatment of cancer or ACS, which included the costs of outpatient visits, admission, laboratory tests, prescription drugs, surgery and procedures (including radiation therapy). The expenditures related to the treatment of cancers or ACS were defined by the diagnostic codes of each medical claim in outpatient visits or hospitalisations. Particularly, we further analysed the sum of all the medication costs, and the sum of anticancer drug costs as the expenditures on anticancer medications were rising due to the increasing price and demands on anticancer medications.⁶ An anticancer drug was defined by the WHO's Anatomical Therapeutic Chemical (ATC) classification system code 'L01', indicating antineoplastic agents (for female breast cancer and prostate cancer, ATC code 'L02', indicating drugs for endocrine therapy, was also included). Anticancer drugs, therefore, included alkylating agents, antimetabolites, vinca alkaloids, taxanes, cytotoxic antibiotics, platinum compounds, monoclonal antibodies, protein kinase inhibitors and so on, which covered conventional chemotherapy and target therapy agents. Direct medical costs were calculated from inpatient admissions and ambulatory visit claims within the first 3 years after diagnosis. The main reason we would like to set up a 3 years postdiagnosis was because that the aim of this study was to estimate the comprehensive economic burden of cancers (direct medical and indirect costs) across 10 different cancers. As the disease progress varied significantly among these cancers, some have long-term survival (such as breast cancer) while some have relatively short survival, we need to set up an equal follow-up period (the concept of landmark analysis) for a fair comparison.

Indirect costs comprised the productivity losses resulting from disease morbidity (morbidity costs) and premature

death (mortality costs). In this study, we adopted the human capital approach to estimate the indirect costs, where future lost earnings were assumed as a proxy of the productivity losses from the perspective of society. In this study, the morbidity costs and mortality costs were calculated using the following equations:

$$\text{Morbidity}C_i = (\text{Out}N_i \times 0.5 + \text{In}daysN_i \times 1) \times \text{D}wage_{jk} \times E_k$$

Morbidity costs were the productivity losses due to outpatient visits and hospitalisation for cancer (or ACS) according to the diagnostic codes in the administrative claims. It was obtained from the lost wages due to absenteeism per patient (i), considering the number of lost workdays, sex (j)-specific and age (k)-specific average daily wage ($\text{D}wage_{jk}$), and age-specific employment rates (E_k). The number of lost workdays due to a certain disease was estimated by summing the number of outpatient visits ($\text{Out}N_i$) multiplied by 0.5 (representing a half-day) and inpatient days ($\text{In}daysN_i$). The average daily wage was calculated from the average monthly wage according to Taiwan National Statistics¹⁹ and divided into 30 days.

$$\text{Mortality}C_i = \sum_{n=1}^m \left(\frac{\text{Death}_i \times Ywage_{j(k+n)} \times E_{(k+n)}}{(1+r)^n} \right)$$

Mortality costs were defined as future income losses after premature death. For the calculation of mortality costs per death (i), we multiplied the life expectancy²⁰ of each case (ie, lost years, m), sex (j)-specific and age-specific average annual expected income¹⁹ ($Ywage_{j(k+n)}$) at the time of $k+n$ (k =age at death; $n=1,2,\dots,m$), and age-specific employment rate²¹ ($E_{(k+n)}$) at the time of $k+n$, with the application of a discount rate of 3% (r), to estimate the total mortality costs.

All cost estimates were normalised to 2018 New Taiwanese dollars using the Consumer Price Index and then converted to US\$ (30 NT\$=US\$1).

Cost driver analysis

Potential cost drivers reported in previous studies, including a year of diagnosis (2007–2010 or 2011–2014), age at diagnosis, sex, tumour metastasis/late stage, Charlson Comorbidity Index (CCI)^{10 22 23} and treatment in a medical centre, were identified in this study. Tumour metastasis was defined by distant metastasis according to the American Joint Committee on Cancer (AJCC)/tumour, node and metastases cancer staging system,^{24 25} while M0 was defined as no metastasis, and M1 was defined as tumour metastasis. For NHL, the definition of tumour metastasis was substituted with late stage (stages III and IV) classified by the Ann Arbor staging system.²⁶ The CCI was calculated from the comorbidities documented in outpatient and inpatient medical claims within the first year after diagnosis. The institution at which the patients received most of their cancer treatment within the first year after diagnosis was categorised into medical centres and non-medical centres. Under Taiwan's National Health Insurance system, all contracted hospitals can be categorised as medical centres, regional hospitals or community

hospitals (accreditation level). In Taiwan, the minimum requirement of medical centres is the capacity of 500 beds, and with at least 23 divisions including general medicine, general surgery, psychiatry, gynaecology and paediatrics. In this study, 'non-medical centres' were regional hospitals and community hospitals. Adjusted analyses were further conducted to examine the impacts of these cost drivers on direct or total costs (direct medical costs and indirect costs). Due to the availability of data in TCRD, the variables assessed in cost driver analyses, such as metastases at diagnosis, were not documented in all types of cancers for the entire study period. The complete registry (including the stages at diagnoses) started from 2008 for oesophageal cancers, gastric cancer and prostate cancer to 2009 for haematology malignancy. Therefore, only patients with complete data for variables included in the cost-driver analysis were kept for this part of analysis.

Statistical analyses

Descriptive statistics, including the mean, SD, median, quartile 1 and quartile 3, were used to describe direct medical costs and indirect costs. The direct medical costs were further stratified into all medication costs and anti-cancer drug costs. The proportions of all medication costs and anticancer drug costs among direct medical costs of different cancers were calculated. Identified patients were further split into an early subset (2007–2010) and late subset (2011–2014) according to the year of diagnosis to conduct a subgroup analysis to test the hypothesis whether the direct medical or indirect costs varied over time. A generalised linear model with a log link function and gamma distribution was used to conduct the cost driver analysis, presented as the beta coefficient estimates. The findings with p values <0.05 were considered significant cost drivers. All analyses were conducted using SAS V.9.4 (SAS Institute) and Microsoft Excel 2019.

Patient and public involvement

No patient involved.

RESULTS

We identified a total of 545 221 cancer patients and 170 879 ACS patients between 2007 and 2014 (table 1). Regarding the cancers, different ages and sex distributions were observed across groups, depending on the features of each cancer. The mean age of diagnosis ranged from 53.7 (female breast cancer) to 73.3 (prostate cancer) years. Regarding the mortality rate during the follow-up period (first 3 years after diagnosis), the highest mortality rate was associated with oesophageal cancer (78.4%), with a mean follow-up period of 1.3 years, while the lowest mortality rate was associated with female breast cancer (8.7%), with a mean follow-up period of 2.9 years. The most commonly diagnosed cancers were colorectal cancer, followed by female breast cancer and liver cancer. Patients with ACS were generally older than patients with

Table 1 Patient characteristics across different cancers

Cancer	Total patients	Age at diagnosis, mean (SD)	Male, %	Follow-up years, mean (SD)	Mortality rate*, %	Age at death, mean (SD)
Colorectal cancer	112 986	65.6 (13.5)	57.8	2.4 (1.0)	33.4	72.1 (13.9)
Liver cancer	90 987	64.6 (12.9)	69.6	1.6 (1.3)	64.1	67.1 (13.4)
Female breast cancer	88 416	53.7 (11.9)	0	2.9 (0.5)	8.7	61.7 (14.4)
Lung cancer	87 568	68.0 (12.9)	62.2	1.4 (1.2)	73.6	71.3 (12.6)
Oral cancer	50 784	55.0 (11.9)	91.4	2.3 (1.1)	39.8	58.5 (12.8)
Prostate cancer	35 086	73.3 (9.1)	100	2.6 (0.8)	23.4	79.5 (8.7)
Gastric cancer	30 659	68.3 (14.2)	63.1	1.7 (1.2)	61.1	72.1 (14.2)
Oesophageal cancer	18 191	58.8 (12.3)	93.2	1.3 (1.1)	78.4	60.7 (12.6)
Non-Hodgkin's lymphoma	16 268	62.2 (16.1)	56.1	2.1 (1.2)	42.2	70.1 (14.8)
Leukaemia	14 276	61.3 (17.6)	58.7	1.7 (1.3)	56.8	67.6 (16.4)
Heart disease						
Acute coronary syndrome	170 879	66.0 (14.2)	67.7	2.4 (1.1)	26.7	76.2 (11.9)

*Mortality within the first 3 years after diagnosis.

cancer, except for prostate cancer, in terms of age at diagnosis (66.0) or age at death (76.2).

Table 2 shows the comprehensive economic burdens of cancers and ACS. The sums of the direct medical and indirect costs were highest for oesophageal cancer (US\$81 775), followed by leukaemia (US\$58 176). On the contrary, the sums of direct medical and indirect costs were lowest for prostate cancer (US\$14 383), followed by female breast cancer (US\$19 650). Across the cancers, the median direct medical cost was highest for oesophageal cancer (US\$17 815) and lowest for liver cancer (US\$7115). The median morbidity cost was highest for oral cancer (US\$937) and lowest for prostate cancer (US\$76). The median mortality costs varied from US\$ 0 to US\$25 379. The mortality rate of some cancers, such as female breast cancer, colorectal cancer, oral cancer, prostate cancer and NHL, was less than 50%, which made the median mortality cost zero. In contrast, the mortality rate was greater than 70% for lung cancer and oesophageal cancer, resulting in increased mortality costs. For most cancers, the indirect costs accounted for over 50% of the total economic burden, except for prostate cancer (22%) and female breast cancer (29%). For ACS, the median of either the direct medical costs or indirect costs were much lower than those associated with cancers.

Further analysis of the sums of all medication costs and the sums of anticancer drug costs are displayed in **table 3**. NHL and lung cancer had the highest sums of all medication costs (US\$4206 and US\$2717, respectively), accounting for more than 40% of the total direct medical costs. In comparison, decreased medication costs were observed for liver cancer and oral cancer (US\$877 and US\$1217, respectively). The gap between the highest and the lowest medication expenditures was nearly fivefold.

The proportion of anticancer drug costs to total direct medical costs was over 30% for lung cancer (42%), leukaemia (35%) and female breast cancer (33%), in contrast to less than 10% for oral cancer and oesophageal cancer.

In the subgroup analysis, as shown in **figure 1**, the direct medical costs of most cancers in 2011–2014 were higher than those in 2007–2011. However, when considering both direct and indirect costs, the economic burden of cancers decreased in 2011–2014 for most cancers and ACS. Online supplementary table S1 reports the variables included in the cost driver analysis. After adjusting for multiple variables (**table 4**), the impact of the year of diagnosis on the direct and indirect costs was statistically significant for only several cancers (decreased for lung cancer, oral cancer and oesophageal cancer; increased for female breast cancer, liver cancer and leukaemia).

Other significant cost drivers included age at diagnosis, which decreased the direct and indirect costs of cancers in those with older ages, while male sex, the occurrence of tumour metastasis, a high CCI score, and treatment in medical centres led to increased total costs.

DISCUSSION

Our study revealed the comprehensive economic burdens of the top 10 high-expenditure cancers as well as ACS from the societal perspective, considering both direct medical costs and indirect costs. The total costs of illness varied substantially by cancer depending on the characteristics of cancer. Among the 10 cancers in this study, oesophageal cancer was associated with the highest economic burden per patient, followed by leukaemia, while prostate cancer was estimated to have the lowest burden. To our

Table 2 Direct and indirect costs in the first 3 years after diagnosis (in US\$)

	Direct medical costs			Indirect costs: morbidity			Indirect costs: mortality			Total costs, mean
	Mean (SD)	Median (Q1–Q3)	%	Mean (SD)	Median (Q1–Q3)	%	Mean (SD)	Median (Q1–Q3)	%	
Cancer										
Lung cancer	18410 (18341)	12238 (5239–26140)	43.3	532 (869)	135 (55–711)	1.3	23540 (41166)	8837 (0–15003)	55.4	42481
Female breast cancer	13946 (15589)	9747 (4256–16885)	71.0	588 (567)	539 (96–838)	3.0	5117 (23162)	0 (0–0)	26.0	19650
Colorectal cancer	11998 (13140)	8427 (4498–15828)	50.8	463 (742)	124 (47–662)	2.0	11143 (32801)	0 (0–7195)	47.2	23604
Liver cancer	10759 (14332)	7115 (3176–13090)	25.5	574 (877)	157 (53–828)	1.4	30837 (53189)	8221 (0–20076)	73.1	42170
Oral cancer	19644 (15305)	17525 (7295–27678)	34.8	1286 (1386)	937 (266–1797)	2.3	35570 (61859)	0 (0–48078)	63.0	56501
Leukaemia	28464 (41967)	9001 (60–40438)	48.9	913 (1800)	94 (1–902)	1.6	28799 (59149)	6687 (0–13756)	49.5	58176
Prostate cancer	11170 (9611)	8397 (4286–16475)	77.7	183 (352)	76 (47–129)	1.3	3030 (9745)	0 (0–0)	21.1	14383
Non-Hodgkin's lymphoma	18050 (18427)	14003 (5972–24351)	50.7	687 (1106)	227 (65–863)	1.9	16830 (44045)	0 (0–9263)	47.3	35567
Gastric cancer	11883 (13170)	8462 (4468–15289)	35.4	526 (872)	140 (58–697)	1.6	21135 (42503)	6850 (0–12289)	63.0	33544
Oesophageal cancer	19816 (14680)	17815 (9368–27619)	24.2	1266 (1364)	932 (158–1935)	1.5	60692 (64510)	25379 (7070–114108)	74.2	81775
Heart disease										
Acute coronary syndrome	6031 (7178)	4724 (1410–7787)	41.5	162 (277)	59 (22–209)	1.1	8327 (24340)	0 (0–7743)	57.3	14520

Table 3 Direct medical costs with specified drug costs in the first 3 years after diagnosis, per patient (in US\$)

	Direct medical cost (A)		Sum of all medication costs (B)		Percent-ages of B/A	Sum of anticancer drug cost (C)		Percentages of C/A
	Mean	Median	Mean	Median		Mean	Median	
Cancer								
Lung cancer	18410	12238	9181	2717	49.9	7641	832	41.5
Female breast cancer	13946	9747	5903	1315	42.3	4667	371	33.5
Colorectal cancer	11998	8427	3977	1304	33.1	2655	0	22.1
Liver cancer	10759	7115	3140	877	29.2	1051	0	9.8
Oral cancer	19644	17525	2359	1217	12.0	638	15	3.2
Leukaemia	28464	9001	17169	2158	60.3	9969	85	35.0
Prostate cancer	11170	8397	4197	2224	37.6	2575	615	23.1
Non-Hodgkin's lymphoma	18050	14003	7975	4206	44.2	4480	1275	24.8
Gastric cancer	11883	8462	3923	1380	33.0	2188	0	18.4
Oesophageal cancer	19816	17815	2660	1706	13.4	294	44	1.5
Heart disease								
Acute coronary syndrome	6031	4724	857	348	14.2	–	–	–

The median cost of anticancer drugs was zero because more than half of the patients did not receive anticancer drugs for cancer treatment.

knowledge, this is the first cost analysis of both the direct and indirect costs of 10 cancers in Taiwan, considering a nationwide population-based cohort study design.

The indirect costs played an important role in the estimation of the economic burden of disease. According to previous studies in the European Union,²⁷ Korea²⁸ and Japan,¹⁴ the proportion of productivity losses due to morbidity and premature death accounted for 41%–68% of the total economic burden of cancers. In one Taiwanese study on advanced gastric cancer, the indirect costs were estimated to be 342 million US\$ at the national-level, approximately 77% of the total costs.¹³ Our results also showed that the indirect costs accounted for the major proportion (over 50%) of the total costs for most cancers, except prostate cancer and female breast cancer, due to their decreased mortality rates and older age at death. Without considering the indirect costs, the risk of underestimating the total economic burden of cancer is high. Additionally, the overall value of new advanced treatment

options could be underestimated if the evaluation is focused on only direct medical costs. The findings of the subgroup analysis in our study showed that the costs of cancers seemed to increase when considering only the direct medical costs, but the total costs demonstrated a decreasing trend when considering indirect costs simultaneously, suggesting the possible benefits of advanced cancer treatments.

In our study, the proportion of anticancer drug costs to the direct medical costs showed a discrepancy for different cancers. Although the costs of each category of anticancer drugs were not differentiated in this study, previous studies have indicated that the costs of targeted therapies, especially oral targeted therapies, comprised a growing share.^{6 29 30} Shih *et al* explored the trends of costs on anticancer medications from 2001 to 2011 in the USA.²⁹ The results showed that the cost share of oral targeted therapies doubled over the 10-year observational period, in contrast to the fair growth of intravenous targeted therapies. Further analyses demonstrated a great financial impact of oral targeted therapies, which was driven by high launch prices of new drugs and constantly increasing drug prices.^{6 30} The findings in our study support these findings, as a relatively high percentage of anticancer drug costs for cancers with available oral targeted therapies, such as lung cancer and leukaemia, was observed; moreover, a relatively low percentage of anticancer drug costs for cancers mainly treated by surgery, such as oral cancer and oesophageal cancer, were observed.

ACS had relatively lower direct medical costs, a smaller proportion of medication costs and lower indirect costs than cancers. The mean total costs of ACS were estimated to be US\$14520 per patient, while the costs of most cancers were over US\$30000 per patient in our study. This gap between cancers and other diseases was

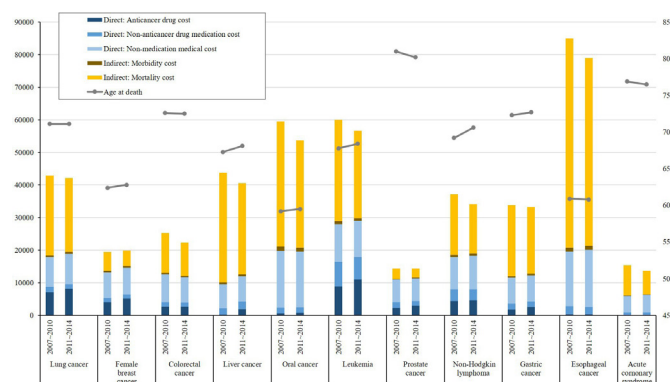


Figure 1 Bar chart of the direct and indirect mean costs in different years of diagnosis, grouped by 4-year intervals (in US\$).

Table 4 Coefficient estimates of the cost drivers considering direct and indirect costs

Cancers	Beta coefficient estimates of direct costs						Beta coefficient estimates of direct and indirect costs					
	Age at diagnosis	Sex†	Year of diagnosis‡	Tumour metastasis§	CCI score	Medical centre	Age at diagnosis	Sex†	Year of diagnosis‡	Tumour metastasis§	CCI score	Medical centre
Lung cancer	-0.0211*	-0.1748*	+0.0310*	-0.0555*	+0.0612*	+0.1020*	-0.0468*	+0.1713*	-0.0150*	+0.2179*	+0.0610*	+0.0406*
Female breast cancer	-0.0112*	N/A	+0.1412*	+0.6429*	+0.1413*	-0.0098	-0.0210*	N/A	+0.0878*	+1.0911*	+0.1662*	-0.0143
Colorectal cancer	-0.0080*	+0.0787*	-0.0108	+0.1764*	+0.0812*	+0.1237*	-0.0271*	+0.1845*	-0.0042	+0.6191*	+0.0985*	+0.0445*
Liver cancer	-0.0190*	+0.0616*	+0.2000*	-0.4449*	+0.0985*	+0.1656*	-0.0574*	+0.3145*	+0.0492*	+0.2585*	+0.0400*	0.0083
Oral cancer	-0.0076*	+0.2327*	-0.0207*	-0.3661*	+0.0862*	+0.0203*	-0.0405*	+0.3793*	-0.0611*	+0.3559*	+0.1378*	-0.0046
Leukaemia	-0.0355*	-0.0185	+0.1205*	N/A	+0.1529	+0.2805*	-0.0487*	+0.1452*	+0.0480*	N/A	+0.0544*	+0.2850*
Prostate cancer	-0.0110*	N/A	+0.0049	+0.3285*	+0.0467*	-0.1101*	-0.0131*	N/A	-0.0156	+0.5274*	+0.0759*	-0.1193*
Non-Hodgkin's lymphoma	-0.0112*	+0.0865*	+0.0161	+0.2696*	+0.0315*	+0.1662*	-0.0285*	+0.2489*	-0.0189	+0.4065*	+0.0157*	+0.0775*
Gastric cancer	-0.0141*	+0.0711*	+0.0518*	-0.1659*	+0.0425*	+0.1009*	-0.0429*	+0.2189*	-0.0165	+0.2968*	+0.0577*	+0.0433*
Oesophageal cancer	-0.0114*	+0.0361	-0.0193	-0.3627*	+0.0362*	+0.1234*	-0.0565*	+0.2012*	-0.0378*	+0.0821*	+0.0278*	+0.0314*

"Bold-shaded" entries were used to highlight the variables with statistical significance.

*P value <0.05.

†Female as reference.

‡2007–2010 as reference.

§Late stage (Ann Arbor stage 3–4) for non-Hodgkin's lymphoma.

CCI, Charlson Comorbidity Index; N/A, not available;.

also observed in a Japanese study, which showed much higher costs for cancer (US\$60 400 per patient) than for heart disease (US\$25 800 per patient) or cardiovascular disease (US\$55 100 per patient) in 2014.¹⁴ The difference between cancers and other diseases mainly resulted from mortality costs due to the relatively young age at death in cancer patients,^{14 27} and therefore reflecting similar costs for prostate cancer and ACS in this study.

Our results of the cost driver analysis are aligned with those of previous studies,^{7 31–33} showing decreasing effects on the total costs of cancer associated with an older age at diagnosis and increasing effects associated with male sex, tumour metastasis, comorbidities and treatment in a medical centre. Regarding the effects on direct medical costs, tumour metastasis showed a noteworthy inconsistency among cancers. For most cancers, such as lung cancer, liver cancer and oral cancer the occurrence of tumour metastasis at diagnosis decreased the direct medical costs due to limited treatment options. In contrast, the direct medical costs of female breast cancer, colorectal cancer, prostate cancer and NHL increased when the patients were diagnosed with late-stage cancer, given the availability of expensive but effective treatments for advanced cancer. Older age at diagnosis significantly decreased the direct costs and total costs of cancers in this study. However, current trends worldwide demonstrate unprecedented age decrease for many non-communicable diseases including cancer that may significantly burden the healthcare economics in a long-term manner.^{34–36} Therefore, the implementation of cost-effective healthcare services based on the principles of 3P medicine, namely predictive diagnostics, targeted prevention and personalisation of the treatment algorithms particularly in case of young subpopulations is recommended.^{34 37 38}

The major strength of this study was the evaluation from a broader societal perspective of both the direct medical and indirect costs of cancers. In addition, the inclusion of high-expenditure but low-prevalence haematologic cancers, such as leukaemia and NHL, was more appropriate for the theme of cost analyses. The population-based study design provides precise information on the treatment costs for each patient, compared with bulk estimated expenditures from the perspective of the payer. For instance, the total medical cost of female breast cancer ranked second among all cancers according to national-level statistics due to the substantial patient number; however, it was relatively inexpensive compared with other cancers at the patient-level. Other advantages of this study include the usage of the most recent nationwide data for representing the current status and the application of human capital methods widely used in cost analyses for comparability with other literature results.

There are some limitations to our study. First, setting up a 3-year postdiagnosis estimates may only capture the high-cost period of cancer. However, as the disease progress varied significantly across different cancers, some have long-term survival (such as breast cancer) while some have relatively short survival, we need to set up an equal

follow-up period (the concept of landmark analysis) for our study cohort to allow fair comparisons of economic burden across different cancers. Also, the costs on specific medical services, such as inpatient hospitalisations and outpatient clinics, were not reported separately (grouped into direct medical costs) in this study because the main focus of estimating direct medical costs was to reveal the role of medications, particularly anti-cancer drugs, on the economic burden of different cancers. The lack of data on out-of-pocket costs due to the natural restriction of NHIRD may also lead to an underestimation of direct medical costs. Second, the morbidity costs in this study covered only the costs of ‘absenteeism’ by calculating the number of outpatient visits and inpatient days from claims data; the costs of ‘presenteeism’, resulting from the physically or mentally unwell still working, were not estimated. Some other costs not covered in this study included direct non-medical costs (transportation costs, informal care costs, etc) and intangible costs (reduced quality of life, pain, anxiety, etc). Third, we did not perform further analyses on each stage or subtype of cancer (eg, non-small-cell lung cancer and small-cell lung cancer), which requires a careful interpretation for different patient characteristics. Fourth, the population in this study was limited to adult patients (≥ 20 years old). Future studies may focus on the economic burdens of cancers in children (< 20 years old), especially in cancers associated with younger ages at diagnosis (< 20 years old), such as leukaemia and female breast cancer. Fifth, all-cause mortality, in replacement of cancer-related death, was used to calculate the mortality costs in this study. However, if we used the specific coding for cause of death, some other cause of death such as organ failure might result in underestimation of mortality costs of cancers.

Using the latest nationwide database, this study demonstrates the direct and indirect costs of the top 10 high-expenditure cancers in Taiwan. Large variation was observed among the cancers based on their different characteristics. These differences are good references for optimising the allocation of national health resources.

Contributors S-YH, K-HL, B-SK and F-YH contributed to the study concept and design. S-YH acquired and analysed the data. S-YH, H-MC, B-SK and F-YH interpreted the data. S-YH drafted the manuscript. F-YH revised the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Because the identification numbers of all subjects in the NHIRD were encrypted to protect individual privacy, this study was exempted from full review by the Institution Review Board of the National Taiwan University Hospital, and the requirement for informed consent was waived. The National Taiwan University Hospital approved this study (20180110W).

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