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Abstract

Aims/Introduction: There is uncertainty about the direct medical costs of type 2 diabetes mellitus (T2DM) patients with cancers.

Materials and Methods: A population-based retrospective cohort of 99915 T2DM patients from Hong Kong Hospital Authority between 2006 and 2017 was assembled. 16869 patients who had initial cancer diagnosis after T2DM were matched with 83046 patients without cancer (controls) using a matching ratio up to one-to-five propensity score-matching method. Patients were divided into four categories according to life expectancy. Healthcare service utilization and direct medical costs during the index year, subsequent years, and mortality year were compared between patients with and without cancer in each category.

Results: Medical costs of cancer patients in index year ranged from US$27533 for patients died <1 year to US$11303 for those survived >3 years. Cancer patients had significantly greater expenditures than controls in index year (all P<0.001) and subsequent years (US$4569 vs. US$4155, P<0.001). Cancer patients also had greater costs in the death year, and the difference was significant for patients who survived >3 years after index year (US$32558 vs. US$28260). For patients in both groups, patients who survived >3 years had significantly lower costs than those died <1 year. Costs incurred in mortality year were greater than those in index year and subsequent years. Hospitalization accounted for >90% of the medical costs for both groups in mortality year.

Conclusions: T2DM patients with cancers incurred greater medical costs in the diagnosis, ensuing, and mortality years than T2DM patients without cancers.

Keywords: Cancer; Type 2 diabetes mellitus; Direct medical costs

Introduction

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Cancer causes a tremendous disease burden worldwide[1]. As the leading cause of death globally, cancer accounts for 18.1 million new cases and 9.6 million deaths in 2018[2]. The incidence of cancer has increased over the years, and its upward trend is partly due to the rising prevalence of risk factors such as diabetes, obesity and other lifestyle factors [1]. An increasing number of studies confirm that type 2 diabetes mellitus (T2DM) is associated with an increased risk of cancer and cancer mortality [3-8]. Indeed, patients with T2DM have higher incidence across all cancer types with Risk ratio of 1.23 for Asian patients and 1.15 for non-Asian patients [9]. For hepatocellular carcinoma, particular, the increased risk among patients with T2DM reaches to 131% [10]. In view of the strong link between diabetes and the incidence of cancer, a joint consensus statement convened by the American Diabetes Association (ADA) and the American Cancer Society stated that T2DM patients are more likely to develop cancers in liver, pancreas, endometrium, colon and rectum, breast and bladder, although they are less likely to develop prostate cancer[11].

The economic burden of cancers is tremendously heavy from either a macroscopic or an individual perspective[12-14]. The estimated direct medical costs and indirect costs resulting from a loss of productivity among cancer patients has reached US$2 trillion globally[15]. At an individual level, up to $81655 was accrued in the post-diagnosis period for each cancer patient who died within 1 year[16]. Of note, oncology patients who died within 1 year after diagnosis tended to have higher medical costs than those who survived beyond 1 year in the post-diagnosis periods[16]. This is probably because the cost of treating cancer increases with the advancement of the disease, as extra treatments, intensive care and expensive drugs are given during the end-of-life care[17,18].

In recent years, the increasing use of computer simulation models of diabetes progression in clinical decision-making processes has addressed clinical questions with long-term simulated results[19]. While diabetes-related complications, including cardiovascular diseases, retinopathy, nephropathy and amputation, have been widely included in existing economic evaluations of interventions for T2DM, none of them considered cancers as one of modelled complications [20], even though the guidelines for economic models of diabetes advocate a compression of multiple diabetes complications[21]. Since T2DM is associated with an increased risk of cancer and the burden of cancer is heavy, diabetes economic models could be further refined by introducing

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cancers. However, no known studies measured the direct medical costs of T2DM patients co-existing with cancer, and thus it remains a great challenge to incorporate cancer into the model.

This population-based cohort study aimed to 1) examine the direct medical costs of T2DM patients with cancers in the year of diagnosis, ensuing years and year of death by their life expectancies; 2) compare the costs of T2DM patients with and without cancers; and 3) assess the impact of patients' baseline covariates on direct medical costs.

Materials and Methods

Study design and population

A retrospective propensity score-matched cohort study was conducted. Patients who used the Hong Kong Hospital Authority (HA) healthcare services between January 2006 and December 2017 were identified from the HA Clinical Management System (CMS). Disease diagnosis was identified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Primary Care, Second Edition (ICPC-2) (**Supplemental Table 1**). A one-year screening period was adopted to exclude patients whose cancer diagnosis was made in or before the year 2006. Patients who had cancer diagnosis on or after the onset date of T2DM were assigned to the cancer group. The index date was defined as the date of the first occurrence of a cancer event during the study period. To fully use the large pool of non-cancer patients, a group of T2DM patients without a recorded cancer diagnosis during the observation period was matched in a ratio up to one-to-five ratio using caliper propensity score matching.

Outcomes

Primary outcomes were the direct medical costs of patients in the cancer and control group incurred in the index year, ensuing years, and the last year of life. For patients in the cancer group, direct medical costs were further measured by tumour sites.

Secondary outcomes included the pattern of use of healthcare services in T2DM patients with and without cancer and the impacts of patients' baseline characteristics on medical costs.

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Estimation of direct medical costs

The dates and types of healthcare service use by patients in both groups during the observation period were retrieved. Cost items included General Outpatient Clinic (GOPC) visits, Specialist Outpatient Clinic (SOPC) visits, Accident & Emergency (A&E) visits, applied health professional visits, and length of stay in a general ward, in an Intensive Care Unit (ICU), in a Coronary Care Unit (CCU), and in a High Dependency Unit (HDU). The unit cost of each type of healthcare services was extracted from the public charges to non-eligible persons listed in the 2017 Government Gazette and HA Ordinance (Chapter 113) (**Supplemental Table 2**)[22]. The pegged exchange rage of US$1=HK$7.80 was used to convert Hong Kong dollars to US dollars[23]. The annual direct medical costs of each patient were calculated by summing up the unit cost of each healthcare service multiplied by the frequency of use of the respective service.

Patients in both groups were divided into four categories by their life expectancies after the index year, including those who 1) died within 1 year after the index date (Category 1); 2) survived over 1 year, but died within 2 years after the index date (Category 2); 3) survived over 2 years, but died within 3 years after the index date (Category 3); and 4) survived over 3 years after the index date (Category 4). Costs in the index year were the costs incurred from the index date to 1 year after the index date, while the costs incurred in the mortality year were the costs incurred from 1 year before the mortality date to the death date. Of note, costs in the index year of patients in Category 1 were also the costs of the mortality year. To avoid duplicate calculations, costs incurred beyond the index year were regarded as the costs in the mortality year for patients in Category 2. Only patients in Category 4 had the costs in the ensuing years, which were the mean value of the costs incurred between 1 year after the index date and 1 year before the death date (for patients who died during the observation period) or the mean value of the costs incurred between 1 year after the index date and the last observation date (for patients who survived during the whole observation period).

Baseline covariates

The baseline covariates included gender (male, female), age (≤75, >75), Charlson Comorbidity Index (CCI) (≤3, 4-6, ≥7), duration of T2DM (≤5, >5 years), presence of comorbidities (including mental health problems, hyperlipidaemia, obstructive sleep apnoea [OSA], gallbladder disease, musculoskeletal and chronic orthopaedic disorders, end-stage renal diseases [ESRD] and

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hypertension), and the use of insulin, oral anti-diabetic drugs, anti-hypertensive drugs and lipid-lowering agents.

Statistical Analysis

Propensity Score Matching Method

Multiple imputation by chained equations was used to address the absence of baseline data [24]. HbA1c, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, total cholesterol, high-density lipoprotein cholesterol, triglyceride and fasting glucose were imputed by demographics (gender and age), body mass index, history of comorbidities (including mental health problems, hyperlipidaemia, OSA, gallbladder diseases, musculoskeletal and chronic orthopaedic disorders, and hypertension), and the use of medications (including insulin, oral antidiabetic drugs, antihypertensive drugs, and lipid-lowering drugs). Missing percentages for HbA1c, systolic blood pressure, diastolic blood pressure, LDL-C, total cholesterol, HDL-C, triglyceride and fasting glucose were 3.97%, 9.34%, 9.42%, 10.12%, 9.53%, 9.97%, 9.97% and 10.62%, respectively. Model parameters estimated from multiple imputed data were used to obtain multiple-imputation linear predictions by applying Rubin's combination rules observation wise to the completed-data predictions[25]. The obtained predictions were then used in propensity score matching. Each patient's propensity score was computed by multivariable logistic regression adjusting for baseline clinical parameters and covariates. Command 'calipmatch' in STATA with a caliper width of 0.05 was used to match cancer patients with controls on a one-to-five basis.

The baseline characteristics of patients before and after matching were presented by frequency with percentages for categorical variables and means with standard deviation (SD) for continuous variables in a table. Independent t-tests or chi-squire tests were used to determine if there were significant differences between cancer and non-cancer patients. Standard mean difference (SMD), a statistic less sensitive to sample size, was calculated for each characteristic. An SMD of <0.2 indicated that the baseline characteristics between cancer patients and controls were well balanced[26].

Generalised linear models

Generalised linear models (GLMs) with log link and gamma distribution were used to explore the effects of patient covariates on direct medical costs. GLMs were constructed separately for each

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Category. Multipliers (exponential value of coefficients), corresponding 95% confidence intervals (CIs) and p-values for each covariate were reported.

All statistical analysis was done with Stata 13.1 (StataCorp LP, College Station, Texas). All significance tests were two-tailed and the p-value <0.05 was statistically significant.

Results

Patient characteristics

A total of 16869 and 83046 eligible cancer and control patients respectively were included in this analysis. (**Supplemental Figure 1**)

Table 1 summarises the baseline characteristics of patients before and after the propensity-score matching. The baseline characteristics of the cancer and control patients were well balanced (**Supplemental Figure 2**). There were 4811, 1377, 725 and 9956 cancer patients with a median follow-up duration of 3, 16, 29, and 41 months in Categories 1 to 4, respectively. There were 2795, 2752, 2575, and 74924 control patients in Categories 1 to 4, respectively. The median follow-up duration of the controls was 5, 17, 29, and 47 months in Categories 1 to 4, respectively.

Utilization of healthcare services

Table 2 summarises the use of healthcare services by patients in the cancer and control groups. Notably, the SOPC was the most frequently used healthcare services by all categories, apart from cancer patients' use of inpatient services. The frequency of SOPC visits by cancer patients ranged from 5.28 to 15.76 times, while those of control patients was less than five times across the four categories. Cancer patients had more SOPC visits than controls within the same category. A&E and allied health professional admissions tended to be more frequent for cancer patients than control patients during the observation period. However, the frequency of visits to GOPCs by patients in the cancer and control groups were similar.

Compared with controls in the same category, cancer patients spent approximately 10 additional nights in general wards in the index year and three extra nights in general wards in the mortality

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year. However, both cancer and control patients in Categories 1-4 spent less than one night in ICU, CCU and HDU wards.

Direct medical costs

Figure 1 shows the mean direct medical costs of cancer and control patients in the index year, subsequent years and the mortality year. For patients in Category 1, the direct medical costs of cancer and control patients in the index year were US$27533 and US$21043, respectively (P<0.001). Hospitalization accounted for the largest proportion (>95%) of the direct medical costs for both groups. Cancer patients in Category 2 had higher medical costs than control patients in both the index year (US$26988 vs. US$15542, P<0.001) and the mortality year ($21790 vs. US$21343, P=0.594). Similarly, cancer patients in Category 3 had higher costs in the index year (US$18695 vs. US$9121, P<0.001) and the mortality year (US$30433 vs. US$29608, P=0.534), but the differences were not significant in the mortality year. For patients in Category 4, the medical costs of cancer patients were significantly higher than those of controls in the index year, subsequent years and the mortality year (all P<0.001). Compared with patients in other categories, patients in Category 4 incurred less expenditure in hospitalization in the index year. However, the costs of hospitalization, again, were in excess of 90% of the total medical costs in the mortality year for patients in both the cancer and control groups. Of note, patients with longer remaining life expectancies had lower medical costs in the index year.

We further grouped the costs incurred in the index year and in the mortality year for patients in all four Categories, and compared their annualised mean costs across patients in the four Categories and between the two groups (**Supplemental Figure 3**). Cancer patients in all four Categories had significantly greater medical costs in the index year than in the mortality year (all P<0.001). In group comparisons, patients in Category 2, more of whom had aggressive cancers with high mortality rates (e.g. cancers in digestive organs and unspecified sites), had the highest medical costs; while patients in Category 4, among who there are less patients with aggressive cancers, had the lowest.

The mean direct medical cost of cancer patients in the index year, subsequent years and mortality year are displayed by tumour sites in **Table 3**. The direct medical costs of patients in Category 1 ranged from US$24478.15 (SD=US$1023.28) in patients with cancers in other and unspecified

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sites to US$42066.32 (SD=US$8380.46) for patients with cancers of the lip, oral cavity and pharynx. The patients in Category 2 with cancers in lymphatic and hematopoietic tissue had the highest costs in the index year (US$33762.93, SD=US$8612.39), and patients with cancers of the lip, oral cavity and pharynx had the highest costs in the mortality year (US$28072.39, SD=US$8233.23). Patients in Category 3 with lymphatic cancers and leukemia had the highest direct medical costs in both the index year (US$28706.56, SD=US$12983.92) and the mortality year (US$39598.94, SD=US$12 817.13). Finally, the medical costs of patients in Category 4 in the index year ranged from US$7133.32 (SD=US$472.55) to US$18429.11 (SD=US$2839.51); the direct medical costs in the subsequent years were around US$4600 per year for all cancer patients.

Effects of patients' covariates on annual direct medical costs

Table 4 shows the influence of baseline patients' covariates on the annual direct medical costs by category. The base-case annual mean medical costs for a T2DM female patient belonging to Category 1, aged ≤75 years, who did not have cancer or other diabetic complications were US$14366.22. Oncology patients incurred significantly greater medical costs than non-cancer patients, with a multiplier of 1.470 (P<0.001). Medical costs were greater for patients aged 75 or under (P<0.001). Compared with patients with a CCI ≤3, patients with a higher CCI had greater medical costs. The presence of gallbladder disease, ESRD and hypertension significantly increased the medical costs for patients in Category 1, while the presence of other diabetic complications did not have and a significant influence on annual costs. Of note, patients using insulin had significantly higher medical costs, while those taking oral anti-diabetic drugs, anti-hypertensives or lipid-lowering agents had significantly lower costs.

The occurrence of cancer in patients of all other categories significantly increased the medical costs in the index year, subsequent years and the mortality years. Generally, a higher CCI, the presence of diabetic complications and the use of insulin increased annual medical costs, while the use of oral anti-diabetic drugs, anti-hypertensives, or lipid-lowering agents decreased them.

Discussion

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This large-scale population-based cohort study estimated the direct medical costs and described the patterns of uptake of healthcare services by patients with both cancer and T2DM. This study also estimated the influence of patients' characteristics on direct medical costs and provided cost information of patients with specific tumours. The use of a propensity-score matching method enabled the cost comparison between cancer and control patients by using real-world data. Results of GLMs facilitated easy estimation of medical costs incurred by patients with different baseline characteristics.

This study filled the research gap and separately reported the medical costs incurred by T2DM patients with and without cancers by years. Several previous health economic evaluations had focused on the medical costs of either cancers or T2DM[12,13,27-30], but none had quantified the impacts of cancer on the direct medical costs and healthcare utilization of T2DM patients, given the intrinsic connections between the two diseases. In addition, few of them reported the medical costs separately by the diagnosis year, subsequent years and mortality year[28,31,32].

This study also showed that greater medical expenditures were incurred in the mortality year. Of special note was that the overall medical and inpatient costs of oncology patients with a remaining life expectancy greater than 3 years had a U-shaped curve, i.e. higher costs were incurred in the year of diagnosis and mortality, while costs were lower in the years in between. In comparison, the medical costs of T2DM patients without cancer showed an increasing trend over the years. Similar findings were supported by previous studies, which found that costs of cancer patients had a typical U-shaped curve while medical costs of T2DM patients increased overtime [28,31]. The increased medical costs in the mortality year were mainly because patients had more hospital stays in their last year of life compared with those in the years preceding the mortality year. This finding was consistent with the observations of previous studies, which confirmed that patients with more hospital stays had significantly greater chance of mortality[33]. Indeed, our study showed that hospitalization accounted for most of the annual medical costs of patients over the years. A previous study also found that inpatient admissions contributed the largest part of the total medical costs for cancer patients, while costs for other services, such as chemotherapy and radiotherapy, accounted for no more than 10% of the total direct medical costs[16]. However, hospitalization costs were only from 38% to 64% of the total costs of oncology patients in Ontario[16], but accounted for up to 96% of the total costs for cancer patients in our study. One possible explanation of this

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discrepancy is that patients who were enrolled in this study were approximately 10 years older than those included in the Ontario study[16]. Since the length of stay in hospitals generally increased with ages[34], higher percentage of medical costs were attributed to hospitalization.

The direct medical costs and survival rates varied across tumour sites. For example, patients with cancers of the lip, oral cavity and pharynx and those with lymphatic and hematopoietic cancers had relatively larger costs compared with patients with other types of cancers. Compared with patients with survivable cancers, those with riskier cancers tended to have a shorter life expectancy. In our analyses, a great percentage (24.19%) of patients with genitourinary cancer survived beyond 3 years after cancer diagnosis, while a large portion (34.11%) of patients with cancer in other and unspecified tumour sites died within 1 year. These results had a message for policy makers to implement early health interventions, such as cancer screening tests, in T2DM patients to prevent cancers; and to provide patients who are at high risks of lower survivable and/or costly cancers with special care. Apart from sites of tumours, patient age is another important factor that affects the life expectancy after cancer diagnosis. Life expectancy in younger cancer patients is expected to be longer than that of older patients with same conditions[35]. Indeed, patients in Category 4, with a mean age of 74.6 years, were significantly younger than patients in Categories 1 to 3 (**Supplemental Table 3**). In addition, a greater percentage of patients in Category 1 had multiple chronic diseases which could contribute to their shorter life expectancy.

Apart from cancers, the presence of comorbidities was another important factor associated with increased healthcare expenditure. This study suggested that patients who had a higher CCI, diabetic complications and used insulin tended to incur higher costs than patients with lower CCI, had no or fewer diabetic complications and used oral antidiabetic drugs. This finding was consistent with previous studies that focused on the effects of comorbidities on medical costs in oncology patients[31,36,37]. For example, a costing analysis calculating the costs of elderly patients with neuroendocrine tumours found that a comorbidity score of 3 or above incrementally increased the monthly medical costs by $1359 for patients who survived beyond 1 year and $4185 for patients who died within 1 year[31]. Also, comorbidity was found to be with higher medical costs for patients with colon, breast and prostate cancers[36].

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Our study showed the importance of involving cancer as one of the health states in diabetes economic models. The current guidelines for computer simulation modelling of diabetes and its complications provide general requirements on model construction, such as considering long-term horizons, including multiple complications and carefully selecting a perspective; but they do not specifically require the inclusion of cancer[19]. However, the reliability and validity of diabetes models are considered questionable if cancers are not incorporated as one of the modelled complications. It is not only because cancers deteriorate the quality of life and largely increase the medical costs of T2DM patients, but also because diabetes is associated with increased risks of different cancer types by 10% to 131%[9,10]. The findings of this study therefore provided suggestions for health economists in refining the current diabetes economic models and can be used for future cost-effectiveness analyses of health interventions for T2DM.

However, several limitations should be acknowledged. First of all, cancer patients and non-cancer patients were not matched separately by categories, leading to imbalanced baseline characteristics of two groups in a same category. Also, cancer patients in Category 1 had fewer matched patients, while those in Category 4 had more matched cases. Secondly, the cost of healthcare services incurred in the private sector and the indirect costs due to loss of productivity were not taken in consideration. Besides, the packaged charges of HA outpatient and inpatient services include pathology investigations, medication within the scale provided at the hospitals or clinics and other necessary examinations, but do not cover the costs of immunology therapies and surgical operations. Therefore, the results of this study may be underestimated. Thirdly, this study assumed that patients enrolled from 2006 to 2017 incurred the same unit cost for each healthcare service, without making an adjustment for inflation over time.

To conclude, T2DM patients with cancers had higher direct medical costs than those who were cancer-free in the year of cancer diagnosis, the years that followed and year of death. Hospitalization accounted for the majority of these direct medical costs.

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organization had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation of the manuscript.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethics approval of this study was granted by Institutional Review Board of the University of Hong Kong /Hospital Authority Hong Kong West Cluster (Ref No. UW 16-1018).

Disclosure statement

The authors have no financial conflicts of interest.

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References

1. Park Y, Colditz GA. Diabetes and adiposity: a heavy load for cancer. *The Lancet Diabetes & Endocrinology.* 2018;6(2):82-83.
2. World Health Organization. WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. In. Geneva: World Health Organization; 2018.
3. Gallagher EJ, LeRoith D. Diabetes, cancer, and metformin: connections of metabolism and cell proliferation. *Ann N Y Acad Sci.* 2011;1243:54-68.
4. Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. *Am J Epidemiol.* 2004;159(12):1160-1167.
5. Everhart J. Diabetes Mellitus as a Risk Factor for Pancreatic Cancer. *JAMA.* 1995;273(20):1605-1609.
6. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. *Int J Cancer.* 2007;121(4):856-862.
7. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst.* 2005;97(22):1679-1687.
8. Shlomai G, Neel B, LeRoith D, Gallagher EJ. Type 2 Diabetes Mellitus and Cancer: The Role of Pharmacotherapy. *J Clin Oncol.* 2016;34(35):4261-4269.
9. Noto H, Tsujimoto T, Noda M. Significantly increased risk of cancer in diabetes mellitus patients: A meta-analysis of epidemiological evidence in Asians and non-Asians. *J Diabetes Investig.* 2012;3(1):24-33.
10. Wang P, Kang D, Cao W, Wang Y, Liu Z. Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and meta-analysis. *Diabetes Metab Res Rev.* 2012;28(2):109-122.
11. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *Diabetes Care.* 2010;33(7):1674-1685.
12. Yabroff KR, Lund J, Kepka D, Mariotto A. Economic burden of cancer in the United States: estimates, projections, and future research. *Cancer Epidemiol Biomarkers Prev.* 2011;20(10):2006-2014.
13. Luengo-Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the European Union: a population-based cost analysis. *The Lancet Oncology.* 2013;14(12):1165-1174.

This article is protected by copyright. All rights reserved

14. Stewart BW, Wild CP. *World Cancer Report 2014.* Lyon: International Agency for Research on Cancer; 2014.
15. Cavalli F, Atun R. Towards a global cancer fund. *The Lancet Oncology.* 2015;16(2):133-134.
16. de Oliveira C, Bremner KE, Pataky R, et al. Understanding the costs of cancer care before and after diagnosis for the 21 most common cancers in Ontario: a population-based descriptive study. *CMAJ Open.* 2013;1(1):E1-8.
17. Sun L, Legood R, Dos-Santos-Silva I, Gaiha SM, Sadique Z. Global treatment costs of breast cancer by stage: A systematic review. *PLoS One.* 2018;13(11):e0207993.
18. Mittmann N, Porter JM, Rangrej J, et al. Health system costs for stage-specific breast cancer: a population-based approach. *Curr Oncol.* 2014;21(6):281-293.
19. Palmer AJ, Si L, Tew M, et al. Computer Modeling of Diabetes and Its Transparency: A Report on the Eighth Mount Hood Challenge. *Value Health.* 2018;21(6):724-731.
20. Govan L, Wu O, Lindsay R, Briggs A. How do diabetes models measure up? A review of diabetes economic models and ADA Guidelines. *Journal of Health Economics and Outcomes Research.* 2015;5:132-152.
21. American Diabetes Association Consensus Panel. Guidelines for computer modeling of diabetes and its complications. *Diabetes Care.* 2004;27(9):2262-2265.
22. Hospital Authority. Hospital Authority Ordiance (Chapter 113) Revision to List of Charges: Public Charges - Non-eligible Persons http://www.ha.org.hk/haho/ho/cs/238767_en.pdf. Published 2017. Accessed.
23. Wong CK, Lam CL, Poon JT, et al. Direct medical costs of care for Chinese patients with colorectal neoplasia: a health care service provider perspective. *J Eval Clin Pract.* 2012;18(6):1203-1210.
24. Royston P, White I. Multiple Imputation by Chained Equations (MICE): Implementation inStata. *Journal of Statistical Software.* 2011;45(4).
25. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med.* 2011;30(4):377-399.
26. Cohen J. *Statistical power analysis for the behavioral sciences.* Routledge; 2013.
27. Chang S, Long SR, Kutikova L, et al. Estimating the cost of cancer: results on the basis of claims data analyses for cancer patients diagnosed with seven types of cancer during 1999 to 2000. *J Clin Oncol.* 2004;22(17):3524-3530.

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28. Wong CKH, Jiao F, Tang EHM, Tong T, Thokala P, Lam CLK. Direct medical costs of diabetes mellitus in the year of mortality and year preceding the year of mortality. *Diabetes Obes Metab.* 2018;20(6):1470-1478.
29. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. *J Cancer Epidemiol.* 2013;2013:965212.
30. American Diabetes Association. Economic Costs of Diabetes in the U.S. in 2017. *Diabetes Care.* 2018;41(5):917-928.
31. Shen C, Chu Y, Halperin DM, et al. Carcinoid Syndrome and Costs of Care During the First Year After Diagnosis of Neuroendocrine Tumors Among Elderly Patients. *Oncologist.* 2017;22(12):1451-1462.
32. Jiao F, Wong CKH, Tang SCW, et al. Annual direct medical costs associated with diabetes-related complications in the event year and in subsequent years in Hong Kong. *Diabet Med.* 2017;34(9):1276-1283.
33. Lingsma HF, Bottle A, Middleton S, Kievit J, Steyerberg EW, Marang-van de Mheen PJ. Evaluation of hospital outcomes: the relation between length-of-stay, readmission, and mortality in a large international administrative database. *BMC Health Serv Res.* 2018;18(1):116.
34. Kwok CL, Lee CK, Lo WT, Yip PS. The Contribution of Ageing to Hospitalisation Days in Hong Kong: A Decomposition Analysis. *Int J Health Policy Manag.* 2016;6(3):155-164.
35. Capocaccia R, Gatta G, Dal Maso L. Life expectancy of colon, breast, and testicular cancer patients: an analysis of US-SEER population-based data. *Ann Oncol.* 2015;26(6):1263-1268.
36. Taplin SH, Barlow W, Urban N, et al. Stage, age, comorbidity, and direct costs of colon, prostate, and breast cancer care. *J Natl Cancer Inst.* 1995;87(6):417-426.
37. Subramanian S, Tangka FK, Sabatino SA, et al. Impact of chronic conditions on the cost of cancer care for Medicaid beneficiaries. *Medicare Medicaid Res Rev.* 2012;2(4).

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Supporting information

Supplemental Figure 1 Flowchart of the study

Supplemental Figure 2 Pyramid of propensity score distribution among T2DM patients with and without cancers.

Supplemental Figure 3 Mean direct medical costs incurred in the index year and in the mortality year among type 2 diabetes mellitus patients with and without cancers

Supplemental Table 1 ICPC-2 and ICD-9-CM diagnosis codes

Supplemental Table 2 Unit cost of healthcare services

Supplemental Table 3 Baseline characteristics of type 2 diabetes mellitus patients with cancers in 4 Categories

Figure legends

Figure 1 Mean direct medical cost (US$) of patients and proportion of costs attributed by hospitalisation in the cancer and control groups in the index year, subsequent year and mortality year

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Table 1 Baseline characteristics of patients in the cancer group and matched control group

Characteristics	Before matching	After 1-to-5 propensity score matching			
	Cancer patients (n = 21327)	Cancer patients (n = 16869)	Matched control patients (n =83046)	P-value	SMD[†]
Demographic					
Female, n (%)	10130 (47.5)	8249 (48.9)	41523 (50.0)	0.013[*]	0.021
Mean age (SD), year	76.70 (10.72)	76.83 (10.33)	76.81 (6.98)	0.714	0.003
Clinical parameters					
Mean HbA1c (SD), %	7.11 (1.35)	7.08 (1.29)	7.08 (1.24)	0.719	0.003
Mean fasting glucose (SD), mmol/L	7.38 (2.44)	7.33 (2.34)	7.32 (2.37)	0.645	0.004
Mean oral glucose tolerance test (OGTT) (SD), mmol/L	9.53 (4.36)	9.57 (4.46)	9.68 (5.20)	0.191	0.022
Mean SBP (SD), mmHg	133.61 (18.49)	133.78 (18.43)	134.26 (16.98)	0.002[*]	0.027
Mean DBP (SD), mmHg	71.79 (10.78)	71.63 (10.69)	71.57 (10.14)	0.460	0.006
Mean total cholesterol (SD), mmol/L	4.26 (1.02)	4.26 (0.98)	4.27 (0.91)	0.100	0.014
Mean HDL-C (SD), mmol/L	1.17 (0.34)	1.19 (0.34)	1.20 (0.32)	0.003[*]	0.026
Mean TC/HDL-C ratio (SD)	3.89 (1.63)	3.81 (1.37)	3.76 (1.18)	<0.001[*]	0.038
Mean LDL-C (SD), mmol/L	2.42 (0.86)	2.41 (0.85)	2.41 (0.77)	0.988	0.000
Mean triglyceride (SD), mmol/L	1.47 (0.88)	1.46 (0.84)	1.46 (0.82)	0.570	0.005
Mean serum creatinine (SD), umol/l	104.02 (90.47)	102.45 (89.32)	102.61 (73.62)	0.808	0.002
Mean eGFR (SD), ml/min/1.73m^2	72.79 (28.50)	73.03 (27.96)	68.60 (53.39)	<0.001[*]	0.104
Comorbidities					
Mean duration of T2DM (SD), year	4.79 (3.22)	5.09 (3.15)	5.07 (2.96)	0.401	0.007

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Insulin used, n (%)	4180 (19.6)	3988 (18.7)	15197 (18.3)	0.201	0.011
Oral anti-diabetic drugs ever used, n (%)	13009 (61.0)	10594 (62.8)	51405 (61.9)	0.028*	0.019
History of hypertension, n (%)	17552 (82.3)	14187 (84.1)	69426 (83.6)	0.084	0.000
Anti-hypertensive drugs ever used, n (%)	16870 (79.1)	13647 (80.9)	65606 (79.0)	<0.001*	0.046
History of hyperlipidemia, n (%)	9832 (46.1)	8097 (48.0)	39613 (47.7)	0.542	0.005
Lipid lowering agents ever used, n (%)	10919 (51.2)	9042 (53.6)	43433 (52.3)	0.003*	0.025
History of mental health problems, n (%)	512 (2.4)	405 (2.4)	2076 (2.5)	0.247	0.010
History of obstructive sleep apnea, n (%)	1088 (5.1)	860 (5.1)	4235 (5.1)	0.776	0.002
History of gallbladder disease, n (%)	981 (4.6)	759 (4.5)	3820 (4.6)	0.713	0.003
History of musculoskeletal and chronic orthopedic disorders, n (%)	4820 (22.6)	3964 (23.5)	19931 (24.0)	0.191	0.011
Charlson Comorbidity Index, n (%)				<0.001*	0.098
≤ 3	130 (0.61)	118 (0.7)	914 (1.1)		
4-6	18687 (87.62)	16565 (98.2)	81800 (98.5)		
≥ 7	2508 (11.76)	186 (1.1)	332 (0.4)		

Notes:

Abbreviations: SMD = Standardized Mean Difference; SD = Standard Deviation; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HDL-C = High-density Lipoprotein Cholesterol; TC = Total Cholesterol; LDL-C = Low-density Lipoprotein Cholesterol; eGFR = estimated glomerular filtration rate; DM = Diabetes Mellitus

*Significant difference (p-value <0.05) detected by independence t tests or by chi square tests.

†SMD <0.200 indicates the balance of baseline covariates.

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Table 2. Mean number of healthcare utilization (visits and length of stays) with standard deviation of cancer and control patients

Patients	Year	N	GOPC	SOPC	A&E	Allied health	Hospitalization utilization[†]	
							General Ward	ICU, CCU and HDU
Cancer patients								
Category 1	Index year	4,811	0.75 (0.04)	5.28 (0.17)	2.53 (0.06)	0.22 (0.03)	38.08 (0.98)	0.45 (0.08)
Category 2	Index year	1,377	2.72 (0.15)	15.76 (0.45)	2.96 (0.17)	0.76 (0.13)	34.79 (2.15)	0.38 (0.08)
	Mortality year	1,377	0.85 (0.09)	5.32 (0.29)	2.35 (0.12)	0.22 (0.06)	30.11 (1.66)	0.27 (0.13)
Category 3	Index year	725	3.01 (0.22)	14.79 (0.60)	1.64 (0.14)	0.58 (0.12)	22.22 (2.21)	0.47 (0.15)
	Mortality year	725	2.14 (0.18)	11.55 (0.54)	3.58 (0.20)	0.39 (0.13)	41.43 (2.73)	0.28 (0.15)
Category 4	Index year	9,956	3.43 (0.06)	11.46 (0.15)	1.07 (0.03)	1.12 (0.07)	12.83 (0.41)	0.24 (0.03)
	Subsequent years	8,256	3.56 (0.07)	7.77 (0.12)	0.95 (0.04)	0.82 (0.07)	4.33 (0.03)	0.04 (0.01)
	Mortality year	1,138	2.15 (0.16)	10.01 (0.41)	3.71 (0.17)	0.51 (0.11)	42.71 (2.51)	0.82 (0.41)
Control patients								
Category 1	Index year	2,795	0.89 (0.08)	2.05 (0.11)	2.33 (0.08)	0.13 (0.03)	26.50 (1.31)	0.97 (0.17)
Category 2	Index year	2,752	2.30 (0.11)	4.56 (0.16)	2.15 (0.10)	0.35 (0.07)	20.68 (1.33)	0.26 (0.07)
	Mortality year	2,752	0.93 (0.08)	1.95 (0.10)	2.28 (0.08)	0.14 (0.03)	27.23 (1.32)	0.93 (0.16)
Category 3	Index year	2,575	2.51 (0.11)	4.43 (0.16)	1.56 (0.10)	0.39 (0.08)	11.70 (0.97)	0.12 (0.04)
	Mortality year	2,575	1.80 (0.10)	4.32 (0.16)	3.56 (0.12)	0.29 (0.05)	39.07 (1.72)	0.90 (0.19)
Category 4	Index year	74,924	3.65 (0.02)	3.02 (0.02)	0.69 (0.01)	0.46 (0.02)	3.16 (0.09)	0.05 (0.01)
	Subsequent years	64,504	3.36 (0.02)	3.41 (0.03)	0.90 (0.01)	0.48 (0.02)	4.78 (0.09)	0.05 (0.00)
	Mortality year	8,990	1.63 (0.05)	3.83 (0.08)	3.53 (0.06)	0.29 (0.03)	38.46 (0.91)	0.60 (0.08)

Notes:

GOPC = General Outpatient Clinic; SOPC = Specialist Outpatient Clinic; A&E = Accident & Emergency; ICU = Intensive Care Unit; CCU = Coronary Care Unit; HDU = High Dependency Unit

Category 1: patients die in the index year; Category 2: patients die in the second year after the index date; Category 3: patients die in the third year after the index date; Category 4: patients survive over 3 years after the index date.

[†]Mean length of stay

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Table 3 Mean direct medical cost (US$) with standard deviation of cancer patients in the diagnosis year, in the subsequent years and in the mortality year by sites of tumor

Sites of tumor	Category 1 (N=4811)		Category 2 (N=1377)			Category 3 (N=725)			Category 4 (N=9956)			
	N (%)	Diagnosis year, US$	N (%)	Diagnosis year, US$	Mortality year	N (%)	Diagnosis year, US$	Mortality year, US$	N (%)	Diagnosis year, US$	Subsequent year, US$	Mortality year, US$
Lip, oral cavity and pharynx (N=561)	97 (2.02)	42066.32 (8380.46)	46 (3.34)	32085.96 (9166.37)	28072.39 (8233.23)	31 (4.28)	28572.1 (12689.65)	32069.94 (12713.72)	387 (3.89)	18429.11 (2839.51)	4287.77 (927.01)	31820.49 (12615.83)
Digestive organs including Esophageal, stomach, pancreatic, liver, gallbladder, colorectal, anal cancer (N=5843)	1839 (38.22)	28721.00 (1199.82)	557 (40.45)	29580.42 (2385.92)	21468.45 (1831.32)	274 (37.79)	21570.43 (2682.81)	29772.51 (3089.45)	3173 (31.87)	15199.79 (576.63)	5116.07 (394.76)	31528.71 (3072.53)
Respiratory system (N=1645)	690 (14.34)	24539.40 (1523.83)	196 (14.23)	20745.52 (2903.76)	22755.97 (3166.10)	92 (12.69)	14907.88 (6090.02)	27270.16 (5013.89)	667 (6.70)	10403.65 (939.00)	4929.98 (907.96)	24753.09 (4050.22)
Bone, skin, soft tissue and breast (N=2539)	98 (2.04)	30130.23 (5256.34)	106 (7.70)	19988.01 (4598.54)	18484.26 (3587.70)	74 (10.21)	11253.2 (2757.01)	28080.38 (5366.14)	2261 (22.71)	7133.32 (472.55)	3694.90 (349.36)	30714.18 (4559.82)
Genitourinary organs including kidney, bladder, ureter, uterus, genitalia, prostate, and ovary (N=3071)	336 (6.98)	32520.42 (3049.85)	187 (13.58)	26570.94 (4161.12)	26221.86 (4265.75)	140 (19.31)	15634.7 (2854.77)	33654.11 (4513.94)	2408 (24.19)	8207.70 (467.62)	4407.84 (352.36)	38124.71 (4988.48)
Lymphatic and hematopoietic tissue (N=424)	110 (2.29)	41647.28 (6277.62)	40 (2.90)	33762.93 (8612.39)	18893.08 (9202.82)	18 (2.48)	28706.56 (12983.92)	39598.94 (12817.13)	256 (2.57)	16653.34 (2526.06)	5681.45 (1279.90)	36635.21 (8207.30)

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Other and unspecified sites (N=2786)	1641 (34.11)	24478.15 (1023.28)	245 (17.79)	27372.49 (3798.34)	19087.67 (2097.52)	96 (13.24)	19249.16 (4525.76)	30220.68 (4566.09)	804 (8.08)	12538.97 (1133.88)	5045.94 (851.01)	31544.20 (6160.39)

Notes: Category 1: patients die in the index year; Category 2: patients die in the second year after the index date; Category 3: patients die in the third year after the index date; Category 4: patients survive over 3 years after the index date.

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Table 4 Effects of cancer and other baseline covariates on costs in the index year, subsequent years and year of death (generalized linear model with log link of Gamma distribution)

A. Category 1 and 2

	Category 1			Category 2					
	Index year			Index year			Mortality year		
Covariates	Multiplier	95% CI	p-value	Multiplier	NA	<0.001*	Multiplier	95% CI	p-value
Constant	NA	NA	<0.001*	NA	(1.934, 2.359)	<0.001*	NA	NA	<0.001*
Cancer (vs. non-cancer)	1.470	(1.386, 1.559)	<0.001*	2.136	(0.866, 1.068)	0.461	1.151	(1.064, 1.245)	<0.001*
Age (vs ≤75)	0.868	(0.822, 0.916)	<0.001*	0.961	(0.906, 1.099)	0.963	0.910	(0.839, 0.988)	0.025*
Male (vs. female)	0.980	(0.934, 1.028)	0.412	0.998	(0.957, 1.156)	0.292	1.027	(0.953, 1.107)	0.487
Duration of T2DM (vs. ≤5 years)	1.006	(0.958, 1.056)	0.822	1.052	(0.398, 1.438)	0.394	0.955	(0.887, 1.028)	0.218
CCI (vs. CCI ≤3)									
4-6	1.638	(0.970, 2.765)	0.065	0.757	(0.772, 3.056)	0.222	1.959	(1.298, 2.957)	0.001*
≥7	1.820	(1.062, 3.120)	0.029*	1.536	(1.136, 1.394)	<0.001*	1.824	(1.130, 2.945)	0.014*
Presence of cardiovascular disease	0.999	(0.949, 1.052)	0.973	1.258	(0.824, 1.390)	0.612	1.054	(0.976, 1.138)	0.182
Presence of mental health problems	0.990	(0.858, 1.141)	0.885	1.070	(0.905, 1.100)	0.962	0.986	(0.792, 1.227)	0.899
Presence of hyperlipidemia	1.015	(0.966, 1.066)	0.560	0.998	(0.959, 1.394)	0.127	0.978	(0.907, 1.054)	0.558
Presence of OSA	1.043	(0.936, 1.162)	0.449	1.156	(0.923, 1.279)	0.319	1.014	(0.875, 1.176)	0.850
Presence of gallbladder disease	1.100	(1.001, 1.208)	0.046*	1.086	(1.054, 1.293)	0.003*	0.982	(0.853, 1.131)	0.801
Presence of musculoskeletal and chronic orthopedic disorders	1.031	(0.976, 1.088)	0.279	1.167	(1.133, 1.428)	<0.001*	0.998	(0.919, 1.084)	0.958
Presence of ESRD	1.127	(1.049, 1.211)	0.001*	1.272	(0.895, 1.159)	0.776	1.196	(1.087, 1.317)	<0.001*
Presence of hypertension	1.154	(1.075, 1.239)	<0.001*	1.019	(0.959, 1.196)	0.222	1.157	(1.045, 1.280)	0.005*
Use of insulin	1.072	(1.014, 1.133)	0.014*	1.071	(0.649, 0.803)	<0.001*	1.111	(1.021, 1.209)	0.014*
Use of oral anti-diabetic drugs	0.806	(0.768, 0.846)	<0.001*	0.722	(0.771, 0.935)	0.001*	0.797	(0.736, 0.864)	<0.001*

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Use of anti-hypertensive drugs	0.821	(0.779, 0.865)	<0.001*	0.849	(0.826, 1.020)	0.113	0.775	(0.718, 0.836)	<0.001*
Use of lipid-lowering agents	0.849	(0.807, 0.894)	<0.001*	0.918	NA	<0.001*	0.856	(0.790, 0.927)	<0.001*

Notes: CI = confidence interval; CCI = Charlson Comorbidity Index; ESRD = End-Stage Renal Disease; OSA = Obstructive Sleep Apnea; T2DM = Type 2 Diabetes Mellitus; NA = Not Applicable.

Category 1: Base cost of index year = US Base cost of the index year = US$14,366.22; Category 2: Base cost of index year = US$18,306.62; Base cost of mortality year = US$12,148.92

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B. Category 3

Covariates	Index year			Mortality year		
	Multiplier	95% CI	p-value	Multiplier	95% CI	p-value
Constant	NA	NA	<0.001*	NA	NA	0.019*
Cancer (vs. non-cancer)	2.478	(2.168, 2.831)	<0.001*	1.162	(1.069, 1.263)	<0.001*
Age (vs ≤75)	0.899	(0.788, 1.026)	0.115	1.012	(0.928, 1.104)	0.783
Male (vs. female)	0.939	(0.825, 1.069)	0.343	0.996	(0.923, 1.074)	0.912
Duration of T2DM (vs. ≤5 years)	0.961	(0.844, 1.094)	0.546	0.975	(0.904, 1.052)	0.512
CCI (vs. CCI ≤3)						
4-6	2.522	(0.641, 9.921)	0.186	2.146	(0.877, 5.255)	0.095
≥7	8.075	(1.861, 35.035)	0.005*	2.961	(1.127, 7.778)	0.028*
Presence of cardiovascular disease	1.365	(1.196, 1.558)	<0.001*	1.099	(1.015, 1.19)	0.020*
Presence of mental health problems	0.839	(0.600, 1.172)	0.303	1.002	(0.842, 1.194)	0.980
Presence of hyperlipidemia	1.007	(0.881, 1.150)	0.920	0.965	(0.894, 1.043)	0.372
Presence of OSA	1.235	(0.996, 1.53)	0.054	1.052	(0.912, 1.214)	0.487
Presence of gallbladder disease	1.294	(1.033, 1.621)	0.025*	0.985	(0.839, 1.155)	0.850
Presence of musculoskeletal and chronic orthopedic disorders	1.204	(1.042, 1.392)	0.012*	1.114	(1.018, 1.219)	0.019*
Presence of ESRD	1.338	(1.157, 1.547)	<0.001*	1.250	(1.142, 1.368)	<0.001*
Presence of hypertension	0.981	(0.842, 1.143)	0.807	0.983	(0.892, 1.083)	0.724
Use of insulin	1.092	(0.945, 1.261)	0.231	1.065	(0.977, 1.162)	0.152
Use of oral anti-diabetic drugs	0.812	(0.705, 0.935)	0.004*	0.793	(0.726, 0.865)	<0.001*
Use of anti-hypertensive drugs	0.878	(0.771, 1.001)	0.052	0.841	(0.777, 0.909)	<0.001*
Use of lipid-lowering agents	0.890	(0.780, 1.016)	0.085	0.896	(0.824, 0.973)	0.009*

Notes: CI = confidence interval; CCI = Charlson Comorbidity Index; ESRD = End-Stage Renal Disease; OSA = Obstructive Sleep Apnea; T2DM = Type 2 Diabetes Mellitus; NA = Not Applicable; Base cost of index year = US$3,446.30; Base cost of mortality year = US$14,987.65

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C. Category 4

Covariates	Index year			Subsequent year			Mortality year		
	Multiplier	95% CI	p-value	Multiplier	95% CI	p-value	Multiplier	95% CI	p-value
Constant	NA	NA	<0.001*	NA	NA	<0.001*	NA	NA	<0.001*
Cancer (vs. non-cancer)	5.042	(4.857, 5.234)	<0.001*	1.352	(1.295, 1.412)	<0.001*	1.213	(1.136, 1.295)	<0.001*
Age (vs ≤75)	1.267	(1.218, 1.318)	<0.001*	1.383	(1.343, 1.424)	<0.001*	0.909	(0.862, 0.959)	<0.001*
Male (vs. female)	0.999	(0.961, 1.038)	0.961	0.990	(0.963, 1.019)	0.494	1.107	(1.059, 1.157)	<0.001*
Duration of T2DM (vs. ≤5 years)	1.129	(1.086, 1.174)	<0.001*	1.062	(1.032, 1.094)	<0.001*	0.949	(0.899, 1.001)	0.055
CCI (vs. CCI ≤3)									
4-6	1.414	(1.218, 1.642)	<0.001*	1.287	(1.036, 1.600)	0.023*	0.960	(0.544, 1.693)	0.887
≥7	4.784	(3.788, 6.042)	<0.001*	1.331	(0.995, 1.781)	0.054	0.865	(0.457, 1.637)	0.655
Presence of cardiovascular disease	1.762	(1.693, 1.833)	<0.001*	1.527	(1.481, 1.575)	<0.001*	1.083	(1.035, 1.134)	0.001*
Presence of mental health problems	1.499	(1.359, 1.654)	<0.001*	1.351	(1.222, 1.494)	<0.001*	0.892	(0.773, 1.029)	0.118
Presence of hyperlipidemia	0.916	(0.879, 0.956)	<0.001*	0.881	(0.855, 0.907)	<0.001*	0.929	(0.885, 0.974)	0.003*
Presence of OSA	1.183	(1.099, 1.272)	<0.001*	1.128	(1.058, 1.203)	<0.001*	0.993	(0.894, 1.103)	0.893
Presence of gallbladder disease	1.333	(1.236, 1.438)	<0.001*	1.131	(1.064, 1.203)	<0.001*	0.986	(0.895, 1.086)	0.769
Presence of musculoskeletal and chronic orthopedic disorders	1.335	(1.280, 1.392)	<0.001*	1.209	(1.170, 1.249)	<0.001*	1.053	(0.996, 1.114)	0.070
Presence of ESRD	2.023	(1.875, 2.184)	<0.001*	1.723	(1.603, 1.852)	<0.001*	1.136	(1.056, 1.221)	0.001*
Presence of hypertension	1.063	(1.007, 1.122)	0.026*	1.080	(1.040, 1.121)	<0.001*	0.939	(0.888, 0.993)	0.028*
Use of insulin	1.503	(1.428, 1.582)	<0.001*	1.607	(1.553, 1.663)	<0.001*	1.127	(1.076, 1.181)	<0.001*
Use of oral anti-diabetic drugs	0.669	(0.640, 0.698)	<0.001*	0.581	(0.563, 0.599)	<0.001*	0.753	(0.717, 0.791)	<0.001*
Use of anti-hypertensive drugs	0.770	(0.725, 0.817)	<0.001*	0.695	(0.668, 0.722)	<0.001*	0.874	(0.835, 0.915)	<0.001*
Use of lipid-lowering agents	0.860	(0.823, 0.898)	<0.001*	0.825	(0.801, 0.851)	<0.001*	0.893	(0.850, 0.938)	<0.001*

Notes: CI = confidence interval; CCI = Charlson Comorbidity Index; ESRD = End-Stage Renal Disease; OSA = Obstructive Sleep Apnea; T2DM = Type 2 Diabetes Mellitus; NA = Not Applicable; Base cost of index year = US$1,818.00; Base cost of subsequent year = US$3,612.85; Base cost of mortality year = US$36,805.40

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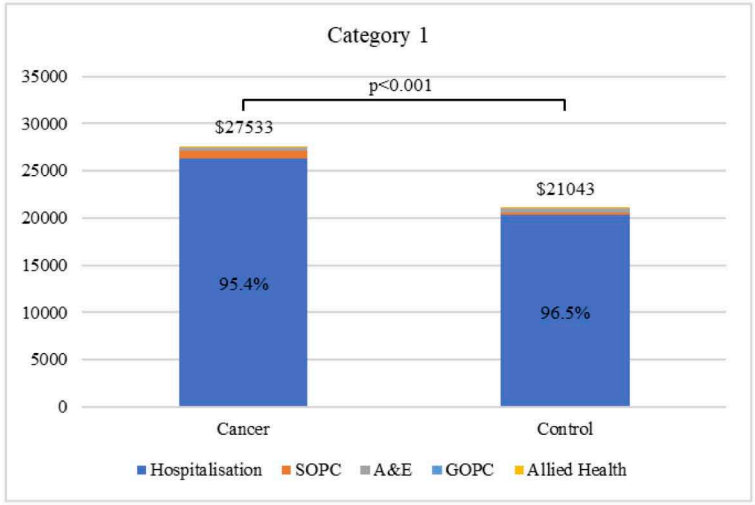
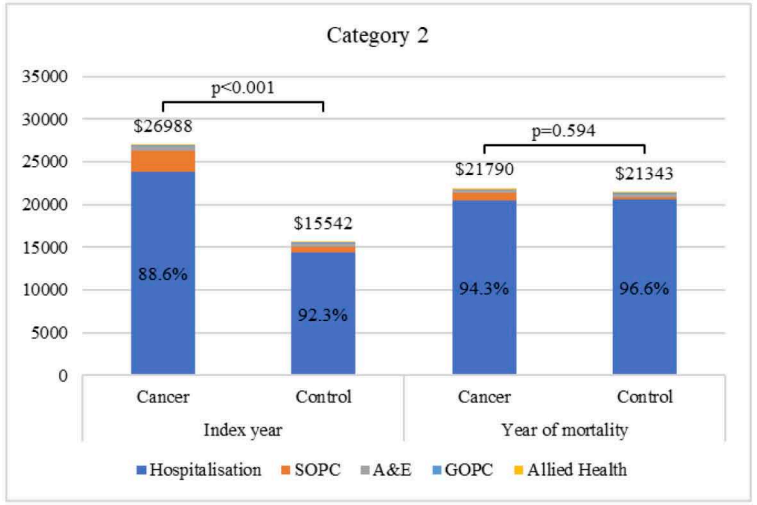
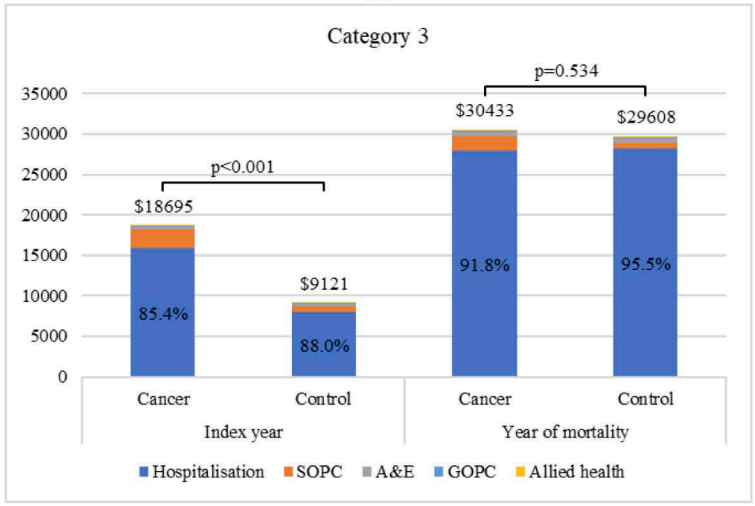
Figure 1 Mean direct medical cost (US$) of patients and proportion of costs attributed by hospitalisation in the cancer and control groups in the index year, subsequent years and mortality year



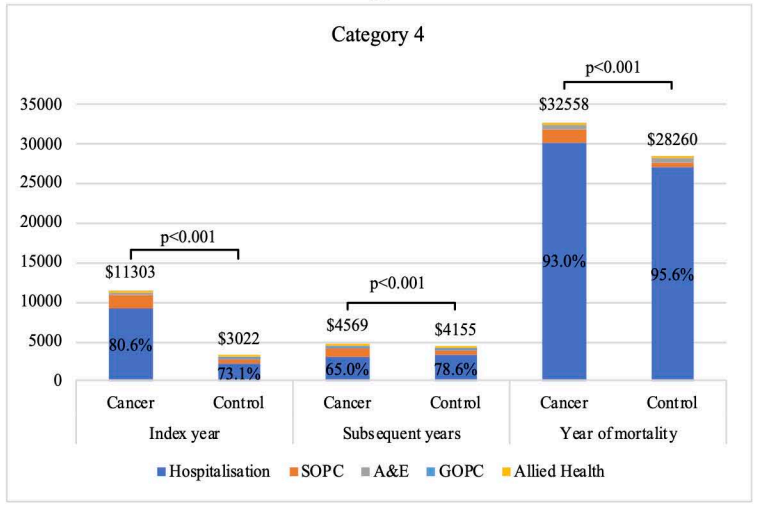
A



B



C



D

Footnotes: Category 1: patients die in the index year; Category 2: patients die in the second year after the index date; Category 3: patients die in the third year after the index date; Category 4: patients survive over 3 years after the index date.