The cancer premium – explaining differences in prices for cancer vs non-cancer drugs with efficacy and epidemiological endpoints in the US, Germany, and Switzerland: a cross sectional study

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Summary

Background High treatment prices of new cancer drugs are a global public health challenge to patients and healthcare systems. Policymakers in the US and Europe are debating reforms to drug pricing. The objective of this study was to assess whether drug efficacy or epidemiological characteristics (prevalence, incidence, mortality) explain the gap in treatment prices between cancer and non-cancer drugs in the US, Germany, and Switzerland.

Methods This cross-sectional study identified all new drugs approved in the US, Germany, and Switzerland between 2011 and 2020. Drug efficacy was extracted from pivotal trials, drug prices from public and commercial databases, and epidemiological characteristics from the Global Burden of Disease (GBD) 2019 study. We used regression models to explain drug prices with drug efficacy and epidemiological characteristics (prevalence, incidence, mortality).

Findings The cohort included 181 drugs, including 68 (37.5%) drugs approved for treatment of cancer. A significant negative correlation was found between incidence/prevalence and treatment prices, and a significant positive correlation was observed between mortality and treatment prices for both, cancer and non-cancer drugs. A significant association between relative drug efficacy and treatment prices of drugs was observed, however, less pronounced for cancer drugs. Our regression estimates indicated that after adjusting for efficacy and epidemiological characteristics, cancer drugs were on average approximately three times more expensive compared to non-cancer drugs in all three countries, indicating a cancer premium; i.e., treatment prices of cancer drugs were on average USD 74,412 (95% CI [62,810; 86,015]) more expensive in the US compared to non-cancer drugs, USD 37,770 (95% CI [26,175; 49,367]) more expensive in Germany, and USD 32,801 (95% CI [27,048; 38,555]) more expensive in Switzerland. Our model explained 72% of the variance in observed prices (R^2).

Interpretation Drug pricing reforms should target the cancer premium to improve access of patients to cancer drugs as well as to achieve equity across the different therapeutic areas and sustainability in the health care systems.

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Keywords: Medicines; Cancer premium; Epidemiologic endpoints

Introduction

Launch prices of new drugs increased over the past years.[1] Among the different therapeutic areas, high prices have especially been attributed to cancer drugs.[1–4] Their high costs are a public health challenge to patients and health care systems across countries.[3–5]

In the US, the term "financial toxicity" has been used to describe the harmful effect that high treatment costs

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Research in context

Evidence before this study

To assess previous research pertaining to the explanation of high cancer drug prices, we conducted a non-systematic PubMed and google scholar search using a combination of terms including, but not limited to, "drug prices", "cancer", "cancer premium." The search included all types of studies from database inception until 10 November 2022. While studies, including from our research group, outline the high prices of cancer drugs, and certain determinants for high treatment prices (such as higher willingness to pay), the explanation for high treatment prices of cancer drugs in comparison to non-cancer drugs remains poorly understood and has not been analysed with the characteristics of this study (drug efficacy and epidemiological characteristics).

Added value of this study

Drug efficacy and epidemiological characteristics (prevalence, incidence, mortality) cannot explain the three-fold difference in treatment prices between cancer and non-cancer drugs. After adjustment, treatment prices of cancer drugs were on average USD 74,412 (95% CI [62,810; 86,015]) more expensive in the US compared to non-cancer drugs, USD 37,770 (95% CI [26,175; 49,367]) more expensive in Germany, and USD 32,801 (95% CI [27,048; 38,555]) more expensive in Switzerland. Our model explained 72% of variance in the observed prices (R^2). This gap –here referred to as the "cancer premium"– was observed both in the US where drug prices can be set freely, and in European countries with price negotiation power.

Implications of all the available evidence

Drug pricing reforms should target the cancer premium to improve access of patients to cancer drugs as well as to achieve equity across the different therapeutic areas and sustainability in the health care systems.

may have on patients' financial stress. Approximately one-half of individuals with cancer face personal economic burdens associated with their disease and treatment.[2,6] Financial toxicity arises, for example, from the out-of-pocket medical spending, employment disruptions, productivity losses, and impaired livelihoods that accompany a cancer diagnosis.[6] Financial toxicity can result in skipping drug doses, increased anxiety, stress or depression, employment loss, reduced food spending, or even bankruptcy.[2]

By contrast to the US, drug prices are negotiated in European countries.[7] Healthcare systems in European countries, such as Germany or Switzerland, are increasingly challenged by the high costs of cancer drugs.[4] Economic theory holds that smaller markets (i.e., smaller population groups) result in higher prices in monopolistic markets, such as the market of new drugs with patent protection.[8–10]

Germany and Switzerland have a universal coverage system with low out-of-pocket spending, which decreases the risk of financial toxicity for patients.[11,12] However, high prices affect the healthcare system since fewer financial resources are finite and high costs result in less resources available for other drugs that are also important for the treatment of diseases.

Policymakers in the US and Europe have been debating reforms targeted at high-priced drugs with a particular focus on cancer drugs.[13,14] It remains unclear how much higher treatment prices for cancer drugs are compared to non-cancer drugs, whether this gap can be explained, and if there are differences between the US and European countries. To inform ongoing policymaking, we analysed in this study how much higher treatment prices of new cancer compared to non-cancer drugs in the US and two European countries (Germany and Switzerland) were and whether this gap can be explained with drug efficacy or epidemiological characteristics (prevalence, incidence, mortality).

Methods

Data sources and extraction

Using FDA's public database, we identified all new drugs approved by the FDA between January 2011 and December 2020, excluding generic, biosimilar, diagnostic, contrast, and imaging agents.[15] We then assessed whether these drugs were also approved in Germany or Switzerland between 2011 and 2020 using the publicly available databases of the EMA and Swissmedic.[16,17] For the identified drugs, we extracted key information, including generic and brand names, therapeutic area (based on the World Health Organization's Anatomic Therapeutic Classification system), date of approval, indication, approval pathway, and orphan designation.

We then extracted launch prices for the US (Truven Micromedex and SSR, in cases of deviation, we included the lowest treatment price in the analysis), Germany (Lauer-Taxe), and Switzerland (Bundesamt für Gesundheit). Treatment prices were calculated for each drug using dosing information from the FDA label and median treatment duration information from the FDA label or pivotal clinical trials. Trial data was obtained using the ClinicalTrials.gov registry from the NIH's US National Library of Medicine. For drugs with multiple dosage forms, we included the cheapest dosage. European prices were converted to USD by applying the exchange rates on 1 January 2022. All prices were adjusted to inflation, using data from the US Bureau of Labor Statistics.

From ClinicalTrials.gov, we further extracted trial design information such as type of hypothesis (classified as superiority or non-inferiority/equivalence), outcomes, number of arms, trial phase, and linked trial results publications. We categorized phase 1/phase 2 trials as phase 2 trials and phase 2/phase 3 trials as phase 3 trials. Outcomes of trials were classified into overall survival measuring changes in quantity of life, quality of life, or surrogate endpoints. We classified the trials into superiority or non-inferiority/equivalence studies. We further categorized the trial efficacy estimates into ratios or differences. For trials that assessed ratios and differences as primary endpoints, we only included those endpoints with ratios to enable aggregation of the results at trial level of the drug. In cases of multiple primary endpoints, we averaged the measures of efficacy and their statistical significance (p-values).

We obtained country-year-specific modeled epidemiological estimates, prevalence, incidence, and mortality rates per 100,000 inhabitants for the US, Germany and Switzerland from the Global Burden of Disease (GBD) 2019 study.[3] We manually linked drug indications to cause-specific epidemiological estimates. Since we were interested in the treatment price at launch, we used the epidemiological data from the previous year to control only for information that was available at the time of launch.

Eventually, we included those drugs in our study cohort approved in the respective country (US, Germany, Switzerland), and for which pricing and epidemiological data was publicly available. The flowchart for the identification and inclusion of the drugs in our study cohort is depicted in Fig. 1.

Statistical analyses

Local regression was used to graphically present temporal trends and differences in drug prices between countries. To assess the adjusted differences between cancer and non-cancer drugs, we used a linear regression model to estimate the inflation-adjusted treatment prices of drugs. Our variables of interest were the interaction between the categorical variable target cancer drugs vs non-cancer drugs, and the categorical variable country (US, Germany, Switzerland). We regressed the price of drug *i*, in country *j*, in year *t*, against a country-specific binary indicator of whether or not a drug has a cancer disorder target. We controlled for country fixed-effects, year fixed-effects. Additionally we adjusted for drug efficacy, measured as trial design (superiority or non-inferiority/equivalence), primary endpoint (overall survival, quality of life, or surrogate endpoints), and the relative effect size (measure as hazard ratio for time-to-event outcomes, relative risk ratio for binary ones, and % of standard deviation in continuous outcomes). We also controlled for epidemiologic characteristics, including prevalence, incidence, and lethality (measured as incidence to mortality ratio), company fixed-effects, small molecule/biologic product fixed-effects, trial phase, and orphan/non-orphan drug designation. Standard errors are clustered at the country level. Additional modelling specifications are described in the supplementary methods section of the appendix. To assess the robustness of our estimates, we performed extensive sensitivity analyses, namely: the estimation of the log-linear model (transforming prices into log-prices), the inclusion of only common drugs across all included countries, and alternative sets of control variables.

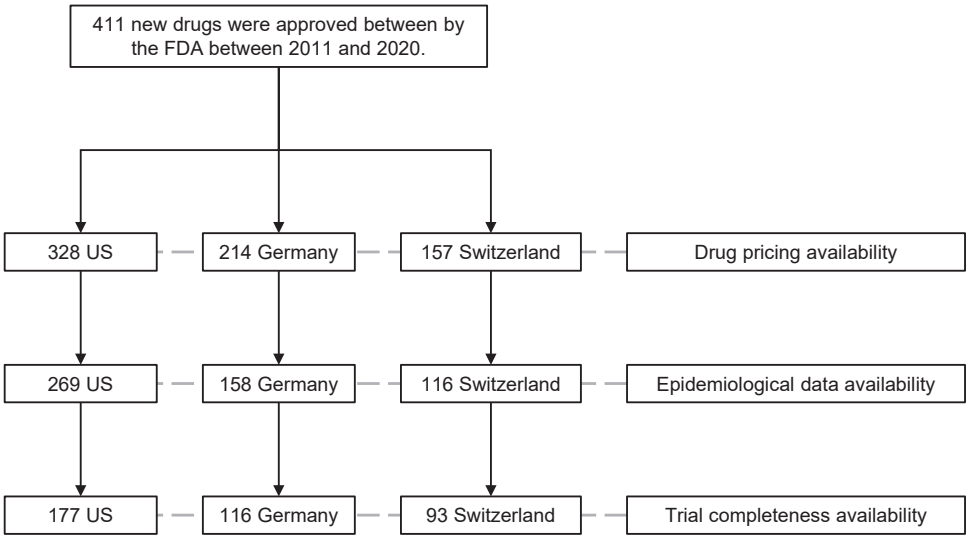

Fig. 1: **Flowchart for identified and included drugs in the study cohort.**

We applied standard descriptive methods to present the data. When appropriate, numerical variables were presented with means and standard deviation or median, interquartile range. Categorical variables were presented as counts and proportions. To summarize the differences across countries, the average standard mean difference across all pairwise comparisons was provided.

The study was deemed exempt from ethical approval because it used nonidentifiable data and did not constitute human participants research.

All statistical analyses were performed in R, version 4.2.2. (R Foundation for Statistical Computing).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the study. All study authors had final responsibility for the decision to submit for publication.

Results

177 drugs were included in our study cohort for the US, 116 for Germany, and 93 for Switzerland (Fig. 1). Of these drugs, 47 (26.6%) were approved for the treatment of cancer disorders in the US, 39 (33.6%) in Germany, and 32 (34.4%) in Switzerland (Table 1).

Treatment prices of cancer drugs vs non-cancer drugs

Overall, the largest observed differences were observed in the distribution of launch prices, with the US having notably higher mean and median prices as compared to the other two countries (see boxplot Fig. S1). Mean treatment prices at launch were USD 100,614 in the US, USD 63,615 in Germany, and USD 49.542 in Switzerland (Table 1).

Launch treatment drug prices have increased significantly over the past decade across all countries but with a more pronounced scaling in the US, specifically for cancer drugs (Fig. S2). In the US, mean treatment prices for non-cancer drugs were USD 26,696 in 2011 and USD 68,979 in 2020, with an annual mean increase of 17.6%. Mean treatment prices for cancer drugs were USD 51,651 in 2011 and USD 197,629 in 2020, with an annual mean increase of 31%. In Germany, mean treatment prices for non-cancer drugs were USD 24,179 in 2011 and USD 41,344 in 2020, with an annual mean increase of 7.9%. Mean treatment prices for cancer drugs were USD 50,149 in 2011 and USD 71,986 in 2020, with an annual mean increase of 4.8%. In Switzerland, mean treatment prices for non-cancer drugs were USD 23,984 in 2011 and USD 30,415 in 2020, with an annual mean increase of 3%. Mean treatment prices for cancer drugs were USD 43,990 in 2011 and USD 76,094 in 2020, with an annual mean increase of 8.1%.

Association between treatment drug prices and epidemiological characteristics and efficacy

A significant association was observed between the epidemiological characteristics (prevalence, incidence, mortality) and the treatment prices of drugs. A negative correlation was found between incidence/prevalence and

	US n = 177	Germany n = 116	Switzerland n = 93	SMD[a]
Drug characteristics				
Oncology target (%)	47 (26.6)	39 (33.6)	32 (34.4)	0.114
Small molecule, NDA (%)	136 (76.8)	84 (72.4)	68 (73.1)	0.068
Orphan designation (%)	79 (44.6)	56 (48.3)	34 (36.6)	0.159
Epidemiology (median [IQR])				
Prevalence per 100,000	332.39 [89.72, 5769.97]	279.36 [95.00, 4222.56]	242.88 [79.53, 4810.67]	0.153
Incidence per 100,000	25.03 [2.86, 196.56]	22.40 [4.45, 84.19]	42.71 [7.79, 78.93]	0.169
Mortality per 100,000	5.45 [1.26, 10.53]	5.44 [1.90, 20.89]	3.92 [1.32, 15.05]	0.106
Trial				
Superiority trial (%)	142 (80.2)	96 (82.8)	79 (84.9)	0.083
Overall survival (%)	13 (7.3)	11 (9.5)	8 (8.6)	0.051
Quality of Life (%)	4 (2.3)	3 (2.6)	3 (3.2)	0.039
Relative Effect size	0.35 [0.13, 0.52]	0.35 [0.18, 0.49]	0.37 [0.23, 0.50]	0.031
Phase (%)				0.25
Phase 1	3 (1.7)	1 (0.9)	1 (1.1)	
Phase 2	15 (8.5)	7 (6.0)	1 (1.1)	
Phase 3	159 (89.8)	108 (93.1)	91 (97.8)	
Pricing USD				
Price *median* [IQR]	45,151 [3627; 134,442]	32,748 [6045; 67,232]	30,135 [4840; 61,190]	0.289
Price *mean* (SD)	100,614 (153,674)	63,615 (102,999)	49,542 (72,622)	0.289

[a]Average standardized mean difference accross all pairwise comparisons.

Table 1: **Characteristics of included drugs by country.**

prices, i.e., lower incidence and prevalence was associated with higher prices. A positive correlation was observed between mortality and prices, i.e., higher mortality was associated with higher prices (Fig. 2). These associations were observed for both cancer and non-cancer drugs.

For example, inotuzumab ozagamicin is indicated for the treatment of acute lymphoid leukemia, a disease with a low incidence and prevalence, and high lethality (in the US prevalence of 4.2/100,000, incidence of 0.98/100,000, and lethality of 60%). Its launch price was USD 190,938 in the US, USD 123,383 in Germany, and USD 105,722 in Switzerland. An example of a drug targeting a disease with high prevalence and incidence, and low lethality is dalbavancin for treatment of MRSA-infection (in the US prevalence of 13,000/100,000, incidence of 8.3%, lethality of 8.3%). Its launch price was USD 5272 in the US and USD 2843 in Germany, no pricing data for Switzerland).

A significant association between relative drug efficacy and treatment prices of drugs was observed, however, less pronounced for cancer drugs (Fig. S3).

Cancer premium

Our regression estimates indicated that after adjusting for efficacy, regulatory, and epidemiological characteristics, we found cancer drugs on average to be approximately 3x more expensive compared to non-cancer drugs in all three countries (Fig. S4). More specifically, treatment prices of cancer drugs were on average USD 74,412 (95% CI [62,810; 86,015]) more expensive in the US compared to non-cancer drugs, USD 37,770 (95% CI [26,175; 49,367]) more expensive in Germany, and USD 32,801 (95% CI [27,048; 38,555]) more expensive in Switzerland (Fig. 3). Our model explained 72% of variance in the observed prices (R^2). Sensitivity analyses yielded similar results (Figs. S4–S8).

Discussion

Launch treatment drug prices have increased significantly over the past decade in the US, Germany, and Switzerland. We found significant associations between the efficacy of drugs and treatment prices, epidemiological characteristics of the diseases and treatment prices. However, these features cannot explain three three-fold difference in treatment prices between cancer and non-cancer drugs. This gap –here referred to as the "cancer premium"– was observed both in the US where drug prices can be set freely, and in European countries with price negotiation power.

Previous studies showed the high prices for cancer drugs.[4,18,19] Aligned with our study results, prior studies have indicated that orphan-designated drugs had a higher median price than drugs not designated with orphan status.[20,21] But even when considering these characteristics, treatment prices for cancer drugs were higher compared to non-cancer drugs. Furthermore, former studies found that the willingness to pay is higher for cancer drugs due to their lethality compared to non-lethal diseases.[3,22] However, even when controlling for lethality, our study indicates a premium for cancer drugs. What factors are driving the cancer premium?

The cancer premium may reflect that public awareness and fear of cancer disorders is greater compared to non-cancer diseases.[3] People across countries may be concerned about having their life expectancy shortened, more than for other diseases. Furthermore, the cancer premium may also be driven by the dread effect, whereby people are particularly fearful of cancer, and their fear may be disproportionate to the actual health impact and risks associated with the disease.[23]

These fear-driven factors are also reflected in initiatives, such as the cancer moonshot, and in drug pricing regulations, such as the separate funding mechanisms or assessment criteria for cancer drugs that some countries have established.[23] For example, in England, extending end of life treatments may be recommended even if they are less cost-effective than is usually considered acceptable. Even though this is not specific to cancer, only cancer drugs have met the criteria for special consideration in practice.[23,24] In addition, a "Cancer Drug Fund" intended to improve access to cancer drugs that have not been recommended by NICE and are not routinely available in the NHS has been introduced in England in 2011.[23] The purpose is to enable cancer treatments to be reimbursed despite having lower overall value compared to other drugs.[23] The Cancer Drug Fund is unique – no other health condition has a fund dedicated to improving drug access.[23] This indicates that policymakers are willing to pay more for cancer treatments than other types of healthcare.[23] Many European countries, such as Germany or Switzerland, do not have such special mechanisms for cancer drugs, but nonetheless, cancer drugs may be more likely than non-cancer drugs to meet the criteria needed to be eligible for a more favorable assessment.[23]

Research and development (R&D) costs of cancer drugs have been estimated to be highest across therapeutic areas.[25,26] It has been argued that such high R&D costs should be reflected in cancer drug prices to recoup the R&D costs and to incentivize the development of new cancer drugs. However, studies have found no association between R&D costs and treatment costs, and cancer drugs have generated returns far in excess of possible R&D costs, contributing to the inefficiencies in R&D of cancer drugs and stifling clinically meaningful innovation.[27,28]

Our study results indicate that patients, countries, and other payers in the US and European countries allocate disproportionate resources toward purchasing cancer drugs. This implies a departure from the goal of maximizing population health,[23] and, moreover is not a

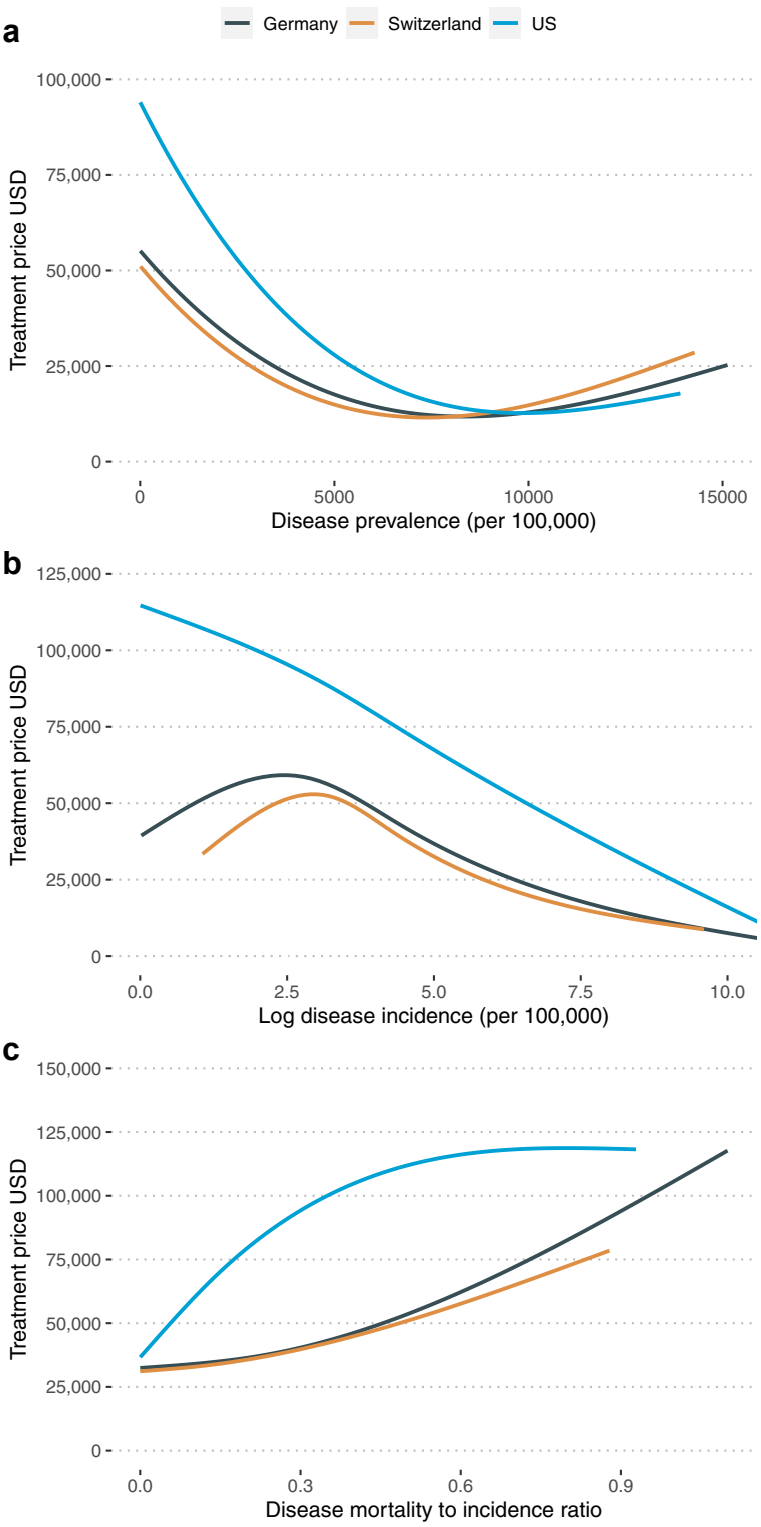

***Fig. 2:* Association between epidemiological characteristics and treatment prices**. *Legend:* Lines represent cubic natural splines of the association. Panel a) presents the association between prevalence and prices, panel b) incidence, and panel c) mortality.

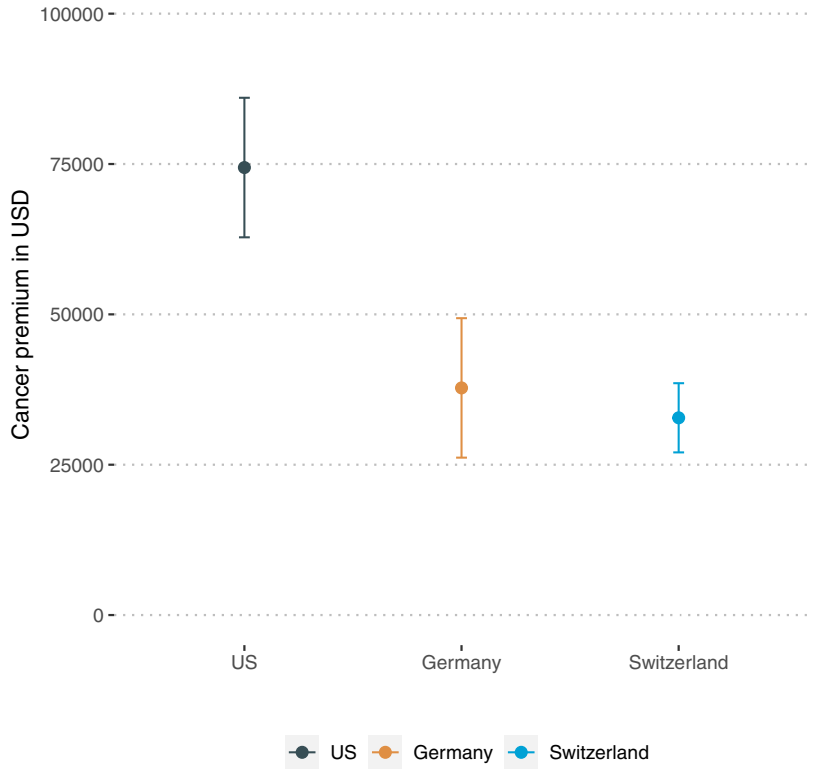

***Fig. 3:* Adjusted estimates of the association between cancer and non-cancer drugs**. *Legend:* Dots present point estimates and whiskers 95% confidence intervals. The estimates present the adjusted difference in mean price between cancer and non-cancer drugs. Explained variance in prices, R^2: 0.72.

sustainable trend given the high number of cancer drugs entering the market and the rising prevalence and incidence of cancer across countries.[29]

The US Inflation Reduction Act will allow Medicare to negotiate drug prices in the US for the first time. The legislation limits the number of drugs that can be negotiated to 10 annually in 2026, increasing to 20 drugs annually by 2029. Drugs will be eligible for negotiation from 9 years after drug approval or 13 years for biologics, until entry of a generic or biosimilar competitor.[30,31] Although negotiation of launch prices is not permitted and that negotiation is limited to a certain number of drugs, the Congressional Budget Office estimates more than USD 100 billion in Medicare savings by 2031.[30] Cancer drugs represent a therapeutic area in which the prospect of price negotiation is particularly alluring[32]; the Inflation Reduction Act is an important step forward. Policies that directly address launch prices will likely require separate legislation.[31]

In European countries, such as Germany and Switzerland, negotiation bodies should also be aware of the cancer premium and consider it in their negotiations with manufacturers. In Germany, manufacturers are permitted to set prices freely during a drug's first year on the market, but the price is subsequently negotiated and established based on a formal assessment of the drug's therapeutic value.[4] In Switzerland, the Federal Office of Public Health negotiates drug prices with manufacturers at launch and reassesses negotiated prices every 3 years after market entry.[33] These differences between both systems may explain the higher launch treatment prices in Germany and Switzerland. A previous study indicated that drug prices in Germany dropped below those in Switzerland after the first negotiation in Germany.[34] Switzerland and Europe are challenged by high-priced cancer drugs and are considering policy changes to meet this challenge. These changes should specifically address the cancer premium in order to improve access of patients to cancer drugs as well as to achieve equity across the different therapeutic areas within these health care systems.

Our study has limitations. Different numbers of drugs were included for the countries. However, when focusing only on those drugs for which data was available in all three countries, the results did not change in the sensitivity analyses. We used the FDA as a reference

to identify approved drugs. Drugs that were approved by the EMA or Swissmedic but were not approved in the US within that time frame were not identified. However, a previous study indicated that few drugs are approved in Europe but not in the US.[35] Another limitation is that our model might not capture all potential characteristics driving the launch treatment prices. However, our modeling approach explains 72% of the variation in launch treatment prices. Lastly, we were unable to match every drug-indication pairing approval due to the lack of fine grain epidemiological estimates of the global burden of disease.

Launch treatment drug prices have increased significantly over the past decade in the US and Europe (Germany, Switzerland). Treatment prices of cancer drugs were approximately three times higher than non-cancer drugs in the US, Germany, and Switzerland). A gap –referred to as the "cancer premium"– that could not be explained with efficacy or epidemiological endpoints such as incidence, prevalence, or mortality.

Drug pricing reforms should target the cancer premium to improve access of patients to cancer drugs as well as to achieve equity across the different therapeutic areas and sustainability in the health care systems.

Contributors

MSB, KNV designed the study; MSB, GP, YL, APM, KNV interpreted the results; MSB, GP, YL collected the data; MSB, GP, YL analysed the data; MSB created the figures; KNV drafted the manuscript. MSB, GP, YL accessed and verified the underlying data. All authors had access to all the data, contributed to the revision of the manuscript and approved the final version.

Data sharing statement

The datasets generated and analysed for this study are available from the corresponding author after publication upon reasonable request.

Declaration of interests

KNV reports grants from the Swiss National Science Foundation (SNSF) and Swiss Cancer Research Foundation (Krebsforschung Schweiz). She also reports institutional consulting fees from the Swiss Federal Office of Public Health, the Swiss Federal Department of Foreign Affairs and santesuisse. APM reports grants from the National Institutes of Health, the National Institute of Health Care Management, the US Department of Defense and payments from the National Institutes of Health and the Institute for Clinical and Economic Review. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102087.

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