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Influence of Government Price Regulation and Deregulation on the Price of Antineoplastic Medications in China

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LWS conceived the study. XDG designed the study. All authors acquired and analysed the data. HW, MCY, SH, DRD and AKW interpreted the findings. XDG and MCY wrote the first draft of the manuscript. DRD, AKW and HW drafted subsequent versions. All authors critically reviewed this report and approved the final version.

Keywords: Price Regulation, Deregulation, Laspeyres index, Antineoplastic Medications

ABSTRACT

Background: In October 2012, the Chinese government established maximum retail prices for specific products, including 30 antineoplastic medications. Three years later, in June 2015, the government abolished price regulation for most medications, including all antineoplastic medications. This study examined the impacts of regulation and subsequent deregulation of prices of antineoplastic medications in China.

Methods: Using hospital procurement data and an interrupted time series (ITS) with comparison series design, we examined the impacts of the policy changes on relative purchase prices, volumes, and spending of 52 antineoplastic medications in 699 hospitals.

Results: We identified three policy periods: prior to the initial price regulation (October 2011 to September 2012); during price regulation (October 2012 to June 2015); and after price deregulation (July 2015 to June 2016). During government price regulation, compared to price-unregulated cancer medications (n = 22 mostly newer targeted therapies), the relative price of price-regulated medications (n = 30 mostly cytotoxic products) decreased significantly (β = -0·081, $P < 0·001$). After the government price deregulation, the relative price of price-unregulated medications decreased significantly (β = -0·013, $P < 0·05$).

Conclusion: Neither government price regulation nor deregulation significantly impacted the average volumes or average spending on all antineoplastic medications immediately after the policy changes or in the longer term ($P > 0·05$). To control the rapid growth of oncology medication expenditures, more effective measures than price regulation of selected products are needed.

Strengths and limitations

- An interrupted time series (ITS) design, with two breakpoints was adopted to assess changes following implementation of two price policies.
- The study added value to the understanding of the effect of government regulation and deregulation of the prices of cancer medications, in the context of provincial policies.
- We were unable to obtain the full list of products under government price regulation since 1996, which could lead to selection bias.
- The comparison group of price-unregulated oncology medications tended to include newer, more expensive products than the price-regulated group
- Given our use of aggregated hospital procurement data, we could not assess factors such as the numbers of patients treated within a given level of medication spending or volume.

Introduction

Cancer medications account for the highest proportion of pharmaceutical spending among all therapeutic classes.[1] Rising cancer medication prices contribute to the rapid rise of medical and pharmaceutical expenditures, drawing criticism from leading academics, patients, cancer specialists, and policy experts.[2,3,4] In response, policy makers are implementing a variety of regulatory controls.[5]

International studies of the roles of regulation and competition in the pharmaceutical market have addressed various challenges and benefits of government price control policies, and results and perspectives are mixed.[6,7]. Srinivasan (2013) argues that the pharmaceutical market requires government regulation because of market failures,[8] such as information asymmetry and perverse incentives which affect pricing, professional ethics and competition.[9] Studies in a number of settings have found that government regulation can be effective in reducing medication prices. [10,11] However, researchers have reported favorable effects of market competition on medication prices and argued that the high price of medications is due in part to interfering government controls.[12] In critics' eyes, government regulation constitutes a barrier to dynamic competition, resulting in consumers not being able benefit fully from competition on pharmaceutical prices. [13]

In China, the government has introduced complex medication price control policies to decrease medication prices. First, after the Urban Employee Basic Medical Insurance (UEBMI) was established in 1998, the National Development and Reform Commission (NDRC) was required to set a highest retail price for each medication listed in the national insurance medication formulary.[14] In addition, because medication expenditures accounted for 40% of total health expenditures and almost 70% of medication sales were in hospitals,[15] since 2010, provinces had to conduct a centralized bidding and tendering process to procure hospital medications, with the intent to decrease prices and curb medication expenditures. [16]

In October 2012, the NDRC established maximum retail prices for specific products listed in the 2009 National Reimbursement List, including 36 antineoplastic medications. Following the central government's requirement to limit regulatory controls in economic management, China loosened administrative controls over medication prices and the NDRC formally abolished price ceiling policies in 2015.[17] Improvement of access to price-regulated medications after the 2012 price regulation and price increases after the 2015 government price deregulation were expected. However, a complicated web of policies influence hospital medication use and spending in China. (Table 1) For example, the price-regulated products were also listed on the insurance reimbursement list and are therefore subject to a hospital spending limit for insurance-reimbursable medications. In addition, all medications procured by hospitals also undergo price negotiation by the provincial government. Lastly, the price-regulated antineoplastic group comprised mostly cytotoxic chemotherapy medications; newer, more costly targeted anticancer medications were not subject to price regulation. The effect of government regulation and deregulation of the prices of cancer medications, in the context of provincial policies, is unknown.

Therefore, we studied impacts of NDRC price regulation and deregulation on the relative prices and sales volume and spending on antineoplastic medications in China.

Table 1. Policies affecting medication sales in Chinese hospitals

	Centralized provincial procurement	Insurance reimbursement listing	Hospital spending limit
Price-regulated medications	√	√	√
Price-unregulated medications	√	×	×

Methods

Study design

We used the strongest quasi-experimental design, an interrupted time series (ITS) design, [18] with two breakpoints to assess changes following implementation of two price policies. The first breakpoint served to assess the effects of the government retail price regulation in October 2012 on the Laspeyeres price (Lp) index for, monthly volumes of and spending on the study medications. The second breakpoint served to assess the effects of government retail price deregulation in June 2015. To compare the effects of each policy intervention, we conducted analyses of medication groups for which 2012 price caps were and were not applied. The intervention group of medications had retail price caps as of October 2012 and the control group was without price caps throughout the study period. (Figure 1) We hypothesized that the impacts of price regulation or deregulation on purchase prices, volumes, and spending would differ between the two groups.

Figure 1. Timeline of price regulation and deregulation of 52 antineoplastic medications

Data source

Data on products purchased between October 2011 and June 2016 were extracted from the observational Chinese Medical Economic Information (CEMI) database of public hospital medication purchasing records.[19] We conducted a search of all antineoplastic medications in the database by ATC code[20] and extracted data for 52 antineoplastic medications (30 medications with retail price caps from October 2012 to June 2015 and 20 medications without any price caps between October 2011 and June 2016, Appendix A) from 699 public hospitals. Data elements extracted for each product comprised the International Nonproprietary Name (INN), dosage form, strength, manufacturer, medication purchase price per package, monthly purchasing volumes and monthly hospital spending.

Outcome measures

The primary outcome was the Lp, which reflects what happens to the price level of a fixed basket of goods in a given period of time, compared to the price of the basket of goods during a previous period. [21] In this study, the Lp was calculated based on equation (1):

$$L_{pt} = \frac{\sum P_{ijt} Q_{ij0}}{\sum P_{ij0} Q i j_0} \qquad (1)$$

where P_{ijt} stands for price of medication i with dosage j in periods t, and Q_{ij0} stands for the volume for this medication used in period 0; *P* and *Q* were calculated in terms of Defined Daily Doses (DDD). The DDD used in this paper were the recommended daily amounts of each study medication based on dosage regimens recommended in the manufacturers' instructions, as approved by China Food and Drug Administration (CFDA). An Lp value of less than 1 means that the price of the basket of goods in a given period of time was lower than that in period 0, and a value of more than 1 means that the basket price in a given period was higher than that in period 0. The currency of price and spending was Chinese Yuan (CNY).[22]

Other outcomes of interest were average monthly purchasing volumes (number of DDD) of and average monthly hospital spending (CNY) on the 30 price-regulated, 22 price-unregulated and all 52 pharmaceuticals. All price and spending data were adjusted to October 2011 prices using the consumer price index for health care.[23]

Statistical Analysis

We assessed outcomes over time for price-regulated medications (intervention group), price-unregulated medications (control group) and all 52 products together. We also modeled intervention effects using the monthly differences in the outcomes in the two groups to estimate the relative impacts of regulation and deregulation among the regulated products, controlling for any other externalities that may have affected outcomes in the control group products.

ITS models were used to estimate levels and trends of the outcomes in the pre-intervention periods and changes in levels and trends in the post-intervention periods. ITS models with two interruption points were formulated to detect the effect on Lp, monthly average purchasing volumes and spending, as in equation (2)[18]:

$$Y_{it} = \beta_0 + \beta_1 \times time_t + \beta_2 \times regulation + \beta_3 \times reg\_trend + \beta_4 \times deregulation + \beta_5 \times der\_trend + \varepsilon_{it} \quad (2)$$

We used β_0 to estimate the baseline purchasing volume and spending; β_1 estimated the pre-regulation trend; β_2 estimated the change in level after the regulation policy; β_3 estimated the change in trend after the regulation policy; β_4 estimated the change in level after the deregulation policy; β_5 estimated the change in trend after the deregulation policy. Key coefficients were β_2, β_3, β_4 and β_5. To estimate the combined level and trend impacts of the policy changes, we calculated the absolute difference in Y_{it} at 12 months after regulation and deregulation, respectively,

compared to the counterfactual, that is, the estimated Y_{it} had the intervention not happened.[18, 24]

We performed the Durbin-Watson test to estimate level of residual autocorrelations[25] and used the Cochrane-Orcutt auto-regression procedure to correct for first order serially correlated errors when needed.[26] All analyses were performed using Stata 14.0.[27]

Study Results

Influence of Government Pricing Policies on Relative Purchase Prices

The Lp declined over time in both intervention and control medication groups (that is, prices decreased relative to baseline) from October 2011 to June 2016 (Table 2, Figure 2). After government price regulation in October 2012, the Lp for price-regulated medications dropped suddenly (β = -0·082, P < 0·001), with significant declines in Lp relative to price-unregulated medications (β = -0.081, P < 0·001). At 12 months after the regulation, there was an estimated reduction in the Lp for price-regulated medications of 0·058 (P < 0·05) and an estimated increase in the Lp for price-unregulated of 0·029 (P < 0·05).

After the government price deregulation in June 2015, the Lp for price-unregulated medications decreased significantly (β = -0·013, P < 0·05), but no significant discontinuities in Lp levels or trends were observed for the price-regulated medications or for their relative change compared to price-unregulated medications. At 12 months after price deregulation, there was no change in Lp for price regulated medications and an estimated reduction in the Lp for price-unregulated medications of 0·043 (P < 0·05).

Table 2. Results of interrupted time series analyses of the impacts of government price regulation and deregulation on Laspeyres Price Index, monthly average purchase volumes and spending for price-regulated, price-unregulated, and all antineoplastic medications, as well as group differences, 2011-2016

	Baseline level	Baseline trend	Post-regulation level change	Post-regulation trend change	Change at 12 months after regulation	Post-deregulation level change	Post-deregulation trend change	Change at 12 months after deregulation
Lp Price Index								
All medications	0·993***	-0·004*	-0·057***	0·001	-0·032	-0·005	0·001	-0·013
Price-regulated medications	0·988***	-0·004*	-0·082***	0·001	-0·058*	-0·003	0·002	0·000
Price-unregulated medications	1·006***	-0·003***	0·002	0·001	0·029*	-0·013*	0·000	-0·043*
Difference between groups	-0·015	-0·002	-0·081***	0·001	-0·071	0·005	0·002	0·043*
Hospital Purchase Volume (Thousand DDD)								
All medications	38·086***	0·915	1·938	-0·525	-4·881	-0·176	-0·311	-4·218
Price-regulated medications	58·502***	1·447	3·325	-0·862	-7·878	-1·605	-0·527	-8·455
Price-unregulated medications	10·242***	0·193	0·004	-0·068	-0·879	1·798	-0·017	1·573
Difference between groups	48·252***	1·258	3·273	-0·798	-7·097	-3·370	-0·510	-10·003
Hospital Purchase Spending (Million CNY)								
All medications	11·129***	0·168	-0·092	-0·083	-0·854	0·257	-0·063	-0·945
Price-regulated medications	12·628***	0·239	-0·778	-0·178	-2·821	-0·323	-0·013	-0·912
Price-unregulated medications	9·085***	0·073	0·832	0·048	1·806	1·052	-0·132	-0·992
Difference between groups	3·614***	0·158*	-1·570**	-0·219**	-4·508*	-1·301*	0·117	0·122

*, P ≤ 0·05; **, P ≤ 0·01; ***, P ≤ 0·001; price-regulated medications: 30 antineoplastic products with price regulation in 2012 and deregulation in 2015; price-unregulated medications: 22 antineoplastic products without price regulation or deregulation; DDD=defined daily doses; CNY = Chinese Yuan (1 CNY = 0·155 US$ in 2011)

Figure 2. Influence of government price regulation and deregulation on monthly Laspeyres index (Lp) among price-regulated medications (n=30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between regulated and unregulated medications, 2011-2016.

Influence of Government Pricing Policies on Average Purchase Volumes

The average volume purchased of all 52 antineoplastic medications, measured in DDD, rose from 33,370 DDD in October 2011 to 66,189 DDD in June 2016 (Table 2,

Figure 3. There were no statistically significant changes in volume levels or trends after government price regulation or deregulation in any group.

Figure 3. Influence of government price regulation and deregulation on monthly average purchase volumes among price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between groups, 2011-2016.

Influence of Government Pricing Policies on Hospital Spending

Average hospital spending on all antineoplastic medications rose from 9.86 million CNY in October 2011 to 17.08 million CNY in June 2016 (Table 2, Figure 4). There were no statistically significant changes in spending levels or trends after government price regulation or deregulation in any of the groups. However, the spending on price-regulated medications decreased and spending on price-unregulated medications increased after both the regulation and deregulation policies, resulting in significant level and trend changes in the differences between the two groups. After government price regulation, the spending difference decreased suddenly (β = -1·570, $P < 0.01$) and increased somewhat more slowly (β = -0·219, $P < 0.01$) than the baseline period. At 12 months after regulation, the absolute spending difference between the groups was significantly lower (-4·508, $P < 0.05$) than would have been expected without the regulation.

After the deregulation policy was implemented, the spending difference dropped again (β = -1·301, $P < 0.01$), although followed by an increasing trend (β = 0·117, $P <$ 0·05). By the end of follow-up, the relative difference between groups had returned to nearly the level expected based on trends at the time of the price deregulation policy.

Figure 4. Influence of government price regulation and deregulation on monthly average spending on price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and difference between groups, 2011-2016.

Discussion

In this study, we investigated the effects of government price regulation and subsequent deregulation for groups of antineoplastic medications in China. We found that after government price regulation, the relative price of regulated products fell more than that of price-unregulated products, and the price of all study medications as a group decreased significantly compared to the 2011 baseline price; after government deregulation, the relative price level of price-unregulated medications decreased. Neither government price regulation nor deregulation significantly affected volumes purchased or spending on regulated or unregulated medications. However, compared to price-unregulated medications, spending on price-regulated medications dropped significantly after price regulation and deregulation.

Our results indicate that, as expected, price regulation was effective in decreasing the price of antineoplastic medications; we have previously shown this effect for

digestive system medications,[28] and others have found similar decreases in price for antihyperlipidemic agents.[29] We did not find the expected price increase after deregulation for the price-regulated medications. This could be due to the fact that medication prices in China are also influenced by the provincial tendering system.[30] Since 2009, the medication tendering process is conducted at the provincial level, with different assessment criteria, usually a composite score of product quality and price, to determine the winner.[31] Hence, the tendering mechanism could have constrained medication price increases after government deregulation.[32] The provincial tendering process could also explain the price decreases in both groups observed prior to the national government price regulation. Further, generic entry, particularly for the older price-regulated cytotoxic medications, may explain why relative medication prices did not increase after government price deregulation. With the Chinese government encouraging the development of pharmaceutical enterprises, more generic medications have come to the market, which might improve the availability and the affordability of antineoplastic agents.[33]

We found no significant changes in purchase volumes or spending on either price-regulated or price-unregulated medications. When prices of regulated products decreased in comparison to price-unregulated products following the introduction of price regulation, we did not observe a compensatory increase in the use of regulated products, but spending on products in the price-regulated group decreased. Medication utilization and spending were likely also affected by reimbursement policies, which restricted the total hospital spending on insurance-listed and price-regulated products but not on unregulated medications.[34,35]

Finally, prescribers may have maintained a preference for the newer, more expensive medications in the price-unregulated group.[36] Studies in China[37], Korea[Error! Bookmark not defined.] and Italy[38], have shown that volume and medication mix, rather than prices, determine overall medication expenditures. This may indicate that it is difficult to manage medication spending increases solely by regulating the prices of some medications in a therapeutic class. Before 2015, China's Drugs Price Addition Policy allowed hospitals to charge and keep 15% of the medication sales budget,[39] and hospitals were incentivized to preferentially prescribe higher priced products.[40] Since 2015, the zero mark-up policy has been gradually introduced for all medications at all public hospitals, presumably eliminating these incentives to use more and higher-priced medications.[41] However, prescribing habits developed prior to the zero mark-up policy may still prevail.

Limitations

The study had some limitations. First, we were unable to obtain the full list of products under government price regulation since 1996, which could lead to selection bias. However, the 30 price-regulated antineoplastic products studied are likely representative of all such products. Second, the comparison group of price-unregulated oncology medications tended to include newer, more expensive products than the price-regulated group. However, the Lp trends observed at baseline in the two groups of products were quite similar, suggesting that differential changes

observed following the government pricing policies were indicative of true differences. Third, given our use of aggregated hospital procurement data, we could not assess factors such as the numbers of patients treated within a given level of medication spending or volume.

Conclusion

Compared to unregulated products, the prices of antineoplastic medications decreased after government price regulation, but did not increase after deregulation. Neither of the two price regulation policies affected volumes purchased or hospital spending on all antineoplastic medications. To control the rapid growth of oncology medication expenditures, more effective measures than price regulation of selected (typically older) antineoplastic medications need to be taken.

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Competing Interests:

The authors declared no competing interests.

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Ethics approval and consent to participate

The study was considered not human subjects research by the Harvard Pilgrim Health Care Institutional Review Board.

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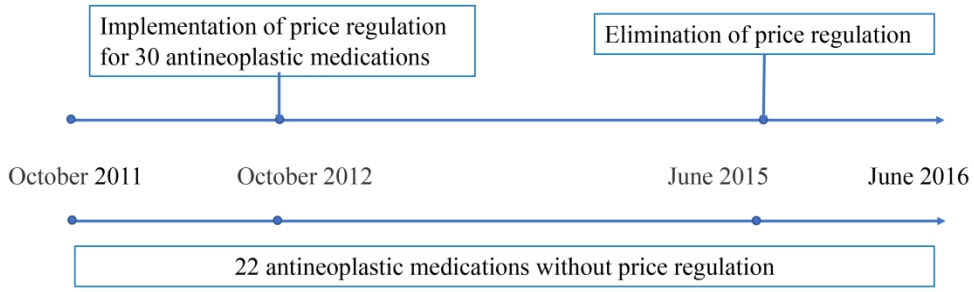

Figure 1. Timeline of price regulation and deregulation of 52 antineoplastic medications

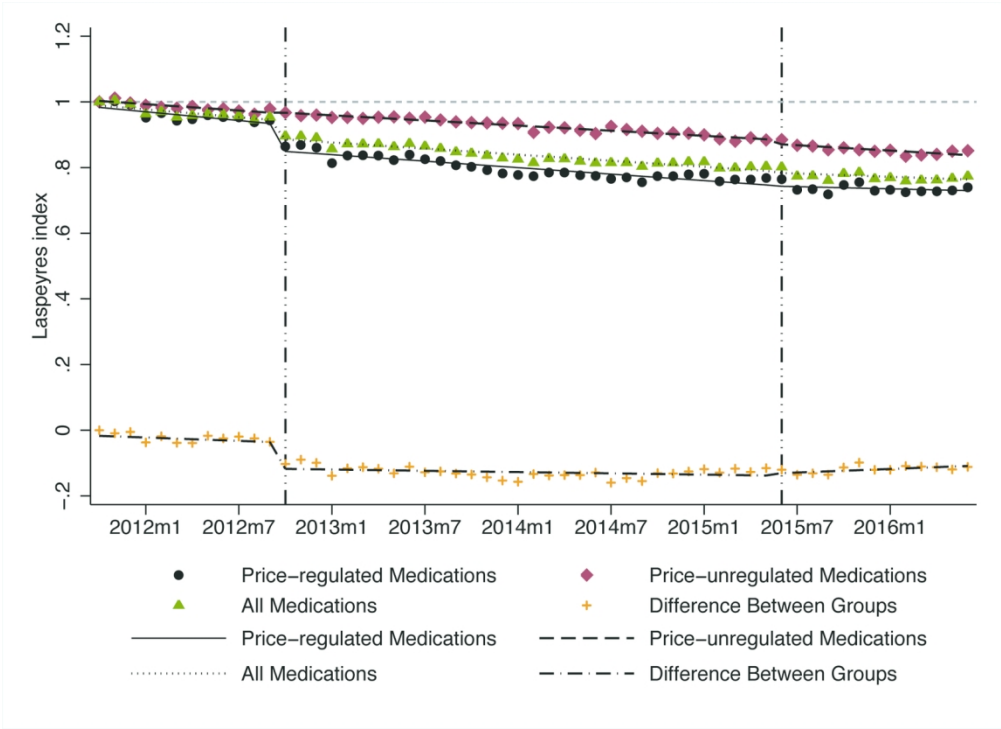

Figure 2. Influence of government price regulation and deregulation on monthly Laspeyres index (Lp) among price-regulated medications (n=30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between regulated and unregulated medications, 2011-2016.

139x101mm (300 x 300 DPI)

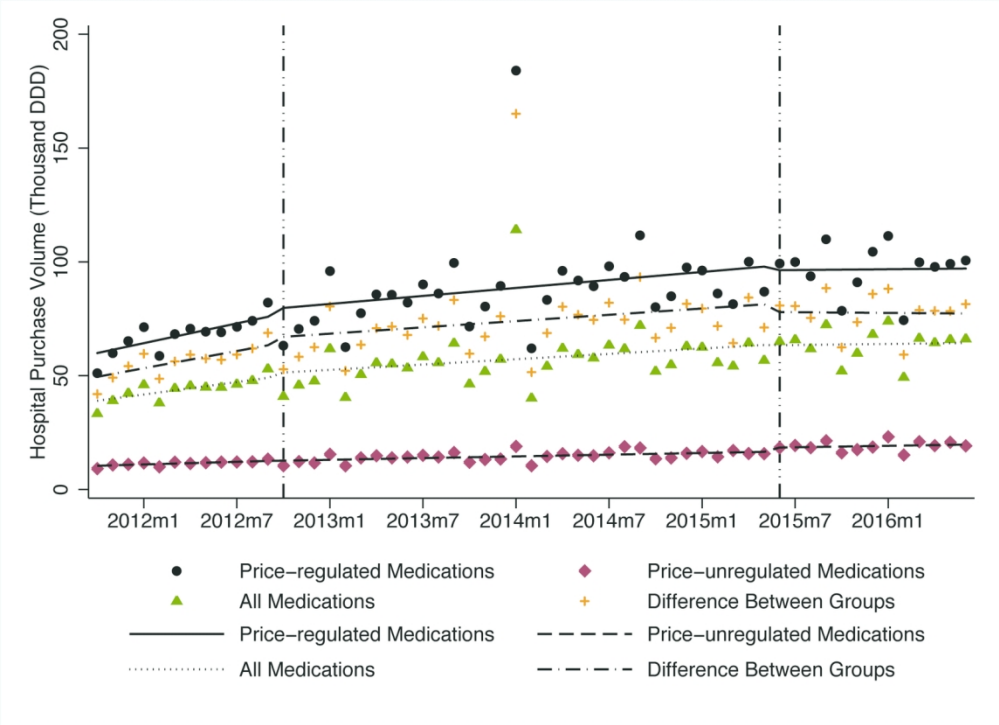

Figure 3. Influence of government price regulation and deregulation on monthly average purchase volumes among price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between groups, 2011-2016.

139x101mm (300 x 300 DPI)

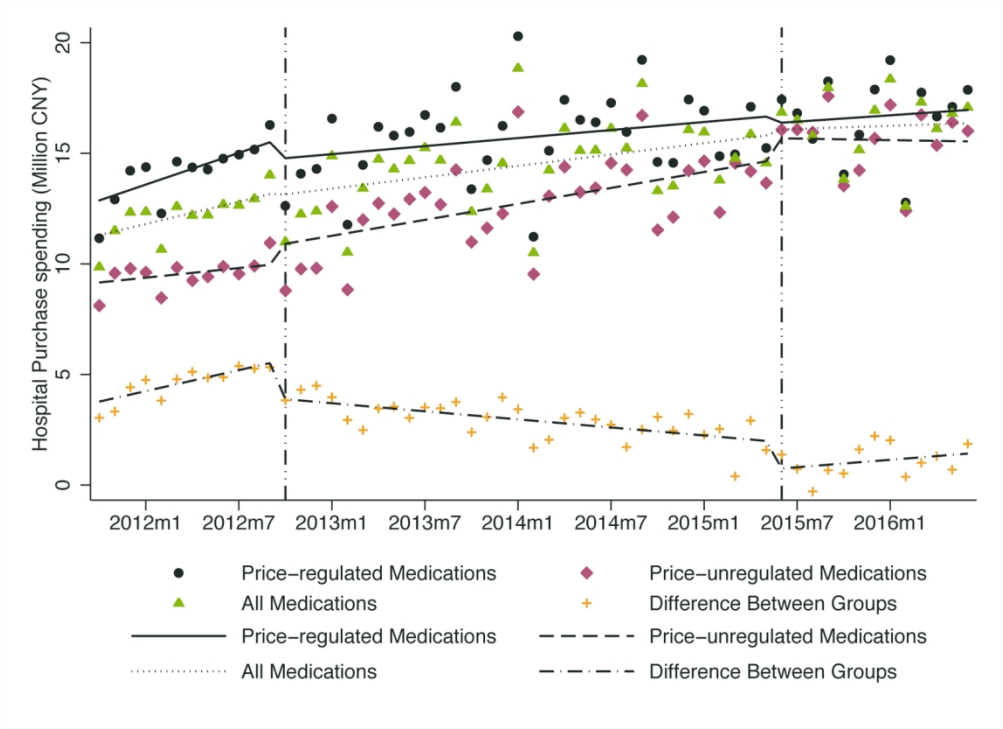

Figure 4. Influence of government price regulation and deregulation on monthly average spending on price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and difference between groups, 2011-2016.

139x101mm (300 x 300 DPI)

Appendix A Antineoplastic medications samples in the price-regulated and price-unregulated groups

Group	Generic name
Price-regulated medications (n=30)	aclarubicin; altretamine; asparaginase; bleomycin; busulfan; carboplatin; carmofur; carmustine; dacarbazine; daunorubicin; docetaxel; doxifluridine; epirubicin; etoposide; fludarabine; fluorouracil; gemcitabine; hydroxycamptothecin; lobaplatin; nedaplatin; nimustine; oxaliplatin; semustine; tegafur; tegafur, gimeracil and oteracil porassium; temozolomide; teniposide; topotecan; vindesine; vinorelbine.
Price-unregulated medications (n=22)	amsacrine; aminolevulinic acid; arsenite; bortezomib; cetuximab; decitabine; doxorubicin; erlotinib; fluorouracil; fluorouracil combinations; gefitinib; idarubicin; imatinib; raltitrexed; rituximab; sunitinib; sorafenib; thioguanine; nilotinib; trastuzumab; thiotepa; vinblastine.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract 【1】
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found 【2】
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported 【3】
Objectives	3	State specific objectives, including any prespecified hypotheses 【4】
Methods		
Study design	4	Present key elements of study design early in the paper 【4】
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection 【4】
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up 【N/A】 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls 【N/A】 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants 【N/A】
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed 【N/A】 *Case-control study*—For matched studies, give matching criteria and the number of controls per case 【N/A】
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable 【5】
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group 【4】
Bias	9	Describe any efforts to address potential sources of bias 【N/A】
Study size	10	Explain how the study size was arrived at 【N/A】
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why 【5】
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding 【5】
		(*b*) Describe any methods used to examine subgroups and interactions 【5】
		(*c*) Explain how missing data were addressed 【5】
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed 【N/A】 *Case-control study*—If applicable, explain how matching of cases and controls was addressed 【N/A】 *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy 【N/A】
		(*e*) Describe any sensitivity analyses 【N/A】

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed【N/A】
		(b) Give reasons for non-participation at each stage【N/A】
		(c) Consider use of a flow diagram【N/A】
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders【N/A】
		(b) Indicate number of participants with missing data for each variable of interest【N/A】
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)【N/A】
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time【N/A】
		Case-control study—Report numbers in each exposure category, or summary measures of exposure【N/A】
		Cross-sectional study—Report numbers of outcome events or summary measures【N/A】
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included【6-10】
		(*b*) Report category boundaries when continuous variables were categorized【6-10】
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period【N/A】
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses【6-10】
Discussion		
Key results	18	Summarise key results with reference to study objectives【10-11】
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias【11】
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence【11】
Generalisability	21	Discuss the generalisability (external validity) of the study results【11】
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based【12】

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Influence of Government Price Regulation and Deregulation on the Price of Antineoplastic Medications in China: A Controlled Interrupted Time Series Study

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Influence of Government Price Regulation and Deregulation on the Price of Antineoplastic Medications in China: A Controlled Interrupted Time Series Study

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Wushouer drafted the initial manuscript. All authors contributed to the critical revision of the manuscript and approved the final version.

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ABSTRACT

Background: In October 2012, the Chinese government established maximum retail prices for specific products, including 30 antineoplastic medications. Three years later, in June 2015, the government abolished price regulation for most medications, including all antineoplastic medications. This study examined the impacts of regulation and subsequent deregulation of prices of antineoplastic medications in China.

Methods: Using hospital procurement data and an interrupted time series (ITS) with comparison series design, we examined the impacts of the policy changes on relative purchase prices (Laspeyeres price index) and volumes, and spending on 52 antineoplastic medications in 699 hospitals. We identified three policy periods: prior to the initial price regulation (October 2011 to September 2012); during price regulation (October 2012 to June 2015); and after price deregulation (July 2015 to June 2016).

Results: During government price regulation, compared to price-unregulated cancer medications (n = 22 mostly newer targeted products), the relative price of price-regulated medications (n = 30 mostly chemotherapeutic products) decreased significantly (β = -0·081, P < 0·001). After the government price deregulation, no significant price change occurred. Neither government price regulation nor deregulation significantly impacted average volumes of or average spending on all antineoplastic medications immediately after the policy changes or in the longer term (P > 0·05).

Conclusion: Compared to unregulated antineoplastic, the prices of regulated antineoplastic medications decreased after setting price caps, but did not increase after deregulation. To control the rapid growth of oncology medication expenditures, more effective measures than price regulation through price caps for traditional chemotherapy are needed.

Strengths and limitations

- An interrupted time series (ITS) design, with two breakpoints was adopted to assess changes in price, volume of use, and spending following implementation of two price policies.
- The study adds value to the understanding of the effect of government regulation and deregulation on the prices of cancer medications.
- We were unable to obtain the full list of products under government price regulation since 1996, which could lead to selection bias.

- Given our use of aggregated hospital procurement data, we could not assess factors such as numbers of patients treated or appropriateness of use at a given level of medication spending or volume.

Introduction

Cancer medications account for the highest proportion of pharmaceutical spending among all therapeutic classes.[1] Rising cancer medication prices contribute to the rapid rise of medical and pharmaceutical expenditures, drawing criticism from leading academics, patients, cancer specialists, and policy experts.[2,3,4] In response, policy makers are implementing a variety of regulatory controls.[5]

International studies of the roles of regulation and competition in the pharmaceutical market have addressed various challenges and benefits of government price control policies, and results and perspectives are mixed.[6,7]. Srinivasan (2013) argues that the pharmaceutical market requires government regulation because of market failures,[8] such as information asymmetry and perverse incentives which affect pricing, professional behavior and competition.[9] Studies in a number of settings have found that direct price-cap government regulation can be effective in reducing medication prices. [10,11,12] However, researchers have reported favorable effects of generic market competition on medication prices[13,14] and argued that the high price of medications is due in part to interfering government controls.[15] In critics' eyes, government regulation, such as price caps, constitutes a barrier to dynamic competition in the generic market, resulting in consumers not being able benefit fully from competition on pharmaceutical prices.[16,17,18]

In China, the government has introduced complex medication price control policies to decrease medication prices. First, after the Urban Employee Basic Medical Insurance (UEBMI) was established in 1998, the National Development and Reform Commission (NDRC) was required to set a highest retail price using a cost-plus calculation for each medication listed in the National Reimbursement Drug List (NRDL).[19,20] And rules for price difference and price ratio of medicines were applied to convert a generic price into different prices for medicines with different dosage forms or specifications.[21] From 1998 to 2015, the NDRC used price caps to reduce drug prices for 31 times, involving 1029 medicines (not including traditional Chinese drugs) in terms of generic name.[22,23] In addition, because medication expenditures accounted for 40.4% of total health expenditures (in 2009) and almost 70% of medication sales were in hospitals (in 2013),[24,25] since 2010, provinces had to conduct a centralized bidding and tendering process to procure all hospital medications, with the intent to decrease prices and curb medication expenditures. [26]

In October 2012, the NDRC established maximum retail prices for specific products listed in the 2009 National Reimbursement List, including 36 antineoplastic medications.[27] Following the central government's requirement to limit regulatory controls in economic management, China loosened administrative controls over

medication prices and the NDRC formally abolished price ceiling policies in 2015.[28] Improvement in access to price-regulated medications after the 2012 price regulation and price increases after the 2015 government price deregulation were expected. However, the effects of government price regulation and deregulation on anticancer medications is unknown. We studied impacts of NDRC price regulation and deregulation on the relative prices and sales volumes and spending on antineoplastic medications in China.

Methods

Study design

We used the strongest quasi-experimental design, an interrupted time series (ITS) design, [29] with two breakpoints to assess changes following implementation of two price policies. The first breakpoint, October 2012, served to assess the effects of the government retail price regulation that was announced on September 14th, 2012 and came into effect on October 8th, 2012. The second breakpoint, June 2015, served to assess the effects of government retail price deregulation that was announced on May 4th, 2015 and came into effect on June 1st, 2015. To compare the effects of each policy intervention, we conducted analyses of medication groups for which 2012 price caps were and were not applied. The intervention group of medications had retail price caps as of October 2012 and the control group was without price caps throughout the study period. We use the term 'price-regulated medications' for the medicines that were under price regulation during the intervention period; these products are no longer price regulated. (Figure 1) We hypothesized that the impacts of price regulation or deregulation on purchase prices, volumes, and spending would differ between the two groups.

Figure 1. Timeline of price regulation and deregulation of 52 antineoplastic medications

Data source

Data on products purchased between October 2011 and June 2016 were extracted from the observational Chinese Medical Economic Information (CMEI) database of public hospital medication purchasing records.[30] We conducted a search of all antineoplastic medications in the database by ATC code (L01).[31] We excluded those antineoplastic medications with missing data and included antineoplastic medications regulated in

October 2012 as intervention group and antineoplastic medications not listed in the NDRL and thus not subject to price caps during the study period as control group. We extracted procurement data for 52 antineoplastic medications (30 medications with retail price caps from October 2012 to June 2015 and 22 medications without any price caps from the year before to the year after the price poly changes, between October 2011 and June 2016, Supplement 1A and 1B) from 699 public hospitals, including 476 tertiary hospitals, 217 secondary hospitals and 6 primary health facilities in 28 provinces. Data elements extracted for each product comprised the International Nonproprietary Name (INN), dosage form, strength, manufacturer, medication purchase price per package, monthly purchasing volumes and monthly hospital spending.

Outcome measures

The primary outcome was the Lp, an index formula used in price statistics for measuring the price development over time of baskets of goods and services consumed in the base period 0 by weighting prices by the volume purchased in period 0. [32] In this study, the Lp was calculated based on equation (1):

$$L_{pt} = \frac{\sum P_{ijt} Q_{ij0}}{\sum P_{ij0} Qij_0} \qquad (1)$$

where P_{ijt} stands for price of medication i with strength j in periods t, and Q_{ij0} stands for the volume for this medication used in period 0; P and Q were calculated in terms of Defined Daily Doses (DDD). The DDD used in this paper were the recommended daily amounts of each study medication based on dosage regimens recommended in the manufacturers' instructions, as approved by China Food and Drug Administration (CFDA). A Lp value of less than 1 means that the price of the basket of goods in a given period of time was lower than that in period 0, and an Lp greater 1 means that the basket price has increased from baseline. The currency of price and spending was Chinese Yuan (CNY).[33]

Other outcomes of interest were average monthly purchasing volumes (number of DDD) of and average monthly hospital spending (CNY) on the 30 price-regulated, 22 price-unregulated and all 52 pharmaceuticals. All price and spending data were adjusted to October 2011 prices using the consumer price index for health care.[34]

Statistical Analysis

We assessed outcomes over time for price-regulated medications (intervention group), price-unregulated medications (control group) and all 52 products together. We also modeled intervention effects using the monthly differences in the outcomes in the two groups to estimate the relative impacts of regulation and deregulation among the

regulated products, controlling for any other externalities that may have affected outcomes in the control group products.

ITS models were used to estimate levels and trends of the outcomes in the pre-intervention periods and changes in levels and trends in the post-intervention periods. ITS models with two interruption points were formulated to detect the effect on Lp, monthly average purchasing volumes and spending, as in equation (2):

$$Y_{it} = \beta_0 + \beta_1 \times time_t + \beta_2 \times regulation + \beta_3 \times reg\_trend + \beta_4 \times deregulation + \beta_5 \times der\_trend + \varepsilon_{it} \quad (2)$$

We used β_0 to estimate the baseline purchasing volume and spending; β_1 estimated the pre-regulation trend; β_2 estimated the change in level after the regulation policy; β_3 estimated the change in trend after the regulation policy; β_4 estimated the change in level after the deregulation policy; β_5 estimated the change in trend after the deregulation policy. Key coefficients were β_2, β_3, β_4 and β_5. To estimate the combined level and trend impacts of the policy changes, we calculated the absolute difference in Y_{it} at 12 months after regulation and after deregulation, respectively, compared to the counterfactual, that is, the estimated Y_{it} had the intervention not happened. [35]

We performed the Durbin-Watson test to estimate level of residual autocorrelations[36] and used the Cochrane-Orcutt auto-regression procedure to correct for first order serially correlated errors when needed.[37] All analyses were performed using Stata 14.0.[38]

Patient and public involvement

There were no patients and public involved in in the design or planning of the study.

Study Results

Influence of Government Pricing Policies on Relative Purchase Prices

The Lp declined over time in both intervention and control medication groups (that is, prices decreased relative to baseline) (Table 1, Figure 2). After government price regulation in October 2012, the Lp for price-regulated medications dropped suddenly (level change β = -0·082, P < 0·001), with significant declines in Lp relative to price-

unregulated medications (β = -0.081, P < 0·001). At 12 months after the regulation, there was an estimated reduction in the Lp for price-regulated medications of 0·058 (P < 0·05) and an estimated increase in the Lp for price-unregulated of 0·029 (P < 0·05).

After the government price deregulation in June 2015, the Lp for price-unregulated medications decreased significantly (level change β = -0·013, P < 0·05), but no significant discontinuities in Lp levels or trends were observed for the price-regulated medications or for the relative change compared to price-unregulated medications. At 12 months after price deregulation, there was no change in Lp for price regulated medications and an estimated reduction in the Lp for price-unregulated medications of 0·043 (P < 0·05).

Table 1. Results of interrupted time series analyses of the impacts of government price regulation and deregulation on Laspeyres Price Index, monthly average purchase volumes and spending for price-regulated, price-unregulated, and all antineoplastic medications, as well as group differences, 2011-2016

	Baseline level	Baseline trend	Post-regulation level change	Post-regulation trend change	Change at 12 months after regulation	Post-deregulation level change	Post-deregulation trend change	Change at 12 months after deregulation
Lp Price Index								
All medications	0·993***	-0·004*	-0·057***	0·001	-0·032	-0·005	0·001	-0·013
Price-regulated medications	0·988***	-0·004*	-0·082***	0·001	-0·058*	-0·003	0·002	0·000
Price-unregulated medications	1·006***	-0·003***	0·002	0·001	0·029*	-0·013*	0·000	-0·043*
Difference between groups	-0·015	-0·002	-0·081***	0·001	-0·071	0·005	0·002	0·043*
Hospital Purchase Volume (Thousand DDD)								
All medications	38·086***	0·915	1·938	-0·525	-4·881	-0·176	-0·311	-4·218
Price-regulated medications	58·502***	1·447	3·325	-0·862	-7·878	-1·605	-0·527	-8·455
Price-unregulated medications	10·242***	0·193	0·004	-0·068	-0·879	1·798	-0·017	1·573
Difference between groups	48·252***	1·258	3·273	-0·798	-7·097	-3·370	-0·510	-10·003
Hospital Purchase Spending (Million CNY)								
All medications	11·129***	0·168	-0·092	-0·083	-0·854	0·257	-0·063	-0·945
Price-regulated medications	12·628***	0·239	-0·778	-0·178	-2·821	-0·323	-0·013	-0·912
Price-unregulated medications	9·085***	0·073	0·832	0·048	1·806	1·052	-0·132	-0·992
Difference between groups	3·614***	0·158*	-1·570**	-0·219**	-4·508*	-1·301*	0·117	0·122

*, P ≤ 0·05; **, P ≤ 0·01; ***, P ≤ 0·001; price-regulated medications: 30 antineoplastic products with price regulation in 2012 and deregulation in 2015; price-unregulated medications: 22 antineoplastic products without price regulation or deregulation; DDD=defined daily doses; CNY = Chinese Yuan (1 CNY = 0·155 US$ in 2011)

Figure 2. Influence of government price regulation and deregulation on monthly Laspeyres index (Lp) among price-regulated medications (n=30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between regulated and unregulated medications, 2011-2016.

Influence of Government Pricing Policies on Average Purchase Volumes

The average volume purchased of all 52 antineoplastic medications, measured in DDD, rose from 33,370 DDD in October 2011 to 66,189 DDD in June 2016 (Table 1, Figure 3. There were no statistically significant changes in volume levels or trends after government price regulation or deregulation in any group.

Figure 3. Influence of government price regulation and deregulation on monthly average purchase volumes among price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between groups, 2011-2016.

Influence of Government Pricing Policies on Hospital Spending

Average hospital spending on all antineoplastic medications rose from 9.86 million CNY in October 2011 to 17.08 million CNY in June 2016 (Table 1, Figure 4). There were no statistically significant changes in spending levels or trends after government price regulation or deregulation in any of the groups. However, the spending on price-regulated medications decreased and spending on price-unregulated medications increased after both the regulation and deregulation policies, resulting in significant level and trend changes in the differences between the two groups. After government price regulation, the spending difference decreased suddenly (level change β = -1·570, P < 0.01) and increased somewhat more slowly (β = -0·219, P < 0.01) than in the baseline period. At 12 months after regulation, the absolute spending difference

between the groups was significantly lower (-4·508 mio CNY, $P < 0.05$) than would have been expected without the regulation.

After the deregulation policy was implemented, the spending difference dropped again (level change $\beta = -1{\cdot}301$, $P < 0.01$), although followed by an increasing trend ($\beta = 0{\cdot}117$, $P < 0{\cdot}05$). By the end of follow-up, the relative difference between groups had returned to nearly the level expected based on the trend at the time of the price regulation policy.

Figure 4. Influence of government price regulation and deregulation on monthly average spending on price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and difference between groups, 2011-2016.

Discussion

In this study, we investigated the effects of maximum retail price regulation and subsequent deregulation for groups of antineoplastic medications in China. We found that after setting maximum retail prices, the relative price of regulated products fell and that of price-unregulated products increased; the price of all study medications as a group decreased significantly compared to the 2011 baseline price; after government deregulation, no significant change occurred in either group. Neither setting maximum retail prices nor price deregulation significantly affected volumes purchased or spending on regulated or unregulated medications. However, compared to price-unregulated medications, spending on price-regulated medications dropped significantly after price regulation and deregulation.

Our results indicate that, as expected, a price-cap policy was effective in decreasing the prices of selected antineoplastic medications. Most medicines in the intervention group were products with intense market competition, possibly facilitating implementation of price caps. This might not be the case for originator products with only one supplier in the market. Such medicines were not price-regulated at the time. We have previously shown this effect for digestive system medications,[39] and others have found similar decreases in price for antihyperlipidemic agents.[40]

We did not find the expected price increase after deregulation for the price-regulated medications. This could be due to the fact that medication prices in China are also influenced by the provincial tendering system. Since 2009, the medication tendering process is conducted at the provincial level, with different assessment criteria, usually a composite score of product quality and price, to determine the winner.[41] Hence, the

tendering mechanism could have constrained medication price increases after government deregulation.[42] The provincial tendering process could also explain the price decreases in both groups observed prior to the national government price regulation. Further, generic entry, particularly for the older price-regulated cytotoxic medications, may explain why relative medication prices did not increase after government price deregulation. With the Chinese government encouraging the development of pharmaceutical enterprises, more generic medications have come to the market, which might improve the availability and the affordability of antineoplastic agents.[43]

We found no significant changes in purchase volumes or spending on either price-regulated or price-unregulated medications. When prices of regulated products decreased in comparison to price-unregulated products following the introduction of maximum retail prices, we did not observe a compensatory increase in the use of regulated products, but spending on products in the price-regulated group decreased. Medication utilization and spending were likely also affected by reimbursement policies, which restricted the total hospital spending on insurance-listed and price-regulated products but not on unregulated medications.[44,45]

Finally, prescribers may have maintained a preference for the newer, more expensive medications in the price-unregulated group.[46] Studies in China[47] and Italy[48], have shown that volume and medication utilization mix, rather than prices, determine overall medication expenditures. This may indicate that it is difficult to manage medication spending increases solely by regulating the prices of some medications in a therapeutic class. Before 2015, China's Drugs Price Addition Policy allowed hospitals to charge and keep 15% of the medication sales budget,[49] and hospitals were incentivized to preferentially prescribe higher priced products.[50] Since 2015, the zero mark-up policy which canceled the mark-up by public health facilities has been gradually introduced for all medications at all public hospitals, presumably eliminating these incentives to use more and higher-priced medications.[51] However, prescribing habits developed prior to the zero mark-up policy may still prevail.

Limitations

The study had some limitations. First, we were unable to obtain the full list of products under government price regulation since 1996, which could lead to selection bias.. Second, the inherent limitation of Laspeyres index may lead to underestimating the price decreases. However, the impact of this limitation was limited, since price elasticity of demand for medicines is relatively small. Third, the comparison group of

price-unregulated oncology medications tended to include newer, more expensive products than the price-regulated group and the two groups differed in other characteristics such as indications and therapeutic status in treatment. However, the Lp trends observed at baseline in the two groups of products were quite similar, suggesting that differential changes observed following the government pricing policies were indicative of true differences. Fourth, given that our analyses are based on procurement data we have not information on indications of use and potential therapeutic substitution. Fifth, some new antineoplastic drugs not included in the NRDL and thus not price-regulated may be made available by manufacturers' access programs (like buy 3 get 3 free) for individual patients. These products would not be part of our price, volume, or spending analyses because they would be transacted directly between individual physicians, their patients, and the manufacturer (or an intermediary). However, the number of patients who participated in access programs was limited and almost 70% of medication sales in China occur in hospitals.[52] Sixth, given our use of aggregated hospital procurement data, we could not assess factors such as the numbers of patients treated or appropriate use given levels of medication spending or volume.

Conclusion

Compared to unregulated antineoplastic, the prices of regulated antineoplastic medications decreased after setting price caps, but did not increase after deregulation. Neither of these policies affected volumes purchased or hospital spending on all antineoplastic medications. To control the rapid growth of oncology medication expenditures, more effective measures than setting price caps for selected (typically older) antineoplastic medications need to be taken.

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Competing Interests:

The authors declared no competing interests.

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Ethics approval and consent to participate

The study was considered not human subjects research by the Harvard Pilgrim Health Care Institutional Review Board.

Data availability statement

Data on products purchased between October 2011 and June 2016 were extracted from the observational Chinese Medical Economic Information (CMEI) database of public hospital medication purchasing records. However, this data are unavailable to the public due to its confidentiality.

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Referenc

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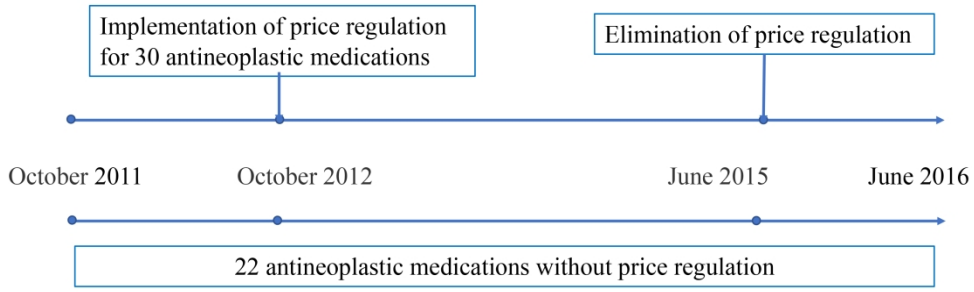

Figure 1. Timeline of price regulation and deregulation of 52 antineoplastic medications

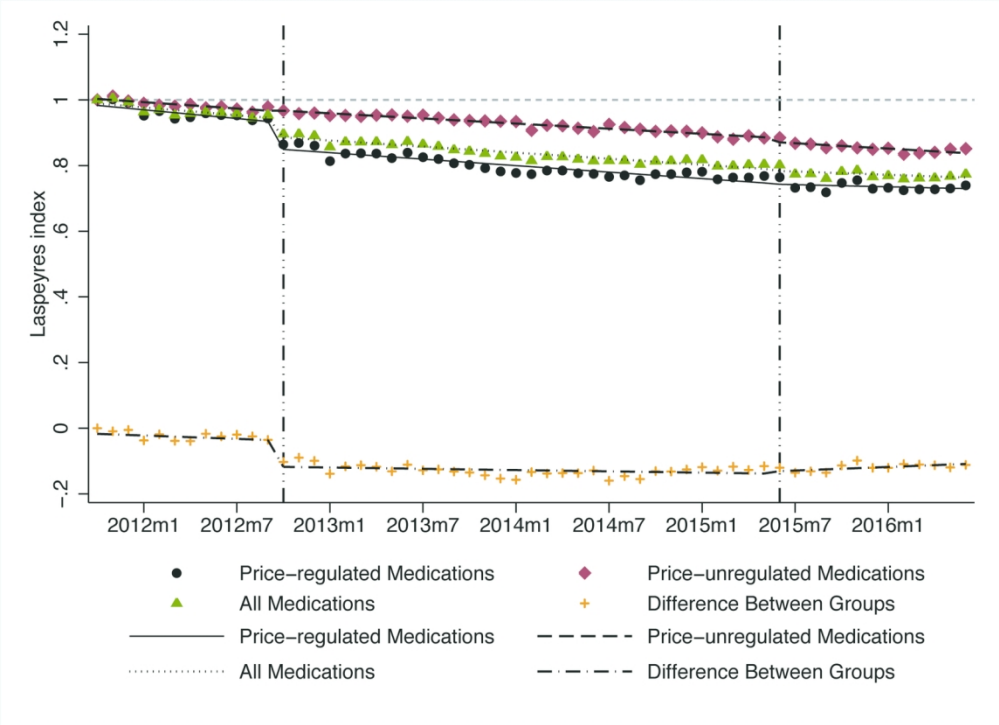

Figure 2. Influence of government price regulation and deregulation on monthly Laspeyres index (Lp) among price-regulated medications (n=30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between regulated and unregulated medications, 2011-2016.

139x101mm (300 x 300 DPI)

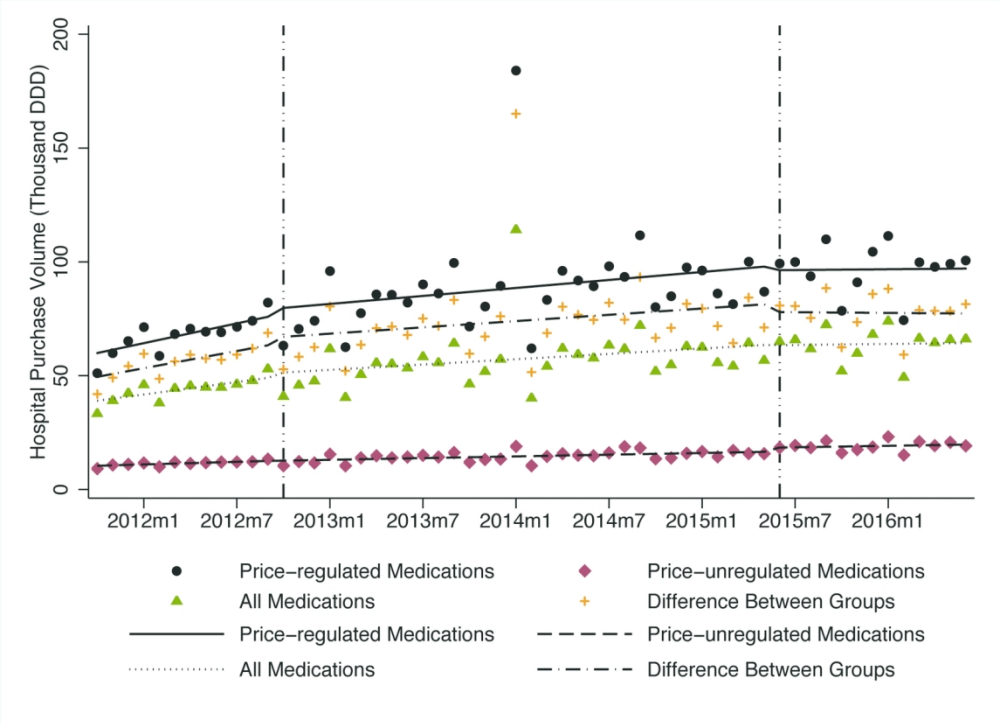

Figure 3. Influence of government price regulation and deregulation on monthly average purchase volumes among price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between groups, 2011-2016.

139x101mm (300 x 300 DPI)

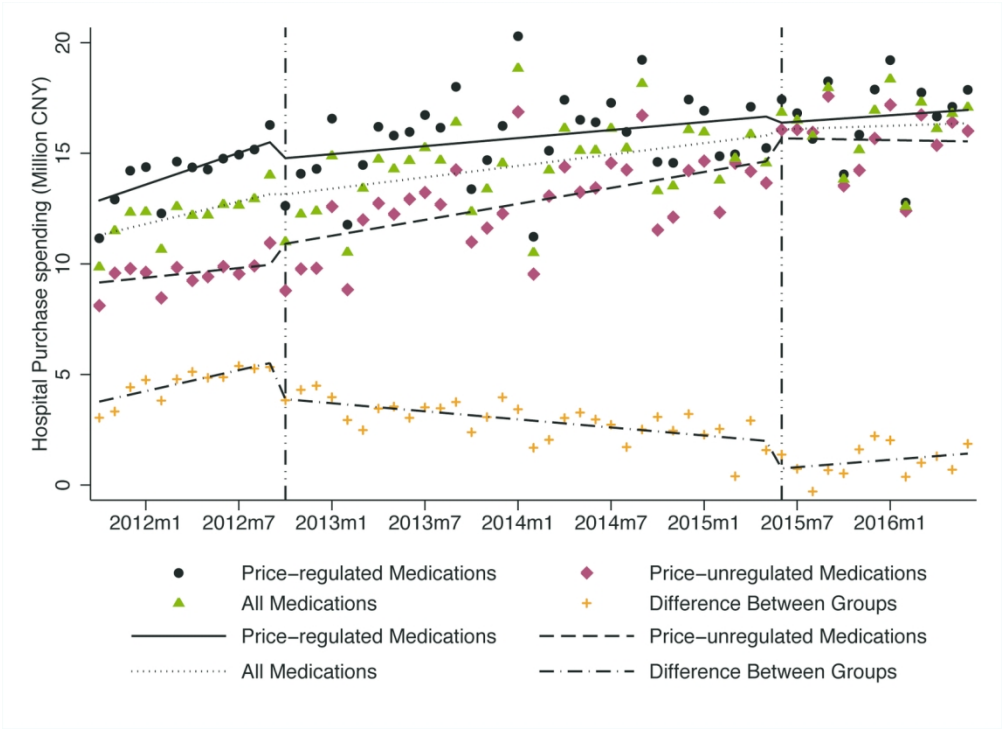

Figure 4. Influence of government price regulation and deregulation on monthly average spending on price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and difference between groups, 2011-2016.

139x101mm (300 x 300 DPI)

Supplement 1A. Antineoplastic medications samples of the intervention group

Generic Name	ATC	Classfication	Manufactures[1]	Indications Approved in China
aclarubicin	L01DB04	chemotherapy	originator only	acute leukemia; malignant lymphoma;
altretamine	L01XX03	chemotherapy	generic only	ovarian cancer; small cell lung cancer; malignant lymphoma; endometrial cancers;
asparaginase	L01XX02	chemotherapy	originator and generic	acute lymphoblastic leukemia, ALL; acute myeloid leukemia, AML; acute monocytic leukemia, AMOL; chronic myeloid leukemia, CML; Hodgkin's lymphoma; non-Hodgkin's lymphoma; melanoma;
bleomycin	L01DC01	chemotherapy	originator and generic	Cutaneous Carcinoma; head and neck cancer; lung cancer; esophageal cancer; malignant lymphoma; cervical carcinoma; neuroglioma; thyroid carcinoma;
busulfan	L01AB01	chemotherapy	originator only	chronic myeloid leukemia; Essential Thrombocythemia, polycythemia vera and other chronic myeloproliferative disorders, CMPDs
carboplatin	L01XA02	chemotherapy	originator and generic	ovarian cancer; small cell lung cancer; head and neck squamous cell carcinoma;
carmofur	L01BC04	chemotherapy	generic only	gastrointestinal cancer(colon cancer, colorectal cancer, gastric cancer, esophagus cancer); breast cancer;
carmustine	L01AD01	chemotherapy	generic only	encephaloma; brain metastases; meningeal leukemia; malignant lymphoma; multiple myeloma; malignant melanoma;
dacarbazine	L01AX04	chemotherapy	generic only	melanoma; soft tissue tumor; malignant lymphoma;

daunorubicin	L01DB02	chemotherapy	generic only	acute myeloid leukemia, AML; acute lymphoblastic leukemia, ALL;
docetaxel	L01CD02	chemotherapy	originator and generic	breast cancer; non-small cell lung cancer;
doxifluridine	/	chemotherapy	generic only	Breast cancer; gastric cancer; colorectal cancer; nasopharyngeal cancer;
epirubicin	L01DB03	chemotherapy	originator and generic	leukemia; malignant lymphoma; multiple myeloma; breast cancer; lung cancer; soft tissue tumor; gastric cancer; liver cancer; colorectal cancer; ovarian cancer;
etoposide	L01CB01	chemotherapy	generic only	small cell lung cancer; malignant lymphoma; leukemia; neuroblastoma; rhabdomyosarcom; gastric cancer; esophageal carcinoma; malignant germ cell tumor; ovarian cancer;
fludarabine	L01BB05	chemotherapy	originator and generic	chronic lymphocytic leukemia;
fluorouracil	L01BC02	chemotherapy	generic only	Gastrointestinal Cancer; chorionepithilioma; breast cancer; Ovarian Carcinoma; lung cancer; cervical carcinoma; bladder cancer; skin cancer;
gemcitabine	L01BC05	chemotherapy	originator and generic	non-small cell lung cancer; pancreatic cancer; breast cancer;
hydroxycamptothecin	/	chemotherapy	originator and generic	primary liver cancer; gastric cancer; bladder cancer; rectal cancer; head and neck epithelial cancer; leukemia and other malignant tumors
lobaplatin	/	chemotherapy	originator only	breast cancer; small cell lung cancer; chronic myeloid leukemia

nedaplatin	/	chemotherapy	generic only	Solid tumors such as head and neck cancer, small cell lung cancer, non-small cell lung cancer and esophageal cancer
nimustine	L01AD06	chemotherapy	originator and generic	brian tumor; gastrointestinal cancer; lung cancer; malignant lymphoma; chronic leukaemia;
oxaliplatin	L01XA03	chemotherapy	originator and generic	colorectal carcinoma; hepatocellular carcinoma, HCC;
semustine	L01AD03	chemotherapy	generic only	brain tumor; malignant lymphoma; gastric cancer; colon cancer; melanoma;
tegafur	L01BC03	chemotherapy	generic only	Gastrointestinal Cancer; breast cancer;
tegafur, gimeracil and oteracil porassium	L01BC53	chemotherapy	generic only	gastrointestinal cancer (gastric cancer; intestinal cancer; pancreatic cancer); breast cancer; liver cancer;
temozolomide	L01AX03	chemotherapy	originator and generic	glioblastoma multiforme, GBM; anaplastic astrocytoma;
teniposide	L01CB02	chemotherapy	originator and generic	malignant lymphoma; central nervous system-tumors; bladder cancer;
topotecan	L01XX17	chemotherapy	originator and generic	small cell lung cancer; ovarian cancer;
vindesine	L01CA03	chemotherapy	generic only	non-small cell lung cancer; small cell lung cancer; malignant lymphoma; breast cancer; esophageal carcinoma; malignant melanoma;
vinorelbine	L01CA04	chemotherapy	originator and generic	non-small cell lung cancer; breast cancer;

[1] Manufactures of specific medications during our study period.

Supplement 1B. Antineoplastic medications samples of the intervention group

Generic Name	ATC	Classfication	Manufactures[1]	Indications Approved in China
actinomycin D	L01DA01	chemotherapy	originator and generic	Hodgkin's disease; neuroblastoma; choriocarcinoma; testicular cancer; Wilm's tumor; Ewing's sarcoma; rhabdomyosarcoma;
amsacrine	L01XX01	chemotherapy	generic only	acute leukemia; malignant lymphoma;
arsenite	L01XX27	chemotherapy	generic only	acute promyelocytic leukemia, APL; liver cancer;
bortezomib	L01XX32	targeted therapy	originator and generic	multiple myeloma; mantle cell lymphoma;
cetuximab	L01XC06	targeted therapy	originator only	colorectal cancer;
decitabine	L01BC08	chemotherapy	originator and generic	myelodysplastic syndrome(MDS);
doxorubicin	L01DB01	chemotherapy	originator and generic	acute myeloid leukemia; lymphoma; soft tissue tumor and osteosarcoma; children malignant tumour; solid tumor in adults; particularly breast cancer and lung cancer;
erlotinib	L01XE03	targeted therapy	originator only	non-small cell lung cancer;
floxuridine	L01BC09	chemotherapy	generic only	liver cancer; rectum cancer; esophageal cancer; gastric cancer; breast cancer;lung cancer;
fluorouracil combinations	L01BC52	chemotherapy	generic only	gastrointestinal cancer; breast cancer; liver cancer;
gefitinib	L01XE02	targeted therapy	originator only	non-small cell lung cancer;
idarubicin	L01DB06	chemotherapy	originator only	acute myeloid leukemia, AML; acute lymphoblastic leukemia, ALL;

imatinib	L01XE01	targeted therapy	originator and generic	chronic myeloid leukemia, CML; gastrointestinal stromal tumors, GIST; acute lymphoblastic leukemia, ALL;
raltitrexed	L01BA03	chemotherapy	originator only	colorectal cancer;
rituximab	L01XC02	targeted therapy	originator only	follicle Center Lymphomas; follicular non-Hodgkin's lymphom; diffuse large B-cell lymphoma;
sunitinib	L01XE04	targeted therapy	originator only	renal cell cancer, RCC; gastrointestinal stromal tumors, GIST; pancreatic neuroendocrine tumors, pNET;
sorafenib	L01XE05	targeted therapy	originator only	renal cell cancer; hepatocellular carcinoma; thyroid cancer;
tioguanine	L01BB03	chemotherapy	generic only	acute lymphocytic leukemia; acute non-lymphocytic leukemia; chronic myeloid leukemia;
nilotinib	L01XE08	targeted therapy	originator only	chronic myeloid leukemia;
trastuzumab	L01XC03	targeted therapy	originator only	breast cancer; gastric cancer;
thiotepa	L01AC01	chemotherapy	generic only	breast cancer; ovarian cancer; bladder cancer; gastrointestinal cancer;
vinblastine	L01CA01	chemotherapy	generic only	acute leukemia; Hodgkin's lymphoma; malignant melanoma; breast cancer; bronchogenic carcinoma; soft tissue sarcoma; neuroblastoma;

[1] Manufactures of specific medications during our study period.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract 【1】
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found 【2】
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported 【3】
Objectives	3	State specific objectives, including any prespecified hypotheses 【4】
Methods		
Study design	4	Present key elements of study design early in the paper 【4】
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection 【4】
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up 【N/A】 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls 【N/A】 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants 【N/A】
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed 【N/A】 *Case-control study*—For matched studies, give matching criteria and the number of controls per case 【N/A】
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable 【5】
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group 【4】
Bias	9	Describe any efforts to address potential sources of bias 【N/A】
Study size	10	Explain how the study size was arrived at 【N/A】
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why 【5】
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding 【5】
		(*b*) Describe any methods used to examine subgroups and interactions 【5】
		(*c*) Explain how missing data were addressed 【5】
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed 【N/A】 *Case-control study*—If applicable, explain how matching of cases and controls was addressed 【N/A】 *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy 【N/A】
		(*e*) Describe any sensitivity analyses 【N/A】

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed【N/A】
		(b) Give reasons for non-participation at each stage【N/A】
		(c) Consider use of a flow diagram【N/A】
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders【N/A】
		(b) Indicate number of participants with missing data for each variable of interest【N/A】
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)【N/A】
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time【N/A】
		Case-control study—Report numbers in each exposure category, or summary measures of exposure【N/A】
		Cross-sectional study—Report numbers of outcome events or summary measures【N/A】
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included【6-10】
		(*b*) Report category boundaries when continuous variables were categorized【6-10】
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period【N/A】
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses【6-10】
Discussion		
Key results	18	Summarise key results with reference to study objectives【10-11】
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias【11】
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence【11】
Generalisability	21	Discuss the generalisability (external validity) of the study results【11】
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based【12】

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Influence of Government Price Regulation and Deregulation on the Price of Antineoplastic Medications in China: A Controlled Interrupted Time Series Study

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Primary Subject Heading:	Health policy
Secondary Subject Heading:	Health policy
Keywords:	Price Regulation, Deregulation, Laspeyres index, Antineoplastic Medications

Influence of Government Price Regulation and Deregulation on the Price of Antineoplastic Medications in China: A Controlled Interrupted Time Series Study

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Keywords: Price Regulation, Deregulation, Laspeyres index, Antineoplastic Medications

ABSTRACT

Background: In October 2012, the Chinese government established maximum retail prices for specific products, including 30 antineoplastic medications. Three years later, in June 2015, the government abolished price regulation for most medications, including all antineoplastic medications. This study examined the impacts of regulation and subsequent deregulation of prices of antineoplastic medications in China.

Methods: Using hospital procurement data and an interrupted time series (ITS) with comparison series design, we examined the impacts of the policy changes on relative purchase prices (Laspeyeres price index) and volumes of and spending on 52 antineoplastic medications in 699 hospitals. We identified three policy periods: prior to the initial price regulation (October 2011 to September 2012); during price regulation (October 2012 to June 2015); and after price deregulation (July 2015 to June 2016).

Results: During government price regulation, compared to price-unregulated cancer medications (n = 22, mostly newer targeted products), the relative price of price-regulated medications (n = 30, mostly chemotherapeutic products) decreased significantly (β = -0·081, $P < 0·001$). After the government price deregulation, no significant price change occurred. Neither government price regulation nor deregulation had a significant impact on average volumes of or average spending on all antineoplastic medications immediately after the policy changes or in the longer term ($P > 0·05$).

Conclusion: Compared to unregulated antineoplastics, the prices of regulated antineoplastic medications decreased after setting price caps and did not increase after deregulation. To control the rapid growth of oncology medication expenditures, more effective measures than price regulation through price caps for traditional chemotherapy are needed.

Strengths and limitations

- An interrupted time series (ITS) design, with two breakpoints was adopted to assess changes in price, volume of use, and spending following implementation of two price policies.
- The study adds value to the understanding of the effects of government regulation and deregulation on the prices of cancer medications.
- We were unable to obtain the full list of products under government price regulation since 1996, which could have led to selection bias.
- Given our use of aggregated hospital procurement data, we could not assess policy impacts on numbers of patients treated or appropriateness of use at a given level of medication spending or use.

Introduction

Cancer medications account for the highest proportion of pharmaceutical spending among all therapeutic classes.[1] Rising cancer medication prices contribute to the rapid rise of medical and pharmaceutical expenditures, drawing criticism from leading academics, patients, cancer specialists, and policy experts.[2,3,4] In response, policy makers are implementing a variety of regulatory controls.[5]

International studies of the roles of regulation and competition in pharmaceutical markets have addressed various challenges and benefits of government price control policies, from different perspectives.[6,7]. Srinivasan (2013) argues that the pharmaceutical market requires government regulation because of market failures,[8] such as information asymmetry and perverse incentives which affect pricing, professional behavior and competition.[9] Studies in a number of settings have found that direct price-cap government regulation can be effective in reducing medication prices. [10,11,12] However, researchers have reported favorable effects of unregulated generic market competition on medication prices[13,14] and argued that the high price of medications is due in part to interfering government controls.[15] In critics' eyes, government regulations, such as price caps, constitute a barrier to dynamic competition in the generics market, resulting in consumers not benefiting fully from competition on pharmaceutical prices.[16,17,18]

In China, the government has introduced complex medication price control policies to decrease medication prices. First, after the Urban Employee Basic Medical Insurance (UEBMI) was established in 1998, the National Development and Reform Commission (NDRC) was required to set a highest retail price using a cost-plus calculation for each medication listed in the National Reimbursement Drug List (NRDL).[19,20] Rules for price differences and price ratios of medicines were applied to convert a substance's price into different prices for medicines with different dosage forms or specifications.[21] From 1998 to 2015, the NDRC used price caps to reduce drug prices 31 times, involving 1029 substances (not including traditional Chinese medicines).[22,23] In addition, because medication expenditures accounted for 40.4% of total health expenditures (in 2009) and almost 70% of medication sales were in hospitals (in 2013),[24,25] since 2010, provinces had to conduct a centralized bidding and tendering process to procure all hospital medications, with the intent to decrease prices and curb medication expenditures. [26]

In October 2012, the NDRC established maximum retail prices for specific products listed in the 2009 National Reimbursement List, including 36 antineoplastic medications.[27] Following the central government's requirement to limit regulatory controls in economic management, China loosened administrative controls over medication prices and the NDRC formally abolished price ceiling policies in 2015.[28] Price decreases and increased use of price-regulated medications after the 2012 price regulation and price increases after the 2015 government price deregulation were expected. However, the effects of government price regulation and deregulation on anticancer medications is unknown. We studied the impacts of NDRC price regulation

and deregulation on the relative prices and sales volumes of and spending on antineoplastic medications in China.

Methods

Study design

We used the strongest quasi-experimental design, an interrupted time series (ITS) design, [29] with two breakpoints to assess changes following implementation of two price policies. The first breakpoint, October 2012, served to assess the effects of the government retail price regulation that was announced on September 14th, 2012 and came into effect on October 8th, 2012. The second breakpoint, June 2015, served to assess the effects of government retail price deregulation that was announced on May 4th, 2015 and came into effect on June 1st, 2015. To compare the effects of each policy intervention, we conducted analyses of medication groups for which 2012 price caps were and were not applied. The intervention group of medications had retail price caps since October 2012 and the control group was without price caps throughout the study period. We use the term 'price-regulated medications' for the medicines that were under price regulation during the intervention period; these products are no longer price regulated. (Figure 1) We hypothesized that the impacts of price regulation or deregulation on purchase prices, volumes, and spending would differ between the two groups.

Figure 1. Timeline of price regulation and deregulation of 52 antineoplastic medications

Data source

Data on products purchased between October 2011 and June 2016 were extracted from the observational Chinese Medical Economic Information (CMEI) database of public hospital medication purchasing records.[30] We conducted a search of all antineoplastic medications in the database by ATC code (L01).[31] We excluded those antineoplastic medications with missing data. We included antineoplastic medications that were regulated in October 2012 as intervention group. Antineoplastic medications which were not listed in the NDRL and thus not subject to price caps during the study period constituted the control group. We extracted procurement data for 52 antineoplastic medications (30 medications with retail price caps from October 2012 to June 2015 and 22 medications without any price caps from the year before to the year after the price policy changes, between October 2011 and June 2016, Supplement 1A and 1B) from 699 public hospitals, including 476 tertiary hospitals, 217 secondary hospitals and 6 primary health facilities in 28 of the 31 provinces in China. Aggregated procurement data was accessed to based on data elements in the dataset for each product comprised the International Nonproprietary Name (INN), dosage form, strength, manufacturer,

medication purchase price per package, monthly purchasing volumes and monthly hospital spending.

Outcome measures

The primary outcome was the Lp, an index formula used in price statistics for measuring the price development over time of baskets of goods and services consumed in the base period 0 by weighting prices by the volume purchased in period 0. [32] In this study, the Lp was calculated based on equation (1):

$$L_{pt} = \frac{\sum P_{ijt} Q_{ij0}}{\sum P_{ij0} Q i j_0} \qquad (1)$$

where P_{ijt} stands for price of medication i with strength j in periods t, and Q_{ij0} stands for the volume for this medication used in period 0; P and Q were calculated in terms of Defined Daily Doses (DDD). The DDD used in this paper were the recommended daily amounts of each study medication based on dosage regimens recommended in the manufacturers' instructions, as approved by China Food and Drug Administration (CFDA). A Lp value of less than 1 means that the price of the basket of goods in a given period of time was lower than that in period 0, and a Lp greater 1 means that the basket price has increased from baseline. The currency of price and spending was Chinese Yuan (CNY).[33]

Other outcomes of interest were average monthly purchasing volumes (number of DDD) of and average monthly hospital spending (CNY) on the 30 price-regulated, 22 price-unregulated and all 52 pharmaceuticals. All price and spending data were adjusted to October 2011 prices using the consumer price index for health care.[34]

Statistical Analysis

We assessed outcomes over time for price-regulated medications (intervention group), price-unregulated medications (control group) and all 52 products together. We also modeled intervention effects using the monthly differences in outcomes in the two groups to estimate the relative impacts of regulation and deregulation among the regulated products, controlling for any other externalities that may have affected outcomes in the control group products.

ITS models were used to estimate levels and trends of the outcomes in the pre-intervention periods and changes in levels and trends in the post-intervention periods. ITS models with two interruption points were formulated to detect the effect on Lp, monthly average purchasing volumes and spending, as in equation (2):

$$Y_{it} = \beta_0 + \beta_1 \times time_t + \beta_2 \times regulation + \beta_3 \times reg\_trend + \beta_4 \times deregulation + \beta_5 \times der\_trend + \varepsilon_{it} \quad (2)$$

We used β_0 to estimate the baseline purchasing volume and spending; β_1 estimated the pre-regulation trend; β_2 estimated the change in level after the regulation policy; β_3 estimated the change in trend after the regulation policy; β_4 estimated the change in level after the deregulation policy; β_5 estimated the change in trend after the deregulation policy. Key coefficients were β_2, β_3, β_4 and β_5. To estimate the combined level and trend impacts of the policy changes, we calculated the absolute difference in Y_{it} at 12 months after regulation and after deregulation, respectively, compared to the counterfactual, that is, the estimated Y_{it} had the intervention not happened. [35]

We performed the Durbin-Watson test to estimate level of residual autocorrelations[36] and used the Cochrane-Orcutt auto-regression procedure to correct for first order serially correlated errors when needed.[37] All analyses were performed using Stata 14.0.[38]

Patient and public involvement

There were no patients and public involved in in the design or planning of the study.

Study Results

Influence of Government Pricing Policies on Relative Purchase Prices

The Lp declined over time in both intervention and control medication groups (that is, prices decreased relative to baseline) (Table 1, Figure 2). After government price regulation in October 2012, the Lp for price-regulated medications dropped suddenly (level change β = -0·082, P < 0·001), with significant declines in Lp relative to price-unregulated medications (β = -0.081, P < 0·001). At 12 months after the regulation, there was an estimated reduction in the Lp for price-regulated medications of 0·058 (P < 0·05) and an estimated increase in the Lp for price-unregulated of 0·029 (P < 0·05).

After the government price deregulation in June 2015, the Lp for price-unregulated medications decreased significantly (level change β = -0·013, P < 0·05), but no significant discontinuities in Lp levels or trends were observed for the price-regulated medications or for the relative change compared to price-unregulated medications. At 12 months after price deregulation, there was no change in Lp for price regulated medications and an estimated reduction in the Lp for price-unregulated medications of 0·043 (P < 0·05).

Table 1. Results of interrupted time series analyses of the impacts of government price regulation and deregulation on Laspeyres Price Index, monthly average purchase volumes and spending for price-regulated, price-unregulated, and all antineoplastic medications, as well as group differences, 2011-2016

	Baseline level	Baseline trend	Post-regulation level change	Post-regulation trend change	Change at 12 months after regulation	Post-deregulation level change	Post-deregulation trend change	Change at 12 months after deregulation
Lp Price Index								
All medications	0·993***	-0·004*	-0·057***	0·001	-0·032	-0·005	0·001	-0·013
Price-regulated medications	0·988***	-0·004*	-0·082***	0·001	-0·058*	-0·003	0·002	0·000
Price-unregulated medications	1·006***	-0·003***	0·002	0·001	0·029*	-0·013*	0·000	-0·043*
Difference between groups	-0·015	-0·002	-0·081***	0·001	-0·071	0·005	0·002	0·043*
Hospital Purchase Volume (Thousand DDD)								
All medications	38·086***	0·915	1·938	-0·525	-4·881	-0·176	-0·311	-4·218
Price-regulated medications	58·502***	1·447	3·325	-0·862	-7·878	-1·605	-0·527	-8·455
Price-unregulated medications	10·242***	0·193	0·004	-0·068	-0·879	1·798	-0·017	1·573
Difference between groups	48·252***	1·258	3·273	-0·798	-7·097	-3·370	-0·510	-10·003
Hospital Purchase Spending (Million CNY)								
All medications	11·129***	0·168	-0·092	-0·083	-0·854	0·257	-0·063	-0·945
Price-regulated medications	12·628***	0·239	-0·778	-0·178	-2·821	-0·323	-0·013	-0·912
Price-unregulated medications	9·085***	0·073	0·832	0·048	1·806	1·052	-0·132	-0·992
Difference between groups	3·614***	0·158*	-1·570**	-0·219**	-4·508*	-1·301*	0·117	0·122

*, P ⩽ 0·05; **, P ⩽ 0·01; ***, P ⩽ 0·001; price-regulated medications: 30 antineoplastic products with price regulation in 2012 and deregulation in 2015; price-unregulated medications: 22 antineoplastic products without price regulation or deregulation; DDD=defined daily doses; CNY = Chinese Yuan (1 CNY = 0·155 US$ in 2011)

Figure 2. Influence of government price regulation and deregulation on monthly Laspeyres index (Lp) among price-regulated medications (n=30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between regulated and unregulated medications, 2011-2016.

Influence of Government Pricing Policies on Average Purchase Volumes

The average volume purchased of all 52 antineoplastic medications, measured in DDD, rose from 33,370 DDD in October 2011 to 66,189 DDD in June 2016 (Table 1, Figure 3. There were no statistically significant changes in volume levels or trends after government price regulation or deregulation in any group.

Figure 3. Influence of government price regulation and deregulation on monthly average purchase volumes among price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between groups, 2011-2016.

Influence of Government Pricing Policies on Hospital Spending

Average hospital spending on all antineoplastic medications rose from 9.86 million CNY in October 2011 to 17.08 million CNY in June 2016 (Table 1, Figure 4). There were no statistically significant changes in spending levels or trends after government price regulation or deregulation in any of the groups. However, the spending on price-regulated medications decreased and spending on price-unregulated medications increased after both the regulation and deregulation policies, resulting in significant level and trend changes in the differences between the two groups. After government price regulation, the spending difference decreased suddenly (level change $\beta = -1{\cdot}570$, $P < 0.01$) and increased somewhat more slowly ($\beta = -0{\cdot}219$, $P < 0.01$) than in the baseline period. At 12 months after regulation, the absolute spending difference between the groups was significantly lower (-4·508 million CNY, $P < 0.05$) than would have been expected without the regulation.

After the deregulation policy was implemented, the spending difference dropped again (level change $\beta = -1{\cdot}301$, $P < 0.01$), although followed by an increasing trend ($\beta = 0{\cdot}117$, $P < 0{\cdot}05$). By the end of follow-up, the relative difference between groups had returned to nearly the level expected based on the trend at the time of the price regulation policy.

Figure 4. Influence of government price regulation and deregulation on monthly average spending on price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and difference between groups, 2011-2016.

Discussion

In this study, we investigated the effects of maximum retail price regulation and subsequent deregulation for groups of antineoplastic medications in China. We found that after setting maximum retail prices, the relative price of regulated products fell and

that of price-unregulated products increased; the price of all studied medications as a group decreased significantly compared to the 2011 baseline price; after government deregulation, no significant change occurred in either group. Neither setting maximum retail prices nor price deregulation significantly affected volumes purchased or spending on regulated or unregulated medications. However, compared to price-unregulated medications, spending on price-regulated medications dropped significantly after price regulation and deregulation.

Our results indicate that, as expected, a price-cap policy was effective in decreasing the prices of selected antineoplastic medications. Most medicines in the intervention group were products with intense market competition, possibly facilitating implementation of price caps. We have previously shown this effect for digestive system medications,[39] and others have found similar decreases in price for antihyperlipidemic agents.[40] This might not be the case for originator products with only one supplier in the market. Such medicines were not price-regulated at the time.

We did not find the expected price increase after deregulation for the price-regulated medications. This could be due to the fact that medication prices in China are also influenced by the provincial tendering system. Since 2009, the medication tendering process is conducted at the provincial level, with different assessment criteria, usually a composite score of product quality and price, to determine the winner.[41] Hence, the tendering mechanism could have constrained medication price increases after government deregulation.[42] The provincial tendering process could also explain the price decreases in both groups observed prior to the national government price regulation. Further, generic entry, particularly for the older price-regulated cytotoxic medications, may explain why relative medication prices did not increase after government price deregulation. With the Chinese government encouraging the development of pharmaceutical enterprises, more generic medications have come to the market, which might improve the availability and the affordability of antineoplastic agents.[43]

We found no significant changes in purchase volumes or spending on either price-regulated or price-unregulated medications. When prices of regulated products decreased in comparison to price-unregulated products following the introduction of maximum retail prices, we did not observe a compensatory increase in the use of regulated products, but spending on products in the price-regulated group decreased. Medication utilization and spending were likely also affected by reimbursement policies, which restricted the total hospital spending on insurance-listed and price-regulated products but not on unregulated medications.[44,45]

Finally, prescribers may have maintained a preference for the newer, more expensive medications in the price-unregulated group.[46] Studies in China[47] and Italy[48], have shown that volume and medication utilization mix, rather than prices, determine overall medication expenditures. This may indicate that it is difficult to manage medication spending increases solely by regulating the prices of some medications in a therapeutic class. Before 2015, China's Drugs Price Mark-up Policy allowed hospitals to charge

and keep 15% of the medication sales budget,[49] and hospitals were incentivized to preferentially prescribe higher priced products.[50] Since 2015, the zero mark-up policy which bans mark-ups by public health facilities has been gradually introduced to all medications at all public hospitals, presumably eliminating these incentives to use more and higher-priced medications.[51] However, prescribing habits developed prior to the zero mark-up policy may still prevail.

Limitations

The study had some limitations. First, we were unable to obtain the full list of products under government price regulation since 1996, which could lead to selection bias. Second, an inherent limitation of the Laspeyres index may lead to underestimating price decreases. However, the impact of this limitation should be limited, since price elasticity of demand for medicines is relatively small. Third, the comparison group of price-unregulated oncology medications tended to include newer, more expensive products than the price-regulated group and the two groups differed in other characteristics such as indications and therapeutic status in treatment. However, the Lp trends observed at baseline in the two groups of products were quite similar, suggesting that differential changes observed following the government pricing policies were indicative of true differences. Fourth, given that our analyses are based on aggregated procurement data, we have no information on indications of use and potential therapeutic substitution and cannot assess impacts of individual product generic and brand status. Fifth, some new antineoplastic drugs are not included in the NRDL and thus are not price-regulated. These drugs may be made available by manufacturers' access programs ("buy 3 get 3 free") for individual patients. These products would not be part of our price, volume, or spending analyses because they would be transacted directly between individual physicians, their patients, and the manufacturer (or an intermediary). However, the number of patients who participate in access programs is limited and almost 70% of medication sales in China occur in hospitals.[52] Sixth, given our use of aggregated hospital procurement data, we could not assess factors such as the numbers of patients treated or appropriate use given levels of medication spending or volume.

Conclusion

Compared to unregulated antineoplastics, the prices of regulated antineoplastic medications decreased after setting price caps and did not increase after deregulation. Neither of these policies affected volumes purchased or hospital spending on antineoplastic medications. To control the rapid growth of oncology medication expenditures, more effective measures than setting price caps for selected (typically older) antineoplastic medications are needed.

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Competing Interests:

The authors declared no competing interests.

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Ethics approval and consent to participate

The study was considered non-human subjects research by the Harvard Pilgrim Health Care Institutional Review Board.

Data availability statement

Data on products purchased between October 2011 and June 2016 were extracted from the observational Chinese Medical Economic Information (CMEI) database of public hospital medication purchasing records. This data is unavailable to the public due to its confidentiality. Researchers interested in the data need to contact Chinese Pharmaceutical Association.

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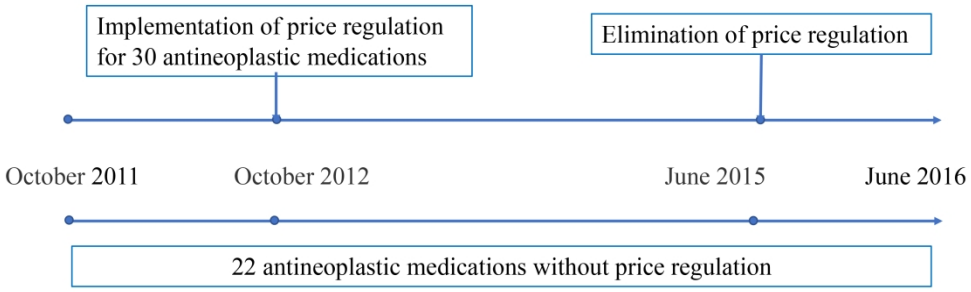

Figure 1. Timeline of price regulation and deregulation of 52 antineoplastic medications

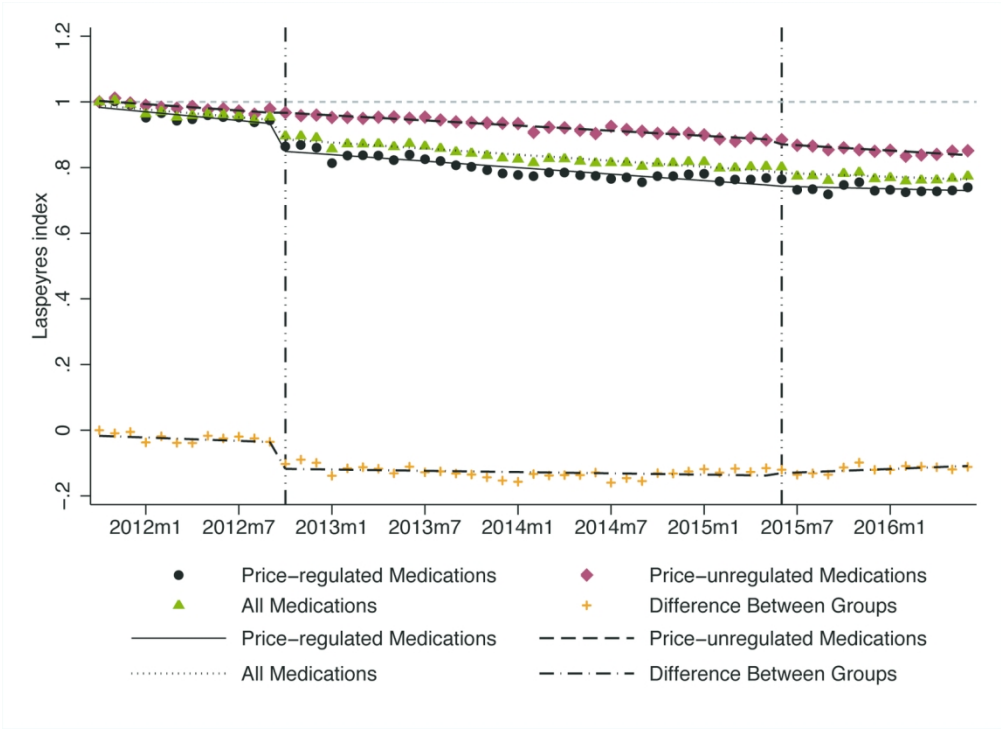

Figure 2. Influence of government price regulation and deregulation on monthly Laspeyres index (Lp) among price-regulated medications (n=30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between regulated and unregulated medications, 2011-2016.

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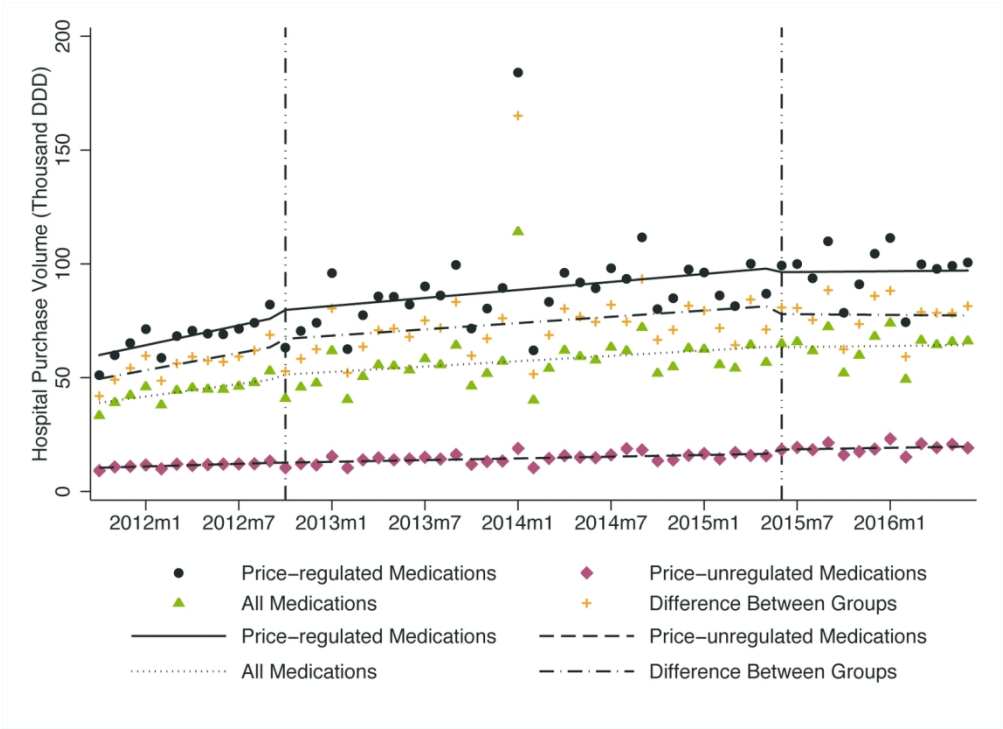

Figure 3. Influence of government price regulation and deregulation on monthly average purchase volumes among price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between groups, 2011-2016.

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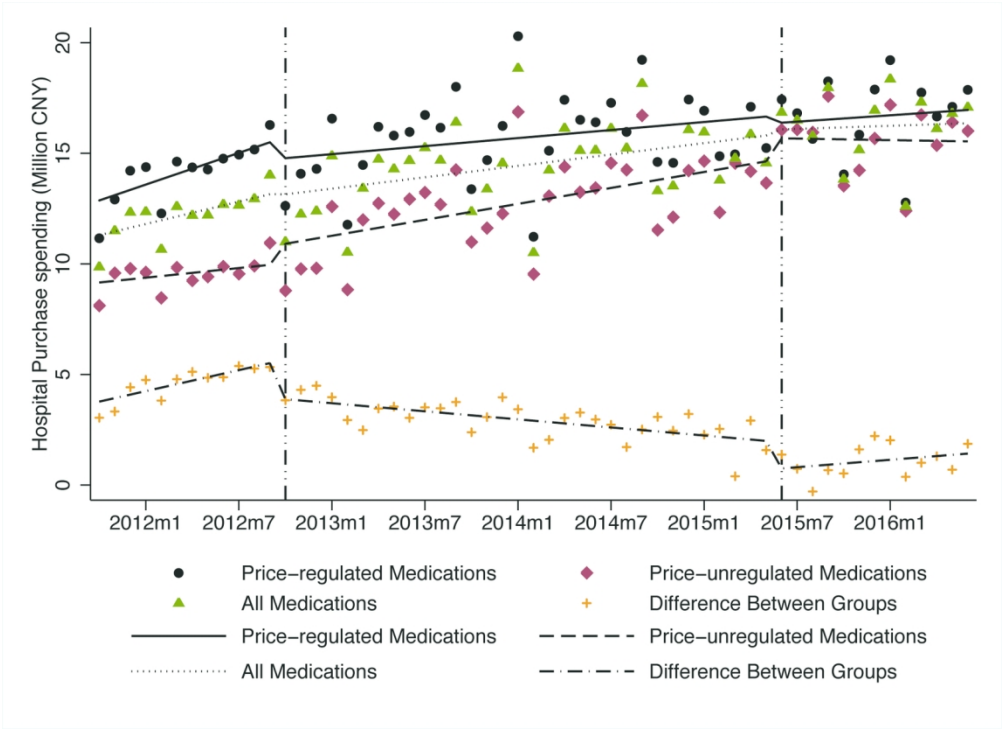

Figure 4. Influence of government price regulation and deregulation on monthly average spending on price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and difference between groups, 2011-2016.

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Supplement 1A. Antineoplastic medications samples of the intervention group

Generic Name	ATC	Classfication	Manufactures[1]	Indications Approved in China
aclarubicin	L01DB04	chemotherapy	originator only	acute leukemia; malignant lymphoma;
altretamine	L01XX03	chemotherapy	generic only	ovarian cancer; small cell lung cancer; malignant lymphoma; endometrial cancers;
asparaginase	L01XX02	chemotherapy	originator and generic	acute lymphoblastic leukemia, ALL; acute myeloid leukemia, AML; acute monocytic leukemia, AMOL; chronic myeloid leukemia, CML; Hodgkin's lymphoma; non-Hodgkin's lymphoma; melanoma;
bleomycin	L01DC01	chemotherapy	originator and generic	Cutaneous Carcinoma; head and neck cancer; lung cancer; esophageal cancer; malignant lymphoma; cervical carcinoma; neuroglioma; thyroid carcinoma;
busulfan	L01AB01	chemotherapy	originator only	chronic myeloid leukemia; Essential Thrombocythemia, polycythemia vera and other chronic myeloproliferative disorders, CMPDs
carboplatin	L01XA02	chemotherapy	originator and generic	ovarian cancer; small cell lung cancer; head and neck squamous cell carcinoma;
carmofur	L01BC04	chemotherapy	generic only	gastrointestinal cancer(colon cancer, colorectal cancer, gastric cancer, esophagus cancer); breast cancer;
carmustine	L01AD01	chemotherapy	generic only	encephaloma; brain metastases; meningeal leukemia; malignant lymphoma; multiple myeloma; malignant melanoma;
dacarbazine	L01AX04	chemotherapy	generic only	melanoma; soft tissue tumor; malignant lymphoma;

daunorubicin	L01DB02	chemotherapy	generic only	acute myeloid leukemia, AML; acute lymphoblastic leukemia, ALL;
docetaxel	L01CD02	chemotherapy	originator and generic	breast cancer; non-small cell lung cancer;
doxifluridine	/	chemotherapy	generic only	Breast cancer; gastric cancer; colorectal cancer; nasopharyngeal cancer;
epirubicin	L01DB03	chemotherapy	originator and generic	leukemia; malignant lymphoma; multiple myeloma; breast cancer; lung cancer; soft tissue tumor; gastric cancer; liver cancer; colorectal cancer; ovarian cancer;
etoposide	L01CB01	chemotherapy	generic only	small cell lung cancer; malignant lymphoma; leukemia; neuroblastoma; rhabdomyosarcom; gastric cancer; esophageal carcinoma; malignant germ cell tumor; ovarian cancer;
fludarabine	L01BB05	chemotherapy	originator and generic	chronic lymphocytic leukemia;
fluorouracil	L01BC02	chemotherapy	generic only	Gastrointestinal Cancer; chorionepithilioma; breast cancer; Ovarian Carcinoma; lung cancer; cervical carcinoma; bladder cancer; skin cancer;
gemcitabine	L01BC05	chemotherapy	originator and generic	non-small cell lung cancer; pancreatic cancer; breast cancer;
hydroxycamptothecin	/	chemotherapy	originator and generic	primary liver cancer; gastric cancer; bladder cancer; rectal cancer; head and neck epithelial cancer; leukemia and other malignant tumors
lobaplatin	/	chemotherapy	originator only	breast cancer; small cell lung cancer; chronic myeloid leukemia

nedaplatin	/	chemotherapy	generic only	Solid tumors such as head and neck cancer, small cell lung cancer, non-small cell lung cancer and esophageal cancer
nimustine	L01AD06	chemotherapy	originator and generic	brian tumor; gastrointestinal cancer; lung cancer; malignant lymphoma; chronic leukaemia;
oxaliplatin	L01XA03	chemotherapy	originator and generic	colorectal carcinoma; hepatocellular carcinoma, HCC;
semustine	L01AD03	chemotherapy	generic only	brain tumor; malignant lymphoma; gastric cancer; colon cancer; melanoma;
tegafur	L01BC03	chemotherapy	generic only	Gastrointestinal Cancer; breast cancer;
tegafur, gimeracil and oteracil porassium	L01BC53	chemotherapy	generic only	gastrointestinal cancer (gastric cancer; intestinal cancer; pancreatic cancer); breast cancer; liver cancer;
temozolomide	L01AX03	chemotherapy	originator and generic	glioblastoma multiforme, GBM; anaplastic astrocytoma;
teniposide	L01CB02	chemotherapy	originator and generic	malignant lymphoma; central nervous system-tumors; bladder cancer;
topotecan	L01XX17	chemotherapy	originator and generic	small cell lung cancer; ovarian cancer;
vindesine	L01CA03	chemotherapy	generic only	non-small cell lung cancer; small cell lung cancer; malignant lymphoma; breast cancer; esophageal carcinoma; malignant melanoma;
vinorelbine	L01CA04	chemotherapy	originator and generic	non-small cell lung cancer; breast cancer;

[1] Manufactures of specific medications during our study period.

Supplement 1B. Antineoplastic medications samples of the control group

Generic Name	ATC	Classfication	Manufactures[1]	Indications Approved in China
actinomycin D	L01DA01	chemotherapy	originator and generic	Hodgkin's disease; neuroblastoma; choriocarcinoma; testicular cancer; Wilm's tumor; Ewing's sarcoma; rhabdomyosarcoma;
amsacrine	L01XX01	chemotherapy	generic only	acute leukemia; malignant lymphoma;
arsenite	L01XX27	chemotherapy	generic only	acute promyelocytic leukemia, APL; liver cancer;
bortezomib	L01XX32	targeted therapy	originator and generic	multiple myeloma; mantle cell lymphoma;
cetuximab	L01XC06	targeted therapy	originator only	colorectal cancer;
decitabine	L01BC08	chemotherapy	originator and generic	myelodysplastic syndrome(MDS);
doxorubicin	L01DB01	chemotherapy	originator and generic	acute myeloid leukemia; lymphoma; soft tissue tumor and osteosarcoma; children malignant tumour; solid tumor in adults; particularly breast cancer and lung cancer;
erlotinib	L01XE03	targeted therapy	originator only	non-small cell lung cancer;
floxuridine	L01BC09	chemotherapy	generic only	liver cancer; rectum cancer; esophageal cancer; gastric cancer; breast cancer;lung cancer;
fluorouracil combinations	L01BC52	chemotherapy	generic only	gastrointestinal cancer; breast cancer; liver cancer;
gefitinib	L01XE02	targeted therapy	originator only	non-small cell lung cancer;
idarubicin	L01DB06	chemotherapy	originator only	acute myeloid leukemia, AML; acute lymphoblastic leukemia, ALL;

imatinib	L01XE01	targeted therapy	originator and generic	chronic myeloid leukemia, CML; gastrointestinal stromal tumors, GIST; acute lymphoblastic leukemia, ALL;
raltitrexed	L01BA03	chemotherapy	originator only	colorectal cancer;
rituximab	L01XC02	targeted therapy	originator only	follicle Center Lymphomas; follicular non-Hodgkin's lymphom; diffuse large B-cell lymphoma;
sunitinib	L01XE04	targeted therapy	originator only	renal cell cancer, RCC; gastrointestinal stromal tumors, GIST; pancreatic neuroendocrine tumors, pNET;
sorafenib	L01XE05	targeted therapy	originator only	renal cell cancer; hepatocellular carcinoma; thyroid cancer;
tioguanine	L01BB03	chemotherapy	generic only	acute lymphocytic leukemia; acute non-lymphocytic leukemia; chronic myeloid leukemia;
nilotinib	L01XE08	targeted therapy	originator only	chronic myeloid leukemia;
trastuzumab	L01XC03	targeted therapy	originator only	breast cancer; gastric cancer;
thiotepa	L01AC01	chemotherapy	generic only	breast cancer; ovarian cancer; bladder cancer; gastrointestinal cancer;
vinblastine	L01CA01	chemotherapy	generic only	acute leukemia; Hodgkin's lymphoma; malignant melanoma; breast cancer; bronchogenic carcinoma; soft tissue sarcoma; neuroblastoma;

[1] Manufactures of specific medications during our study period.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract 【1】
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found 【2】
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported 【3】
Objectives	3	State specific objectives, including any prespecified hypotheses 【4】
Methods		
Study design	4	Present key elements of study design early in the paper 【4】
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection 【4】
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up 【N/A】 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls 【N/A】 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants 【N/A】
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed 【N/A】 *Case-control study*—For matched studies, give matching criteria and the number of controls per case 【N/A】
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable 【5】
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group 【4】
Bias	9	Describe any efforts to address potential sources of bias 【N/A】
Study size	10	Explain how the study size was arrived at 【N/A】
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why 【5】
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding 【5】
		(*b*) Describe any methods used to examine subgroups and interactions 【5】
		(*c*) Explain how missing data were addressed 【5】
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed 【N/A】 *Case-control study*—If applicable, explain how matching of cases and controls was addressed 【N/A】 *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy 【N/A】
		(*e*) Describe any sensitivity analyses 【N/A】

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed【N/A】
		(b) Give reasons for non-participation at each stage【N/A】
		(c) Consider use of a flow diagram【N/A】
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders【N/A】
		(b) Indicate number of participants with missing data for each variable of interest【N/A】
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)【N/A】
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time【N/A】
		Case-control study—Report numbers in each exposure category, or summary measures of exposure【N/A】
		Cross-sectional study—Report numbers of outcome events or summary measures【N/A】
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included【6-10】
		(*b*) Report category boundaries when continuous variables were categorized【6-10】
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period【N/A】
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses【6-10】
Discussion		
Key results	18	Summarise key results with reference to study objectives【10-11】
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias【11】
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence【11】
Generalisability	21	Discuss the generalisability (external validity) of the study results【11】
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based【12】

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.