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

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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.

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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, 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 ($\beta = -0.081$, $P < 0.001$). After the government price deregulation, the relative price of price-unregulated medications decreased significantly ($\beta = -0.013$, $P < 0.05$).

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 (L_p) 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 code²⁰ 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 L_p , 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 L_p was calculated based on equation (1):

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

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 L_p 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 L_p , 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,

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3 compared to the counterfactual, that is, the estimated Y_{it} had the intervention not
4 happened.^{18, 24}

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6 We performed the Durbin-Watson test to estimate level of residual autocorrelations²⁵
7 and used the Cochrane-Orcutt auto-regression procedure to correct for first order
8 serially correlated errors when needed.²⁶ All analyses were performed using Stata
9 14.0.²⁷
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12 **Study Results**

13 **Influence of Government Pricing Policies on Relative Purchase Prices**

14 The Lp declined over time in both intervention and control medication groups (that is,
15 prices decreased relative to baseline) from October 2011 to June 2016 (Table 2,
16 Figure 2). After government price regulation in October 2012, the Lp for
17 price-regulated medications dropped suddenly ($\beta = -0.082$, $P < 0.001$), with
18 significant declines in Lp relative to price-unregulated medications ($\beta = -0.081$, $P <$
19 0.001). At 12 months after the regulation, there was an estimated reduction in the Lp
20 for price-regulated medications of 0.058 ($P < 0.05$) and an estimated increase in the
21 Lp for price-unregulated of 0.029 ($P < 0.05$).
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24 After the government price deregulation in June 2015, the Lp for price-unregulated
25 medications decreased significantly ($\beta = -0.013$, $P < 0.05$), but no significant
26 discontinuities in Lp levels or trends were observed for the price-regulated
27 medications or for their relative change compared to price-unregulated medications.
28 At 12 months after price deregulation, there was no change in Lp for price regulated
29 medications and an estimated reduction in the Lp for price-unregulated medications of
30 0.043 ($P < 0.05$).
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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

*, $P \leq 0.05$; **, $P \leq 0.01$; ***, $P \leq 0.001$; 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,

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3 Figure 3. There were no statistically significant changes in volume levels or trends
4 after government price regulation or deregulation in any group.
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7 Figure 3. Influence of government price regulation and deregulation on monthly
8 average purchase volumes among price-regulated medications (n = 30),
9 price-unregulated medications (n = 22), all medications (n = 52), and the difference
10 between groups, 2011-2016.
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13 **Influence of Government Pricing Policies on Hospital Spending**

14 Average hospital spending on all antineoplastic medications rose from 9.86 million
15 CNY in October 2011 to 17.08 million CNY in June 2016 (Table 2, Figure 4). There
16 were no statistically significant changes in spending levels or trends after government
17 price regulation or deregulation in any of the groups. However, the spending on
18 price-regulated medications decreased and spending on price-unregulated medications
19 increased after both the regulation and deregulation policies, resulting in significant
20 level and trend changes in the differences between the two groups. After government
21 price regulation, the spending difference decreased suddenly ($\beta = -1.570$, $P < 0.01$)
22 and increased somewhat more slowly ($\beta = -0.219$, $P < 0.01$) than the baseline period.
23 At 12 months after regulation, the absolute spending difference between the groups
24 was significantly lower (-4.508 , $P < 0.05$) than would have been expected without the
25 regulation.
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28 After the deregulation policy was implemented, the spending difference dropped
29 again ($\beta = -1.301$, $P < 0.01$), although followed by an increasing trend ($\beta = 0.117$, $P <$
30 0.05). By the end of follow-up, the relative difference between groups had returned to
31 nearly the level expected based on trends at the time of the price deregulation policy.
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37 Figure 4. Influence of government price regulation and deregulation on monthly
38 average spending on price-regulated medications (n = 30), price-unregulated
39 medications (n = 22), all medications (n = 52), and difference between groups,
40 2011-2016.
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44 **Discussion**

45 In this study, we investigated the effects of government price regulation and
46 subsequent deregulation for groups of antineoplastic medications in China. We found
47 that after government price regulation, the relative price of regulated products fell
48 more than that of price-unregulated products, and the price of all study medications as
49 a group decreased significantly compared to the 2011 baseline price; after government
50 deregulation, the relative price level of price-unregulated medications decreased.
51 Neither government price regulation nor deregulation significantly affected volumes
52 purchased or spending on regulated or unregulated medications. However, compared
53 to price-unregulated medications, spending on price-regulated medications dropped
54 significantly after price regulation and deregulation.
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58 Our results indicate that, as expected, price regulation was effective in decreasing the
59 price of antineoplastic medications; we have previously shown this effect for
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3 digestive system medications,²⁸ and others have found similar decreases in price for
4 antihyperlipidemic agents.²⁹ We did not find the expected price increase after
5 deregulation for the price-regulated medications. This could be due to the fact that
6 medication prices in China are also influenced by the provincial tendering system.³⁰
7 Since 2009, the medication tendering process is conducted at the provincial level,
8 with different assessment criteria, usually a composite score of product quality and
9 price, to determine the winner.³¹ Hence, the tendering mechanism could have
10 constrained medication price increases after government deregulation.³² The
11 provincial tendering process could also explain the price decreases in both groups
12 observed prior to the national government price regulation. Further, generic entry,
13 particularly for the older price-regulated cytotoxic medications, may explain why
14 relative medication prices did not increase after government price deregulation. With
15 the Chinese government encouraging the development of pharmaceutical enterprises,
16 more generic medications have come to the market, which might improve the
17 availability and the affordability of antineoplastic agents.³³

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

32 Finally, prescribers may have maintained a preference for the newer, more expensive
33 medications in the price-unregulated group.³⁶ Studies in China³⁷, Korea^{Error! Bookmark}
34 not defined. and Italy³⁸, have shown that volume and medication mix, rather than prices,
35 determine overall medication expenditures. This may indicate that it is difficult to
36 manage medication spending increases solely by regulating the prices of some
37 medications in a therapeutic class. Before 2015, China's Drugs Price Addition Policy
38 allowed hospitals to charge and keep 15% of the medication sales budget,³⁹ and
39 hospitals were incentivized to preferentially prescribe higher priced products.⁴⁰ Since
40 2015, the zero mark-up policy has been gradually introduced for all medications at all
41 public hospitals, presumably eliminating these incentives to use more and
42 higher-priced medications.⁴¹ However, prescribing habits developed prior to the zero
43 mark-up policy may still prevail.

50 **Limitations**

51 The study had some limitations. First, we were unable to obtain the full list of
52 products under government price regulation since 1996, which could lead to selection
53 bias. However, the 30 price-regulated antineoplastic products studied are likely
54 representative of all such products. Second, the comparison group of
55 price-unregulated oncology medications tended to include newer, more expensive
56 products than the price-regulated group. However, the Lp trends observed at baseline
57 in the two groups of products were quite similar, suggesting that differential changes
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3 observed following the government pricing policies were indicative of true
4 differences. Third, given our use of aggregated hospital procurement data, we could
5 not assess factors such as the numbers of patients treated within a given level of
6 medication spending or volume.
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10 11 **Conclusion**

12 Compared to unregulated products, the prices of antineoplastic medications decreased
13 after government price regulation, but did not increase after deregulation. Neither of
14 the two price regulation policies affected volumes purchased or hospital spending on
15 all antineoplastic medications. To control the rapid growth of oncology medication
16 expenditures, more effective measures than price regulation of selected (typically
17 older) antineoplastic medications need to be taken.
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38 **Ethics approval and consent to participate**

39 The study was considered not human subjects research by the Harvard Pilgrim Health
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Figure 1. Timeline of price regulation and deregulation of 52 antineoplastic medications

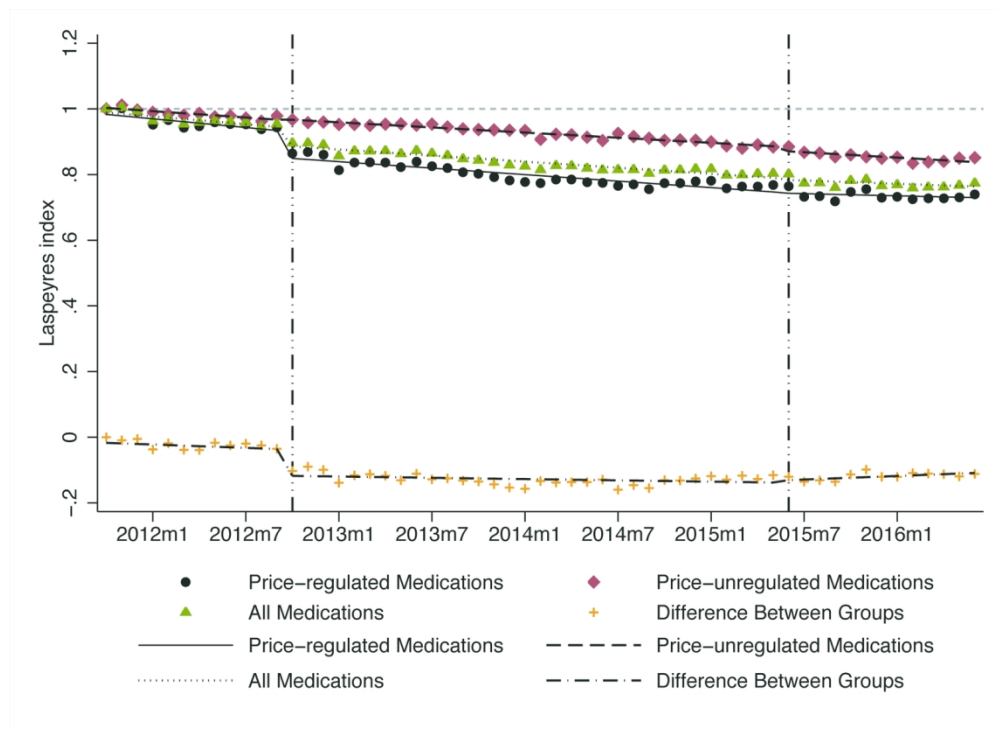


Figure 2. Influence of government price regulation and deregulation on monthly Laspeyres index (Lp) among price-regulated medications (n=30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between regulated and unregulated medications, 2011-2016.

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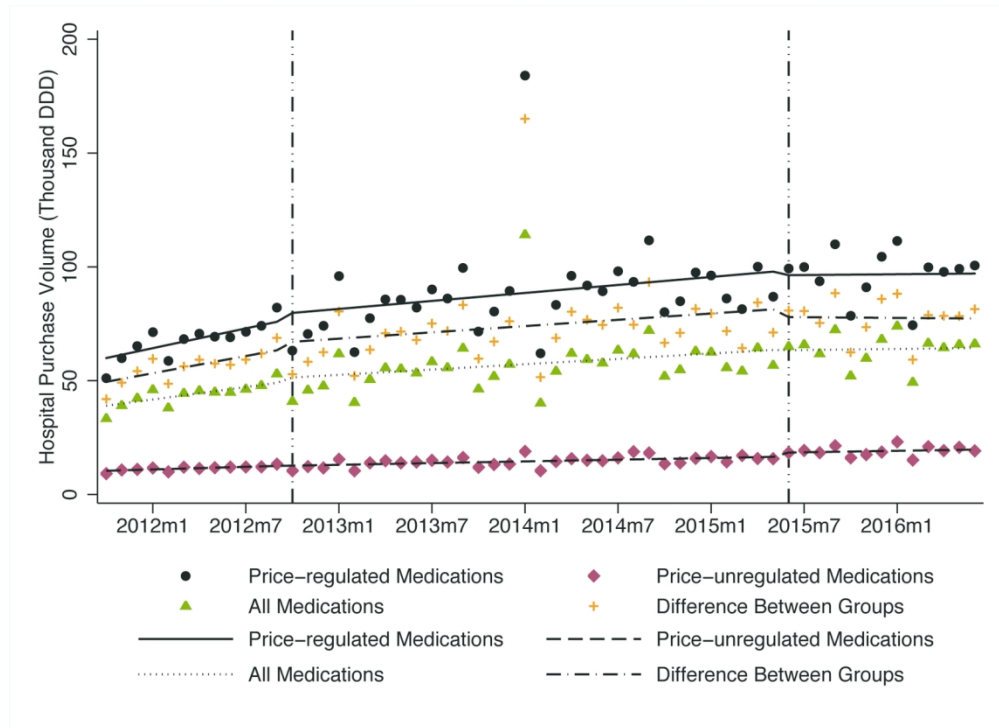


Figure 3. Influence of government price regulation and deregulation on monthly average purchase volumes among price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between groups, 2011-2016.

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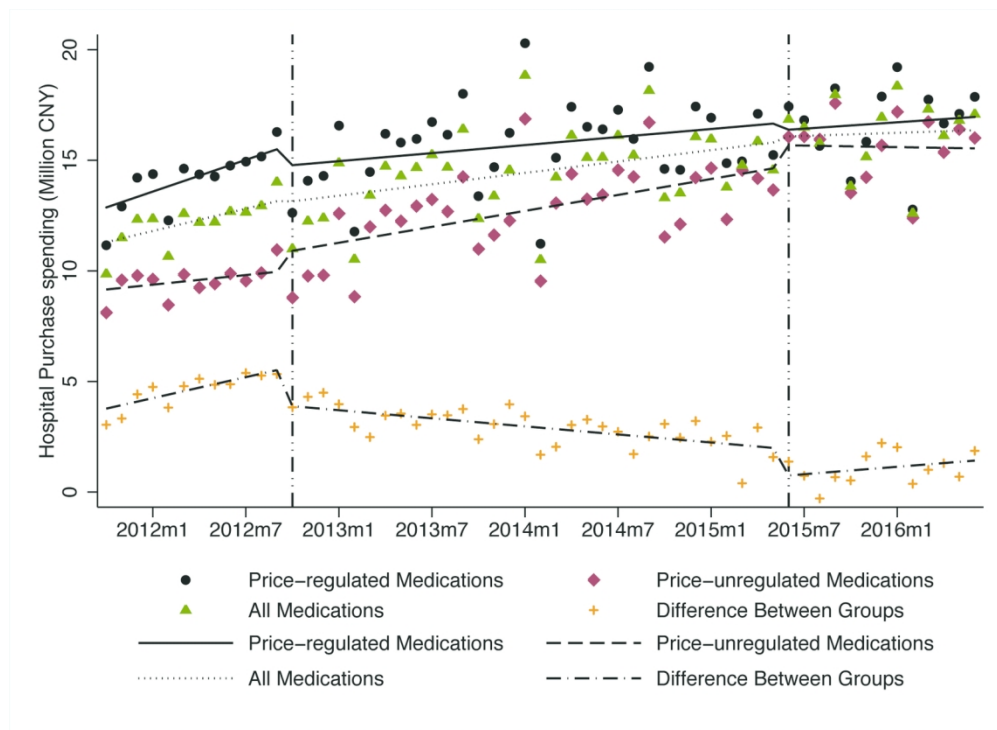


Figure 4. Influence of government price regulation and deregulation on monthly average spending on price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and difference between groups, 2011-2016.

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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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up 【N/A】 <i>Case-control study</i> —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】 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants 【N/A】 (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed 【N/A】 <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed 【N/A】 <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed 【N/A】 <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy 【N/A】 (e) Describe any sensitivity analyses 【N/A】

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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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) 【N/A】
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time 【N/A】 <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure 【N/A】 <i>Cross-sectional study</i> —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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Secondary Subject Heading:	Health policy
Keywords:	Price Regulation, Deregulation, Laspeyres index, Antineoplastic Medications

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4 **Influence of Government Price Regulation and Deregulation on the Price of**
5 **Antineoplastic Medications in China: A Controlled Interrupted Time Series**
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7 **Study**
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57 Mingchun Yang conducted the final analyses. Xiaodong Guan and Haishaerjiang
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3 Wushouer drafted the initial manuscript. All authors contributed to the critical revision
4 of the manuscript and approved the final version.
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9 **Keywords:** Price Regulation, Deregulation, Laspeyres index, Antineoplastic
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1 ABSTRACT

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

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

13 Results: During government price regulation, compared to price-unregulated cancer
14 medications (n = 22 mostly newer targeted products), the relative price of price-
15 regulated medications (n = 30 mostly chemotherapeutic products) decreased
16 significantly ($\beta = -0.081$, $P < 0.001$). After the government price deregulation, no
17 significant price change occurred. Neither government price regulation nor
18 deregulation significantly impacted average volumes of or average spending on all
19 antineoplastic medications immediately after the policy changes or in the longer term
20 ($P > 0.05$).

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

26 27 **Strengths and limitations**

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

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4 35 ● Given our use of aggregated hospital procurement data, we could not assess factors
5 36 such as numbers of patients treated or appropriateness of use at a given level of
6 37 medication spending or volume.
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39 **Introduction**

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

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

58 In China, the government has introduced complex medication price control policies to
59 decrease medication prices. First, after the Urban Employee Basic Medical Insurance
60 (UEBMI) was established in 1998, the National Development and Reform Commission
61 (NDRC) was required to set a highest retail price using a cost-plus calculation for each
62 medication listed in the National Reimbursement Drug List (NRDL).^{19,20} And rules for
63 price difference and price ratio of medicines were applied to convert a generic price
64 into different prices for medicines with different dosage forms or specifications.²¹
65 From 1998 to 2015, the NDRC used price caps to reduce drug prices for 31 times,
66 involving 1029 medicines (not including traditional Chinese drugs) in terms of generic
67 name.^{22,23} In addition, because medication expenditures accounted for 40.4% of total
68 health expenditures (in 2009) and almost 70% of medication sales were in hospitals (in
69 2013),^{24,25} since 2010, provinces had to conduct a centralized bidding and tendering
70 process to procure all hospital medications, with the intent to decrease prices and curb
71 medication expenditures.²⁶

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

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3 76 medication prices and the NDRC formally abolished price ceiling policies in 2015.²⁸
4 77 Improvement in access to price-regulated medications after the 2012 price regulation
5 78 and price increases after the 2015 government price deregulation were expected.
6 79 However, the effects of government price regulation and deregulation on anticancer
7 80 medications is unknown. We studied impacts of NDRC price regulation and
8 81 deregulation on the relative prices and sales volumes and spending on antineoplastic
9 82 medications in China.

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17 84 **Methods**

18 85 **Study design**

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20 86 We used the strongest quasi-experimental design, an interrupted time series (ITS)
21 87 design,²⁹ with two breakpoints to assess changes following implementation of two
22 88 price policies. The first breakpoint, October 2012, served to assess the effects of the
23 89 government retail price regulation that was announced on September 14th, 2012 and
24 90 came into effect on October 8th, 2012. The second breakpoint, June 2015, served to
25 91 assess the effects of government retail price deregulation that was announced on May
26 92 4th, 2015 and came into effect on June 1st, 2015. To compare the effects of each policy
27 93 intervention, we conducted analyses of medication groups for which 2012 price caps
28 94 were and were not applied. The intervention group of medications had retail price caps
29 95 as of October 2012 and the control group was without price caps throughout the study
30 96 period. We use the term ‘price-regulated medications’ for the medicines that were under
31 97 price regulation during the intervention period; these products are no longer price
32 98 regulated. (Figure 1) We hypothesized that the impacts of price regulation or
33 99 deregulation on purchase prices, volumes, and spending would differ between the two
34 100 groups.

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

51 105 **Data source**

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53 106 Data on products purchased between October 2011 and June 2016 were extracted from
54 107 the observational Chinese Medical Economic Information (CMEI) database of public
55 108 hospital medication purchasing records.³⁰ We conducted a search of all antineoplastic
56 109 medications in the database by ATC code (L01).³¹ We excluded those antineoplastic
57 110 medications with missing data and included antineoplastic medications regulated in

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4 111 October 2012 as intervention group and antineoplastic medications not listed in the
5 112 NDRL and thus not subject to price caps during the study period as control group. We
6 113 extracted procurement data for 52 antineoplastic medications (30 medications with
7 114 retail price caps from October 2012 to June 2015 and 22 medications without any price
8 115 caps from the year before to the year after the price poly changes, between October
9 116 2011 and June 2016, Supplement 1A and 1B) from 699 public hospitals, including 476
10 117 tertiary hospitals, 217 secondary hospitals and 6 primary health facilities in 28
11 118 provinces. Data elements extracted for each product comprised the International
12 119 Nonproprietary Name (INN), dosage form, strength, manufacturer, medication
13 120 purchase price per package, monthly purchasing volumes and monthly hospital
14 121 spending.

122 **Outcome measures**

123 The primary outcome was the L_p , an index formula used in price statistics for
124 measuring the price development over time of baskets of goods and services consumed
125 in the base period 0 by weighting prices by the volume purchased in period 0.³² In this
126 study, the L_p was calculated based on equation (1):

$$127 L_{pt} = \frac{\sum P_{ijt} Q_{ij0}}{\sum P_{ij0} Q_{ij0}} \quad (1)$$

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

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

141 **Statistical Analysis**

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

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4 146 regulated products, controlling for any other externalities that may have affected
5 147 outcomes in the control group products.

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7 148 ITS models were used to estimate levels and trends of the outcomes in the pre-
8 149 intervention periods and changes in levels and trends in the post-intervention periods.
9 150 ITS models with two interruption points were formulated to detect the effect on Lp,
10 151 monthly average purchasing volumes and spending, as in equation (2):

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$$153 Y_{it} = \beta_0 + \beta_1 \times time_t + \beta_2 \times regulation + \beta_3 \times reg_trend + \beta_4 \\ 154 \times deregulation + \beta_5 \times der_trend + \varepsilon_{it} \quad (2)$$

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21 156 We used β_0 to estimate the baseline purchasing volume and spending; β_1 estimated
22 157 the pre-regulation trend; β_2 estimated the change in level after the regulation policy;
23 158 β_3 estimated the change in trend after the regulation policy; β_4 estimated the change
24 159 in level after the deregulation policy; β_5 estimated the change in trend after the
25 160 deregulation policy. Key coefficients were β_2 , β_3 , β_4 and β_5 . To estimate the
26 161 combined level and trend impacts of the policy changes, we calculated the absolute
27 162 difference in Y_{it} at 12 months after regulation and after deregulation, respectively,
28 163 compared to the counterfactual, that is, the estimated Y_{it} had the intervention not
29 164 happened.³⁵

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35 165 We performed the Durbin-Watson test to estimate level of residual autocorrelations³⁶
36 166 and used the Cochrane-Orcutt auto-regression procedure to correct for first order
37 167 serially correlated errors when needed.³⁷ All analyses were performed using Stata
38 168 14.0.³⁸

39 169 **Patient and public involvement**

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45 170 There were no patients and public involved in in the design or planning of the study.

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51 173 **Study Results**

52 174 **Influence of Government Pricing Policies on Relative Purchase Prices**

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55 175 The Lp declined over time in both intervention and control medication groups (that is,
56 176 prices decreased relative to baseline) (Table 1, Figure 2). After government price
57 177 regulation in October 2012, the Lp for price-regulated medications dropped suddenly
58 178 (level change $\beta = -0.082$, $P < 0.001$), with significant declines in Lp relative to price-

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4 179 unregulated medications ($\beta = -0.081$, $P < 0.001$). At 12 months after the regulation,
5 180 there was an estimated reduction in the Lp for price-regulated medications of 0.058 (P
6 181 < 0.05) and an estimated increase in the Lp for price-unregulated of 0.029 ($P < 0.05$).

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9 182 After the government price deregulation in June 2015, the Lp for price-unregulated
10 183 medications decreased significantly (level change $\beta = -0.013$, $P < 0.05$), but no
11 184 significant discontinuities in Lp levels or trends were observed for the price-regulated
12 185 medications or for the relative change compared to price-unregulated medications. At
13 186 12 months after price deregulation, there was no change in Lp for price regulated
14 187 medications and an estimated reduction in the Lp for price-unregulated medications of
15 188 0.043 ($P < 0.05$).

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191 Table 1. Results of interrupted time series analyses of the impacts of government price
 192 regulation and deregulation on Laspeyres Price Index, monthly average purchase
 193 volumes and spending for price-regulated, price-unregulated, and all antineoplastic
 194 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

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4 195 *, $P \leq 0.05$; **, $P \leq 0.01$; ***, $P \leq 0.001$; price-regulated medications: 30 antineoplastic products with
5 196 price regulation in 2012 and deregulation in 2015; price-unregulated medications: 22 antineoplastic
6 197 products without price regulation or deregulation; DDD=defined daily doses; CNY = Chinese Yuan (1
7 198 CNY = 0.155 US\$ in 2011)

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14 201 Figure 2. Influence of government price regulation and deregulation on monthly
15 202 Laspeyres index (Lp) among price-regulated medications (n=30), price-unregulated
16 203 medications (n = 22), all medications (n = 52), and the difference between regulated
17 204 and unregulated medications, 2011-2016.

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22 206 **Influence of Government Pricing Policies on Average Purchase Volumes**

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25 207 The average volume purchased of all 52 antineoplastic medications, measured in DDD,
26 208 rose from 33,370 DDD in October 2011 to 66,189 DDD in June 2016 (Table 1, Figure
27 209 3. There were no statistically significant changes in volume levels or trends after
28 210 government price regulation or deregulation in any group.

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34 212 Figure 3. Influence of government price regulation and deregulation on monthly
35 213 average purchase volumes among price-regulated medications (n = 30), price-
36 214 unregulated medications (n = 22), all medications (n = 52), and the difference between
37 215 groups, 2011-2016.

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42 217 **Influence of Government Pricing Policies on Hospital Spending**

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44 218 Average hospital spending on all antineoplastic medications rose from 9.86 million
45 219 CNY in October 2011 to 17.08 million CNY in June 2016 (Table 1, Figure 4). There
46 220 were no statistically significant changes in spending levels or trends after government
47 221 price regulation or deregulation in any of the groups. However, the spending on price-
48 222 regulated medications decreased and spending on price-unregulated medications
49 223 increased after both the regulation and deregulation policies, resulting in significant
50 224 level and trend changes in the differences between the two groups. After government
51 225 price regulation, the spending difference decreased suddenly (level change $\beta = -1.570$,
52 226 $P < 0.01$) and increased somewhat more slowly ($\beta = -0.219$, $P < 0.01$) than in the
53 227 baseline period. At 12 months after regulation, the absolute spending difference

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228 between the groups was significantly lower (-4.508 mio CNY, $P < 0.05$) than would
229 have been expected without the regulation.

230 After the deregulation policy was implemented, the spending difference dropped again
231 (level change $\beta = -1.301$, $P < 0.01$), although followed by an increasing trend ($\beta = 0.117$,
232 $P < 0.05$). By the end of follow-up, the relative difference between groups had returned
233 to nearly the level expected based on the trend at the time of the price regulation policy.

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235 Figure 4. Influence of government price regulation and deregulation on monthly
236 average spending on price-regulated medications ($n = 30$), price-unregulated
237 medications ($n = 22$), all medications ($n = 52$), and difference between groups, 2011-
238 2016.

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240 Discussion

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

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

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

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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 China⁴⁷ and Italy⁴⁸, 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.

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293 **Limitations**

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

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3 299 price-unregulated oncology medications tended to include newer, more expensive
4 300 products than the price-regulated group and the two groups differed in other
5 301 characteristics such as indications and therapeutic status in treatment. However, the Lp
6 302 trends observed at baseline in the two groups of products were quite similar, suggesting
7 303 that differential changes observed following the government pricing policies were
8 304 indicative of true differences. Fourth, given that our analyses are based on procurement
9 305 data we have not information on indications of use and potential therapeutic substitution.
10 306 Fifth, some new antineoplastic drugs not included in the NRDL and thus not price-
11 307 regulated may be made available by manufacturers' access programs (like buy 3 get 3
12 308 free) for individual patients. These products would not be part of our price, volume, or
13 309 spending analyses because they would be transacted directly between individual
14 310 physicians, their patients, and the manufacturer (or an intermediary). However, the
15 311 number of patients who participated in access programs was limited and almost 70% of
16 312 medication sales in China occur in hospitals.⁵² Sixth, given our use of aggregated
17 313 hospital procurement data, we could not assess factors such as the numbers of patients
18 314 treated or appropriate use given levels of medication spending or volume.

315

316 **Conclusion**

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

323

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326 in data access and analysis.

327

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329 The authors declared no competing interests.

330

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11 337 **Ethics approval and consent to participate**

12 338 The study was considered not human subjects research by the Harvard Pilgrim Health
13 339 Care Institutional Review Board.
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16 341 **Data availability statement**

17 342 Data on products purchased between October 2011 and June 2016 were extracted from
18 343 the observational Chinese Medical Economic Information (CMEI) database of public
19 344 hospital medication purchasing records. However, this data are unavailable to the
20 345 public due to its confidentiality.
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36 359 **Referenc**

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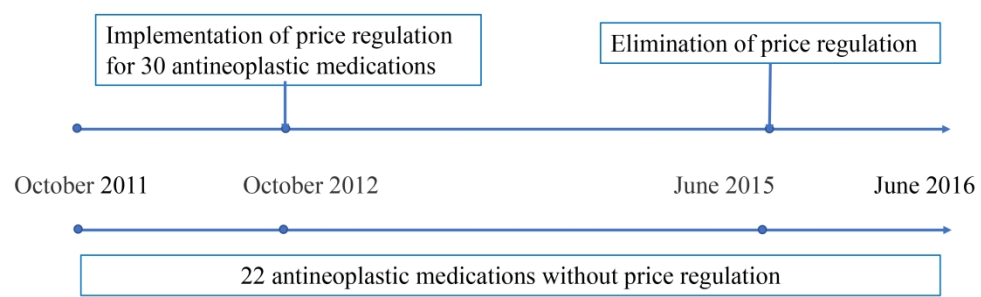


Figure 1. Timeline of price regulation and deregulation of 52 antineoplastic medications

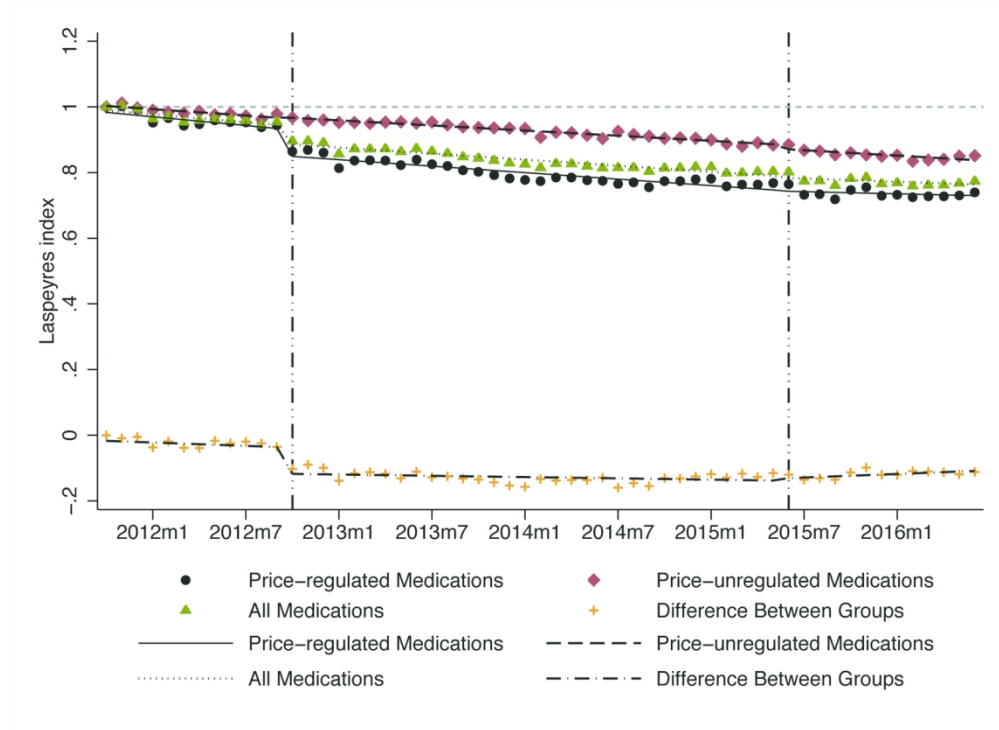


Figure 2. Influence of government price regulation and deregulation on monthly Laspeyres index (Lp) among price-regulated medications (n=30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between regulated and unregulated medications, 2011-2016.

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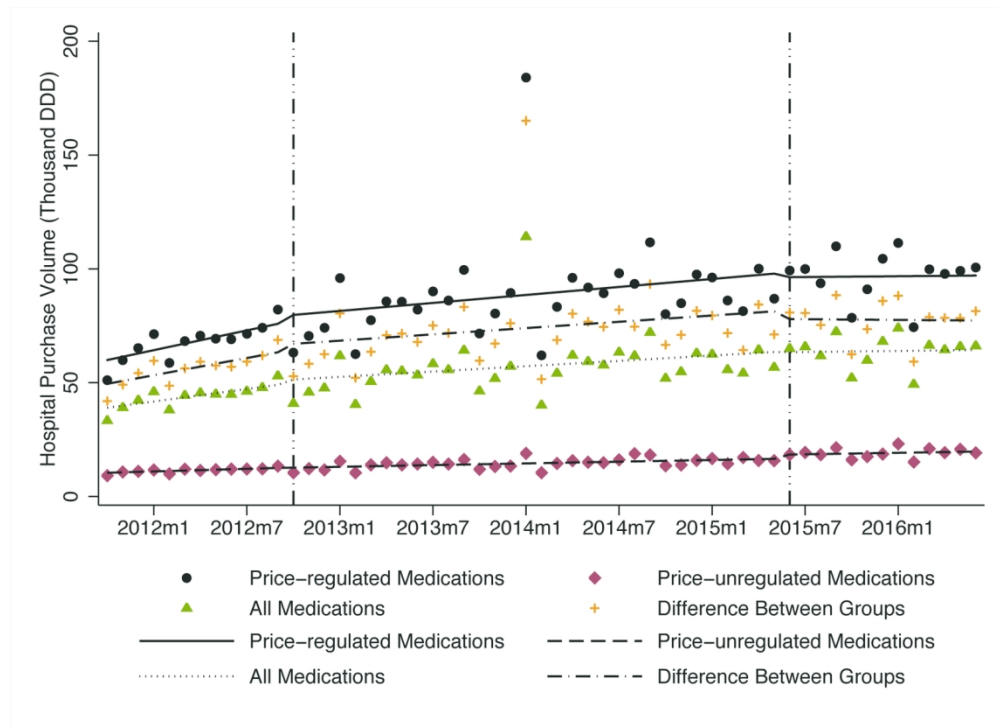


Figure 3. Influence of government price regulation and deregulation on monthly average purchase volumes among price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between groups, 2011-2016.

139x101mm (300 x 300 DPI)

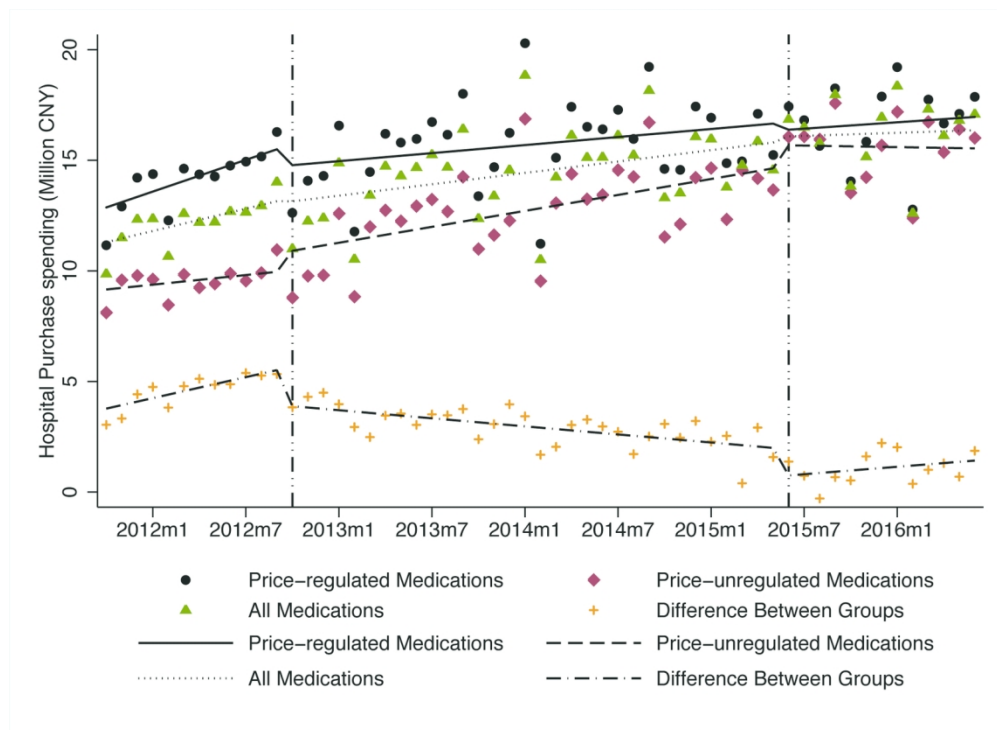


Figure 4. Influence of government price regulation and deregulation on monthly average spending on price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and difference between groups, 2011-2016.

139x101mm (300 x 300 DPI)

Supplement 1A. Antineoplastic medications samples of the intervention group

Generic Name	ATC	Classification	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;

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5	daunorubicin	L01DB02	chemotherapy	generic only	acute myeloid leukemia, AML; acute lymphoblastic leukemia, ALL;
6					
7					
8	docetaxel	L01CD02	chemotherapy	originator and generic	breast cancer; non-small cell lung cancer;
9					
10					
11	doxifluridine	/	chemotherapy	generic only	Breast cancer; gastric cancer; colorectal cancer; nasopharyngeal cancer;
12					
13					
14	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;
15					
16					
17					
18	etoposide	L01CB01	chemotherapy	generic only	small cell lung cancer; malignant lymphoma; leukemia; neuroblastoma; rhabdomyosarcom; gastric cancer; esophageal carcinoma; malignant germ cell tumor; ovarian cancer;
19					
20					
21					
22					
23	fludarabine	L01BB05	chemotherapy	originator and generic	chronic lymphocytic leukemia;
24					
25					
26					
27	fluorouracil	L01BC02	chemotherapy	generic only	Gastrointestinal Cancer; chorionepithelioma; breast cancer; Ovarian Carcinoma; lung cancer; cervical carcinoma; bladder cancer; skin cancer;
28					
29					
30	gemcitabine	L01BC05	chemotherapy	originator and generic	non-small cell lung cancer; pancreatic cancer; breast cancer;
31					
32					
33					
34	hydroxycamptothecin	/	chemotherapy	originator and generic	primary liver cancer; gastric cancer; bladder cancer; rectal cancer; head and neck epithelial cancer; leukemia and other malignant tumors
35					
36					
37	lobaplatin	/	chemotherapy	originator only	breast cancer; small cell lung cancer; chronic myeloid leukemia
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5	nedaplatin	/	chemotherapy	generic only	Solid tumors such as head and neck cancer, small cell lung cancer, non-small cell lung cancer and esophageal cancer
6					
7					
8	nimustine	L01AD06	chemotherapy	originator and generic	brain tumor; gastrointestinal cancer; lung cancer; malignant lymphoma; chronic leukemia;
9					
10					
11	oxaliplatin	L01XA03	chemotherapy	originator and generic	colorectal carcinoma; hepatocellular carcinoma, HCC;
12					
13					
14	semustine	L01AD03	chemotherapy	generic only	brain tumor; malignant lymphoma; gastric cancer; colon cancer; melanoma;
15					
16	tegafur	L01BC03	chemotherapy	generic only	Gastrointestinal Cancer; breast cancer;
17	tegafur, gimeracil and oteracil porassium	L01BC53	chemotherapy	generic only	gastrointestinal cancer(gastric cancer; intestinal cancer; pancreatic cancer); breast cancer; liver cancer;
18					
19					
20					
21	temozolomide	L01AX03	chemotherapy	originator and generic	glioblastoma multiforme, GBM; anaplastic astrocytoma;
22					
23					
24	teniposide	L01CB02	chemotherapy	originator and generic	malignant lymphoma; central nervous system-tumors; bladder cancer;
25					
26					
27	topotecan	L01XX17	chemotherapy	originator and generic	small cell lung cancer; ovarian cancer;
28					
29					
30	vindesine	L01CA03	chemotherapy	generic only	non-small cell lung cancer; small cell lung cancer; malignant lymphoma; breast cancer; esophageal carcinoma; malignant melanoma;
31					
32					
33	vinorelbine	L01CA04	chemotherapy	originator and generic	non-small cell lung cancer; breast cancer;
34					

¹ Manufactures of specific medications during our study period.

Supplement 1B. Antineoplastic medications samples of the intervention group

Generic Name	ATC	Classification	Manufactures ¹	Indications Approved in China
actinomycin D	L01DA01	chemotherapy	originator and generic	Hodgkin's disease; neuroblastoma; choriocarcinoma; testicular cancer; Wilms'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;

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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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up 【N/A】 <i>Case-control study</i> —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】 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants 【N/A】 (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed 【N/A】 <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed 【N/A】 <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed 【N/A】 <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy 【N/A】 (e) Describe any sensitivity analyses 【N/A】

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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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) 【N/A】
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time 【N/A】 <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure 【N/A】 <i>Cross-sectional study</i> —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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Keywords:	Price Regulation, Deregulation, Laspeyres index, Antineoplastic Medications

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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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Contributors: Luwen Shi, Xiaodong Guan, Dennis Ross-Degnan and Anita Katharina Wagner conceptualised and designed the study. Sheng Han and Mingchun Yang contributed to analysis of the data. Xiaodong Guan, Haishaerjiang Wushouer and Mingchun Yang conducted the final analyses. Xiaodong Guan and Haishaerjiang Wushouer drafted the initial manuscript. All authors contributed to the critical revision of the manuscript and approved the final version.

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3 **Keywords:** Price Regulation, Deregulation, Laspeyres index, Antineoplastic
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1 ABSTRACT

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

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

13 Results: During government price regulation, compared to price-unregulated cancer
14 medications (n = 22, mostly newer targeted products), the relative price of price-
15 regulated medications (n = 30, mostly chemotherapeutic products) decreased
16 significantly ($\beta = -0.081$, $P < 0.001$). After the government price deregulation, no
17 significant price change occurred. Neither government price regulation nor
18 deregulation had a significant impact on average volumes of or average spending on all
19 antineoplastic medications immediately after the policy changes or in the longer term
20 ($P > 0.05$).

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

26 Strengths and limitations

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

39 Introduction

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

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

58 In China, the government has introduced complex medication price control policies to
59 decrease medication prices. First, after the Urban Employee Basic Medical Insurance
60 (UEBMI) was established in 1998, the National Development and Reform Commission
61 (NDRC) was required to set a highest retail price using a cost-plus calculation for each
62 medication listed in the National Reimbursement Drug List (NRDL).^{19,20} Rules for
63 price differences and price ratios of medicines were applied to convert a substance's
64 price into different prices for medicines with different dosage forms or specifications.²¹
65 From 1998 to 2015, the NDRC used price caps to reduce drug prices 31 times, involving
66 1029 substances (not including traditional Chinese medicines).^{22,23} In addition,
67 because medication expenditures accounted for 40.4% of total health expenditures (in
68 2009) and almost 70% of medication sales were in hospitals (in 2013),^{24,25} since 2010,
69 provinces had to conduct a centralized bidding and tendering process to procure all
70 hospital medications, with the intent to decrease prices and curb medication
71 expenditures.²⁶

72 In October 2012, the NDRC established maximum retail prices for specific products
73 listed in the 2009 National Reimbursement List, including 36 antineoplastic
74 medications.²⁷ Following the central government's requirement to limit regulatory
75 controls in economic management, China loosened administrative controls over
76 medication prices and the NDRC formally abolished price ceiling policies in 2015.²⁸
77 Price decreases and increased use of price-regulated medications after the 2012 price
78 regulation and price increases after the 2015 government price deregulation were
79 expected. However, the effects of government price regulation and deregulation on
80 anticancer medications is unknown. We studied the impacts of NDRC price regulation

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3 81 and deregulation on the relative prices and sales volumes of and spending on
4 82 antineoplastic medications in China.
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8 84 **Methods**

10 85 **Study design**

12 86 We used the strongest quasi-experimental design, an interrupted time series (ITS)
13 87 design,²⁹ with two breakpoints to assess changes following implementation of two
14 88 price policies. The first breakpoint, October 2012, served to assess the effects of the
15 89 government retail price regulation that was announced on September 14th, 2012 and
16 90 came into effect on October 8th, 2012. The second breakpoint, June 2015, served to
17 91 assess the effects of government retail price deregulation that was announced on May
18 92 4th, 2015 and came into effect on June 1st, 2015. To compare the effects of each policy
19 93 intervention, we conducted analyses of medication groups for which 2012 price caps
20 94 were and were not applied. The intervention group of medications had retail price caps
21 95 since October 2012 and the control group was without price caps throughout the study
22 96 period. We use the term ‘price-regulated medications’ for the medicines that were under
23 97 price regulation during the intervention period; these products are no longer price
24 98 regulated. (Figure 1) We hypothesized that the impacts of price regulation or
25 99 deregulation on purchase prices, volumes, and spending would differ between the two
26 100 groups.
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37 103 Figure 1. Timeline of price regulation and deregulation of 52 antineoplastic
38 104 medications
39
40 105 **Data source**

41 106 Data on products purchased between October 2011 and June 2016 were extracted from
42 107 the observational Chinese Medical Economic Information (CMEI) database of public
43 108 hospital medication purchasing records.³⁰ We conducted a search of all antineoplastic
44 109 medications in the database by ATC code (L01).³¹ We excluded those antineoplastic
45 110 medications with missing data. We included antineoplastic medications that were
46 111 regulated in October 2012 as intervention group. Antineoplastic medications which
47 112 were not listed in the NDRL and thus not subject to price caps during the study period
48 113 constituted the control group. We extracted procurement data for 52 antineoplastic
49 114 medications (30 medications with retail price caps from October 2012 to June 2015 and
50 115 22 medications without any price caps from the year before to the year after the price
51 116 policy changes, between October 2011 and June 2016, Supplement 1A and 1B) from
52 117 699 public hospitals, including 476 tertiary hospitals, 217 secondary hospitals and 6
53 118 primary health facilities in 28 of the 31 provinces in China. Aggregated procurement
54 119 data was accessed to based on data elements in the dataset for each product comprised
55 120 the International Nonproprietary Name (INN), dosage form, strength, manufacturer,

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

123 **Outcome measures**

124 The primary outcome was the Lp, an index formula used in price statistics for
125 measuring the price development over time of baskets of goods and services consumed
126 in the base period 0 by weighting prices by the volume purchased in period 0.³² In this
127 study, the Lp was calculated based on equation (1):

$$128 \quad L_{pt} = \frac{\sum P_{ijt} Q_{ij0}}{\sum P_{ij0} Q_{ij0}} \quad (1)$$

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

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

142 **Statistical Analysis**

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

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

$$153 \quad Y_{it} = \beta_0 + \beta_1 \times time_t + \beta_2 \times regulation + \beta_3 \times reg_trend + \beta_4 \\ 154 \quad \times deregulation + \beta_5 \times der_trend + \varepsilon_{it} \quad (2)$$

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3 157 We used β_0 to estimate the baseline purchasing volume and spending; β_1 estimated
4 158 the pre-regulation trend; β_2 estimated the change in level after the regulation policy;
5 159 β_3 estimated the change in trend after the regulation policy; β_4 estimated the change
6 160 in level after the deregulation policy; β_5 estimated the change in trend after the
7 161 deregulation policy. Key coefficients were β_2 , β_3 , β_4 and β_5 . To estimate the
8 162 combined level and trend impacts of the policy changes, we calculated the absolute
9 163 difference in Y_{it} at 12 months after regulation and after deregulation, respectively,
10 164 compared to the counterfactual, that is, the estimated Y_{it} had the intervention not
11 165 happened.³⁵

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15 166 We performed the Durbin-Watson test to estimate level of residual autocorrelations³⁶
16 167 and used the Cochrane-Orcutt auto-regression procedure to correct for first order
17 168 serially correlated errors when needed.³⁷ All analyses were performed using Stata
18 169 14.0.³⁸

19 20 21 22 170 **Patient and public involvement**

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24 171 There were no patients and public involved in in the design or planning of the study.
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28 29 173 **Study Results**

30 31 174 **Influence of Government Pricing Policies on Relative Purchase Prices**

32 175 The Lp declined over time in both intervention and control medication groups (that is,
33 176 prices decreased relative to baseline) (Table 1, Figure 2). After government price
34 177 regulation in October 2012, the Lp for price-regulated medications dropped suddenly
35 178 (level change $\beta = -0.082$, $P < 0.001$), with significant declines in Lp relative to price-
36 179 unregulated medications ($\beta = -0.081$, $P < 0.001$). At 12 months after the regulation,
37 180 there was an estimated reduction in the Lp for price-regulated medications of 0.058 (P
38 181 < 0.05) and an estimated increase in the Lp for price-unregulated of 0.029 ($P < 0.05$).

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42 182 After the government price deregulation in June 2015, the Lp for price-unregulated
43 183 medications decreased significantly (level change $\beta = -0.013$, $P < 0.05$), but no
44 184 significant discontinuities in Lp levels or trends were observed for the price-regulated
45 185 medications or for the relative change compared to price-unregulated medications. At
46 186 12 months after price deregulation, there was no change in Lp for price regulated
47 187 medications and an estimated reduction in the Lp for price-unregulated medications of
48 188 0.043 ($P < 0.05$).

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191 Table 1. Results of interrupted time series analyses of the impacts of government price
 192 regulation and deregulation on Laspeyres Price Index, monthly average purchase
 193 volumes and spending for price-regulated, price-unregulated, and all antineoplastic
 194 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

195 *, P ≤ 0.05; **, P ≤ 0.01; ***, P ≤ 0.001; price-regulated medications: 30 antineoplastic products
 196 with price regulation in 2012 and deregulation in 2015; price-unregulated medications: 22 antineoplastic
 197 products without price regulation or deregulation; DDD=defined daily doses; CNY = Chinese Yuan (1
 198 CNY = 0.155 US\$ in 2011)

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

205

206 **Influence of Government Pricing Policies on Average Purchase Volumes**

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

211
212 Figure 3. Influence of government price regulation and deregulation on monthly
213 average purchase volumes among price-regulated medications (n = 30), price-
214 unregulated medications (n = 22), all medications (n = 52), and the difference between
215 groups, 2011-2016.

217 **Influence of Government Pricing Policies on Hospital Spending**

218 Average hospital spending on all antineoplastic medications rose from 9.86 million
219 CNY in October 2011 to 17.08 million CNY in June 2016 (Table 1, Figure 4). There
220 were no statistically significant changes in spending levels or trends after government
221 price regulation or deregulation in any of the groups. However, the spending on price-
222 regulated medications decreased and spending on price-unregulated medications
223 increased after both the regulation and deregulation policies, resulting in significant
224 level and trend changes in the differences between the two groups. After government
225 price regulation, the spending difference decreased suddenly (level change $\beta = -1.570$,
226 $P < 0.01$) and increased somewhat more slowly ($\beta = -0.219$, $P < 0.01$) than in the
227 baseline period. At 12 months after regulation, the absolute spending difference
228 between the groups was significantly lower (-4.508 million CNY, $P < 0.05$) than would
229 have been expected without the regulation.

230 After the deregulation policy was implemented, the spending difference dropped again
231 (level change $\beta = -1.301$, $P < 0.01$), although followed by an increasing trend ($\beta = 0.117$,
232 $P < 0.05$). By the end of follow-up, the relative difference between groups had returned
233 to nearly the level expected based on the trend at the time of the price regulation policy.

234
235 Figure 4. Influence of government price regulation and deregulation on monthly
236 average spending on price-regulated medications (n = 30), price-unregulated
237 medications (n = 22), all medications (n = 52), and difference between groups, 2011-
238 2016.

240 **Discussion**

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

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3 244 that of price-unregulated products increased; the price of all studied medications as a
4 245 group decreased significantly compared to the 2011 baseline price; after government
5 246 deregulation, no significant change occurred in either group. Neither setting
6 247 maximum retail prices nor price deregulation significantly affected volumes purchased
7 248 or spending on regulated or unregulated medications. However, compared to price-
8 249 unregulated medications, spending on price-regulated medications dropped
9 250 significantly after price regulation and deregulation.

13 251 Our results indicate that, as expected, a price-cap policy was effective in decreasing
14 252 the prices of selected antineoplastic medications. Most medicines in the intervention
15 253 group were products with intense market competition, possibly facilitating
16 254 implementation of price caps. We have previously shown this effect for digestive
17 255 system medications,³⁹ and others have found similar decreases in price for
18 256 antihyperlipidemic agents.⁴⁰ This might not be the case for originator products with
19 257 only one supplier in the market. Such medicines were not price-regulated at the time.

23 258 We did not find the expected price increase after deregulation for the price-regulated
24 259 medications. This could be due to the fact that medication prices in China are also
25 260 influenced by the provincial tendering system. Since 2009, the medication tendering
26 261 process is conducted at the provincial level, with different assessment criteria, usually
27 262 a composite score of product quality and price, to determine the winner.⁴¹ Hence, the
28 263 tendering mechanism could have constrained medication price increases after
29 264 government deregulation.⁴² The provincial tendering process could also explain the
30 265 price decreases in both groups observed prior to the national government price
31 266 regulation. Further, generic entry, particularly for the older price-regulated cytotoxic
32 267 medications, may explain why relative medication prices did not increase after
33 268 government price deregulation. With the Chinese government encouraging the
34 269 development of pharmaceutical enterprises, more generic medications have come to
35 270 the market, which might improve the availability and the affordability of
36 271 antineoplastic agents.⁴³

41 272 We found no significant changes in purchase volumes or spending on either price-
42 273 regulated or price-unregulated medications. When prices of regulated products
43 274 decreased in comparison to price-unregulated products following the introduction of
44 275 maximum retail prices, we did not observe a compensatory increase in the use of
45 276 regulated products, but spending on products in the price-regulated group decreased.
46 277 Medication utilization and spending were likely also affected by reimbursement
47 278 policies, which restricted the total hospital spending on insurance-listed and price-
48 279 regulated products but not on unregulated medications.^{44,45}

52 280 Finally, prescribers may have maintained a preference for the newer, more expensive
53 281 medications in the price-unregulated group.⁴⁶ Studies in China⁴⁷ and Italy⁴⁸, have
54 282 shown that volume and medication utilization mix, rather than prices, determine overall
55 283 medication expenditures. This may indicate that it is difficult to manage medication
56 284 spending increases solely by regulating the prices of some medications in a therapeutic
57 285 class. Before 2015, China's Drugs Price Mark-up Policy allowed hospitals to charge

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

292

293 **Limitations**

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

317

318 **Conclusion**

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

325

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26 339 **Ethics approval and consent to participate**
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28 340 The study was considered non-human subjects research by the Harvard Pilgrim Health
29 341 Care Institutional Review Board.
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33 343 **Data availability statement**
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35 344 Data on products purchased between October 2011 and June 2016 were extracted from
36 345 the observational Chinese Medical Economic Information (CMEI) database of public
37 346 hospital medication purchasing records. This data is unavailable to the public due to its
38 347 confidentiality. Researchers interested in the data need to contact Chinese
39 348 Pharmaceutical Association.
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Figure 1. Timeline of price regulation and deregulation of 52 antineoplastic medications

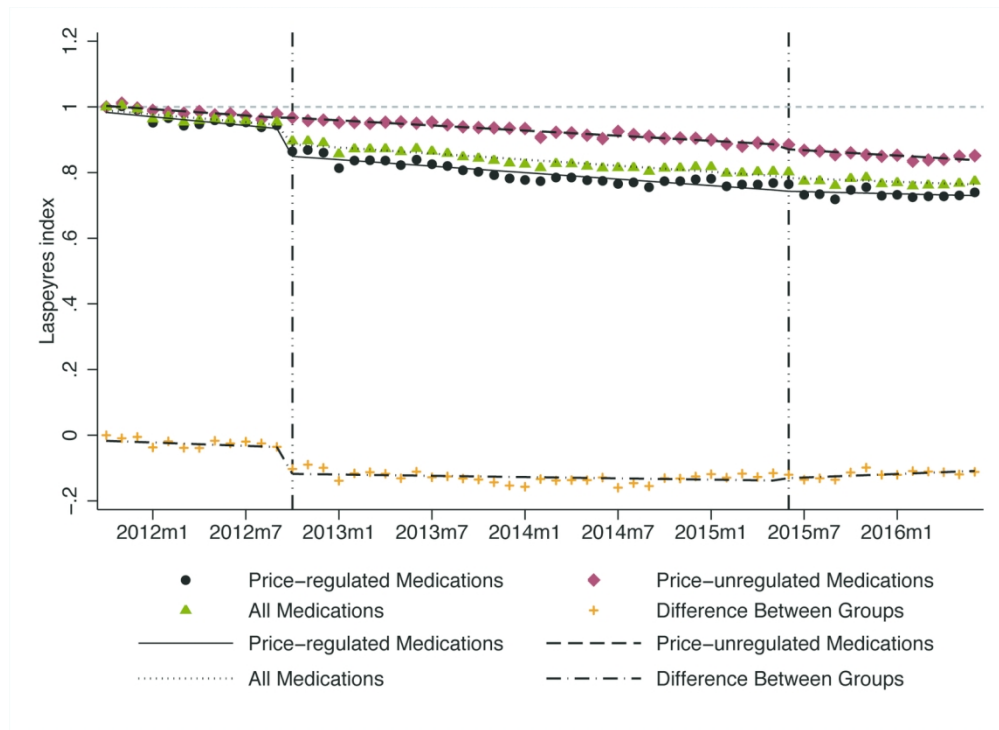


Figure 2. Influence of government price regulation and deregulation on monthly Laspeyres index (Lp) among price-regulated medications (n=30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between regulated and unregulated medications, 2011-2016.

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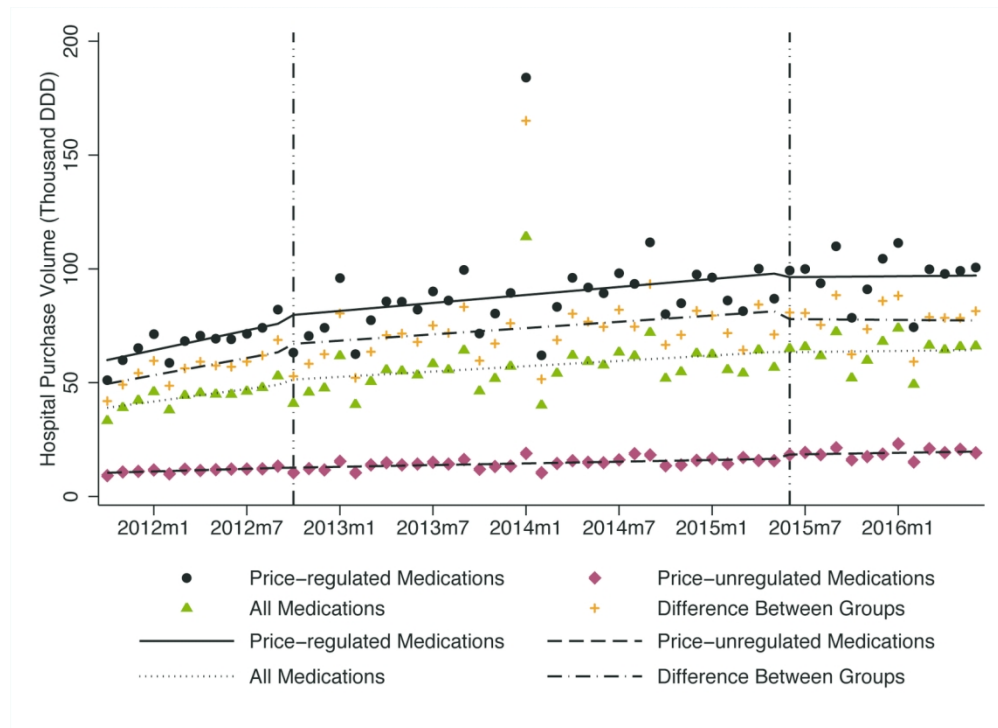


Figure 3. Influence of government price regulation and deregulation on monthly average purchase volumes among price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between groups, 2011-2016.

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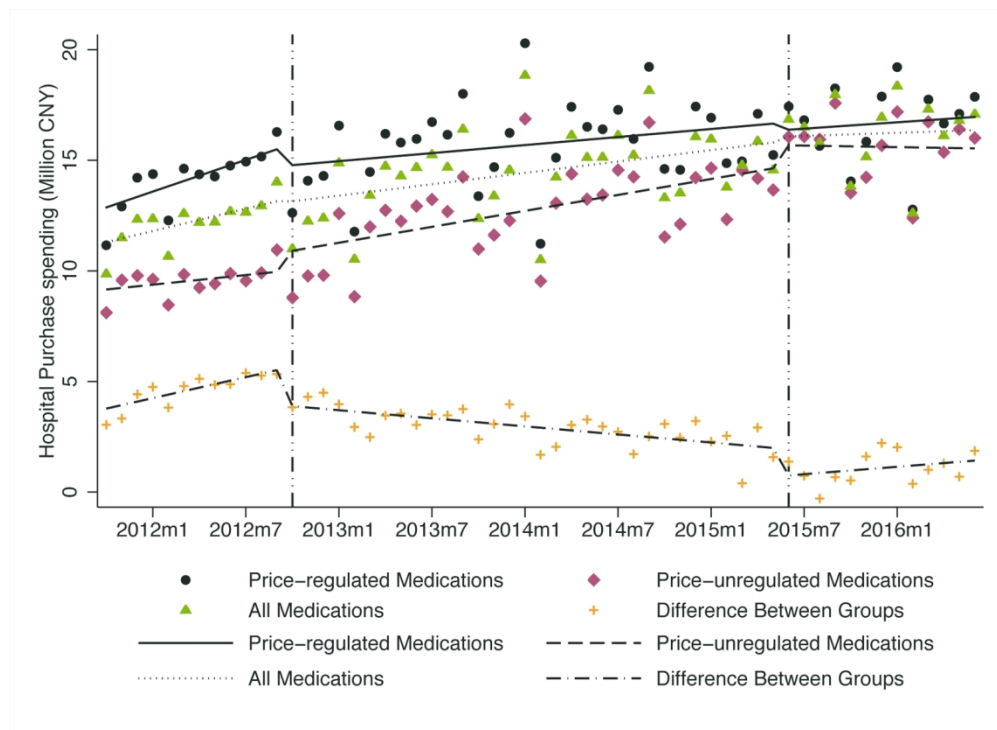


Figure 4. Influence of government price regulation and deregulation on monthly average spending on price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and difference between groups, 2011-2016.

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Supplement 1A. Antineoplastic medications samples of the intervention group

Generic Name	ATC	Classification	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;

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5	daunorubicin	L01DB02	chemotherapy	generic only	acute myeloid leukemia, AML; acute lymphoblastic leukemia, ALL;
6					
7					
8	docetaxel	L01CD02	chemotherapy	originator and generic	breast cancer; non-small cell lung cancer;
9					
10					
11	doxifluridine	/	chemotherapy	generic only	Breast cancer; gastric cancer; colorectal cancer; nasopharyngeal cancer;
12					
13					
14	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;
15					
16					
17					
18	etoposide	L01CB01	chemotherapy	generic only	small cell lung cancer; malignant lymphoma; leukemia; neuroblastoma; rhabdomyosarcom; gastric cancer; esophageal carcinoma; malignant germ cell tumor; ovarian cancer;
19					
20					
21					
22					
23	fludarabine	L01BB05	chemotherapy	originator and generic	chronic lymphocytic leukemia;
24					
25					
26					
27	fluorouracil	L01BC02	chemotherapy	generic only	Gastrointestinal Cancer; chorionepithelioma; breast cancer; Ovarian Carcinoma; lung cancer; cervical carcinoma; bladder cancer; skin cancer;
28					
29					
30	gemcitabine	L01BC05	chemotherapy	originator and generic	non-small cell lung cancer; pancreatic cancer; breast cancer;
31					
32					
33					
34	hydroxycamptothecin	/	chemotherapy	originator and generic	primary liver cancer; gastric cancer; bladder cancer; rectal cancer; head and neck epithelial cancer; leukemia and other malignant tumors
35					
36					
37	lobaplatin	/	chemotherapy	originator only	breast cancer; small cell lung cancer; chronic myeloid leukemia
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5	nedaplatin	/	chemotherapy	generic only	Solid tumors such as head and neck cancer, small cell lung cancer, non-small cell lung cancer and esophageal cancer
6					
7					
8	nimustine	L01AD06	chemotherapy	originator and generic	brain tumor; gastrointestinal cancer; lung cancer; malignant lymphoma; chronic leukemia;
9					
10					
11	oxaliplatin	L01XA03	chemotherapy	originator and generic	colorectal carcinoma; hepatocellular carcinoma, HCC;
12					
13					
14	semustine	L01AD03	chemotherapy	generic only	brain tumor; malignant lymphoma; gastric cancer; colon cancer; melanoma;
15					
16	tegafur	L01BC03	chemotherapy	generic only	Gastrointestinal Cancer; breast cancer;
17	tegafur, gimeracil and oteracil porassium	L01BC53	chemotherapy	generic only	gastrointestinal cancer(gastric cancer; intestinal cancer; pancreatic cancer); breast cancer; liver cancer;
18					
19					
20	temozolomide	L01AX03	chemotherapy	originator and generic	glioblastoma multiforme, GBM; anaplastic astrocytoma;
21					
22					
23	teniposide	L01CB02	chemotherapy	originator and generic	malignant lymphoma; central nervous system-tumors; bladder cancer;
24					
25					
26	topotecan	L01XX17	chemotherapy	originator and generic	small cell lung cancer; ovarian cancer;
27					
28					
29	vindesine	L01CA03	chemotherapy	generic only	non-small cell lung cancer; small cell lung cancer; malignant lymphoma; breast cancer; esophageal carcinoma; malignant melanoma;
30					
31					
32					
33	vinorelbine	L01CA04	chemotherapy	originator and generic	non-small cell lung cancer; breast cancer;
34					

¹ Manufactures of specific medications during our study period.

Supplement 1B. Antineoplastic medications samples of the control group

Generic Name	ATC	Classification	Manufactures ¹	Indications Approved in China
actinomycin D	L01DA01	chemotherapy	originator and generic	Hodgkin's disease; neuroblastoma; choriocarcinoma; testicular cancer; Wilms'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;

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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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up 【N/A】 <i>Case-control study</i> —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】 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants 【N/A】 (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed 【N/A】 <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed 【N/A】 <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed 【N/A】 <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy 【N/A】 (e) Describe any sensitivity analyses 【N/A】

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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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) 【N/A】
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time 【N/A】 <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure 【N/A】 <i>Cross-sectional study</i> —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.