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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.

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

ABSTRACT

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

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

Results: We identified three policy periods: prior to the initial price regulation (October 2011 to September 2012); during price regulation (October 2012 to June 2015); and after price deregulation (July 2015 to June 2016). During government price regulation, compared to price-unregulated cancer medications (n = 22 mostly newer targeted therapies), the relative price of price-regulated medications (n = 30 mostly cytotoxic products) decreased significantly (β = -0.081, P < 0.001). After the government price deregulation, the relative price of price-unregulated medications decreased significantly (β = -0.013, P < 0.05).

Conclusion: Neither government price regulation nor deregulation significantly impacted the average volumes or average spending on all antineoplastic medications immediately after the policy changes or in the longer term (P > 0.05). To control the rapid growth of oncology medication expenditures, more effective measures than price regulation of selected products are needed.

Strengths and limitations

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

Introduction

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

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

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

In October 2012, the NDRC established maximum retail prices for specific products listed in the 2009 National Reimbursement List, including 36 antineoplastic medications. Following the central government's requirement to limit regulatory controls in economic management, China loosened administrative controls over medication prices and the NDRC formally abolished price ceiling policies in 2015.¹⁷ Improvement of access to price-regulated medications after the 2012 price regulation and price increases after the 2015 government price deregulation were expected. However, a complicated web of policies influence hospital medication use and spending in China. (Table 1) For example, the price-regulated products were also listed on the insurance reimbursement list and are therefore subject to a hospital spending limit for insurance-reimbursable medications. In addition, all medications procured by hospitals also undergo price negotiation by the provincial government. Lastly, the price-regulated antineoplastic group comprised mostly cytotoxic chemotherapy medications; newer, more costly targeted anticancer medications were not subject to price regulation. The effect of government regulation and deregulation of the prices of cancer medications, in the context of provincial policies, is unknown.

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

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

Table 1. Policies	affecting	medication	sales in	Chinese	hospitals
	ancoung	incurcation	sales III	Chinese	nospitais

Methods

Study design

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

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

Data source

Data on products purchased between October 2011 and June 2016 were extracted from the observational Chinese Medical Economic Information (CEMI) database of public hospital medication purchasing records.¹⁹ We conducted a search of all antineoplastic medications in the database by ATC 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 Lp, which reflects what happens to the price level of a fixed basket of goods in a given period of time, compared to the price of the basket of goods during a previous period. ²¹ In this study, the Lp was calculated based on equation (1):

$$L_{pt} = \frac{\sum P_{ijt} Q_{ij0}}{\sum P_{ij0} Q_{ij0}} \tag{1}$$

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

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

Statistical Analysis

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

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

$$\begin{split} Y_{it} &= \beta_0 + \beta_1 \times time_t + \beta_2 \times regulation + \beta_3 \times reg_trend + \beta_4 \\ &\times deregulation + \beta_5 \times der_trend + \varepsilon_{it} \ (2) \end{split}$$

We used β_0 to estimate the baseline purchasing volume and spending; β_1 estimated the pre-regulation trend; β_2 estimated the change in level after the regulation policy; β_3 estimated the change in trend after the regulation policy; β_4 estimated the change in level after the deregulation policy; β_5 estimated the change in trend after the deregulation policy. Key coefficients were β_2 , β_3 , β_4 and β_5 . To estimate the combined level and trend impacts of the policy changes, we calculated the absolute difference in Y_{it} at 12 months after regulation and deregulation, respectively, compared to the counterfactual, that is, the estimated Y_{it} had the intervention not happened.^{18, 24}

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

Study Results

Influence of Government Pricing Policies on Relative Purchase Prices

The Lp declined over time in both intervention and control medication groups (that is, prices decreased relative to baseline) from October 2011 to June 2016 (Table 2, Figure 2). After government price regulation in October 2012, the Lp for price-regulated medications dropped suddenly ($\beta = -0.082$, P < 0.001), with significant declines in Lp relative to price-unregulated medications ($\beta = -0.081$, P < 0.001). At 12 months after the regulation, there was an estimated reduction in the Lp for price-regulated medications of 0.058 (P < 0.05) and an estimated increase in the Lp for price-unregulated of 0.029 (P < 0.05).

After the government price deregulation in June 2015, the Lp for price-unregulated medications decreased significantly ($\beta = -0.013$, P < 0.05), but no significant discontinuities in Lp levels or trends were observed for the price-regulated medications or for their relative change compared to price-unregulated medications. At 12 months after price deregulation, there was no change in Lp for price regulated medications and an estimated reduction in the Lp for price-unregulated medications of 0.043 (P < 0.05).

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2 3 4 5 6 7 8	Table 2. Re price regula purchase ve antineoplast	ation and olumes and	deregulatior	n on Laspe for price-1	eyres Price regulated,	Index, n price-unreg	nonthly a	verage	
9 10 11 12 13 14		Baseline level	Baseline trend	Post-regula tion level change	Post-regul ation trend change	Change at 12 months after regulation	Post-dere gulation level change	Post-dere gulation trend change	Change at 12 months after deregulation
15 16	Lp Price Index								rote
17	All medications	0.993***	-0.004*	-0.057***	0.001	-0.032	-0.002	0.001	-0·013 G
18	Price-regulated medications	0.988***	-0.004*	-0.082***	0.001	-0.058*	-0.003	0.002	0.000 Å
19 20 21	Price-unregulated medications	1.006***	-0.003***	0.002	0.001	0.029*	-0.013*	0.000	-0·043* copy ri
21	Difference between groups	-0.015	-0.002	-0.081***	0.001	-0.071	0.005	0.002	0.043* ght
23 24 25	Hospital Purchase Volume (Thousand DDD)								Protected by copyright -0·013 0·000 0·0043* by copyright 0·043* 0·043* -4·218 copyright -8·455 1:573
25 26	All medications	38.086***	0.915	1.938	-0.525	-4.881	-0.176	-0.311	-4·218 ng
27	Price-regulated medications	58.502***	1.447	3.325	-0.862	-7.878	-1.605	-0.527	-8·455 o
28 29 30	Price-unregulated medications	10.242***	0.193	0.004	-0.068	-0.879	1.798	-0.017	1·573
31	Difference between groups	48.252***	1.258	3.273	-0.798	-7.097	-3.370	-0.510	-10.003
32 33 34	Hospital Purchase Spending (Million CNY)								to text
35	All medications	11.129***	0.168	-0.092	-0.083	-0.854	0.257	-0.063	-0·945 and
36	Price-regulated medications	12.628***	0.239	-0.778	-0.178	-2.821	-0.323	-0.013	-0·912 da
37 38 39	Price-unregulated medications	9.085***	0.073	0.832	0.048	1.806	1.052	-0.132	-0.945 and data -0.912 data -0.992 mining 0.122 ,
40	Difference between groups	3.614***	0.158*	-1.570**	-0.219**	-4.508*	-1.301*	0.117	0·122 g
41 -	* $P < 0.05 \cdot *$	* $P < 0.01 \cdot **$	* $P < 0.001$	nrice_regulate	d medications	· 30 antineor	lastic produ	cts with	ž –

*, $P \le 0.05$; **, $P \le 0.01$; ***, $P \le 0.001$; 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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Figure 3. There were no statistically significant changes in volume levels or trends after government price regulation or deregulation in any group.

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

Influence of Government Pricing Policies on Hospital Spending

Average hospital spending on all antineoplastic medications rose from 9.86 million CNY in October 2011 to 17.08 million CNY in June 2016 (Table 2, Figure 4). There were no statistically significant changes in spending levels or trends after government price regulation or deregulation in any of the groups. However, the spending on price-regulated medications decreased and spending on price-unregulated medications increased after both the regulation and deregulation policies, resulting in significant level and trend changes in the differences between the two groups. After government price regulation, the spending difference decreased suddenly ($\beta = -1.570$, P < 0.01) and increased somewhat more slowly ($\beta = -0.219$, P < 0.01) than the baseline period. At 12 months after regulation, the absolute spending difference between the groups was significantly lower (-4.508, P < 0.05) than would have been expected without the regulation.

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

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

Discussion

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

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

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

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

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

Limitations

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

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

Conclusion

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

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Competing Interests:

The authors declared no competing interests.

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Ethics approval and consent to participate

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

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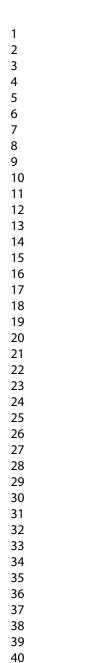
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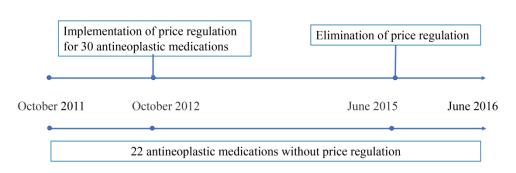
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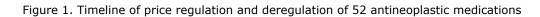
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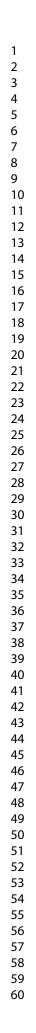
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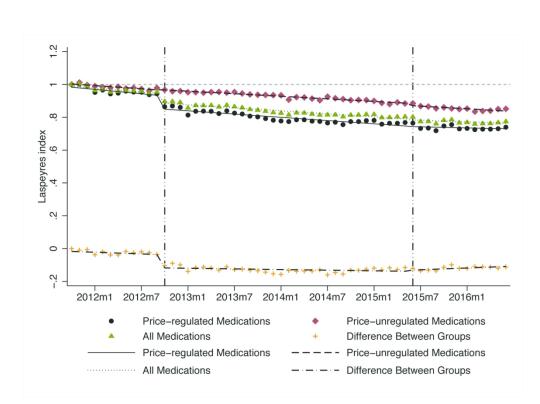
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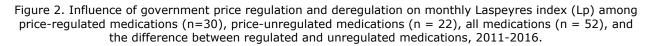












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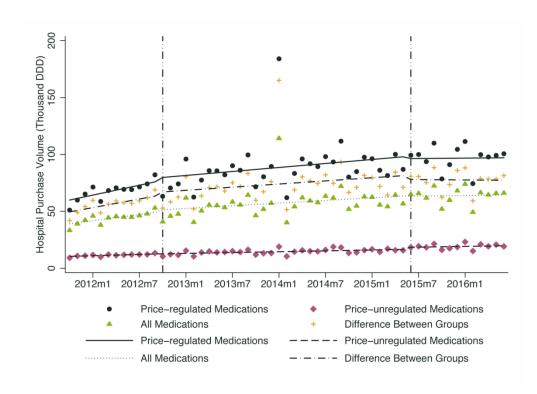


Figure 3. Influence of government price regulation and deregulation on monthly average purchase volumes among price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between groups, 2011-2016.

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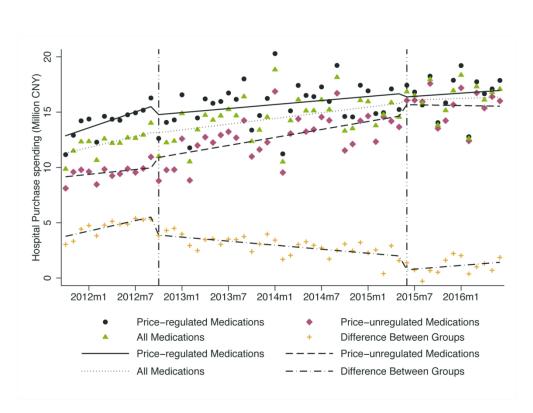


Figure 4. Influence of government price regulation and deregulation on monthly average spending on priceregulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and difference between groups, 2011-2016.

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

unregulated groups

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

e.

	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,
C		exposure, follow-up, and data collection [4]
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of
1		selection of participants. Describe methods of follow-up [N/A]
		Case-control study—Give the eligibility criteria, and the sources and methods of
		case ascertainment and control selection. Give the rationale for the choice of cases
		and controls [N/A]
		Cross-sectional study-Give the eligibility criteria, and the sources and methods of
		selection of participants [N/A]
		(b) Cohort study—For matched studies, give matching criteria and number of
		exposed and unexposed [N/A]
		Case-control study-For matched studies, give matching criteria and the number of
		controls per case [N/A]
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect
		modifiers. Give diagnostic criteria, if applicable [5]
Data sources/	8*	For each variable of interest, give sources of data and details of methods of
measurement		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]
		(<i>d</i>) Cohort study—If applicable, explain how loss to follow-up was addressed [N/A]
		Case-control study-If applicable, explain how matching of cases and controls was
		addressed [N/A]
		Cross-sectional study-If applicable, describe analytical methods taking account of
		sampling strategy [N/A]
		sampling strategy TN/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*	Cohort study—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]
		Cross-sectional study—Report numbers of outcome events or summary measures [N/A]
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their
		precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included [6-10]
		(b) Report category boundaries when continuous variables were categorized [6-10]
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period [N/A]
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses [6-10]
Discussion		
Key results	18	Summarise key results with reference to study objectives [10-11]
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.
		Discuss both direction and magnitude of any potential bias [11]
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity
		of analyses, results from similar studies, and other relevant evidence [11]
Generalisability	21	Discuss the generalisability (external validity) of the study results [11]
Other informati	on	
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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Author: Complete List of Authors:	
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	Depertment of Pharmacy Adiministration and Clinical Pharmacy; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Wushouer, Haishaerjiang; Chinese Academy of Engineering, Center for Strategic Studies; Tsinghua University, School of Medicine Yang, Mingchun; School of Pharmceutial Sciences, Peking University, Depertment of Pharmacy Adiministration and Clinical Pharmacy Han, Sheng; Peking University, International Research Center for Medicinal Administration Shi, Luwen; School of Pharmceutial Sciences, Peking University, Depertment of Pharmacy Adiministration and Clinical Pharmacy Ross-Degnan, Dennis; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Wagner, Anita; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine
Primary Subject Heading :	Health policy
Secondary Subject Heading:	Health policy
	Price Regulation, Deregulation, Laspeyres index, Antineoplastic Medications



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

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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

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

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

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1 ABSTRACT

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

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

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

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.

27 Strengths and limitations

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

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

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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

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

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

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

medication prices and the NDRC formally abolished price ceiling policies in 2015.²⁸ Improvement in access to price-regulated medications after the 2012 price regulation and price increases after the 2015 government price deregulation were expected. However, the effects of government price regulation and deregulation on anticancer medications is unknown. We studied impacts of NDRC price regulation and deregulation on the relative prices and sales volumes and spending on antineoplastic medications in China.

84 Methods

85 Study design

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

Figure 1. Timeline of price regulation and deregulation of 52 antineoplasticmedications

105 Data source

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

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

122 Outcome measures

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

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

)

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

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

141 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

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

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

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

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

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

- **Patient and public involvement**
- 170 There were no patients and public involved in in the design or planning of the study.

 173 Study Results

174 Influence of Government Pricing Policies on Relative Purchase Prices

The Lp declined over time in both intervention and control medication groups (that is, prices decreased relative to baseline) (Table 1, Figure 2). After government price regulation in October 2012, the Lp for price-regulated medications dropped suddenly (level change $\beta = -0.082$, 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 6	180	there was an estimated reduction in the Lp for price-regulated medications of 0.058 (P
7	181	< 0.05) and an estimated increase in the Lp for price-unregulated of 0.029 (P < 0.05).
8 9	182	After the government price deregulation in June 2015, the Lp for price-unregulated
10	183	medications decreased significantly (level change β = -0.013, P < 0.05), but no
11 12	184	significant discontinuities in Lp levels or trends were observed for the price-regulated
13	185	medications or for the relative change compared to price-unregulated medications. At
14 15	186	12 months after price deregulation, there was no change in Lp for price regulated
16	187	medications and an estimated reduction in the Lp for price-unregulated medications of
17 18	188	0.043 (P < 0.05).
19	190	0.043 (P < 0.05).
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Table 1. Results of interrupted time series analyses of the impacts of government price regulation and deregulation on Laspeyres Price Index, monthly average purchase volumes and spending for price-regulated, price-unregulated, and all antineoplastic medications, as well as group differences, 2011-2016

9 10 11 12 13 14 15 16 17		Baseline level	Baseline trend	Post- regulation level change	Post- regulation trend change	Change at 12 months after regulation	Post- deregulat ion level change	Post- deregulat ion trend change	Change a 12 mon after deregulat	nths
18 19	Lp Price Index									by cc
20 21	All medications	0.993***	-0.004*	-0.057***	0.001	-0.032	-0.002	0.001	-0.013	pyrigh
22 23	Price-regulated medications	0.988***	-0.004*	-0.082***	0.001	-0.058*	-0.003	0.002	0.000	וt, incl
24 25 26 27	Price-unregulated medications	1.006***	-0.003***	0.002	0.001	0.029*	-0.013*	0.000	-0.043*	uding for u
28 29 30	Difference between groups	-0.012	-0.002	-0.081***	0.001	-0.071	0.005	0.002	0.043*	Enseiç ses re
30 31 32 33 34 35 36	Hospital Purchase Volume (Thousand DDD)								after deregulat -0·013 0·000 -0·043* 0·043* -4·218	nement Sul lated to text
	All medications	38.086***	0.915	1.938	-0.525	-4.881	-0.176	-0.311	-4·218	perieu and d
37 38	Price-regulated medications	58.502***	1.447	3-325	-0.862	-7.878	-1.605	-0.527	-8-455	r (ABE lata mi
39 40 41 42	Price-unregulated medications	10.242***	0.193	0.004	-0.068	-0.879	1.798	-0·017	1.573	ur (ABES) . data mining, Al training,
43 44	Difference between groups	48.252***	1.258	3.273	-0.798	-7.097	-3.370	-0.510	-10.003	ining, i
45 46 47 48	Hospital Purchase Spending (Million CNY)									and similar technologies
49 50	All medications	11.129***	0.168	-0.092	-0.083	-0.854	0.257	-0.063	-0.945	techn
51 52 53	Price-regulated medications	12.628***	0.239	-0.778	-0.178	-2.821	-0.323	-0.013	-0.912	ologie
53 54 55 56 57 58 59	Price-unregulated medications	9.085***	0.073	0.832	0.048	1.806	1.052	-0.132	-0.992	ŝ
	Difference between groups	3.614***	0.158*	-1.570**	-0.219**	-4.508*	-1.301*	0.117	0.122	
60										d

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195*, $P \le 0.05$; **, $P \le 0.01$; ***, $P \le 0.001$; price-regulated medications: 30 antineoplastic products with196price regulation in 2012 and deregulation in 2015; price-unregulated medications: 22 antineoplastic197products without price regulation or deregulation; DDD=defined daily doses; CNY = Chinese Yuan (1198CNY = 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.

206 Influence of Government Pricing Policies on Average Purchase Volumes

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

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

217 Influence of Government Pricing Policies on Hospital Spending

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

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

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

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

240 Discussion

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

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

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

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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.

293 Limitations

The study had some limitations. First, we were unable to obtain the full list of products under government price regulation since 1996, which could lead to selection bias.. Second, the inherent limitation of Laspeyres index may lead to underestimating the price decreases. However, the impact of this limitation was limited, since price elasticity of demand for medicines is relatively small. Third, the comparison group of price-unregulated oncology medications tended to include newer, more expensive products than the price-regulated group and the two groups differed in other characteristics such as indications and therapeutic status in treatment. However, the Lp trends observed at baseline in the two groups of products were quite similar, suggesting that differential changes observed following the government pricing policies were indicative of true differences. Fourth, given that our analyses are based on procurement data we have not information on indications of use and potential therapeutic substitution. Fifth, some new antineoplastic drugs not included in the NRDL and thus not price-regulated may be made available by manufacturers' access programs (like buy 3 get 3 free) for individual patients. These products would not be part of our price, volume, or spending analyses because they would be transacted directly between individual physicians, their patients, and the manufacturer (or an intermediary). However, the number of patients who participated in access programs was limited and almost 70% of medication sales in China occur in hospitals.⁵² Sixth, given our use of aggregated hospital procurement data, we could not assess factors such as the numbers of patients treated or appropriate use given levels of medication spending or volume.

316 Conclusion

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

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- - **Competing Interests:**
 - 329 The authors declared no competing interests.
- ⁵⁹ 331 **Funding**

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337 Ethics approval and consent to participate

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

341 Data availability statement

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

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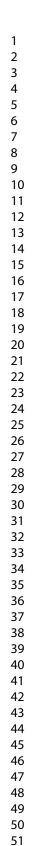
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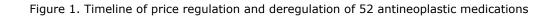
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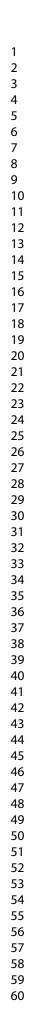
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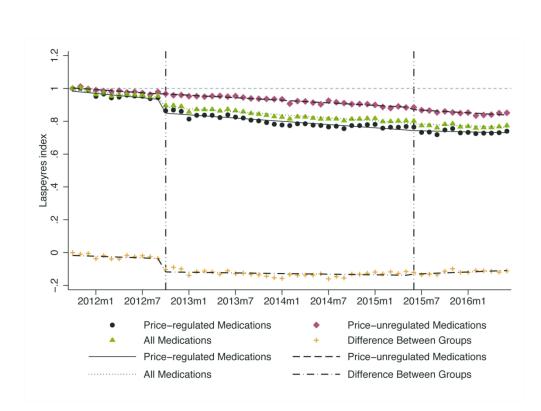
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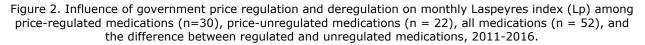












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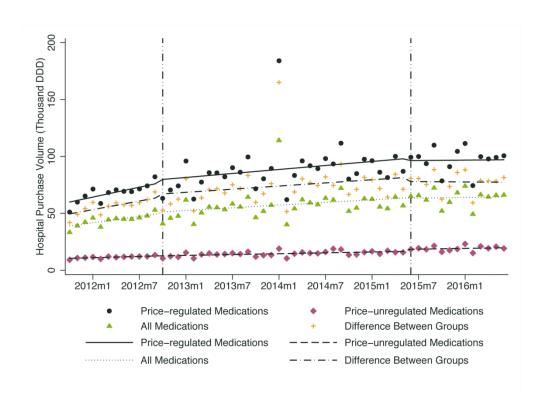


Figure 3. Influence of government price regulation and deregulation on monthly average purchase volumes among price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between groups, 2011-2016.

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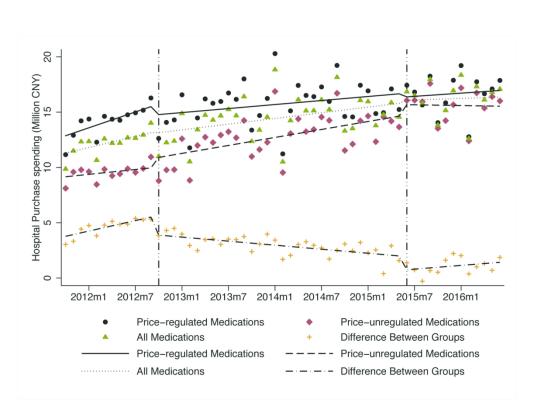
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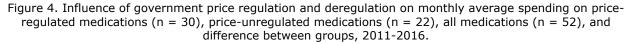
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7 8	Generic Name	ATC	Classfication	Manufactures ¹	Indications Approved in China
9	aclarubicin	L01DB04	chemotherapy	originator only	acute leukemia; malige
10 11 12	altretamine	L01XX03	chemotherapy	generic only	ovarian cancer; small and grading cancer; malignant lymphoma; endometria
13 14 15 16 17	asparaginase	L01XX02	chemotherapy	originator and generic	acute lymphoblastic log fennia, ALL; acute myeloid leukemia, AML; acute moocytic leukemia, AMOL; chronic myeloid leukemia, CML; Hodgkin's lymphoma; non-Hodgkin's lymphona;
18 19 20 21 22	bleomycin	L01DC01	chemotherapy	originator and generic	Cutaneous Carcinoma head and neck cancer; lung cancer; esophageal cancer; makignant lymphoma; cervical carcinoma; neurogliona ;
23 24 25 26	busulfan	L01AB01	chemotherapy	originator only	chronic myeloid leuke Enia Essential Thrombocythemia, polycythemia vera and other chronic myeloproliferative disorders, CMPDs
27 28 29	carboplatin	L01XA02	chemotherapy	originator and generic	ovarian cancer; small را المجود المعنية squamous cell carcino والمجود المعنية squamous cell carcino والمجود المحافظة المح
30 31 32	carmofur	L01BC04	chemotherapy	generic only	gastrointestinal cancer colorectal cancer, gastric cancer, esophagus cancer); breast cancer;
33 34 35	carmustine	L01AD01	chemotherapy	generic only	encephaloma; brain motastases; meningeal leukemia; malignant lymphoma; muttiple myeloma; malignant melanoma;
36 37 38 39	dacarbazine	L01AX04	chemotherapy	generic only	melanoma; soft tissue tumor; malignant lymphoma;
40 41 42 43 44			For peer review only - h	ttp://bmjopen.bmj.com/	iographique /site/about/guidelines.xhtml de

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			BMJ Open	acute myeloid leukemin, AML; acute lymphoblastic
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				acute myeloid leukema. AML: acute lymphoblastic
daunorubicin	L01DB02	chemotherapy	generic only	leukemia, ALL;
docetaxel	L01CD02	chemotherapy	originator and generic	breast cancer; non-small coll lung cancer;
doxifluridine	1	chemotherapy	generic only	Breast cancer; gastrig backcer; colorectal cancer; nasopharyngeal cancer;
epirubicin	L01DB03	chemotherapy	originator and	leukemia; malignant ly for the source in the source is the source in the source is the source in the source is the
.L			generic	cancer; colorectal can e avarian cancer;
				small cell lung cancer : small cell lung
etoposide	L01CB01	chemotherapy	generic only	esophageal carcinoma
				cancer; fra ni
fludarabine	L01BB05	chemotherapy	originator and generic	chronic lymphocytic le ukemia;
a				Gastrointestinal Cancer;
fluorouracil	L01BC02	chemotherapy	generic only	Ovarian Carcinoma; ling cancer; cervical carcinoma; bladder cancer; skin cancer;
gemcitabine	L01BC05	chemotherapy	originator and	non-small cell lung care pancreatic cancer; breast
8			generic	cancer; \overline{g} , \overline{g} primary liver cancer; \overline{g} astoc cancer; bladder cancer; rectal
hydroxycamptothecin	/	chemotherapy	originator and generic	cancer; head and neck epithelial cancer; leukemia and other malignant tumors
lobaplatin	/	chemotherapy	originator only	breast cancer; small cell lung cancer; chronic myeloid leukemia
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nedaplatin	/	chemotherapy	generic only	Solid tumors such as la ad and neck cancer, small cell lung
neuupiuum	,	enemetapy	generie only	cancer, non-small cell ung cancer and esophageal cancer
nimustine	L01AD06	chemotherapy	originator and	brian tumor; gastroint g g g g l cancer; lung cancer; malignant
	Lonie	enemetapy	generic	lymphoma; chronic le
oxaliplatin	L01XA03	chemotherapy	originator and generic	colorectal carcinoma; HCC;
semustine	L01AD03	chemotherapy	generic only	brain tumor; malignan geographoma; gastric cancer; colon
		6		cancer; melanoma;
tegafur	L01BC03	chemotherapy	generic only	Gastrointestinal Cancer;
tegafur, gimeracil and	L01BC53	chemotherapy	generic only	gastrointestinal cancer
oteracil porassium		F)		pancreatic cancer); br and ancer; liver cancer;
temozolomide	L01AX03	chemotherapy	originator and generic	glioblastoma multiforme, BM; anaplastic astrocytoma;
teniposide	L01CB02	chemotherapy	originator and	malignant lymphoma; zengral nervous system-tumors;
temposide	LUICDUZ	enemotierapy	generic	bladder cancer; B
topotecan	L01XX17	chemotherapy	originator and generic	small cell lung cancer
				non-small cell lung carge small cell lung cancer;
vindesine	L01CA03	chemotherapy	generic only	malignant lymphoma; Freast cancer; esophageal carcinoma;
				malignant melanoma; 🖉
vinorelbine	L01CA04	chemotherapy	originator and generic	non-small cell lung cancer breast cancer;
¹ Manufactures of specific	e medications	during our study period	1.	Agence
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plement 1B. Antin	eoplastic medic	ations samples of the in	tervention group	jopen-2019-031658 on 28 l by copyright, including fc
Generic Name	ATC	Classfication	Manufactures ¹	Indications Approved in China
actinomycin D	L01DA01	chemotherapy	originator and generic	Hodgkin's disease; testicular cancer; Wall by tumor; Ewing's sarcoma; rhabdomyosarcoma
amsacrine	L01XX01	chemotherapy	generic only	acute leukemia; ma
arsenite	L01XX27	chemotherapy	generic only	acute promyelocytize wakemia, APL; liver cancer;
bortezomib	L01XX32	targeted therapy	originator and generic	multiple myeloma;
cetuximab	L01XC06	targeted therapy	originator only	colorectal cancer;
decitabine	L01BC08	chemotherapy	originator and generic	myelodysplastic symplece(MDS);
doxorubicin	L01DB01	chemotherapy	originator and generic	acute myeloid leuk min lymphoma; soft tissue tumor ar osteosarcoma; chlicken malignant tumour; solid tumor in adults; particularly greast cancer and lung cancer;
erlotinib	L01XE03	targeted therapy	originator only	non-small cell lung
floxuridine	L01BC09	chemotherapy	generic only	liver cancer; rectume cancer; esophageal cancer; gastric cancer; breast cancer; http://www.seconder.com/seconder/
fluorouracil combinations	L01BC52	chemotherapy	generic only	gastrointestinal canger; greast cancer; liver cancer;
gefitinib	L01XE02	targeted therapy	originator only	non-small cell lung canger;
idarubicin	L01DB06	chemotherapy	originator only	acute myeloid leukemia AML; acute lymphoblastic leukemia, ALL;
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1 2					njopen-2019-031658 c 1 by copyright, includ
3					1658 (includ
4 5 6 7	imatinib	L01XE01	targeted therapy	originator and generic	chronic myeloid let en a, CML; gastrointestinal stromal tumors, GIST; acute phoblastic leukemia, ALL;
7 8	raltitrexed	L01BA03	chemotherapy	originator only	colorectal cancer;
9 10 11	rituximab	L01XC02	targeted therapy	originator only	follicle Center Lymel and has; follicular non-Hodgkin's lymphom; diffuse la get -cell lymphoma;
12 13 14	sunitinib	L01XE04	targeted therapy	originator only	renal cell cancer, RCC, astrointestinal stromal tumors, GIST; pancreatic neugos ndocrine tumors, pNET;
15 16	sorafenib	L01XE05	targeted therapy	originator only	renal cell cancer; has a second cancer; has a second cancer in the secon
17 18 19	tioguanine	L01BB03	chemotherapy	generic only	acute lymphocytic grading acute non-lymphocytic leukemia; chronic grading acute leukemia;
20 21	nilotinib	L01XE08	targeted therapy	originator only	chronic myeloid leux erisia;
22	trastuzumab	L01XC03	targeted therapy	originator only	breast cancer; gastre concer;
23 24 25	thiotepa	L01AC01	chemotherapy	generic only	breast cancer; ovarian cancer; bladder cancer; gastrointestinal caner;
26 27 28 29	vinblastine	L01CA01	chemotherapy	generic only	acute leukemia; Hoggkon's lymphoma; malignant melanoma; breast cancer; bronchogenic carcinoma; soft tissue sarcoma; neugoblastoma;
	¹ Manufactures of spe	ecific medications	s during our study perio	od.	ne 7, hnold
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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
		(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,
0		exposure, follow-up, and data collection [4]
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of
		selection of participants. Describe methods of follow-up [N/A]
		<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]
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of
		selection of participants [N/A]
		(b) Cohort study—For matched studies, give matching criteria and number of
		exposed and unexposed [N/A]
		Case-control study—For matched studies, give matching criteria and the number of
		controls per case [N/A]
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effec
		modifiers. Give diagnostic criteria, if applicable [5]
Data sources/	8*	For each variable of interest, give sources of data and details of methods of
measurement		assessment (measurement). Describe comparability of assessment methods if there
		is more than one group [4]
Bias	9	Describe any efforts to address potential sources of bias [N/A]
Study size	10	Explain how the study size was arrived at [N/A]
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,
		describe which groupings were chosen and why [5]
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		[5]
		(b) Describe any methods used to examine subgroups and interactions [5]
		(c) Explain how missing data were addressed [5]
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed
		[N/A]
		Case-control study—If applicable, explain how matching of cases and controls was
		addressed [N/A]
		Cross-sectional study-If applicable, describe analytical methods taking account of
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy [N/A]

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			of analyses, results from similar studies, and other relevant evidence [11]
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	Other informatio	n	
Funding 22 Give the source of funding and the role of the funders for the present study and, if appli	unding	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]			for the original study on which the present article is based [12]

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

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

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

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

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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.

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

ABSTRACT

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

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

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

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

Strengths and limitations

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

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

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

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

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

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

84 Methods

85 Study design

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

Figure 1. Timeline of price regulation and deregulation of 52 antineoplasticmedications

105 Data source

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

medication purchase price per package, monthly purchasing volumes and monthly

hospital spending. **Outcome measures**

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

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

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

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

Statistical Analysis

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

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

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

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

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

- 170 Patient and public involvement
- 171 There were no patients and public involved in in the design or planning of the study.

173 Study Results

174 Influence of Government Pricing Policies on Relative Purchase Prices

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

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

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

and unregulated medications, 2011-2016.

194	medications,	, as well as g	group differe							
				Post-	Post-	Change at	Post-	Post-	Change a	
		Baseline	Baseline	regulation	regulation	12 months	deregulat	deregulat	12 mor	nths
		level	trend	level	trend	after	ion level	ion trend	after	
				change	change	regulation	change	change	deregula	tion
Lp Price Ind										P
All medicati		0.993***	-0.004*	-0.057***	0.001	-0.032	-0.002	0.001	-0.013	Protected
Price-regular	ted medications	0.988***	-0.004*	-0.082***	0.001	-0.058*	-0.003	0.002	0.000	cted
Price-unregu	ılated	1.006***	-0.003***	0.002	0.001	0.029*	-0.013*	0.000	-0.043*	l by
medications		1 000	0 0 0 0 0	0 002	0 001	0 02)	0 015	0 000		cop
Difference b	etween groups	-0.012	-0.002	-0.081***	0.001	-0.071	0.005	0.002	0.043*	yrig
Hospital Pu	urchase Volume									ght,
(Thousand E	DDD)									by copyright, including for
All medicati	ons	38.086***	0.915	1.938	-0.525	-4.881	-0.176	-0.311	-4.218	udii
Price-regular	ted medications	58.502***	1.447	3.325	-0.862	-7.878	-1.605	-0.527	-8.455	ng f
Price-unregulated		10.242***	0.193	0.004	-0.068	-0.879	1.798	-0.017	1.573	or u
medications		10 242	0 175	0 004	0 000	0 017	1 / 70	0 017	1 575	ses
Difference b	etween groups	48.252***	1.258	3.273	-0.798	-7.097	-3.370	-0.510	-10.003	<u>rel</u>
Hospital Put	rchase Spending									ated
(Million CN	Y)									to
All medicati	ons	11.129***	0.168	-0.092	-0.083	-0.854	0.257	-0.063	-0.945	uses related to text and data mining,
Price-regulat	ted medications	12.628***	0.239	-0.778	-0.178	-2.821	-0.323	-0.013	-0.912	and
Price-unregu	ılated	9.085***	0.073	0.832	0.048	1.806	1.052	-0.132	-0.992	dat
medications		9 005	0 075	0 832	0 040	1 800	1 052	-0 132	-0 992	ia m
Difference b	etween groups	3.614***	0.158*	-1.570**	-0.219**	-4.508*	-1.301*	0.117	0.122	inir
195	*, P $\leq 0.05;$	**, $P \leq 0.01$	$;***,P \leq 0$	001; price-reg	ulated medica	ations: 30 anti	neoplastic pr	oducts		, ',
196	with price regu	lation in 2012	and deregulati	on in 2015; pr	ice-unregulate	ed medication	s: 22 antineo	plastic		l tr
197	products witho	ut price regula	tion or deregu	lation; DDD=	defined daily	doses; CNY	= Chinese Y	uan (1		Al training,
198	CNY = 0.155 U	US\$ in 2011)								
100										and
199										sin
200										ıilar
201	Figure 2 L	fluonco of	govornmon	t price rem	ulation and	dorogulati	on on ma	nthly		tec
201	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									
202	medications			-			-			logi
203 204	and unregula	· · · · · · · · · · · · · · · · · · ·		· · · · · · · · · · · · · · · · · · ·	and the di	nerence de	tween regt	inated		ies.
204	and unregula	aled medicat	ions /UII-	/010						

206 Influence of Government Pricing Policies on Average Purchase Volumes

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

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

217 Influence of Government Pricing Policies on Hospital Spending

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

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

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

Discussion

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

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

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

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

Finally, prescribers may have maintained a preference for the newer, more expensive medications in the price-unregulated group.⁴⁶ Studies in 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 Mark-up Policy allowed hospitals to charge

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

293 Limitations

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

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.

2		
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9	329	
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23		
24 25	338	
26	339	Ethics approval and consent to participate
27		
28 29	340	The study was considered non-human subjects research by the Harvard Pilgrim Health
30	341	Care Institutional Review Board.
31	342	
32 33		
34	343	Data availability statement
35	344	Data on products purchased between October 2011 and June 2016 were extracted from
36 37	345	the observational Chinese Medical Economic Information (CMEI) database of public
38	346	hospital medication purchasing records. This data is unavailable to the public due to its
39	347	confidentiality. Researchers interested in the data need to contact Chinese
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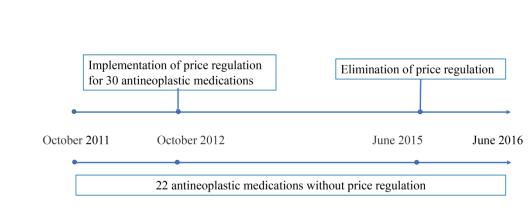
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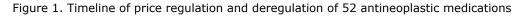
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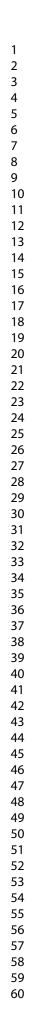
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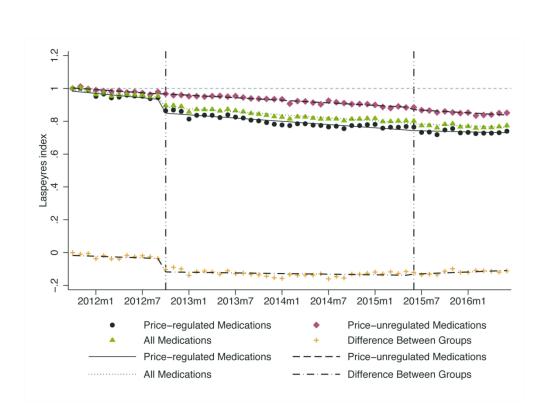
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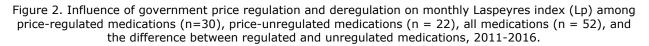
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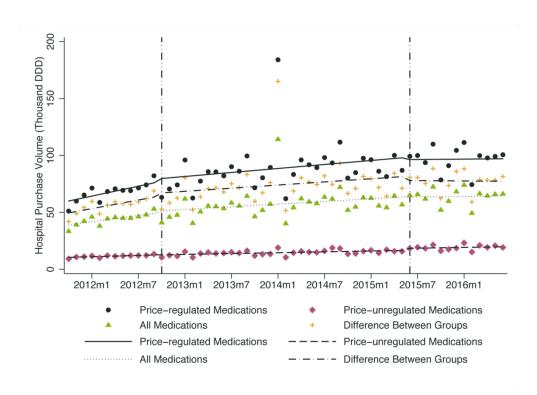


Figure 3. Influence of government price regulation and deregulation on monthly average purchase volumes among price-regulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and the difference between groups, 2011-2016.

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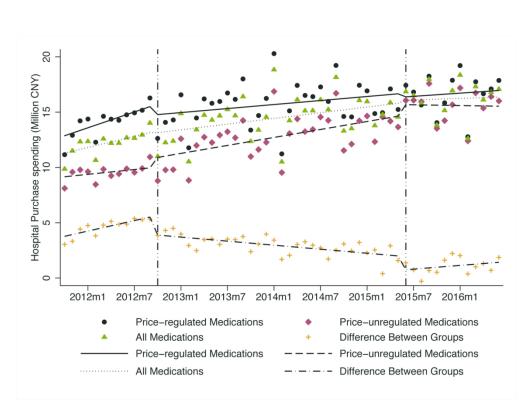


Figure 4. Influence of government price regulation and deregulation on monthly average spending on priceregulated medications (n = 30), price-unregulated medications (n = 22), all medications (n = 52), and difference between groups, 2011-2016.

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9	aclarubicin	L01DB04	chemotherapy	originator only	acute leukemia; maligeda elymphoma;
10 11 12	altretamine	L01XX03	chemotherapy	generic only	ovarian cancer; small and sing cancer; malignant lymphoma; endometria
13 14 15 16 17 18	asparaginase	L01XX02	chemotherapy	originator and generic	acute lymphoblastic log segnia, ALL; acute myeloid leukemia, AML; acute moocytic leukemia, AMOL; chronic myeloid leukemia, CML; Hodgkin's lymphoma; non-Hodgkin's lymphona;
19 20 21 22	bleomycin	L01DC01	chemotherapy	originator and generic	Cutaneous Carcinoma here and neck cancer; lung cancer; esophageal cancer; makignant lymphoma; cervical carcinoma; neurogliona;
23 24 25 26	busulfan	L01AB01	chemotherapy	originator only	chronic myeloid leukenia Essential Thrombocythemia, polycythemia vera and other chronic myeloproliferative disorders, CMPDs
27 28 29	carboplatin	L01XA02	chemotherapy	originator and generic	ovarian cancer; small را المجود المجلس squamous cell carcino المجلس squamous cell carcino المجلس squamous cell carcino المجلس عنه المحافظة المح
30 31 32	carmofur	L01BC04	chemotherapy	generic only	gastrointestinal cancer colorectal cancer, gastric cancer, esophagus cancer); breast cancer; encephaloma; brain metasuses; meningeal leukemia;
33 34 35	carmustine	L01AD01	chemotherapy	generic only	malignant lymphoma; multiple myeloma; malignant melanoma;
36 37 38	dacarbazine	L01AX04	chemotherapy	generic only	melanoma; soft tissue tumor; malignant lymphoma;
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daunorubicin	L01DB02	chemotherapy	generic only	acute myeloid leukemai, AML; acute lymphoblastic leukemia, ALL;
docetaxel	L01CD02	chemotherapy	originator and generic	breast cancer; non-small cancer;
doxifluridine	1	chemotherapy	generic only	Breast cancer; gastrig adcer; colorectal cancer; nasopharyngeal cance
epirubicin	L01DB03	chemotherapy	originator and generic	leukemia; malignant lähen beast cancer; lung cancer; so fatte sue tumor; gastric cancer; liver cancer; colorectal cange avarian cancer;
etoposide	L01CB01	chemotherapy	generic only	small cell lung cancer
fludarabine	L01BB05	chemotherapy	originator and generic	chronic lymphocytic leukemia;
fluorouracil	L01BC02	chemotherapy	generic only	Gastrointestinal Cancer; chorionepithilioma; breast cancer; Ovarian Carcinoma; lung cancer; cervical carcinoma; bladder cancer; skin cancer;
gemcitabine	L01BC05	chemotherapy	originator and generic	non-small cell lung cage pancreatic cancer; breast cancer;
hydroxycamptothecin	/	chemotherapy	originator and generic	primary liver cancer; state cancer; bladder cancer; rectal cancer; head and neck epithelial cancer; leukemia and other malignant tumors
lobaplatin	/	chemotherapy	originator only	breast cancer; small cell lung cancer; chronic myeloid leukemia
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nedaplatin	/	chemotherapy	generic only	Solid tumors such as la ad and neck cancer, small cell lung
1		17		cancer, non-small cell q un g cancer and esophageal cancer
nimustine	L01AD06	chemotherapy	originator and	brian tumor; gastroint 🖓 🖫 al cancer; lung cancer; malignant
			generic	lymphoma; chronic le國委員道;
oxaliplatin	L01XA03	chemotherapy	originator and generic	colorectal carcinoma; HCC;
semustine	L01AD03	chemotherapy	generic only	brain tumor; malignan brain tumor; malignan brain tumor; malignan brain brain tumor; colon cancer; colon cancer; melanoma;
togefur		ah am ath arany	conorio only	Gastrointestinal Cancer;
tegafur	L01BC03	chemotherapy	generic only	
tegafur, gimeracil and oteracil porassium	L01BC53	chemotherapy	generic only	gastrointestinal cancer f
temozolomide	L01AX03	chemotherapy	originator and generic	glioblastoma multiforme, BM; anaplastic astrocytoma;
teniposide	L01CB02	chemotherapy	originator and	malignant lymphoma; zeneral nervous system-tumors;
1		15	generic	bladder cancer;
topotecan	L01XX17	chemotherapy	originator and generic	small cell lung cancer
				non-small cell lung cancer;
vindesine	L01CA03	chemotherapy	generic only	malignant lymphoma; Freast cancer; esophageal carcinoma;
				malignant melanoma; 🖉
vinorelbine	L01CA04	chemotherapy	originator and generic	り、 いう
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Generic Name	ATC	Classfication	Manufactures ¹	Indications Approved in China
actinomycin D	L01DA01	chemotherapy	originator and generic	Hodgkin's disease; see blastoma; choriocarcinoma; testicular cancer; Walk blastoma; Ewing's sarcoma; rhabdomyosarcoma
amsacrine	L01XX01	chemotherapy	generic only	acute leukemia; ma
arsenite	L01XX27	chemotherapy	generic only	acute promyelocytize w kemia, APL; liver cancer;
bortezomib	L01XX32	targeted therapy	originator and generic	multiple myeloma;
cetuximab	L01XC06	targeted therapy	originator only	colorectal cancer; $\frac{1}{20}$
decitabine	L01BC08	chemotherapy	originator and generic	myelodysplastic symplece (MDS);
doxorubicin	L01DB01	chemotherapy	originator and generic	acute myeloid leuk min lymphoma; soft tissue tumor and osteosarcoma; chlicken malignant tumour; solid tumor in adults; particularly great cancer and lung cancer;
erlotinib	L01XE03	targeted therapy	originator only	non-small cell lung and er;
floxuridine	L01BC09	chemotherapy	generic only	liver cancer; rectume cancer; esophageal cancer; gastric cancer; breast cancer; lugg cancer;
fluorouracil combinations	L01BC52	chemotherapy	generic only	gastrointestinal canger; greast cancer; liver cancer;
gefitinib	L01XE02	targeted therapy	originator only	non-small cell lung canger;
idarubicin	L01DB06	chemotherapy	originator only	acute myeloid leukemia leukemia, ALL; #/about/guidelines.xhtml
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4 5 6 7	imatinib	L01XE01	targeted therapy	originator and generic	chronic myeloid leukemia, CML; gastrointestinal stromal tumors, GIST; acute phoblastic leukemia, ALL;
7 8	raltitrexed	L01BA03	chemotherapy	originator only	colorectal cancer; $\[\] \[\] \[\] \] \[\] \] \] \] \] \] \] \] \] \] \] \] \] $
9 10 11	rituximab	L01XC02	targeted therapy	originator only	follicle Center Lymologianas; follicular non-Hodgkin's lymphom; diffuse lage B-cell lymphoma;
12 13 14	sunitinib	L01XE04	targeted therapy	originator only	renal cell cancer, RCE gastrointestinal stromal tumors, GIST; pancreatic nation de gastrointe tumors, pNET;
15 16 17	sorafenib	L01XE05	targeted therapy	originator only	renal cell cancer; has a cellular carcinoma; thyroid cancer;
18 19	tioguanine	L01BB03	chemotherapy	generic only	acute lymphocytic 🔤 🦉 gmia; acute non-lymphocytic leukemia; chronic 🗝 🙀 d leukemia;
20 21	nilotinib	L01XE08	targeted therapy	originator only	chronic myeloid leuxeria;
22	trastuzumab	L01XC03	targeted therapy	originator only	breast cancer; gastrige concer;
23 24 25	thiotepa	L01AC01	chemotherapy	generic only	breast cancer; ovarian cancer; bladder cancer; gastrointestinal canger;
26 27 28 29	vinblastine	L01CA01	chemotherapy	generic only	acute leukemia; Hoggkon's lymphoma; malignant melanoma; breast cance; bronchogenic carcinoma; soft tissue sarcoma; neugoblastoma;
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	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,
C		exposure, follow-up, and data collection [4]
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of
		selection of participants. Describe methods of follow-up [N/A]
		Case-control study—Give the eligibility criteria, and the sources and methods of
		case ascertainment and control selection. Give the rationale for the choice of cases
		and controls [N/A]
		Cross-sectional study-Give the eligibility criteria, and the sources and methods of
		selection of participants [N/A]
		(b) Cohort study—For matched studies, give matching criteria and number of
		exposed and unexposed [N/A]
		Case-control study—For matched studies, give matching criteria and the number of
		controls per case [N/A]
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable [5]
Data sources/	8*	For each variable of interest, give sources of data and details of methods of
measurement		assessment (measurement). Describe comparability of assessment methods if there
		is more than one group [4]
Bias	9	Describe any efforts to address potential sources of bias [N/A]
Study size	10	Explain how the study size was arrived at [N/A]
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,
		describe which groupings were chosen and why [5]
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding[5]
		(b) Describe any methods used to examine subgroups and interactions [5]
		(c) Explain how missing data were addressed [5]
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed [N/A]
		Case-control study-If applicable, explain how matching of cases and controls was
		addressed [N/A]
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy [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	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information
data		on exposures and potential confounders [N/A]
		(b) Indicate number of participants with missing data for each variable of interest [N/A]
		(c) Cohort study—Summarise follow-up time (eg, average and total amount) [N/A]
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time [N/A]
		Case-control study-Report numbers in each exposure category, or summary measures of
		exposure [N/A]
		Cross-sectional study—Report numbers of outcome events or summary measures [N/A]
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their
		precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and
		why they were included [6-10]
		(b) Report category boundaries when continuous variables were categorized [6-10]
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful
		time period [N/A]
Other analyses	17	Report other analyses done-eg analyses of subgroups and interactions, and sensitivity
		analyses [6-10]
Discussion		
Key results	18	Summarise key results with reference to study objectives [10-11]
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.
		Discuss both direction and magnitude of any potential bias [11]
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity
		of analyses, results from similar studies, and other relevant evidence [11]
Generalisability	21	Discuss the generalisability (external validity) of the study results [11]
Other informati	on	
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.