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Association Between the Number of Suppliers for Critical Antineoplastics and Drug Shortages: Implications for Future Drug Shortages and Treatment

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QUESTION ASKED: Cancer drug shortages remain common in the United States and may force oncologists to prioritize patients for treatment, improvise standard treatment regimens, and potentially choose unproven treatment options for patients with curable disease. Because increased competition may reduce drug shortages, the objective of our study was to investigate the association between the number of suppliers for first-line breast, colon, and lung antineoplastics and resulting drug shortages.

SUMMARY ANSWER: Among 35 antineoplastic drugs approved for first-line treatment of breast, colon, and lung cancer, we saw an overall increase in drug shortages over time (12.5%, 33.3%, and 0% of breast, colon, and lung cancer drugs experienced shortages in 2003 *v* 40.0%, 37.5%, and 54.5% in 2014). Having a small number of drug suppliers more than doubled the odds of shortages compared with a large number of suppliers (five or more, Table 1), although the results were only statistically significant with three to four suppliers (odds ratio = 2.6; $P = .049$) but not with one to two suppliers (odds ratio = 3.49; $P = .105$); however, one of the strongest risk factors for drug shortages was the age of the drug, with older drugs significantly more likely to experience shortages ($P < .001$).

METHODS: Using the 2003-2014 Redbook and national drug shortage data from the University of Utah's Drug Information Service, we used exploratory analysis and generalized mixed models to (1) quantify time trends in first-line drug suppliers and shortages by cancer site and (2) examine the association between the number of suppliers for individual drugs and resulting drug shortages.

BIAS, CONFOUNDING FACTOR(S), DRAWBACKS: Although our study provides insights into the relationship between suppliers and drug shortages, we acknowledge the following drawbacks: (1) Information about the supply chain of raw materials, which may affect drug shortages, was not available. (2) As a result of sample size limitations, we were unable to conduct stratified analysis by cancer site. (3) As there is no regulatory requirement to disclose the manufacturer of a product, we could not distinguish drug suppliers from manufacturers as many suppliers participate in contract manufacturing. Despite these limitations, our analysis provides initial insights into the complicated relationship between drug shortages for first-line cancer treatment and the number of companies supplying these drugs.

REAL-LIFE IMPLICATIONS: We found that having few drug suppliers (three to four) was associated with increased likelihood of shortages compared with having a large number (five or more) of suppliers, but the relationship was nonlinear. However, we saw that older drugs were the most likely to experience drug shortages. This suggests that policies focused predominately on promoting increases in distinct suppliers and competition may not alleviate shortages of critical cancer drugs. Given the continued

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significant impact of these shortages on patient care, future policies should promote targeted efforts to understand underlying causes of shortages in older drugs in order to evaluate contributors to and predictors of shortages in the oncology community. These finding are important for oncologists as they demonstrate that current strategies for preventing drug shortages have limited effect. Oncologists and patient advocates can help push for more effective policy initiatives and research aimed at understanding drug shortages. JOP

Table 1. Association Between the Number of Suppliers and Reported Shortages* for FDA-Approved Antineoplastics Drugs for First-Line Treatment of Breast, Colon, and Lung Cancer (2003-2014)

	Model 1 All Drugs		Model 2 Drugs with Generic Equivalent	
Fixed Effects	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
No. of suppliers†				
1-2	3.49 (0.77 to 15.82)	.105	3.67 (0.80 to 16.89)	.095
3-4	2.60 (1.01 to 6.70)	.049	2.67 (1.02 to 7.02)	.046
5+ (reference)	1.00		1.00	
Year of observation	1.53 (1.32 to 1.78)	< .001	1.54 (1.31 to 1.80)	< .001
Year of approval‡	0.81 (0.74 to 0.89)	< .001	0.81 (0.74 to 0.89)	< .001
Cancer site				
Breast	0.97 (0.35 to 2.67)	.949	0.96 (0.34 to 2.75)	.939
Colon	2.33 (0.62 to 8.73)	.210	2.07 (0.50 to 8.00)	.330
Lung (reference)	1.00		1.00	
Had generic equivalent				
Yes	32.17 (1.96 to 527.99)	.015	—	
No (reference)	1.00		—	

NOTE. Three hundred forty-two observations for 35 drugs over a 12-year period (model 1); 191 observations for 21 drugs over a 12-year period (model 2). Model 1: Random slope model adjusting for the number of suppliers, year of observation, year of approval, cancer site and if a generic equivalent of the drug was on the market in a given year for all drugs. Model 2: Random slope model adjusting for the number of suppliers, year of observation, year of approval, and cancer site for drugs which had a generic equivalent was on the market during a given year.

Abbreviations: FDA, US Food and Drug Administration; OR, odds ratio.

*Information about reported drug shortages obtained from the University of Utah's Drug Information System.

†Information about the number of suppliers obtained from the 2003-2009 Redbook: Pharmacy's Fundamental Resource and the RED BOOK Online Database for subsequent years.

‡Year of FDA Approval for use of drug for specific cancer site based on drug information from the National Cancer Institute's website http://www.cancer.gov/cancertopics/druginfo/alphalist; drugs approved before 1984 were assigned the value of 1984 as year of approval.

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Abstract

Purpose

Congress has identified the critical need to evaluate contributors to ongoing cancer drug shortages. Because increased competition may reduce drug shortages, we investigated the association between the number of suppliers for first-line breast, colon, and lung antineoplastics and drug shortages.

Data and Methods

Using the 2003 to 2014 Red Book and national drug shortage data from the University of Utah's Drug Information Service, we used exploratory analysis to quantify time trends in first-line drug suppliers and shortages by cancer site. Generalized mixed models were used to examine the association between the number of suppliers for individual drugs and resulting drug shortages.

Results

Among 35 antineoplastic drugs approved for first-line treatment of breast, colon, and lung cancer, the number of unique suppliers varied greatly (range, 1 to 19). In 2003, 12.5%, 33.3%, and 0% of breast, colon, and lung cancer drugs, respectively, experienced shortages, which increased overall by 2014, to 40.0%, 37.5%, and 54.5%, respectively. Having a small number of drug suppliers more than doubled the odds of shortages compared with a large number of suppliers (≥ 5), although the results were only statistically significant with three to four suppliers (odds ratio = 2.6, $P = .049$) but not with one to two suppliers (odds ratio = 3.49, $P = .105$). One of the strongest risk factors for drug shortages was the age of the drug, with older drugs significantly more likely to experience shortages ($P < .001$).

Conclusion

Cancer drugs with a small number of suppliers had a higher risk of drug shortages than did those with ≥ 5 suppliers, but the relationship was nonlinear. Because the age of the drug is the strongest risk factor, future studies should explore underlying causes of shortages in older drugs.

ASSOCIATED CONTENT

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INTRODUCTION

In 2012, the U.S. Food and Drug Administration (FDA) identified 117 reported drug shortages, 84 of which involved sterile injectable drugs.[1,2] Although shortages seem to have decreased in 2013 and 2014,

the FDA continues to see high levels of drugs shortages, particularly for older sterile injectable drugs, such as cancer drugs.[1-3] These shortages may force oncologists to prioritize patients for treatment, improvise standard treatment regimens, and potentially choose unproven treatment options for patients with curable disease.[3-6] The underlying reasons for drug shortages are complex and may be caused by any number of factors, including manufacturing problems, business decisions, unanticipated changes in demand, difficulty acquiring raw materials, or other regulatory issues.[6-11] Another contributing factor may include the recent consolidation of several pharmaceutical suppliers to combine resources and maximize revenue in an era of declining profit margins,[12] potentially as a result of reimbursement policy changes and patent expirations.[10,13-18] Several studies have examined the effect on drug suppliers when patents expire,[13,14] identifying that older, generic drugs forming the mainstay cancer treatment regimens are increasingly being discontinued or have faced reduced production by companies in favor of newer, more profitable drugs.[1,12]

Recently, Congress identified the critical need to evaluate contributors to ongoing cancer drug shortages. One option proposed by policymakers to reduce the prevalence of drug shortages is to promote competition in drug manufacturing by encouraging more suppliers for critical chemotherapy drugs.[7,19,20] Currently, few suppliers produce generic drugs,[21] likely because other suppliers may have little financial incentive to initiate production of off-patent medications, including injectable oncology medications (which top the list of common drug shortages).[21-23] Because production of injectable oncology medications is lengthy and complicated, additional suppliers may not be willing or able to initiate or increase production in response to shortages.[21] Although the impact of oncology drug shortages on cancer care has been increasingly documented,[3-5,24] these studies have not addressed the implications of oncology manufacturing availability on drug shortages.[3] In 2011, the Office of the Assistant Secretary for Planning and Evaluation conducted an economic analysis of the causes of drug shortages and noted that ongoing oncology shortages were related to an expansion of products produced without corresponding increases in manufacturing capacity.[25] Therefore, using comprehensive data on the number of oncology drug suppliers, as well as information on the scope and timing of antineoplastic drug shortages, we examined the association between the number of drug suppliers for specific cancer drugs and occurrence of drug shortages. We hypothesized that drugs with a larger number of distinct suppliers would experience fewer shortages over time.

DATA AND METHODS

Data

We conducted a retrospective observational study using information from the 2003 to 2014 Red Book and national drug shortage data from the University of Utah's Drug Information Service (DIS).[11,26,27] The Red Book is a widely used resource that provides National Drug Codes, supplier names, deactivation status, generic status, and pricing history for all FDA-approved drugs in a given year.[26] Annual supplier information was available in paperback until 2009 and was changed to an online format in 2010.

Beginning in 2001, the DIS began nationally tracking drug shortages, defined as supply problems that could affect patient care or how the pharmacy would prepare the drug.[11] Under contract from the American Society of Health-System Pharmacists (ASHP), the DIS reported national shortages to ASHP's Drug Product Shortages Management Resource Center, beginning in 2001. Although the process for identifying and verifying shortage data has been previously described in detail,[11] in brief, once shortages are identified, the DIS verifies that a shortage exists by directly contacting the supplier.

Included Drugs and Shortage Information

We abstracted complete information from the Red Book on the number of distinct suppliers for FDA-approved cancer drugs for the treatment of colon, lung, and breast cancer, the three most common cancers in the United States.[28,29] We limited our analysis to drugs used in the first-line treatment of each cancer based on information published by the National Cancer Institute and National Comprehensive Cancer Network Guidelines and approved before 2014 (end of study). We then abstracted all information on reported drug shortages for each drug by year from the DIS drug shortage data and year of drug approval and approved cancer site from the National Cancer Institute.[11,26,28,30] Included drugs and associated numbers of suppliers are described in the online only Appendix Table A1.

Analytic Approach

Exploratory data analysis was used to quantify trends in suppliers and drug shortages by cancer site over time. For each

cancer site and year, we report the total number of FDA-approved drugs, number with reported shortages, and median number and range of suppliers. We also report the average percentage of suppliers identifying shortages in each year and percentage of approved drugs with shortages (Table 1).

Our analytic dataset included one observation per agent per year approved. To account for these repeated measures, we used generalized linear mixed models (GLMMs) with a random slope for year of observation per agent to examine the association between the occurrence of drug shortages (yes *v* no) and the number of suppliers for individual antineoplastic drugs. We estimated a model containing the number of suppliers as an independent variable (Table 2, Model 1), adjusting for the year of drug approval (continuous), year of observation (continuous), whether the drug had a generic equivalent on the market in a given year (yes *v* no), and cancer site for which the drug was approved (breast colon *v* lung). We included suppliers in the model as a continuous variable and categorized this variable into three or four groups using approximate tertiles and quartiles. Modeling the number of suppliers categorized into three groups (1-2, 3-4, and 5-19) produced the best model fit (ie, lowest pseudo Akaike's information criterion) and was therefore chosen as the final model. To account for the fact that most drugs experiencing shortages had a generic equivalent, we then fit a separate GLMM examining the association between suppliers and drug shortages for drugs that had a generic equivalent in a given year, adjusting for the same factors as Model 1(Table 2, Model 2). All analyses were conducted using SAS (version 9.3, 2012; SAS Institute, Cary NC).

Because methotrexate sodium, fluorouracil, paclitaxel, and bevacizumab have been approved for the first-line treatment of more than one of the cancer sites included in the analysis, these data are represented twice in our data (under each cancer site for which they are approved). However, FDA approval for a given cancer site may have taken place at different times. Therefore, we conducted sensitivity analyses including these drugs for only one cancer site for analysis and found that our results remained unchanged.

RESULTS

Trends in FDA-Approved Antineoplastics, Suppliers, and Drug Shortages

From 2003 to 2014, we identified 35 antineoplastic drugs approved for first-line treatment of breast, colon, and lung cancer (methotrexate sodium, fluorouracil, paclitaxel, and bevacizumab were approved for more than one site). Fifteen of these drugs were approved for use in breast cancer patients, eight for colon cancer, and 12 for lung cancer.

In 2003, eight drugs were approved for treatment of breast cancer, one of which experienced a reported drug shortage (fluorouracil; 12.5%; Table 1). By 2014, 15 drugs were FDA-approved, with shortages reported for fluorouracil, doxorubicin, methotrexate sodium, cyclophosphamide, tamoxifen, and paclitaxel (40.0%). Three drugs were approved for first-line treatment of colon cancer in 2003, with one reported shortage (fluorouracil; 33.3%). By 2014, eight drugs were FDA approved, with three reported shortages for fluorouracil, irinotecan, and leucovorin calcium (25.0%). Finally, in 2003, there were six FDA-approved lung cancer drugs, with no reported shortages. By 2014, 11 drugs were FDA approved (accounting for discontinuation of gefitinib in 2011), with six (paclitaxel, cisplatin, gemcitabine, carboplatin, methotrexate sodium, and etoposide/etoposide phosphate) experiencing shortages (54.6%).

The number of suppliers for FDA-approved antineoplastics also varied over time. The median number of suppliers for breast cancer drugs was 2.5 (range, 1 to 6) in 2003, increasing to 4.0 (range, 1 to 19) by 2014, as new drugs and generic equivalents were approved (Table 1). For colon cancer drugs, the median number of suppliers was three (range, 1 to 3) in 2003 versus two in 2014 (range, 1 to 10). Finally, for lung cancer, the median number of suppliers was four in 2003 (range, 1 to 8) and 2014 (range, 1 to 12). Across all three cancer sites, we first saw an overall decrease in the median number of suppliers through 2009, followed by a subsequent increase in median suppliers from 2010 to 2014.

Finally, among drugs experiencing a shortage, an average of 67% to 100% of breast and colon cancer drug suppliers and 80% to 100% of lung cancer drug suppliers reported a shortage across all years (Table 1). In other words, if there was a shortage reported for a drug in a given year, this shortage affected most, if not all, suppliers of that drug in that year.

Association Between Drug Suppliers and Shortages

GLMMs demonstrated a nonlinear relationship between the number of suppliers and drug shortages. Having a small number of drug suppliers more than doubled the odds of shortages compared with a large number of suppliers (≥ 5), although the results were only statistically significant with three to four suppliers (odds ratio [OR] = 2.6, $P = .049$) but not

Table 1. FDA-Approved Antineoplastic Drugs for the First-Line Treatment of Breast, Colon, and Lung Cancer: No. of Drugs Approved, No. of Drugs With Reported Shortages, and No. of Suppliers of These Drugs in 2003 to 2014

Cancer Site	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Breast cancer												
No. of drugs approved	8	8	10	12	13	14	14	14	14	14	15	15
No. of drugs with shortages*	1	3	3	3	4	5	3	5	7	6	6	6
% of drugs in shortage	12.5	37.5	30.0	25.0	30.8	35.7	21.4	35.7	50.0	42.9	40.0	40.0
Median no. of suppliers† (min, max)	2.5 (1, 6)	3.0 (1, 6)	2.5 (1, 6)	1.5 (1, 6)	2.0(1, 5)	1.5 (1, 7)	1.0 (1, 7)	1.0 (1, 7)	2.0 (1, 16)	4.0 (1, 19)	4.0 (1, 19)	4.0 (1, 19)
Among drugs with shortages, average % of suppliers reporting shortages (SD)	66.7 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	84.3 (14.4)	73.8 (25.1)	83.1 (18.1)	91.1 (11.9)	91.7 (12.9)	91.7 (12.9)	95.8 (10.2)
Colon cancer												
No. of drugs approved	3	3	6	7	8	8	8	8	8	8	8	8
No. of drugs with shortages*	1	1	1	1	1	2	2	3	4	3	3	3
% of drugs in shortage	33.3	33.3	16.7	14.3	12.5	25.0	25.0	37.5	50.0	37.5	37.5	37.5
Median no. of suppliers (min, max)	3.0 (1, 3)	3.0 (1, 4)	1.0 (1, 4)	1.0 (1, 3)	1.0 (1, 3)	1.0 (1, 4)	1.0 (1, 9)	1.5 (1, 8)	1.5 (1, 9)	1.5 (1, 8)	2.0 (1, 10)	2.0 (1, 10)
Among drugs with shortages, average % of suppliers reporting shortages (SD)	66.7 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	87.5 (17.7)	75.0 (35.4)	83.3 (14.4)	82.6 (21.6)	87.5 (21.7)	90.0 (17.3)	90.0 (17.3)
Lung cancer												
No. of drugs approved	6	7	8	8	9	9	10	10	10	10	10	11
No. of drugs with shortages*	0	1	2	2	1	3	3	5	5	5	4	6
% of drugs in shortage	0.0	14.3	25.0	25.0	11.1	33.3	30.0	50.0	50.0	50.0	40.0	54.6
Median no. of suppliers (min, max)	4.0 (1, 8)	3.0 (1, 7)	4.0 (1, 6)	3.5 (1, 8)	3.0 (1, 9)	3.0 (1, 8)	2.0 (1, 9)	2.0 (1, 7)	3.0 (1, 6)	3.5 (1, 11)	3.5 (1, 11)	4.0 (1, 12)
Among drugs with shortages, average % of suppliers reporting shortages (SD)	—	100.0 (0.0)	80.0 (28.3)	87.5 (17.7)	100.0 (0.0)	93.3 (11.5)	83.8 (14.7)	87.0 (12.7)	88.7 (17.6)	89.3 (15.3)	91.7 (16.7)	91.7 (13.9)

Abbreviations: FDA, US Food and Drug Administration; max, maximum; min, minimum; SD, standard deviation.

*Information about reported drug shortages obtained from the University of Utah's Drug Information Service.

†Information about number of suppliers obtained from the 2003 to 2009 *Red Book: Pharmacy's Fundamental Reference* and the RED BOOK Online Database for subsequent years.

Table 2. Association Between the No. of Suppliers and Reported Shortages* for FDA-Approved Antineoplastic Drugs for First-Line Treatment of Breast, Colon, and Lung Cancer (2003 to 2014)

	Model 1: All Drugs		Model 2: Drugs With Generic Equivalent	
Fixed Effects	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
No. of suppliers†				
1-2	3.49 (0.77 to 15.82)	.105	3.67 (0.80 to 16.89)	.095
3-4	2.60 (1.01 to 6.70)	.049	2.67 (1.02 to 7.02)	.046
≥ 5 (reference)	1.00		1.00	
Year of observation	1.53 (1.32 to 1.78)	< .001	1.54 (1.31 to 1.80)	< .001
Year of approval‡	0.81 (0.74 to 0.89)	< .001	0.81 (0.74 to 0.89)	< .001
Cancer site				
Breast	0.97 (0.35 to 2.67)	.949	0.96 (0.34 to 2.75)	.939
Colon	2.33 (0.62 to 8.73)	.210	2.07 (0.50 to 8.00)	.330
Lung (reference)	1.00		1.00	
Had generic equivalent				
Yes	32.17 (1.96 to 527.99)	.015	—	
No (reference)	1.00		—	

NOTE. Three hundred forty-two observations for 35 drugs over a 12-year period (Model 1); 191 observations for 21 drugs over a 12-year period (Model 2). Model 1: Random slope model adjusting for the number of suppliers, year of observation, year of approval, cancer site, and whether a generic equivalent of the drug was on the market in a given year for all drugs. Model 2: Random slope model adjusting for the number of suppliers, year of observation, year of approval, and cancer site for drugs that had a generic equivalent on the market during a given year.

Abbreviations: FDA, Food and Drug Administration; OR, odds ratio.

*Information about reported drug shortages obtained from the University of Utah's Drug Information System.

†Information about the number of suppliers obtained from the 2003 to 2009 *Red Book: Pharmacy's Fundamental Resource* and the RED BOOK Online Database for subsequent years.

‡Year of FDA approval for use of drug for specific cancer site based on drug information from the National Cancer Institute's website; drugs approved before 1984 were assigned the value of 1984 as year of approval.

with one to two suppliers (OR = 3.49, $P = .105$, Table 2, Model 1). In addition, drug shortages were more likely to occur over time (OR = 1.53, $P < .001$). Further, newer drugs (ie, those with more recent FDA approval) were less likely to experience a drug shortage (OR = 0.81, $P < .001$). Drugs with a generic equivalent on the market were much more likely to report shortages (OR = 32.17, $P = .015$). There was no significant association between cancer site and reported drug shortages. Because of the strong association between reported shortages and having a generic equivalent, we conducted a sensitivity analysis excluding drugs without a generic equivalent. We continued to find the same nonlinear relationship between the number of suppliers and drug shortages (Table 2, Model 2).

DISCUSSION

We found that although many first-line antineoplastics for colon, lung, and breast cancer had multiple suppliers, the extent of suppliers fluctuated greatly over time. Cancer drugs with a small number of suppliers had a higher risk of drug shortages than did those with five or more suppliers, but the relationship was nonlinear. However, one of the strongest risk factors for drug shortages was the age of the drug, with older drugs significantly more likely to experience shortages. Overall, our analyses indicate that future policies promoting only an increase in distinct manufacturing entities for injectable drugs may not alleviate ongoing shortage problems. Rather than a concentrated effort to promote an increase in distinct suppliers, our results suggest that targeted efforts to understand underlying causes of shortages in older drugs, one of the strongest risk factors for shortages, may provide significant opportunities to alleviate these shortages.

Recently, several commentaries have noted continued trends in consolidation of pharmaceutical suppliers.[12,31-34] One analysis suggests that over the past 30 years, approximately 110 biopharmaceutical companies have consolidated to about 30, a 70% reduction in distinct suppliers in a relatively short period.[32] These mergers and acquisitions may occur for

any number of reasons, but much discussion surrounding underlying motivations has focused on the need for these companies to combine resources and maximize revenue in an era of declining profit margins.[12] Over the past decade, several blockbuster drugs have undergone patent expirations, while suppliers have faced increased pressure to achieve economies of scale with recent health policy and reimbursement changes.[12,31,32,34] Our findings support these trends, identifying a declining number of antineoplastic suppliers for three of the most common cancers in the United States until 2009, with a subsequent increase from 2010 to 2014, coinciding with increased national attention on drug shortages and their potential impact on care.[3,5,8,24] The initial decline in suppliers is likely due to new drugs, such as lapatinib or pemetrexed disodium, entering the market under patent from a single supplier, whereas the increase in suppliers after 2009 is likely due to approval of generic equivalents for drugs, including gemcitabine and anastrozole. Interestingly, we found that if drug shortages occurred, most, if not all, suppliers of that drug were affected by this shortage.

Despite variation in available suppliers, we also observed overall increases in drug shortages from 2003 to 2014. Specifically, we identifed time (ie, more recent years of observation) as one of the strongest predictors of shortages in our study. This trend is well documented across the United States, predominantly due to increased tracking efforts from the University of Utah's DIS, the ASHP, and the FDA.[7,11,19,35] In two separate surveys of more than 1,000 health systems between 2010 and 2011, more than 99% of hospitals surveyed reported experiencing more than one drug shortage in the prior 6 months, with more than 66% experiencing oncology drug shortages.[35] By the end of our study period (2014), we continued to see drug shortages affecting more than 48% of first-line treatments for colon, lung, and breast cancer. Combined with prior research demonstrating that these treatments in shortage have led directly to regimen and dosage changes as well as treatment delays, our findings suggest that these shortages remain a significant public health concern for a broad range of cancer patients.[4,36,37] These findings identify the continued need for the FDA and partnering organizations to work with suppliers to prevent new shortages and mitigate those that are not preventable by understanding the underlying contributors to these shortages.[2]

The original motivation for this study was to understand how a proposed approach to reduce these shortages, by promoting more suppliers for first-line antineoplastics, might help to alleviate new shortages. However, we found no evidence of a clear relationship between increasing the number of cancer drug suppliers and a reduced risk of shortages. Rather, we found that although having a small number of drug suppliers (three to four) was associated with an increased likelihood of shortages, there was no statistical difference in shortages among drugs with a large number of suppliers compared with those with one to two suppliers, even after accounting for the availability of generics. Although this study did not specifically examine the reasons underlying this nonlinear relationship, future studies should evaluate whether systematic differences exist in capacity and responsiveness to market needs when drug suppliers are concentrated (one to two suppliers), have some variability (three to four suppliers), or are a diffuse set of suppliers (five or more). Ideally, increasing the number of suppliers for cancer drugs would lead to greater capacity, more strategic purchasing, and decline of the gray market (ie, purchase of drugs not approved for import or sale in the United States). However, the nonlinear relationship we identified between suppliers and drug shortages suggests that simply increasing suppliers may not reduce shortages, demonstrating the need to understand other potential contributing factors, such as quality issues, hoarding, and rise of the gray market that the FDA has targeted for future initiatives.[38]

Furthermore, one of the most important factors predicting increased risk of shortages was whether the drug was part of an older therapy (ie, was not FDA approved more recently for cancer therapy). The reasons behind this association may stem from several interrelated issues. Previous work on the issue of underlying causes behind drug shortages has indicated that the most common reasons for shortages in 2011 were manufacturing problems (23%), supply or demand issues (13%), discontinuation (6%), or raw material issues (3%).[7] The challenge with addressing the primary known causes of drug shortages, namely manufacturing or raw material issues, is that even if there is more than one known supplier for a particular oncology drug (as is commonly the case with generics), they may all receive raw materials from a single source; therefore, interruption in the supply of raw materials would affect all producers of the final product.[7] Additionally, many of the older oncology drugs are now off patent and available for generic production, the market for which has seen a series of rapid changes, including consolidation of buyers, merging suppliers, and outsourcing of drug components.[12] This may reduce financial incentives to produce older generic drugs.[7,10,12] However, it is important to note that more

than 55% of shortages in 2011 had an "unknown/other" cause, as reported by the supplier, which can only be further understood with more stringent and transparent shortage reporting requirements. Overall, this points toward the continued need to understand factors besides unique supply entities that may alleviate these shortages in the future, including the effects of market consolidations, business decisions, and drug shortage notification processes.[7,12]

Although our study provides insights into the relationship between suppliers and drug shortages, we acknowledge the following limitations. First, we have no information about the supply chain of raw materials and other resources needed for manufacturing these drugs, which may affect drug shortages. Second, because of sample size limitations, we were unable to conduct stratified analysis by cancer site. Third, there is no regulatory requirement to disclose the manufacturer of a product. As such, we are unable to disentangle suppliers and manufacturers because many suppliers participate in contract manufacturing. Fourth, we have no data on suppliers' market share of drugs. For example, a product may have three suppliers, but each may supply a different percentage of the market. It is not uncommon for suppliers to supply more than 75% of the market. Despite these limitations, our analysis provides initial insights into the complicated relationship between drug shortages for first-line cancer treatment and the number of companies supplying these drugs, which can be a starting point for future analyses.

In conclusion, we found that having few drug suppliers (three to four) was associated with an increased likelihood of shortages compared with having a large number (more than five) of suppliers, but the relationship was nonlinear; however, one of the strongest risk factors for drug shortages was the age of the drug. This suggests that policies focused predominantly on promoting increases in distinct suppliers may not alleviate shortages. Given the continued significant impact of these shortages on patient care,[4,37] future policies should promote targeted efforts to understand underlying causes of shortages in older drugs to evaluate contributors to and predictors of shortages in the oncology community. JOP

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Authors' Disclosures of Potential Conflicts of Interest

Disclosures provided by the authors are available with this article at www.jop.org

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Association Between the Number of Suppliers for Critical Antineoplastics and Drug Shortages: Implications for Future Drug Shortages and Treatment

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Appendix

Table A1. Included FDA-Approved Drugs for the First-Line Treatment of Breast, Colon, and Lung Cancer With Number of Suppliers Over Time

	No. of Suppliers by Drug and Year											
	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Breast cancer drugs												
Anastrozole	1	1	1	1	1	1	1	1	16	19	19	19
Cyclophosphamide	2	1	2	2	2	2	1	1	1	1	1	1
Docetaxel			1	1	1	1	1	1	1	6	7	8
Doxorubicin hydrochloride	2	3	3	3	3	4	3	3	3	4	4	6
Epirubicin hydrochloride	1	1	1	1	2	7	7	7	8	7	7	8
Exemestane				1	1	1	1	1	1	3	3	3
Fluorouracil	3	3	3	3	3	4	4	4	4	3	3	3
Lapatinib						1	1	1	1	1	1	1
Letrozole			1	1	1	1	1	1	1	9	10	10
Methotrexate sodium	3	3	3	3	3	4	4	5	5	5	6	6
Paclitaxel	5	5	5	4	4	6	7	6	5	6	7	7
Paclitaxel protein-bound		1	1	1	1	1	1	1	1	1	1	1
Pertuzumab											1	1
Tamoxifen	6	6	6	6	5	5	4	4	4	4	4	4
Trastuzumab					1	1	1	1	1	1	1	1
Colon cancer drugs												
Bevacizumab			1	1	1	1	1	1	1	1	1	1
Capecitabine				1	1	1	1	1	1	1	1	1
Cetuximab			1	1	1	1	1	1	1	1	1	1
Fluorouracil	3	3	3	3	3	4	4	4	4	3	3	3
Irinotecan	1	1	1	1	1	2	9	8	9	8	10	10
Leucovorin calcium	3	4	4	3	2	2	2	2	2	2	3	3
Oxaliplatin			1	1	1	1	1	4	5	5	7	7
Panitumumab					1	1	1	1	1	1	1	1
Lung cancer drugs												
Afatinib dimaleate												1
Bevacizumab					1	1	1	1	1	1	1	1
Carboplatin	1	1	5	8	9	8	9	7	6	5	4	5
Cisplatin	5	5	5	4	3	3	3	3	3	2	3	4
Crizotinib										1	1	1
Erlotinib hydrochloride			1	1	1	1	1	1	1	1	1	1
Etoposide and etoposide phosphate	8	7	6	6	5	5	5	5	5	6	6	6
Gefitinib		1	1	1	1	1	1	1	1			
Gemcitabine	1	1	1	1	1	1	1	1	3	11	11	12
Methotrexate sodium	3	3	3	3	3	4	4	5	5	5	6	6
Paclitaxel	5	5	5	4	4	6	7	6	5	6	7	7
Pemetrexed disodium							1	1	1	1	1	1

NOTE. Information about the number of suppliers was obtained from the 2003-2009 Red Book: Pharmacy's Fundamental Resource and the RED BOOK Online Database for subsequent years.
Abbreviation: FDA, US Food and Drug Administration.