

GYNECOLOGY

Total and out-of-pocket costs of different primary management strategies in ovarian cancer



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BACKGROUND: Communicating healthcare costs to patients is an important component of delivering high-quality value-based care, yet cost data are lacking. This is especially relevant for ovarian cancer, where no clinical consensus on optimal first-line treatment exists.

OBJECTIVE: The objective of this study was to generate cost estimates of different primary management strategies in ovarian cancer.

STUDY DESIGN: All women who underwent treatment for ovarian cancer from 2006–2015 were identified from the MarketScan database ($n=12,761$) in this observational cohort study. Total and out-of-pocket costs were calculated with the use of all claims within 8 months from initial treatment and normalized to 2017 US dollars. The generalized linear model method was used to assess cost by strategy.

RESULTS: Among patients who underwent neoadjuvant chemotherapy and those who underwent primary debulking, mean adjusted total costs were \$113,660 and \$107,153 ($P<.001$) and mean out-of-pocket costs were \$2519 and \$2977 ($P<.001$), respectively. Total costs for patients who had intravenous standard, intravenous dose-

dense, and intraperitoneal/intravenous chemotherapy were \$105,047, \$115,099, and \$121,761 ($P<.001$); and out-of-pocket costs were \$2838, \$3405, and \$2888 ($P<.001$), respectively. Total costs for regimens that included bevacizumab were higher than those without it (\$171,468 vs \$104,482; $P<.001$); out-of-pocket costs were \$3127 vs \$2898 ($P<.001$). Among patients who did not receive bevacizumab, 25% paid \geq \$3875, and 10% paid \geq \$6265. For patients who received bevacizumab, 25% paid \geq \$4480, and 10% paid \geq \$6635. Among patients enrolled in high-deductible health plans, median out-of-pocket costs were \$4196, with 25% paying \geq \$6680 and 10% paying \geq \$9751.

CONCLUSION: Costs vary across different treatment strategies, and patients bear a significant out-of-pocket burden, especially those enrolled in high-deductible health plans.

Key words: bevacizumab, chemotherapy, cost, high-deductible health plan, out-of-pocket cost, ovarian cancer

In 2016, healthcare costs comprised 17.9% of the gross domestic product in the United States. Projections from the Center for Medicare and Medicaid Services suggest that medical costs will reach 20% of the gross domestic product by 2026.¹ The costs of cancer care have been rising disproportionately over the past decade, with total and out-of-pocket costs becoming a major burden for both the healthcare system and patients.² With increasing costs, insurers have shifted more of the financial burden to patients, who often face unpredictable or uncontrollable costs, that include high deductibles or co-insurance.³ Financial toxicity or financial distress as an adverse effect of cancer treatment has been associated with greater symptom

burden, poorer quality of life, and increased risk of death.^{4,5}

Communicating healthcare costs to patients is an important component of delivering high-quality value-based care. Given the potential significant impact of costs on patients and their families, the Institute of Medicine recommends providing them with information on the cost of care.⁶ This is especially relevant for patients with ovarian cancer, where no clinical consensus on optimal first-line treatment exists. Patients may be treated with primary debulking surgery followed by adjuvant chemotherapy or neoadjuvant chemotherapy followed by interval debulking surgery.⁷ Chemotherapy may be administered intravenously every 3 weeks, intravenously every week, or intraperitoneally.^{8,9} Additionally, regimens may or may not include bevacizumab, which is an angiogenesis inhibitor.¹⁰ All of these treatment approaches are approved by the current National Comprehensive Cancer Network guidelines for ovarian cancer.¹¹ Despite the recommendation to share cost information with patients,

cost data are lacking. Therefore, the objective of our study was to generate total and out-of-pocket cost estimates of different primary management strategies in ovarian cancer.

Materials and Methods

This was a retrospective cohort study that used the Truven Health Analytics MarketScan (Truven Health Analytics, Ann Arbor, MI) database, a commercial healthcare claims database. It contains deidentified claims data on 240 million patients in the United States who are enrolled in commercial health insurance plans that are sponsored by >100 payers since 1995.¹² The database includes monthly enrollment data, inpatient admission records, outpatient services, outpatient prescription drug claims, and costs of services, with robust longitudinal follow up. We used a combination of International Classification of Diseases, 9th revision (ICD-9), diagnosis codes, Common Procedural Terminology codes, and Healthcare Common Procedure Coding System codes to identify relevant covariates,

Cite this article as: Suidan RS, He W, Sun CC, et al. Total and out-of-pocket costs of different primary management strategies in ovarian cancer. *Am J Obstet Gynecol* 2019;221:136.e1-9.

0002-9378/\$36.00

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<https://doi.org/10.1016/j.ajog.2019.04.005>

AJOG at a Glance

Why was this study conducted?

Although communicating healthcare costs to patients is an important component of delivering value-based care, cost data are lacking. Our objective was to generate cost estimates of different primary management strategies in ovarian cancer.

Key findings

We described total and out-of-pocket cost estimates of different treatment approaches and types of chemotherapy regimens that are administered. The range of out-of-pocket payments was large for patients who received bevacizumab: although the mean payment was \$3127, 25% paid \geq \$4480, and 10% paid \geq \$6635. Patients enrolled in high-deductible health plans had significantly higher out-of-pocket expenses, with 25% paying \geq \$6680, and 10% paying \geq \$9751.

What does this add to what is known?

Costs vary across different treatment strategies, and patients bear a significant out-of-pocket burden, especially those enrolled in high-deductible plans.

treatments, and outcomes (Supplementary Table). Institutional Review Board approval was obtained.

We aimed to assess claims data for women who underwent primary treatment for epithelial ovarian cancer (ICD-9 codes 183.0, 183.2, 183.8). Patients were included if they underwent both surgery and chemotherapy, if they received platinum-based chemotherapy (considered standard of care), if they had 2 inpatient diagnoses claims for ovarian cancer or at least 2 outpatient diagnosis claims that were >30 days apart, and if they had complete healthcare coverage for 8 months after the diagnosis. We considered 8 months to be an appropriate time interval for receipt of surgery, postoperative recovery, and receipt of neoadjuvant or adjuvant chemotherapy. Because our goal was to identify costs that were associated with primary therapy only, we chose not to extend this time limit because that would risk including the costs of treatment for disease progression or recurrence. We identified a total of 36,853 patients who underwent primary treatment from January 2006 to December 2015. The year 2006 was chosen as the starting year for data collection because that was when a landmark study that reported on the use of intraperitoneal/intravenous chemotherapy was published.⁹ We sequentially excluded 513 patients who received bleomycin/etoposide (considered as treatment for non-epithelial ovarian cancer), 1203 patients with ICD-9 codes for “personal history of malignant neoplasm of ovary” (V10.43), 305 patients who received chemotherapy or surgery before 2006, 13,175 patients who did not get both surgery and chemotherapy within 8 months after the diagnosis, and 7545 patients who did not have complete coverage 6 months before and 8 months after the diagnosis. Our study population was comprised of the remaining 12,761 patients.

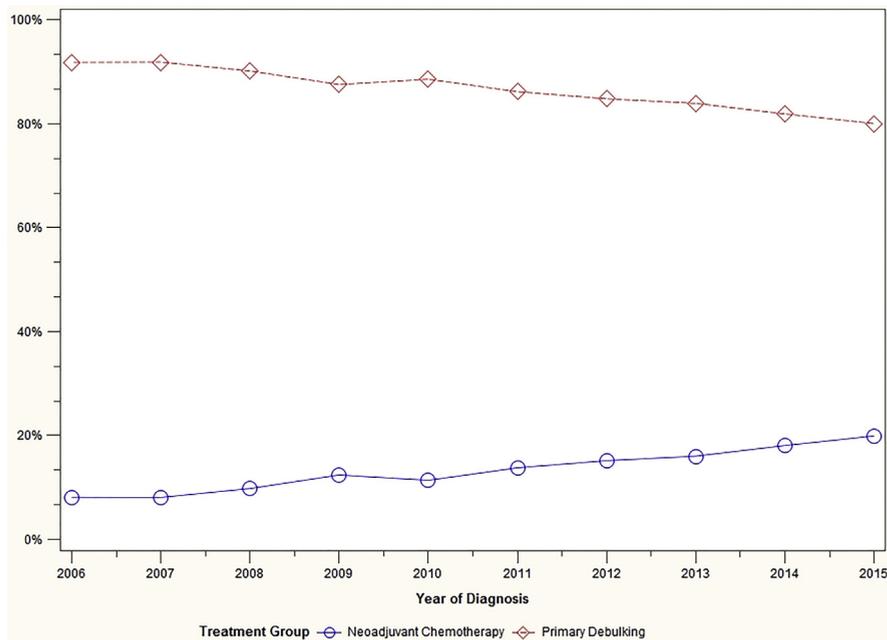
Patients were classified based on (1) whether they underwent primary debulking surgery followed by postoperative chemotherapy or neoadjuvant chemotherapy followed by interval

TABLE 1
Patient characteristics (n = 12,761)

Characteristic	N	%
Age, y		
≤ 49	2,404	19
50–59	4,788	37
60–69	3,697	29
≥ 70	1,872	15
Charlson comorbidity index		
0	11,010	86
1	1,425	11
≥ 2	326	3
Year of diagnosis		
2006–2008	3,041	24
2009–2011	5,263	41
2012–2015	4,457	35
Insurance plan		
Health Maintenance Organization	1,447	11
Preferred Provider Organization	7,469	59
Other	3,845	30
Region of care		
Northeast	2,595	20
North Central	3,353	27
South	4,367	34
West	2,303	18
Unknown	148	1

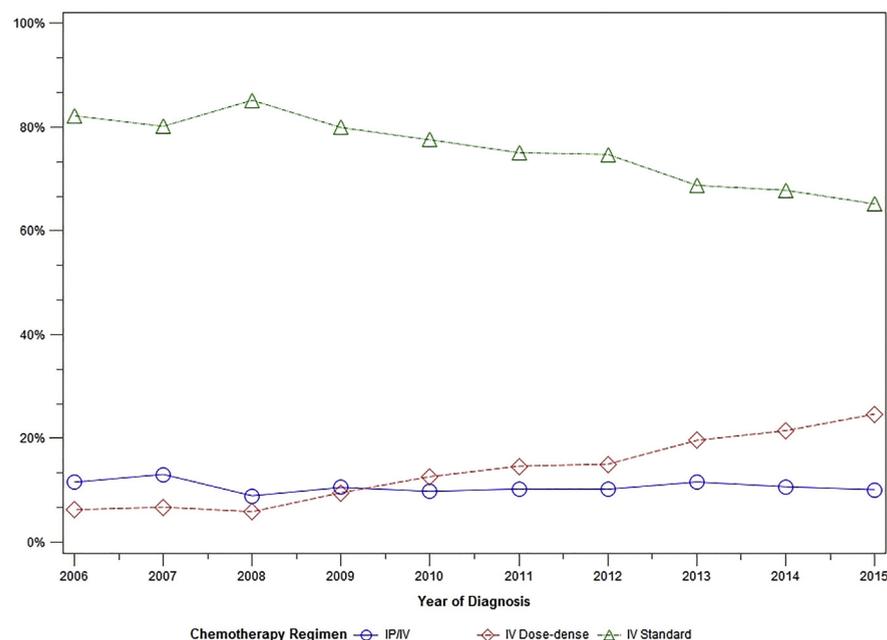
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FIGURE 1
Trend in treatment approach over time



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FIGURE 2
Chemotherapy regimen use over time



IP, intraperitoneal; IV, intravenous.

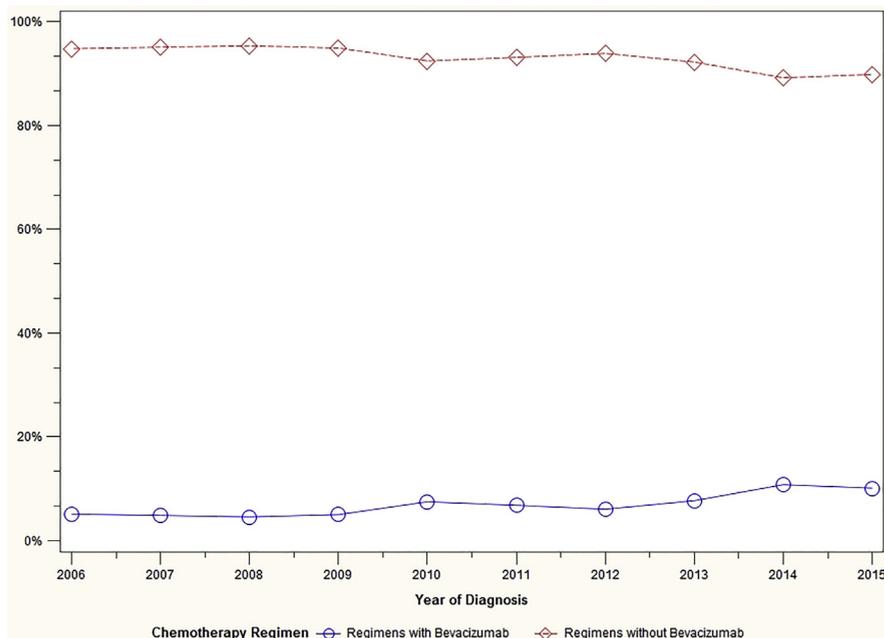
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debulking surgery, (2) the type of chemotherapy regimen administered (intravenous every 3 weeks [standard], intravenous every week [dose-dense], or intraperitoneal/intravenous), and (3) if regimens included bevacizumab (Supplementary Table). Patients were considered to have had neoadjuvant chemotherapy if there was at least 1 billing code for a chemotherapeutic agent before a surgical code. Patients were classified as having received intraperitoneal chemotherapy based on the presence of at least 1 billing code for the intraperitoneal delivery of a chemotherapeutic drug. Patients without a code for intraperitoneal chemotherapy were classified as having received either dose-dense or standard chemotherapy based on the administration schedule. Dose-dense chemotherapy is typically administered as a platinum agent every 3 weeks in combination with a weekly taxane. However, because some women may not receive a taxane every week because of toxicity, dose-dense chemotherapy was defined as a ratio of ≥ 1.5 of taxane-to-platinum (patients who received standard chemotherapy would have a ratio of 1:1).^{8,13} Patients who did not meet the criteria for either dose-dense or intraperitoneal chemotherapy were considered to have had standard chemotherapy.

Patient-level variables that were collected included age at diagnosis (grouped as ≤ 49 , 50–59, 60–69, ≥ 70 years), Charlson comorbidity index, year of diagnosis (2006–2008, 2009–2011, 2012–2015), region of treatment (northeast, north central, south, west), and insurance type (health maintenance organization, preferred provider organization, other). We used the Klabunde modification of the Charlson comorbidity index to assess patient comorbidity, using claims in the 6 months before cancer diagnosis.¹⁴ To prevent overestimation, a patient's comorbidity diagnosis had to appear on at least 2 different claims that were >30 days apart.

The primary outcomes of this study were total and out-of-pocket costs within 8 months from initial treatment that were stratified by treatment strategy. The starting time to calculate costs

FIGURE 3
Trend in bevacizumab use over time



Suidan et al. *Costs of initial care in ovarian cancer. Am J Obstet Gynecol* 2019.

was the initial treatment claim, whether it was a billing code for a chemotherapeutic agent or a surgical code. A secondary outcome was the analysis of costs of patients who were enrolled in high-deductible health plans. High-deductible plans were coded as an

insurance type in the MarketScan database. Costs were defined as reimbursed costs (not charges) and were calculated with the use of all inpatient, outpatient, and prescription claims within that time period. Out-of-pocket costs were calculated as the sum of coinsurance,

copayments, and deductibles. Total costs consisted of patient out-of-pocket expenses, in addition to insurance payments made. All cost estimates were normalized to 2017 US dollars with the use of the medical care component of the consumer price index.¹⁵ Mean and median costs were calculated. Because of the skewed and nonnormal distribution of cost, a generalized linear model with a gamma family and log link function was used to assess cost by strategy, with adjustment for clinical and demographic factors (age, Charlson comorbidity index, region of care, insurance plan, year of diagnosis). All these covariates were associated significantly with cost variability on univariate analysis. All statistical tests were 2-sided, with a probability value of <.05 considered significant. Analysis was performed with SAS software (version 9.4; SAS Institute, Cary, NC).

Results

A total of 12,761 patients met eligibility criteria. Patient characteristics are shown in [Table 1](#). Trends in treatment variability over time are shown in [Figures 1–3](#). The use of neoadjuvant chemotherapy increased over time, from 8% in 2006 to 20% in 2015. The use of intravenous standard chemotherapy decreased from 82% to 65% during that

TABLE 2
Total costs (\$US dollars) by treatment approach, chemotherapy regimen, and inclusion of bevacizumab (n = 12,761)

Variable	N (%)	Unadjusted total costs		Adjust total costs ^a		
		Median	Mean	Mean	95% Confidence interval	P value
Primary debulking	11,091 (87)	\$89,228	\$109,745	\$107,153	\$105,962–\$108,357	<.001
Neoadjuvant chemotherapy	1670 (13)	\$92,770	\$112,879	\$113,660	\$110,404–\$117,012	
Chemotherapy regimen						<.001
Intravenous standard	9739 (76)	\$85,879	\$106,753	\$105,047	\$103,799–\$106,309	
Intravenous dose-dense	1679 (13)	\$95,136	\$117,729	\$115,099	\$111,798–\$118,497	
Intraperitoneal/intravenous	1343 (11)	\$109,995	\$125,359	\$121,761	\$117,890–\$125,760	
Bevacizumab						<.001
Regimens without	11,912 (93)	\$86,859	\$105,525	\$104,482	\$103,362–\$105,613	
Regimens with	849 (7)	\$153,389	\$175,122	\$171,468	\$164,650–\$178,567	

^a Costs were adjusted for age, Charlson comorbidity index, region of care, insurance plan, and year of diagnosis.

Suidan et al. *Costs of initial care in ovarian cancer. Am J Obstet Gynecol* 2019.

TABLE 3

Out-of-pocket costs (\$US dollars) by treatment approach, chemotherapy regimen, and inclusion of bevacizumab (n = 12,761)

Variable	N (%)	Unadjusted out-of-pocket costs		Adjusted out-of-pocket costs ^a		
		Median	Mean	Mean	95% Confidence interval	P value
Primary debulking	11,091 (87)	\$2111	\$3021	\$2977	\$2923–\$3031	<.001
Neoadjuvant chemotherapy	1670 (13)	\$1489	367	\$2519	\$2403–\$2640	
Chemotherapy regimen						<.001
Intravenous standard	9739 (76)	\$1982	\$2870	\$2838	\$2784–\$2893	
Intravenous dose-dense	1679 (13)	\$2103	\$3279	\$3405	\$3250–\$3571	
Intraperitoneal/intravenous	1343 (11)	\$2145	\$2981	\$2888	\$2742–\$3042	
Bevacizumab						<.001
Regimens without	11,912 (93)	\$1982	\$2917	\$2898	\$2848–\$2948	
Regimens with	849 (7)	\$2449	\$3197	\$3127	\$2931–\$3336	

^a Costs were adjusted for age, Charlson comorbidity index, region of care, insurance plan, and year of diagnosis.

Suidan et al. Costs of initial care in ovarian cancer. *Am J Obstet Gynecol* 2019.

time period; the use of intravenous dose-dense chemotherapy administration increased from 6% to 25%. Intraperitoneal/intravenous chemotherapy use

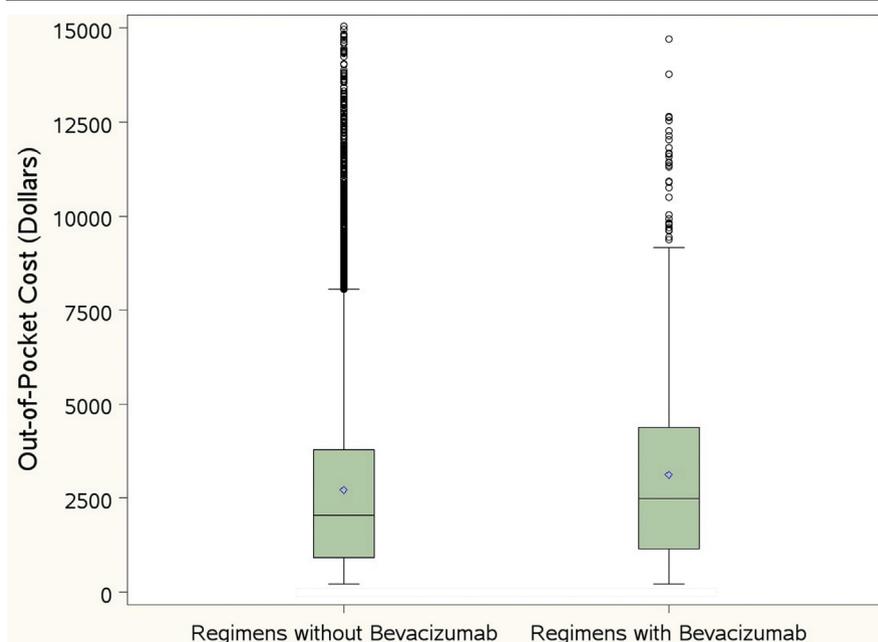
remained stable during the study period (11% to 10%). Bevacizumab use rose gradually from 5% in 2006 to 10% in 2015.

Total and out-of-pocket costs by treatment approach, chemotherapy regimen, and inclusion of bevacizumab are shown in Tables 2 and 3. Among patients who underwent neoadjuvant chemotherapy and those who underwent primary debulking, mean adjusted total costs were \$113,660 and \$107,153 ($P < .001$), and mean adjusted out-of-pocket costs were \$2519 and \$2977 ($P < .001$), respectively. Mean adjusted total costs were highest for patients who had intraperitoneal/intravenous chemotherapy (\$121,761), followed by intravenous dose-dense (\$115,099), and intravenous standard chemotherapy (\$105,047; $P < .001$). Mean adjusted out-of-pocket costs were highest for the intravenous dose-dense group (\$3405), followed by intraperitoneal/intravenous (\$2888) and intravenous standard chemotherapy (\$2838) ($P < .001$). Mean adjusted total costs for regimens that included bevacizumab were higher than those without it (\$171,468 vs \$104,482; $P < .001$), as were out-of-pocket costs (\$3127 vs \$2898; $P < .001$).

The distribution of out-of-pocket costs by receipt of bevacizumab is shown in Figure 4. Overall, 7% of the cohort received a chemotherapy regimen

FIGURE 4

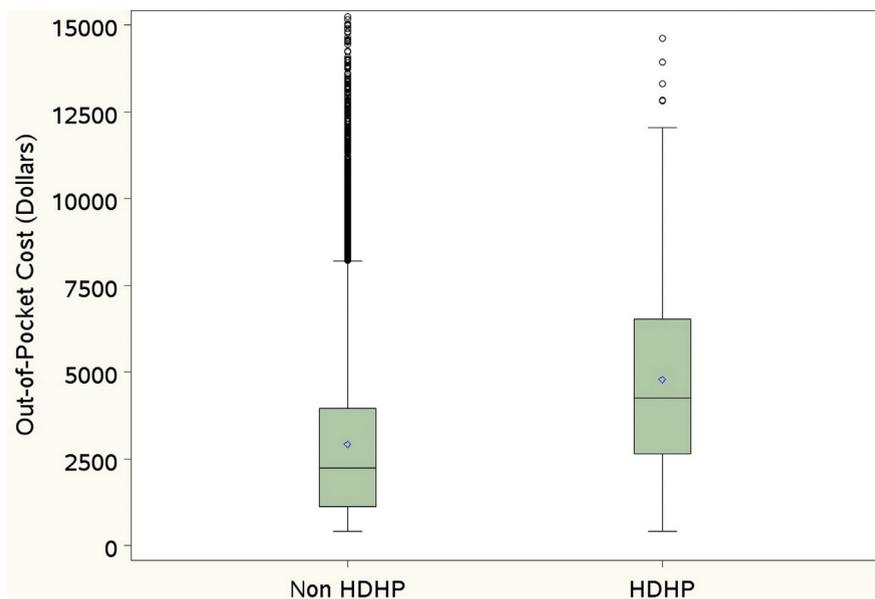
Out-of-pocket costs for regimens with or without bevacizumab



The box indicates 25–75% percentiles; the bold horizontal line indicates median cost; the dot indicates mean cost; the circles indicate outliers.

Suidan et al. Costs of initial care in ovarian cancer. *Am J Obstet Gynecol* 2019.

FIGURE 5
Out-of-pocket costs for high-deductible health plans and non-high-deductible health plans



The box indicates 25–75% percentiles; the bold horizontal line indicates median cost; the dot indicates mean cost; the circles indicate outliers.

HDHP, high-deductible health plan.

Suidan et al. Costs of initial care in ovarian cancer. *Am J Obstet Gynecol* 2019.

with bevacizumab. As seen in the Figure, the range of out-of-pocket payments was quite large. Among the patients who did not receive bevacizumab, 25% paid >\$3875, and 10% paid >\$6265. For patients who received bevacizumab, 25% paid more than >\$4480, and 10% paid at least \$6635.

Patients who were enrolled in high-deductible health plans made up 2% of our cohort. Among these patients, median out-of-pocket costs were \$4196, with 25% paying >\$6680 and 10% paying at least \$9751 (Figure 5). In this cohort, mean adjusted out-of-pocket costs were higher for patients who underwent primary surgery compared with neoadjuvant chemotherapy (\$5238 vs 2989; $P=.004$). Intraperitoneal/intravenous chemotherapy was associated with the highest mean adjusted out-of-pocket costs (\$6156), compared with intravenous dose-dense chemotherapy (\$4896) and intravenous standard (\$4754). However, this difference was not significant ($P=.18$). In comparison, among patients who were not enrolled in high-

deductible health plans, median out-of-pocket costs were \$1983, with 25% paying >\$3852 and 10% paying at least \$6219.

Comment

In this study, we described total and out-of-pocket cost estimates of different primary management strategies in ovarian cancer. The costs of cancer care have been rising steadily in the United States and are estimated to reach \$158 billion by 2020.¹⁶ To address these increasing costs, the American Society of Clinical Oncology has developed a framework to assess and compare the value of cancer treatment options. This framework has defined value by emphasizing 3 critical elements: clinical benefit, complications, and cost.¹⁷ Our data not only add to the growing literature on the costs of cancer care to patients but also can help inform discussions regarding the relative value of different interventions.

With rising coinsurance costs and deductibles, patients have picked up an

ever-increasing share of this financial burden.³ Rising out-of-pocket costs can lead to financial toxicity, which has been associated with adverse clinical outcomes and reduced quality of life.⁵ There is increasing awareness of the need to communicate healthcare costs to patients and their families, as a component of delivering quality care. In a survey that asked 5000 patients to identify key characteristics of high-value healthcare, a plurality (45%) chose “my out-of-pocket costs are affordable.”¹⁸ This is particularly relevant when there is no consensus on optimal treatment strategies, as in ovarian cancer.

In our study, neoadjuvant chemotherapy followed by surgery was associated with higher mean total costs than primary debulking surgery that was followed by chemotherapy. These results are comparable with those published by Urban et al¹⁹ and Forde et al,²⁰ who both used the SEER-Medicare database for their analysis. Total costs were highest for patients who had intraperitoneal/intravenous chemotherapy, followed by intravenous dose-dense and intravenous standard chemotherapy. This is in-line with the report by Wright and et al.¹³ On the other hand, primary debulking, intravenous dose-dense chemotherapy, and receipt of bevacizumab were all associated with higher out-of-pocket costs. Although Bercow et al²¹ assessed the costs of care within the first year of diagnosis of ovarian cancer, to our knowledge, no other studies have compared out-of-pocket costs of different interventions in this population.

Bevacizumab is a monoclonal antibody that is directed against vascular endothelial growth factor. It recently was approved by the Food and Drug Administration in the United States for the front-line treatment of ovarian cancer, based on 2 phase-3 clinical trials.^{10,22} Importantly, these trials showed only a progression-free survival benefit and no overall survival benefit. The adjusted mean difference in out-of-pocket costs for regimens with bevacizumab vs those without was \$229 (\$3127 vs \$2898). Although

that may not appear to be a large difference, it is important to note that the range of out-of-pocket payments was quite large for patients who received bevacizumab, with 25% paying >\$4480, and 10% paying at least \$6635. When we looked at total costs that included insurance payments, the difference was substantial (\$171,468 vs \$104,482). This calls into question the use of an agent with such high costs but no overall survival benefit. This issue becomes even more significant when quality of life is taken into account. In a cost-utility analysis of bevacizumab use in the primary treatment of ovarian cancer, regimens that included bevacizumab were not cost-effective compared with regimens without it when evaluating quality-adjusted life expectancy.²³ Of note, the Food and Drug Administration recently approved Mvasi (bevacizumab-awwb) as a biosimilar to bevacizumab for the treatment of colorectal, lung, brain, kidney, and cervical cancers. Although it has not been approved for ovarian cancer, future approval and use in this disease could lead to lower healthcare costs.

Patients enrolled in high-deductible health plans had significantly higher out-of-pocket expenses than the rest of the cohort. Twenty-five percent of these patients paid >\$6680, and 10% paid at least \$9751. Given the unclear survival benefit of different therapeutic strategies, it may be helpful to pursue treatment options with a lower out-of-pocket burden for these patients. This also applies to some patients who were not in high-deductible health plans. Although the median out-of-pocket payment was \$1983, 25% paid >\$3852, and 10% paid at least \$6219. Hunter et al²⁴ showed that even brief conversations between oncologists and patients about cancer costs may help reduce treatment expenses.

The strengths of this study lie in the fact that our cost data were based on actual inpatient and outpatient insurance reimbursements made to both hospitals and providers. We also evaluated the global 8-month period after diagnosis, which takes into account the

cost of the entire hospital stay for surgery, the management of complications, emergency room visits, and readmissions. Additionally, the MarketScan database includes patients who are enrolled in commercial insurance plans that are sponsored by >100 payers, which allowed us to examine costs nationally. Our study is limited by the fact that, because costs were based on insurance reimbursements, they reflect the payer's perspective, which may or may not reflect the cost of delivering care from a provider/hospital perspective. MarketScan lacks information regarding certain demographic and tumor variables such as race, histologic evidence, grade, and stage, which precluded us from assessing the association of these factors with costs. Additionally, because the database includes only patients who are commercially insured, these results may not be generalizable to other populations.

In conclusion, the costs of initial treatment of ovarian cancer vary across different treatment strategies and patients bear a significant out-of-pocket burden, especially those enrolled in high-deductible plans. As no consensus exists on optimal first-line management, these data may help inform value-based discussions between providers and patients. ■

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Received Jan. 14, 2019; revised April 1, 2019; accepted April 3, 2019.

Supported in part by the Duncan Family Institute, a Cancer Center Support Grant (CCSG) for National Cancer Institute—designated Cancer Centers (#CA016672), and a National Cancer Institute grant (#P30 CA016672); by a National Institutes of Health T32 grant (#5T32 CA101642) to R.S.S.; by a National Cancer Institute K award (#K07 CA201013) to L.A.M., and by a Cancer Prevention and Research Institute of Texas grant (#RP160674) and Komen grant (#SAC150061) to S.H.G.

Dr Meyer has received research support from AstraZeneca and has been a consultant for Clovis Oncology. Dr Sun has received research support from AstraZeneca. The remaining authors report no conflict of interest.

Presented at at the American Society of Clinical Oncology Annual Meeting, Chicago, IL, June 2–6 2017.

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SUPPLEMENTARY TABLE

International Classification of Diseases, 9th revision, and Common Procedural Terminology/Healthcare Common Procedure Coding System codes

	International Classification of Diseases, 9th revision, code	Common Procedural Terminology/Healthcare Common Procedure Coding System code
Debulking surgery	54.4, 65.2, 65.3, 65.31, 65.39, 65.4, 65.41, 65.49, 65.5, 65.51, 65.52, 65.53, 65.54, 65.6, 65.61, 65.62, 65.63, 65.64, 68.3, 68.31, 68.39, 68.4, 68.41, 68.49, 68.5, 68.51, 68.59, 68.6, 68.71, 68.79, 68.7, 68.71, 68.79, 68.8, 68.9, 70.32	56303, 56307, 56308, 57531, 58150, 58152, 58200, 58210, 58240, 58262, 58263, 58720, 58920, 58940, 58943, 58950, 58951, 58952, 58953, 58954, 58960
Intravenous administration of chemotherapy	99.25	96408, 96409, 96410, 96411, 96412, 96413, 96414, 96415, 96416, 96417, 96501, 96504, 96505, 96508, 96509, 96510, 96511, 96512, C8953, C8954, C8955, G0359, G0360, G0361, Q0083, Q0084, Q0085, S9330, S9331
Intraperitoneal administration of chemotherapy	54.97	96445, 96446
Chemotherapeutic agents		Carboplatin: J9045 Cisplatin: J9060, J9062 Oxaliplatin: J9263 Paclitaxel: J9254, J9265, J9267 Docetaxel: J9170, J9171 Bleomycin: J9040 Etoposide: J9181, J9182 Bevacizumab: J9035

Suidan et al. Costs of initial care in ovarian cancer. Am J Obstet Gynecol 2019.