Direct Health Care Costs of Metastatic Ovarian Cancer in a Commercially-Insured Population: A Retrospective Database Analysis

Lauren Mika Chin

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Committee:

Josh J. Carlson

Ryan N. Hansen

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Abstract

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Lauren Mika Chin

Chair of the Supervisory Committee:

Josh J. Carlson, MPH, PhD

Department of Pharmacy

Background: Ovarian cancer is the 10th most common type of cancer and the 5th leading cause of cancer death among women in the United States (U.S.). The majority of incident ovarian cancer cases are diagnosed in individual less than 65 years of age, but little evidence exists regarding the economic burden of ovarian cancer in this age group.

Objectives: The primary objectives of this study were to estimate the mean annual all-cause direct total costs of metastatic ovarian cancer, to compare costs of metastatic ovarian cancer patients to costs in patients without cancer (i.e. controls), and to identify factors associated with high annual all-cause direct total costs (i.e., individuals among the upper quintile) of metastatic ovarian cancer.

Methods: We conducted a retrospective claims analysis using the MarketScan Commercial Claims and Encounters Database. Metastatic ovarian cancer patients were identified based on having a combination of diagnosis codes for a secondary malignancy and ovarian cancer (earliest date of secondary malignancy defined as the index date) between January 1, 2011 through December 31, 2015, ≥18 years old on the index date, ≥12 months of continuous enrollment prior to the index date, and ≥1 month of continuous enrollment after the index date. Controls were randomly selected and matched to metastatic ovarian cancer patients based on age, region, index date, number of months of continuous enrollment after the index date, and propensity score. Mean annual all-cause total costs and ovarian cancer-related total costs were estimated and compared for each cohort by using the Kaplan-Meier sample average technique to account for censoring after the index date. Patient demographic and clinical characteristics were evaluated using a logistic regression model to determine if any variables were significantly associated with the upper quintiles of annual all-cause total costs and ovarian cancer-related total costs.

Results: The mean (95% CI) annual all-cause total costs in the 12-month post-index period were $149,133 ($144,873-153,330) for metastatic ovarian cancer patients and $36,566 ($33,542-39,548) for controls; the resulting mean (95% CI) difference in annual all-cause total costs was $112,567 ($109,589-115,649). The mean (95% CI) annual ovarian cancer-related total costs in the 12-month post-index period were $91,855 ($87,078-96,595) for metastatic ovarian cancer patients and $0 ($0) for controls. No patient characteristics were found to be significantly associated with the upper quintiles of annual all-cause total costs and ovarian cancer-related total costs.

Conclusions: Patients less than 65 years old (i.e. the working age population) with metastatic ovarian cancer have significantly higher costs compared to those without cancer. Given that the

majority of ovarian cancer patients are diagnosed at less than 65 years of age, these findings contribute to the understanding of the burden of illness in a patient population where little evidence currently exists on the economic consequences of the disease.

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1. Introduction

Among women in the United States (U.S.), ovarian cancer is the 10th most common type of cancer and the 5th leading cause of cancer death. In 2017, there were an estimated 22,440 new cases and 14,080 deaths attributable to ovarian cancer in the U.S. The 5-year relative survival of advanced ovarian cancer is 29.2%. It is unclear as to what proportion of patients initially present with metastatic ovarian cancer, however, estimates range from 59 to 80%.[1,2]

There are several known risk factors for ovarian cancer. Modifiable risk factors include obesity, nulliparity, and the use of unopposed estrogen therapy. Women of advanced age and those whom are carriers of mutations in *BRCA1/2* are also at an increased risk of developing the disease.[1] In the general population, the average age of onset is 63 years and the lifetime risk is approximately 1.3%. Conversely, *BRCA1/2* carriers have an estimated lifetime risk of 44% and 17% by 80 years of age and a mean age of onset of 50 and 54.5 years, respectively.[3,4] Based on Surveillance, Epidemiology, and End Results (SEER) data from 2011 to 2015, 54.9% of patients were younger than 65 years at the time of diagnosis.[5]

For the majority of newly diagnosed cases, first-line treatment generally involves surgery and/or interval debulking followed by chemotherapy, depending on surgical candidacy but without regards to stage at initial presentation.[6] Newer targeted therapies have improved the treatment landscape for individuals with susceptible tumor types, but the associated cost remains disproportionately high relative to the marginal improvement in outcomes provided by these treatment agents.[7]

Recent studies have evaluated the initial cost of ovarian cancer and costs incurred among the Medicare population, but given that both the majority of cases are diagnosed at an advanced stage and more than half of incident cases are diagnosed at less than 65 years of age, it is

important to establish the cost of the disease in its relevant epidemiological context.[8,9] We sought to estimate the mean annual direct total costs in metastatic ovarian cancer patients, to compare the costs of metastatic ovarian cancer patients to costs in patients without cancer, and to identify factors associated with high costs (i.e., individuals among the upper quintile) of metastatic ovarian cancer.

2. Objectives

The primary objectives of this study were to estimate the mean annual all-cause direct total cost of metastatic ovarian cancer and to determine the incremental mean annual all-cause direct total cost of metastatic ovarian cancer patients compared to the corresponding costs of patients without cancer in the commercially-insured U.S. population. Additionally, we sought to identify factors associated with high annual all-cause direct total costs among metastatic ovarian cancer patients. The secondary objectives of this study were to estimate the mean annual ovarian cancer-related direct total costs in metastatic ovarian cancer patients and to identify factors associated with high annual ovarian cancer-related direct total costs among metastatic ovarian cancer patients.

3. Methods

3.1 Data Source

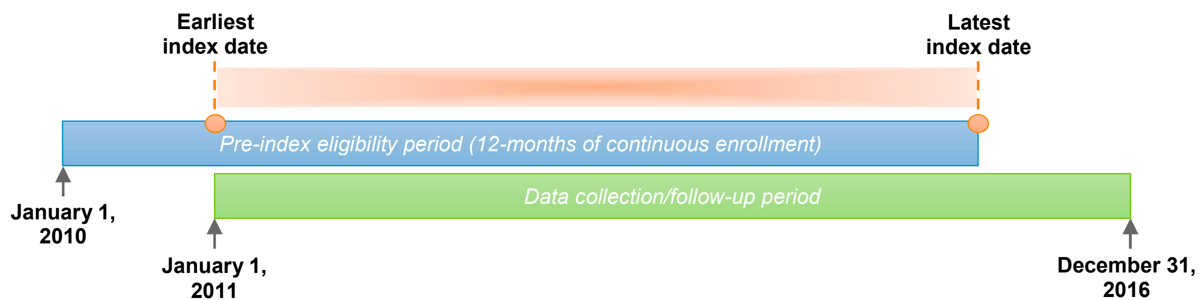
This retrospective study used administrative claims from the Truven Health MarketScan® Commercial Claims and Encounters Database from January 1, 2010 through December 31, 2016. MarketScan® aggregates paid claims data from over 100 employer-sponsored insurance plans across the U.S. The MarketScan® database contains records of inpatient and outpatient encounters, pharmacy claims, and patient demographics for over 45 million commercially-insured individuals, which include active employees, early retirees, COBRA (Consolidated

Omnibus Budget Reconciliation Act) continuees, spouses, and dependents. All patient records are de-identified; a unique identifier links each patient's associated medical claims, pharmacy claims, and enrollment information.[10,11] Since this study utilized only de-identified patient records, pursuant to the Health Insurance Portability and Accountability Act of 1996, this study did not require institutional review board waiver nor approval.

3.2 Study Design

This study was a retrospective database analysis that evaluated all-cause costs, ovarian cancer-related costs, and factors associated with high costs (all-cause and ovarian cancer-related) among patients with metastatic ovarian cancer in the 12-month period following diagnosis of metastases. Eligible patients were identified through MarketScan® from January 1, 2011 through December 31, 2015 and selected based on predefined inclusion criteria (*Figure 1*).

Figure 1. Study participant identification period



3.3 Study Sample

Patients in the metastatic ovarian cancer cohort were first identified based on having ≥1 medical claim with a secondary malignancy diagnosis (ICD-9-CM: 196.xx-198.xx; ICD-10-CM: C77.xx-C79.xx) in the primary position from January 1, 2011 through December 31, 2015 (index identification period); the date of the earliest claim with a secondary malignancy diagnosis (i.e.

metastases) in the index period was defined as the index date (*Figure 2*). Additionally, patients must have also been female on the index date, ≥18 years old on the index date, had ≥12 months of continuous enrollment before the index date, had ≥1 month of continuous enrollment after the index date, and had ≥1 inpatient medical claim or ≥2 outpatient medical claims ≥30 days apart with an ovarian cancer diagnosis (ICD-9-CM: 183.xx, ICD-10-CM: C56.xx) in any claim position within 60 days before or 30 days after the index date. Patients were excluded if they had a medical claim with a cancer diagnosis (ICD-9-CM: 140.xx-239.xx; ICD-10-CM: C00.xx-D49.xx) except for ovarian cancer in any claim position during the 12-month pre-index period. The last selection criterion was utilized in order to focus the analysis on incident metastatic ovarian cancer patients.

Figure 2. Patient identification criteria for inclusion

Patients in the control cohort were first identified based on having ≥1 medical claim during the index period using a random sample of patients derived from 25,000 random inpatient claims and 25,000 random outpatient claims from each index year (2011, 2012, 2013, 2014, 2015). Patients must have also been female on the index date, ≥18 years old on the index date, and had ≥12 months of continuous enrollment prior to the index date. Patients were excluded if

they had ≥1 medical claim with a cancer diagnosis in any position in the 12 months before the index date, on the index date, or in the 12 months after the index date.

After the selection of patients for the control cohorts, we derived a propensity score for each metastatic ovarian cancer patient (n = 2,991) and control (n = 67,914) using a logistic regression model in which metastatic ovarian cancer status was regressed on the following baseline clinical and demographic characteristics:

- Age [continuous variable]
- Region [Northeast, North Central, South, West, Unknown]
- Plan type [Basic/major medical, Comprehensive, Exclusive provider organization (EPO), Health maintenance organization (HMO), Point of service (POS), preferred provider organization (PPO), POS with capitation, Consumer-driven health plan (CDHP), High-deductible health plan (HDHP), Unknown]
- Polycystic ovarian syndrome [Yes, No]
- Hypertension [Yes, No]
- Ischemic heart disease [Yes, No]
- Diabetes mellitus [Yes, No]
- Endometriosis [Yes, No]
- Asthma [Yes, No]
- Autoimmune diseases [Yes, No]
- Depression [Yes, No]
- Anxiety [Yes, No]
- Osteoporosis [Yes, No]
- Kidney disease [Yes, No]

- Liver disease [Yes, No]
- Gallbladder disease [Yes, No]
- Pain [Yes, No]

Each patient (metastatic ovarian cancer patients and controls) had a predicted probability, ranging from 0 through 1, of being a metastatic ovarian cancer patient based on her individual demographic and clinical characteristics. Note that the Deyo-Charlson Comorbidity Index (CCI) score was not included in the logistic regression model for propensity score estimation, as it was highly correlated with the outcome (i.e. all metastatic ovarian cancer patients received at least six CCI score points for having a diagnosis of cancer and/or metastases in the 12-month pre-index period, while all controls were not allowed to have any diagnosis of cancer in the 12-month pre-index period based on the selection criteria). A randomly selected subset of control patients were then matched to the metastatic ovarian cancer patients in a 1:1 manner based on age (±5 years), region, index date (± 30 days), number of months of continuous enrollment after the index date, and $logit$ of the propensity score (± 0.2 of the standard deviation [SD]). All matching variables were weighted equally, which meant that controls were matched exactly to metastatic ovarian cancer patients based on the aforementioned parameters.

3.4 Subgroup with ≥12 Months of Continuous Enrollment after the Index Date

Subgroup analyses were conducted in which only patients with at least 12 months of continuous enrollment after the index date were included. Therefore, all patients were required to have survived and remain enrolled throughout the 12-month follow-up period due to having continuous enrollment throughout this post-index period. The purpose of this subgroup analysis was to evaluate the outcomes of interest in a patient sample that was not lost to follow-up within 12 months after the index date.

3.5 Study Variables

Demographic characteristics, including age (continuous; 18-34, 35-44, 45-54, 55-65 years), region (Northeast, North Central, South, West, Unknown), and plan type (Basic/major medical, Comprehensive, EPO, HMO, PPO, POS with capitation, CDHP, HDHP, Unknown) were measured on the index date for the metastatic ovarian cancer patients and controls. Clinical characteristics were also measured in the 12-month pre-index period, inclusive of the index date, for each cohort. The CCI score (continuous; 0, 1, 2-4, ≥5), along with general comorbid conditions (i.e. polycystic ovarian syndrome [Yes/No], hypertension [Yes/No], ischemic heart disease [Yes/No], diabetes mellitus [Yes/No], endometriosis [Yes/No], asthma [Yes/No], autoimmune diseases [Yes/No], depression [Yes/No], anxiety [Yes/No], osteoporosis [Yes/No], kidney disease [Yes/No], liver disease [Yes/No], gallbladder disease [Yes/No], and pain [Yes/No]),[13,14] were evaluated for each patient.

Outcomes of interest included mean annual all-cause total costs (i.e. costs due to any reason; summation of patient-paid and plan-paid medical and pharmacy costs) and annual ovarian cancer-related total costs (i.e. costs based on claims with an ovarian cancer diagnosis in any position or pharmacy claims for treatments that can be used for ovarian cancer [rucaparib, olaparib, niraparib, anastrozole, tamoxifen citrate, letrozole, exemestane, leuprolide acetate, megestrol acetate, pazopanib]; summation of patient-paid and plan-paid medical and pharmacy costs), which were measured in the 12-month post-index period for both cohorts. Costs were presented as unadjusted costs, and also by sub-components (e.g. medical costs [patient-paid and plan-paid], pharmacy costs [patient-paid and plan-paid]); medical costs were also further presented as outpatient costs (patient-paid and plan-paid) and inpatient costs (patient-paid and plan-paid). Additionally, the incremental all-cause costs and ovarian cancer-related costs for

metastatic ovarian cancer patients versus controls were presented for each cost variable. Note that no adjusted costs (i.e. costs taking into account controlling for potential confounders) were presented since patient characteristics for metastatic ovarian cancer patients and controls were balanced as a result of matching.

3.5 Statistical Analyses

All baseline demographic and clinical characteristics were evaluated descriptively for each cohort. Continuous variables were summarized as means and SDs, and categorical variables were summarized as frequencies and percentages. Student's *t*-tests were used to compare differences between cohorts for continuous variables and Chi-square tests were used to compare differences between cohorts for categorical variables.

3.5.1 Study Sample

To evaluate differences in annual costs between the metastatic ovarian cancer patients and controls and account for varying lengths of post-index follow-up time, we applied the Kaplan-Meier sample average (KMSA) estimator to assess the annual costs per cohort in the presence of censoring after the index date. The per-cohort costs for each of the 12 monthly intervals after the index date were first estimated by averaging the monthly costs for each interval for each cohort. For example, post-index *month one* costs for metastatic ovarian cancer patients were estimated by averaging the *month one* costs for metastatic ovarian cancer patients with at least one month of continuous enrollment after the index date; note that all patients with at least one month of continuous enrollment after the index date were alive at the beginning of the one month after the index date. Post-index *month two* costs for the same cohort were then calculated by averaging the costs in post-index *month two* for patients with at least two months of continuous enrollment after the index date. Each monthly interval was associated with an equal or lesser value for the

denominator (n) in subsequent months; the denominator for the average monthly cost varied based on month.

For each cohort:

$$\textbf{\textit{Annual Cost}} = \sum_{i=1}^{n} \frac{\text{Cost}_i}{n}$$

Where i is the corresponding month, n is the number of patients with continuous enrollment after the index date up to month i

The KMSA method involves multiplying the probability of surviving to the start of each time interval (i.e. post-index month) by the costs incurred during the corresponding time interval conditional on surviving to the start of that interval. The KMSA approach addresses right censoring and nonstandard distributions.[15,16]

For each cohort:

$$\textbf{\textit{KMSA Annual Cost}} = \sum_{i=1}^{12} \frac{\text{Cost}_i}{n} * \text{Pr}_i$$

Where i is the corresponding month, n is the number of patients with continuous enrollment after the index date up to month i, and Pr is the probability of surviving to the start of month i

Using the study data, Kaplan-Meier survival curves were constructed using censored data (i.e. no additional continuous enrollment after a certain post-index month without evidence of death) and death (an inpatient claim with a discharge diagnosis of death). In order to compare the mean

annual all-cause costs and ovarian cancer-related costs for each cohort while accounting for censoring and death after the index date, the average monthly cost for each cohort (12 in total) were summed to calculate the point estimate for the annual costs.

For each cohort:

$$\textit{KMSA Annual Cost} = \sum_{i=1}^{12} \textit{KMSA Average Cost}_i$$

Where *i* is the corresponding month

Ninety-five percent confidence intervals (CIs) for the annual post-index costs for each cohort were calculated by using a bootstrap approach with 1,000 iterations in which 1,000 pairs of matched metastatic ovarian cancer patients and controls were sampled with equal probability and without replacement (i.e. simple random sampling) from the original cohorts. For each bootstrap sample, the annual cost was calculated via summation of monthly costs (the KMSA estimator was applied to the mean cost at each monthly interval). More details are provided in the below example of one bootstrap iteration.

- *Sample without replacement 1,000 pairs of matched metastatic ovarian cancer patients and controls; each metastatic ovarian cancer patients was previously matched to a control based on the selection criteria*
- *Estimate annual costs by applying the KMSA technique*
- *Repeat 999 more times*

A bootstrap approach was used since individual annual costs could not be calculated for each patient due to varying lengths of post-index follow-up time.

3.5.2 Subgroup with ≥12 Months of Continuous Enrollment after the Index Date

Among metastatic ovarian cancer patients and controls with at least 12 months of continuous enrollment after the index date, annual all-cause costs and ovarian cancer-related costs (based on the 12 months after the index date) were summarized as means and 95% CIs and compared using Student's *t*-tests. Among metastatic ovarian cancer patients with at least 12 months of continuous enrollment after the index date, logistic regression models were also used to identify factors significantly associated with the upper quintile versus the lower quintiles of annual all-cause and ovarian cancer-related total costs after controlling for the aforementioned covariates (age [continuous variable], region [Northeast, North Central, South, West, Unknown], plan type [Basic/major medical, Comprehensive, EPO, HMO, POS, PPO, POS with capitation, CDHP, HDHP, Unknown], polycystic ovarian syndrome [Yes, No], hypertension [Yes, No], ischemic heart disease [Yes, No], diabetes mellitus [Yes, No], endometriosis [Yes, No], asthma [Yes, No], autoimmune diseases [Yes, No], depression [Yes, No], anxiety [Yes, No], osteoporosis [Yes, No], kidney disease [Yes, No], liver disease [Yes, No], gallbladder disease [Yes, No], and pain [Yes, No]).

4. Results

4.1 Baseline Characteristics

A total of 2,991 metastatic ovarian cancer patients and 2,991 matched controls were included in this study (Table 1, Table 2). Both demographic and clinical characteristics were not significantly different between both cohorts with the exception of CCI score. Patients in the metastatic ovarian cancer cohort had a mean (SD) age of 54.37 (8.45) years and controls had a mean (SD) age of 54.18 (8.38) years; 58.78% and 58.58% of metastatic ovarian cancer patients and controls, respectively, were 55 to 65 years old. All patients were female and matched on

region, with the South and North Central regions as the most represented regions (34.50% and 24.31%, respectively, for both cohorts). The majority of patients in both cohorts had insurance coverage through a PPO plan type (47.21% and 49.62% for metastatic ovarian cancer patients and controls, respectively) (Table 3).

The mean (SD) CCI score was 6.68 (3.06) for metastatic ovarian cancer patients and 0.79 (1.34) for controls ($p<0.05$); note that all metastatic ovarian cancer patients had at least six CCI points due to having metastases on the index date. In relation to comorbidities, both cohorts were balanced and the most prevalent conditions were hypertension, diabetes mellitus, and ischemic heart disease. All other comorbidities of interest had a prevalence of less than 2% (asthma, autoimmune diseases, anxiety, and kidney disease) or less than 1% (polycystic ovary syndrome, endometriosis, depression, osteoporosis, liver disease, gallbladder disease, and pain) (Table 3).

4.2 Annual Costs

4.2.1 Primary Analyses

The mean (95% CI) annual all-cause total costs in the 12-month post-index period were $149,133 ($144,873-153,330) for the metastatic ovarian cancer patients and $36,566 ($33,542-39,548) for the controls; the resulting mean (95% CI) difference in annual all-cause total costs was $112,567 ($109,589-115,649). The mean (95% CI) annual ovarian cancer-related total costs in the 12-month post-index period were $91,855 ($87,078-96,595) for the metastatic ovarian cancer patients and $0 ($0) for the controls; note that controls were not expected to have any ovarian cancer-related costs since all patients with a cancer diagnosis any time during the study period were excluded. The majority of all-cause and ovarian cancer-related total costs in the follow-up period were driven by medical costs for both cohorts. Pharmacy costs contributed only a small percentage to all-cause and ovarian cancer-related total costs for both cohorts (Table 4).

4.2.2 Subgroup Analyses

When excluding patients without at least 12 months of continuous enrollment after the index date, 1,945 patients remained in both the metastatic ovarian cancer and control cohorts (Table 1, Table 2). Baseline characteristics, with the exception of CCI score, were not significantly different between cohorts.

The mean (95% CI) annual all-cause total costs in the 12-month post-index period were $165,619 ($160,363-170,875) for the metastatic ovarian cancer patients and $36,625 ($33,437-39,813) for the controls; the resulting difference in annual all-cause total costs was a mean (95% CI) of $128,994 ($122,846-135,142). The mean (95% CI) annual ovarian cancer-related total costs in the follow-up period were $105,477 ($101,382-109,572) for the metastatic ovarian cancer patients and $0 ($0) for the controls. The majority of all-cause and ovarian cancer-related costs in the follow-up period were driven by medical costs for both cohorts, of which the majority were outpatient costs for metastatic ovarian cancer patients and inpatient costs for controls. Pharmacy costs contributed only a small percentage to all-cause costs and ovarian cancer-related total costs for both cohorts (Table 4).

4.2.2 Factors Associated with High Costs

The upper quintile of annual all-cause total costs was $233,131 and the upper quintile of annual ovarian cancer-related total costs was $160,474 for the metastatic ovarian cancer cohort. When controlling for all demographic and clinical characteristics, there were not any factors found to be significantly associated with the upper quintile of annual all-cause total costs. In relation to annual ovarian cancer-related total costs, however, POS plan type (OR: 0.44 [95% CI: 0.23-0.88] vs. Comprehensive), PPO plan type (OR: 0.57 [95% CI: 0.34-0.95] vs. Comprehensive), and

anxiety (OR: 2.35 [95% CI: 1.04-5.28]) were found to be significantly associated with the upper quintile (Table 7, Table 8).

5. Discussion

Ovarian cancer remains a substantial clinical and economic burden in the U.S. Our primary objectives were to estimate the mean annual all-cause direct total costs in metastatic ovarian cancer patients, to compare the costs of metastatic ovarian cancer patients to costs in patients without cancer, and to identify factors associated with high annual all-cause direct total costs. We found that the mean annual all-cause total cost of patients with metastatic ovarian cancer was approximately $149,000 in the primary analysis, with the majority of costs related to ovarian cancer. When compared to controls that were matched on baseline demographic and clinical characteristics, metastatic ovarian cancer patients incurred approximately $113,000 greater all-cause total costs compared to controls. Based on demographic and clinical characteristics available in the claims data, we did not find any variables to be significantly associated with high annual all-cause direct total costs, indicating the value of additional research on this topic.

To our knowledge, this is the first study to describe the annual costs of metastatic ovarian cancer in women less than 65 years of age in a commercially-insured population. Prior studies have evaluated the costs of ovarian cancer, but have been limited to older data or patients aged 65 years and older.[1,8] This study demonstrates the economic burden of an understudied patient population that may be inherently more complex or incur higher costs due to earlier disease onset and more aggressive treatment approaches used in this population. One study that evaluated patients 65 years or older with advanced ovarian cancer reported mean annual total costs ranging from $85,987 to $89,149.[9] A recent study also found that costs across different types of cancer were higher for patients less than 65 years old compared to those greater than 65 years old.[15]

Future research focused on this younger patient population will provide greater context for our results and better understanding of the drivers of high costs associated with this younger age group.

All-cause costs were driven primarily by medical costs. This is consistent with findings from a previous study which found that inpatient and outpatient services accounted for nearly all of the mean $93,632 in total expenditures during the 12-month postoperative period for patients newly-diagnosed with ovarian cancer.[8] Pharmacy costs were much lower in comparison, which is representative of the limited number of treatments available for metastases that can be self-administered by patients (e.g. oral poly ADP-ribose polymerase inhibitors).[16] Patients with metastatic ovarian cancer are typically treated with a combination of surgery and chemotherapy, which would not involve medication dispensing from a pharmacy or other pharmacy services (e.g. medication therapy management). Additionally, metastatic ovarian cancer patients incurred substantially higher costs unrelated to ovarian cancer compared to controls. This may be due to the impact of ovarian cancer on other comorbidities or potential under-coding of ovarian cancer in claims data.

Costs of controls in this study may appear relatively high, even for patients without cancer, and may not be representative of the typical patient without cancer. Per-person national health expenditures in 2012, for example, were estimated to be $6,632 per working-age individual and $18,988 for those 65 years and older.[17] The results of this study are most likely due to the fact that controls were matched to metastatic ovarian cancer patients on age and propensity score, which led to balanced demographic and clinical characteristics between both cohorts with the exception of cancer status. Nonetheless, the objectives of this study were to determine the incremental annual all-cause total costs and ovarian cancer-related total costs due

to metastatic ovarian cancer. Matching of controls to the metastatic ovarian cancer patients helped achieve these objectives by controlling for potential confounders.

When comparing the costs of metastatic ovarian cancer patients with at least one month of continuous enrollment after the index date versus those of metastatic ovarian cancer patients with at least 12 months of continuous enrollment after the index date, the mean annual all-cause total costs of the former were approximately 10% less; results were similar for controls. One potential reason for why costs were higher among metastatic ovarian cancer patients with at least 12 months of continuous enrollment after the index date is that patients who survived longer were able to incur greater costs. In the event that costs were lower for these patients, which may potentially occur in other datasets, it may be due to patients incurring high costs in the months leading up to death from ovarian cancer.

The logistic regression models used in this study to evaluate factors associated with the upper quintile of annual all-cause total costs and the upper quintile of annual ovarian cancer-related total costs for metastatic ovarian cancer patients indicated that only POS plan type, PPO plan type, and anxiety were significantly associated with the upper quintile of ovarian cancer-related total costs. These findings may be due to lower reimbursement from POS and PPO plan types compared to other plan types; anxiety can also have negative effects on the quality of life of patients with cancer, which may lead to poorer health and greater consumption of healthcare resources.[18] Despite the findings of this study, it should be noted that many clinically-relevant variables are unavailable in claims data. One example is disease severity, which is likely associated with higher costs. Genetic profiles of patients may also influence responses to ovarian cancer therapy and subsequently costs associated with the disease. In the case of all-cause total costs, the lack of claims-based variables found to be significantly associated with high costs in

the logistic regression model indicates that other important variables (e.g. disease severity) are likely missing from the models.

This study has several limitations associated with the use of retrospective claims data. First, disease severity (e.g. tumor staging) is not available, which limits the ability of the logistic regression models to control for an important confounder that can drive costs. Second, patients may have been diagnosed with ovarian cancer more than 12 months prior to the index date but gone into remission; patients with recurrent ovarian cancer may thus have been included in this analysis, which intended only to include incident cases. Third, the lack of complete data on mortality in the MarketScan® data precludes an accurate assessment of annual costs after an incident diagnosis of metastatic ovarian cancer. Therefore, we utilized the KMSA technique to estimate costs and account for patients that were lost to follow-up. Fourth, there is limited data surrounding relevant confounders in the context of metastatic ovarian cancer. We accounted for comorbidities in this study based on the literature, however, more studies need to be conducted in order to assess the strength of association between the included comorbidities and metastatic ovarian cancer. Fifth, the study sample was limited to patients 65 years or less with commercial insurance, and findings may not be generalizable to older patients or those covered primarily by public health plans. Lastly, 432 patients were excluded from the metastatic ovarian cancer cohort when the inclusion criteria of female gender was applied. These patients were coded as males, which may represent either miscoding or potentially those who had underwent gender reassignment.

6. Conclusions

Patients less than 65 years old (i.e. the working age population) with metastatic ovarian cancer have significantly higher costs compared to those without cancer. Given that the majority of

ovarian cancer patients are diagnosed at less than 65 years of age, these findings contribute to the understanding of the burden of illness in a patient population where little evidence currently exists in regards to the economic consequences of the disease.

Table 1. Attrition Table – Metastatic Ovarian Cancer Patients

Inclusion Criteria	*n* (% of above)
≥1 medical claim with a secondary malignancy diagnosis in the primary position from January 1, 2011 to December 31, 2015	10,406 (100.00%)
Female gender on the index date	9,974 (95.85%)
≥18 years old on the index date	9,965 (99.91%)
≥12 months of continuous enrollment before the index date	6,277 (62.99%)
≥1 inpatient medical claim or ≥2 outpatient medical claims ≥30 days apart with an ovarian cancer diagnosis in any position 60 days pre- or 30 days post-index date	5,477 (87.26%)
Without ≥1 medical claim with a cancer diagnosis other than ovarian cancer in any position in the 12-month pre-index period	3,465 (63.26%)
≥1 months of continuous enrollment after the index date	2,991 (86.32%)
Subgroup analyses only: ≥12 months of continuous enrollment after the index date	1,945 (65.03%)

Table 2. Attrition Table – Controls

Inclusion Criteria	*n* (% of above)
≥1 medical claim from January 1, 2011 to December 31, 2015	286,580* (100.00%)
Female gender on the index date	142,024 (49.56%)
≥18 years old on the index date	126,278 (88.91%)
≥12 months of continuous enrollment before the index date	89,993 (71.27%)
Without ≥1 medical claim with a cancer diagnosis in any position in the 12-month pre-index period, on the index date, or in the 12-month post-index period	67,914 (75.47%)
Matched 1:1 to metastatic ovarian cancer patients based on gender, age (±5 years), region, index date (±30 days), follow-up months with continuous enrollment, and logit of the propensity score (±0.2 of the SD)	2,991 (4.40%)
Subgroup analyses only: ≥12 months of continuous enrollment after the index date	1,945 (65.03%)

*Based on 25,000 random inpatient claims and 25,000 random outpatient claims each year

Table 3. Baseline Characteristics

	Metastatic Ovarian Cancer (*n* = 2,991)	Controls (*n* = 2,991)	*p*-value
Age, mean (SD)	54.37 (8.45)	54.18 (8.38)	0.37
Age Group, *n* (%)			
18-34	91 (3.04%)	91 (3.04%)	1.00*
35-44	260 (8.69%)	262 (8.76%)	

45-54	882 (29.49%)	886 (29.62%)	
55-65	1,758 (58.78%)	1,752 (58.58%)	
Region, *n* (%)			
Northeast	613 (20.49%)	613 (20.49%)	0.57
North Central	272 (24.31%)	272 (24.31%)	
South	1,032 (34.50%)	1,032 (34.50%)	
West	578 (19.32%)	578 (19.32%)	
Unknown	41 (1.37%)	41 (1.37%)	
Plan Type, *n* (%)			
Comprehensive	107 (3.58%)	99 (3.31%)	0.10
EPO	32 (1.07%)	35 (1.17%)	
HMO	275 (9.19%)	295 (9.86%)	
POS	177 (5.92%)	175 (5.85%)	
PPO	1,412 (47.21%)	1,484 (49.62%)	
POS with capitation	19 (0.64%)	13 (0.43%)	
CDHP	195 (6.52%)	169 (5.65%)	
HDHP	94 (3.14%)	61 (2.04%)	
Unknown	680 (22.73%)	660 (22.07%)	
CCI Score, mean (SD)	6.68 (3.06)	0.79 (1.34)	<0.05
CCI Score, *n* (%)			
0	0 (0.00%)	1,757 (58.74%)	<0.05
1	0 (0.00%)	721 (24.11%)	
2-4	931 (31.13%)	428 (14.31%)	
≥5	2,060 (68.87%)	85 (2.84%)	
Comorbidities, *n* (%)			
Polycystic ovary syndrome	16 (0.53%)	11 (0.37%)	0.33
Hypertension	1,074 (35.91%)	1,059 (35.41%)	0.69
Ischemic heart disease	144 (4.81%)	132 (4.41%)	0.46
Diabetes mellitus	384 (12.84%)	371 (12.40%)	0.61
Endometriosis	3 (0.10%)	2 (0.07%)	0.65
Asthma	42 (1.40%)	46 (1.54%)	0.67
Autoimmune diseases	30 (1.00%)	37 (1.24%)	0.39
Depression	5 (0.17%)	4 (0.13%)	0.78
Anxiety	44 (1.47%)	47 (1.57%)	0.75
Osteoporosis	13 (0.43%)	17 (0.57%)	0.46
Kidney disease	35 (1.17%)	37 (1.24%)	0.81
Liver disease	25 (0.84%)	20 (0.67%)	0.45
Gallbladder disease	7 (0.23%)	7 (0.23%)	1.00
Pain	19 (0.64%)	19 (0.64%)	1.00

CCI – Deyo-Charlson Comorbidity Index, CDHP – Consumer-driven health plan, EPO – Exclusive provider organization, HDHP – High-deductible health plan, HMO – Health maintenance organization, POS – Point of service, PPO – Preferred provider organization, SD – Standard deviation

*Rounded to 1.00

Table 4. Annual Follow-Up Costs

	Metastatic Ovarian Cancer	Controls	Difference (Metastatic Ovarian Cancer vs. Controls)	*p*-value
Annual All-Cause Costs, mean (95% CI)				
Total costs	$149,133 ($144,873-153,330)	$36,566 ($33,542-39,548)	$112,567 ($109,589-115,649)	<0.05
Medical costs	$145,008 ($138,924-151,218)	$34,211 ($30,025-38,386)	$110,797 ($105,529-116,107)	<0.05
Pharmacy costs	$4,125 ($3,667-4,570)	$2,356 ($2,052-2,682)	$1,770 ($1,362-2,159)	<0.05
Annual Ovarian Cancer-Related Costs, mean (95% CI)				
Total costs	$91,855 ($87,078-96,595)	$0 (0)	$91,855 ($88,430-95,093)	<0.05

CI – Confidence interval

Table 5. Baseline Characteristics for Subgroup With ≥12 Months of Follow-Up

	Metastatic Ovarian Cancer (*n* = 1,945)	Controls (*n* = 1,945)	*p*-value
Age, mean (SD)	54.49 (8.16)	54.31 (8.06)	0.48
Age Group, *n* (%)			
18-34	53 (2.72%)	54 (2.78%)	1.00*
35-44	150 (7.71%)	151 (7.76%)	
45-54	580 (29.82%)	586 (30.13%)	
55-65	1,162 (59.74%)	1,154 (59.33%)	
Northeast	377 (19.38%)	377 (19.38%)	1.00
North Central	470 (24.16%)	470 (24.16%)	
South	669 (34.40%)	669 (34.40%)	
West	395 (20.31%)	395 (20.31%)	
Unknown	34 (1.75%)	34 (1.75%)	
Plan Type, *n* (%)			
Comprehensive	84 (4.32%)	81 (4.16%)	0.17
EPO	23 (1.18%)	26 (1.34%)	
HMO	223 (11.47%)	228 (11.72%)	
POS	134 (6.89%)	125 (6.43%)	
PPO	1,023 (52.60%)	1,089 (55.99%)	
POS with capitation	14 (0.72%)	9 (0.46%)	
CDHP	127 (6.53%)	130 (6.68%)	
HDHP	69 (3.55%)	45 (2.31%)	
Unknown	248 (12.75%)	212 (10.90%)	
CCI Score, mean (SD)	6.62 (3.04)	0.74 (1.28)	<0.05
CCI Score, *n* (%)			
0	0 (0%)	1,169 (60.10%)	<0.05

1	0 (0%)	467 (24.10%)	
2-4	612 (31.47%)	261 (13.42%)	
≥5	1,333 (68.53%)	48 (2.47%)	
Comorbidities, *n* (%)			
Polycystic ovary syndrome	10 (0.51%)	8 (0.41%)	0.64
Hypertension	680 (34.96%)	665 (34.19%)	0.61
Ischemic heart disease	98 (5.04%)	82 (4.22%)	0.22
Diabetes mellitus	239 (12.29%)	239 (12.29%)	1.00
Endometriosis	2 (0.10%)	1 (0.05%)	0.56
Asthma	18 (0.93%)	26 (1.34%)	0.23
Autoimmune diseases	13 (0.67%)	16 (0.82%)	0.58
Depression	4 (0.21%)	1 (0.05%)	0.18
Anxiety	28 (1.44%)	20 (1.03%)	0.25
Osteoporosis	8 (0.41%)	9 (0.46%)	0.81
Kidney disease	18 (0.93%)	21 (1.08%)	0.63
Liver disease	14 (0.72%)	13 (0.67%)	0.85
Gallbladder disease	3 (0.15%)	3 (0.15%)	1.00
Pain	11 (0.57%)	8 (0.41%)	0.49

CCI – Deyo-Charlson Comorbidity Index, CDHP – Consumer-driven health plan, EPO – Exclusive provider organization, HDHP – High-deductible health plan, HMO – Health maintenance organization, POS – Point of service, PPO – Preferred provider organization, SD – Standard deviation
*Rounded to 1.00

Table 6. Annual Follow-Up Costs for Subgroup With ≥12 Months of Follow-Up

	Metastatic Ovarian Cancer (*n* = 1,945)	Controls (*n* = 1,945)	Difference (Metastatic Ovarian Cancer vs. Controls)	*p*-value
Annual All-Cause Costs, mean (95% CI)				
Total costs	$165,619 ($160,363-170,875)	$36,625 ($33,437-39,813)	$128,994 ($122,846-135,142)	<0.05
Medical costs	$160,515 ($155,358-165,672)	$33,708 ($30,594-36,822)	$126,807 ($120,783-132,821)	<0.05
Inpatient costs	$68,648 ($65,230-72,066)	$21,434 ($18,789-24,079)	$47,214 ($42,892-51,536)	<0.05
Outpatient costs	$91,867 ($88,451-95,283)	$12,274 ($11,297-13,250)	$79,594 ($76,041-83,146)	<0.05
Pharmacy costs	$5,104 ($4,632-5,575)	$2,917 ($2,589-3,245)	$2,187 ($1,612-2,761)	<0.05
Annual Ovarian Cancer-Related Costs, mean (95% CI)				
Total costs	$105,477 ($101,382-109,572)	0 (0)	$105,477 ($101,382-109,572)	<0.05
Medical costs	$105,470 ($101,375-109,565)	0 (0)	$105,470 ($101,375-109,565)	<0.05
Inpatient costs	$44,512 ($42,145-46,879)	0 (0)	$44,512 ($42,145-46,879)	<0.05

Outpatient costs	$60,958 ($58,019-63,898)	0 (0)	$60,958 ($58,019-63,898)	<0.05
Pharmacy costs	$6 ($3-10)	0 (0)	$6 ($3-10)	<0.05

CI – Confidence interval
*Rounded to 0

Table 7. Adjusted Odds Ratios for Factors Associated With High (i.e. Upper Quintile) All-Cause Total Costs for Metastatic Ovarian Cancer Patients

Variable	Odds Ratio	Lower 95% CI	Upper 95% CI
35-44 vs. 18-34 years	1.27	0.85	1.91
45-54 vs. 18-34 years	1.07	0.83	1.37
55-64 vs. 18-34 years	1.04	0.86	1.25
EPO vs. Comprehensive	0.84	0.27	2.58
HMO vs. Comprehensive	0.85	0.46	1.54
POS vs. Comprehensive	0.63	0.32	1.24
PPO vs. Comprehensive	0.70	0.41	1.18
POS with capitation vs. Comprehensive	0.24	0.03	1.98
CDHP vs. Comprehensive	0.88	0.45	1.70
HDHP vs. Comprehensive	1.15	0.55	2.40
Unknown vs. Comprehensive	0.94	0.52	1.70
Polycystic ovarian syndrome	0.85	0.17	4.23
Diabetes mellitus	1.37	0.97	1.94
Hypertension	0.88	0.68	1.14
Ischemic heart disease	1.23	0.74	2.05
Endometriosis	<0.001	<0.001	>999.999
Asthma	0.62	0.14	2.79
Autoimmune disease	0.34	0.04	2.68
Depression	<0.001	<0.001	>999.999
Anxiety	2.27	0.99	5.20
Kidney disease	0.19	0.02	1.47
Liver disease	2.18	0.71	6.70
Pain	0.40	0.05	3.18
Osteoporosis	1.41	0.27	7.31
Gallbladder disease	<0.001	<0.001	>999.999

CI – Confidence interval, CCI – Deyo-Charlson Comorbidity Index, CDHP – Consumer-driven health plan, EPO – Exclusive provider organization, HDHP – High-deductible health plan, HMO – Health maintenance organization, POS – Point of service, PPO – Preferred provider organization
*p <0.05 vs. metastatic ovarian cancer; **Value is rounded to 1.00

Table 8. Adjusted Odds Ratios for Factors Associated With High (i.e. Upper Quintile) Ovarian Cancer-Related Total Costs for Metastatic Ovarian Cancer Patients

Variable	Odds Ratio	Lower 95% CI	Upper 95% CI
35-44 vs. 18-34 years	1.00	0.68	1.47
45-54 vs. 18-34 years	0.94	0.74	1.19
55-64 vs. 18-34 years	0.97	0.82	1.15
EPO vs. Comprehensive	0.54	0.16	1.77
HMO vs. Comprehensive	0.62	0.35	1.12
POS vs. Comprehensive*	0.44	0.23	0.88
PPO vs. Comprehensive*	0.57	0.34	0.95
POS with capitation vs. Comprehensive	0.41	0.08	2.07
CDHP vs. Comprehensive	0.84	0.45	1.58
HDHP vs. Comprehensive	1.08	0.53	2.20
Unknown vs. Comprehensive	0.79	0.45	1.39
Polycystic ovarian syndrome	0.39	0.05	3.21
Diabetes mellitus	1.24	0.87	1.76
Hypertension	0.97	0.75	1.26
Ischemic heart disease	1.41	0.87	2.30
Endometriosis	<0.001	<0.001	>999.999
Asthma	0.92	0.26	3.31
Autoimmune disease	0.33	0.04	2.63
Depression	<0.001	<0.001	>999.999
Anxiety*	2.35	1.04	5.28
Kidney disease	0.39	0.08	1.76
Liver disease	1.42	0.43	4.71
Pain	1.60	0.42	6.13
Osteoporosis	1.46	0.28	7.71
Gallbladder disease	6.49	0.56	75.28

CI – Confidence interval, CCI – Deyo-Charlson Comorbidity Index, CDHP – Consumer-driven health plan, EPO – Exclusive provider organization, HDHP – High-deductible health plan, HMO – Health maintenance organization, POS – Point of service, PPO – Preferred provider organization

*$p < 0.05$ vs. metastatic ovarian cancer

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