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Impact of Rurality on Stage IV Ovarian Cancer at Diagnosis: A Midwest Cancer Registry Cohort Study

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Abstract

Purpose: We aim to understand if rurality impacts patients' odds of presenting with stage IV ovarian cancer at diagnosis independent of distance to primary care provider and the socioeconomic status of a patient's residential census tract.

Methods: A cohort of 1,000 women with ovarian cancer in Iowa, Kansas, and Missouri were sampled and analyzed from the cancer registries' statewide population data. The sample contained those with a histologically confirmed primary ovarian cancer diagnosis in 2011–2012. All variables were captured through an extension of standard registry protocol using standardized definitions and abstraction manuals. Chi-square tests and a multivariable logistic regression model were used.

Findings: At diagnosis, 111 women in our sample had stage IV cancer and 889 had stage I-III. Compared to patients with stage I-III cancer, patients with stage IV disease had a higher average age, more comorbidities, and were more often living in rural areas. Multivariate analysis showed that rural women (vs metropolitan) had a greater odds of having stage IV ovarian cancer at diagnosis (odds ratio = 2.41 and 95% confidence interval = 1.33–4.39).

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Conclusion: Rural ovarian cancer patients have greater odds of having stage IV cancer at diagnosis in Midwestern states independent of the distance they lived from their primary care physician and the socioeconomic status of their residential census tract. Rural women's greater odds of stage IV cancer at diagnosis could affect treatment options and mortality. Further investigation is needed into reasons for these findings.

Keywords

cancer stage; epidemiology; geographic disparities; health disparities; ovarian cancer

Introduction

When compared to nonrural adults, rural adults have poorer cancer outcomes, including decreased overall survival.[1,2] The effect of rurality on cancer outcomes has been related to less access to health care services and an unhealthier, lower socioeconomic status population.[2–4]

Rural ovarian cancer patients may not be impacted by the screening and population differences of other cancers. The United States Preventive Services Task Force recommends against screening women for ovarian cancer.[5,6] Thus, rural women's potential for decreased access to cancer screenings likely has little impact on disparities in ovarian cancer patients. Likewise, the lifestyle factors more prevalent in rural populations, such as smoking, obesity, and physical inactivity, are not prominent risk factors of ovarian cancer. Although this could create an incident disparity, it is likely not creating geographical survival and diagnostic disparities.[7–11] Moreover, ovarian cancer is a cancer of older women, with a median age at diagnosis of 63 years.[12,13] Close to half of women will be Medicare eligible by the time they are diagnosed, which should reduce the socioeconomic burden rural women potentially experience.

Rural ovarian cancer patients have been shown to have less access to specialty surgical care and treatment once they are diagnosed with cancer.[4,14–19] Additionally, they may have less access to diagnosing physicians. Undiagnosed women with ovarian cancer often need the skills of a perceptive primary care physician to discriminate their symptoms, which can be nonspecific and present months to years before a patient is diagnosed.[20,21] Rural patients may have a greater travel distance to their primary care provider. This could delay their time to diagnosis by limiting their abilities to travel to appointments to discuss their symptoms with their primary care provider and to receive a well-check where their symptoms could be recognized.[2,4,16,17,22]

Given that stage of cancer at diagnosis is one of the strongest predictors of survival outcomes in ovarian cancer, we aim to determine if stage at diagnosis varies in ovarian patients by the rurality of where they are living when diagnosed. Particularly, we aim to understand if rurality impacts ovarian cancer patients' odds of presenting with stage IV ovarian cancer at diagnosis, which from 2000 to 2015 had a 5-year survival rate of only 29%.[12,13] We also aim to assess the impact of rurality on stage IV cancer at diagnosis independent of distance to primary care provider and other covariates associated with

rurality, such as the socioeconomic status of the census tract where a woman lived when diagnosed.

Methods

Study Sample

Our analysis utilized data collected through the study, *Patterns of Ovarian Cancer Care and Survival in the Midwestern Region of the United States—a CDC Investigation*.[23] The Midwestern region of the United States was investigated due to the diversity in rurality of ovarian cancer patients' place of residence at time of cancer diagnosis. The data were collected through the central cancer registries in Iowa, Kansas, and Missouri. One thousand and three ovarian cancer patients (roughly 334 from each registry) were sampled from the registries' statewide population data. Inclusion criteria were diagnosis of a first primary, histologically confirmed epithelial, sex-cord, or germ cell cancer (ICD-O-3 8000–8576, 8930–9110) of the ovary, fallopian tube, or primary peritoneum (ICD-O-3 C56.9, C57.0, C48.1, C48.2, and C48.8); malignant behavior; diagnosis in 2011 or 2012; age at diagnosis of 18–89 years; and resident of Iowa, Kansas, or Missouri at diagnosis. Exclusion criteria included low malignant potential histology (ICD-O-3 codes 8442, 8451, 8462, 8472, and 8473); diagnosis at autopsy or by death certificate only; and those with synchronous tumors within 6 months of eligible cancer diagnosis.

All variables were captured through an extension of standard registry protocol using standardized definitions/abstraction manuals and trained coders to complete medical record abstractions. Abstractors attempted to obtain all data from existing patient medical records. When data were not available from the medical record, alternatives such as follow-up with patient providers in each state were pursued. Data abstraction occurred over the course of 18 months.

This study protocol was approved by an institutional review board (IRB) at the CDC as well as by IRBs at each of the 3 field sites.

Measurements

The outcome of interest was International Federation of Gynecology and Obstetrics (FIGO; www.figo.org) stage IV ovarian cancer at diagnosis. FIGO stage was directly coded from the medical record and FIGO stage IV was defined as disease that had metastasized outside the peritoneal cavity to areas of the liver, lung, brain, and/or bones. We defined women diagnosed with FIGO stages I through III (including A through C substages) as having nonmetastatic disease at diagnosis.

The rurality variable was created from the six-category National Center for Health Statistics urban-rural classification scheme framework.[24] The primary exposure of rurality was analyzed as a three-level categorical variable (metropolitan vs micropolitan vs rural) based on the census tract where the patient lived at diagnosis. Metropolitan census tracts were those in a central or fringe metropolitan area with greater than 1 million population or a metropolitan area with a 50,000–999,999 population. Micropolitan census tracts were

nonmetropolitan populations with an urban cluster population of 10,000–49,999 persons. Rural census tracts were nonmetropolitan/noncore populations.

Other covariates included age, insurance status, race, comorbidities, histology, site of origin, distance to primary care physician, census tract income, and census tract education. Age at diagnosis was categorized as (1) 18–45 years, (2) 46–60 years, (3) 61–75 years, and (4) 76–89 years. Insured persons included anyone with any form of private, managed care, or public insurance; all others were classified as uninsured. Race was determined by review of the medical record and, due to small numbers of non-white patients, was categorized as white versus non-white. The Charlson index was calculated based on patient comorbidities.[25–27] The Charlson index score was broken into 3 categories of 0, 1, and 2 or greater. Histologic codes were categorized as epithelial or nonepithelial disease in accordance with ICD-0–3 morphology codes.[28,29] The site of origin of a tumor cell was categorized as ovarian (ICD-O-3 code C56.9), fallopian tube (C57.0), or primary peritoneal cancers (C48.1, C48.2, and C48.8). Distance to primary care physician was calculated from the latitudes and longitudes of the patient's residence and her primary care physician's clinic. Great Circle Distance in ArcGIS was used, and straight distance miles were categorized as (1) 0–15 miles, (2) 16–30 miles, (3) 31–60 miles, and (4) greater than 60 miles. If the patient visited more than 1 primary care provider, the office of the managing, recurrent physician was used. The median annual household income of the census tract of a patient residence at diagnosis was categorized as (1) less than $40,000, (2) $40,000–50,999, (3) $51,000–65,999, and (4) greater than $66,000. The percentage of people with less than a high school education within the census tract of the patient at time of diagnosis was categorized as (1) 0%−10%, (2) 11%−20%, and (3) 21% or greater.

Statistical Analysis

Chi-square tests were used to compare the demographic and clinical characteristics between patients who presented with metastatic versus nonmetastatic disease at diagnosis. A multivariable logistic regression model was created using a backward selection method to remove covariates until all values in the model were significant (alpha <.05). We were primarily interested in the association between rurality and odds of metastatic disease. Therefore, hypothesized confounders were added to the model 1 at a time starting with rurality, then social and geographical factors, followed by tumor characteristics. If adding a hypothesized confounder changed the parameter estimate of rurality more than 10%, it was considered a true confounder and included in the model. Age was added into the final model. Data were suppressed to protect patient confidentiality if any cell had an $n < 4$.

Results

Three cases were excluded from our analysis due to missing census tract variables including rurality. Therefore, the total analytic sample was 1,000 women. Of the 1,000 women in our sample, overall most were white, insured, and residing in metropolitan areas (Table 1). A total of 111 women were diagnosed with stage IV disease and 889 were diagnosed with stage I-III disease (Table 2).

Compared to patients without stage IV disease at diagnosis, patients with stage IV disease had a significantly higher average age (66.9 years vs 63.2 years). Stage IV patients (vs stage I-III) also were significantly more likely to reside in rural areas (28% vs 17%, $P = .022$), have 2 or more comorbidities (14% vs 7%, $P = .013$), and have nonepithelial cancer (6% vs 3%, $P = .049$). Patient census variables (median income and education), distance to primary care physician, insurance status, race, and tumor primary site were similar among patients with stage IV and stages I-III disease.

Results of the multivariate analysis showed that rural women were 2.41 times as likely to have stage IV ovarian cancer at diagnosis than metropolitan women after adjusting for other factors (95% confidence interval [CI], 1.33–4.39) (Table 3). Women who lived 31–60 miles away from their primary care physician were significantly less likely to have stage IV disease at presentation (odds ratio [OR] = 0.42; 95% CI, 0.19–0.90) compared to those who lived 0–15 miles away. There was a nonsignificant association for stage IV diagnosis among women who lived farther than 60 miles away from their primary care physician (OR = 0.60; 95% CI, 0.30–1.20). Additionally, histology, insurance status, race, age, and census tract-based variables (median income and percentage with less than a high school education) did not have a significant impact on having metastatic ovarian cancer at diagnosis. Women with 2 or more comorbidities had nonsignificantly elevated odds of stage IV cancer (OR = 1.86; 95% CI, 0.97–3.56). When rurality was removed from the model, all odds ratios including distance to primary care physician became insignificant.

Discussion

Our results, from a sample of women in 3 Midwestern states, indicate that rural women were more likely than those not living in rural areas to present with stage IV ovarian cancer at diagnosis. This is the first population-based analysis showing an effect of rurality on stage at diagnosis for ovarian cancer patients in these states. Results are somewhat consistent with previous findings examining other cancers. Prior cancer studies showed that rural cancer patients are more likely to have late stage diagnoses and poorer cancer outcomes.[2,30–35]

The association between rurality and stage IV cancer diagnosis persisted even when controlling for distance to primary care physician. Living a greater distance from her primary care physician did not increase an ovarian cancer patient’s odds of having stage IV cancer at diagnosis. In fact, women who lived the second farthest (31–60 miles) from their primary care physician were less likely to have stage IV disease (vs those that lived 0–15 miles away). Women that lived more than 60 miles away had a nonsignificant lower odds of stage IV disease. These findings suggest the rural disparity is likely not a direct result of distance to ovarian cancer patients’ primary care providers, and that the rural disparity exists independent of distance to primary care provider. These findings encourage investigation of causes other than the distance to care. One reason for this discrepancy could be differences in distance to obstetric gynecologist care providers (vs primary care providers). Urban women may be more able to access obstetric gynecologists, and obstetric gynecologists may be able to recognize gynecologic malignancy symptoms sooner in a disease course due to their training and their clinical resources.

We also found that women with 2 or more comorbidities may be more likely to present with stage IV disease. Prior research on the impact of comorbidities on stage at diagnosis has yielded inconsistent findings, but our results align with much of the ovarian cancer-specific research.[36–39] Prior research has found that having multiple comorbidities is associated with advanced stage at diagnosis and less aggressive treatment courses for ovarian cancer; both have been shown to increase the risk of death from ovarian cancer by 40%.[36–39] Our nonsignificant findings also align with the theory of competing demand, which postulates comorbidities distract patients and physicians from noticing tumor growth and cancer symptoms.[36,40,41] Given that screening for ovarian cancer in asymptomatic women is not the standard of care, we did not expect to see a surveillance effect, or early diagnosis of women with worse comorbidities.[36]

The underlying reasons for the association between rurality and stage IV ovarian cancer are unclear and warrant further investigation. It is possible that rural women have additional physical, behavioral, physiological, or health care-related factors that contribute to their advanced stage at diagnosis.[2,30] Physically, it is possible that rural women's higher obesity rates are contributory to delayed presentation.[1] Abdominal obesity could delay patients' and physicians' ability to notice relatively asymptomatic abdominal masses and ovarian cancer-related ascites (the accumulation of intraabdominal fluid).[42] Additionally, rural women of all ages are more likely to rate their health as poor compared to their metropolitan counterparts.[1,43] Thus, it is plausible that rural women have comorbid conditions and health concerns that mask the symptoms of ovarian cancer and contribute to a delayed diagnosis.

Behaviorally, it is possible that rural women are less likely to go to the doctor even when they notice their symptoms.[2,16,32] Their willingness to go to a primary care doctor may be independent of their ability to financially or geographically seek care. Some past research demonstrated that rural cancer patients are more at risk of making adverse health choices, such as refusing preventive or early medical care.[1] Research on colorectal cancer patients in a different Midwestern state than those studied here found that rural patients were more embarrassed by cancer screening procedures and were less likely to identify medical or emotional benefits in preventive checkups with physicians than their urban counterparts.[44] The ability of rural women to communicate their symptoms with their doctors may be limited by social isolation, educational barriers, personal comfort, and fear of stigma in a small community.[45,46] If health behaviors or communication disparities are found to delay diagnosis in rural women, public health efforts could target education of rural women and rural-practicing physicians.

Finally, health system differences could contribute to this rural disparity. Past research found the number of providers available to rural patients could be just as limiting as the travel distance to a provider.[47] The paucity of rural providers could limit the timeliness of appointments. Even when a physician is available locally, rural women can have longer time-to-diagnosis and time-to-initiation-of-treatment after their initial medical appointment due to financial limitations, difficulty obtaining transportation, and referral difficulties within a rural health care network.[17,45] Likewise, greater time lags may occur because more physicians or health systems may be involved in a rural patient's care compared with women who receive all their care at a metropolitan comprehensive cancer hospital. For example,

rural patients may have their symptoms evaluated at their local care provider, and then be sent to distant tertiary care centers or single-specialty regional medical practices for diagnosis, chemotherapy, and surgery.[4] Prior general cancer research has found that about one-fifth of rural women bypass their closest cancer care provider for diagnosis and treatment.[22] Public health efforts that promote patient navigation for ovarian cancer patients in rural communities may help alleviate some of these issues.

Strengths and Limitations

The primary strength of this study was the quality and population representativeness of the data. This dataset was created from statewide central cancer registry data in 3 Midwestern states that have highly trained and experienced cancer registrars. In addition, these registrars participated in extensive training for medical record abstraction of specific study variables using a standardized tool, and they conducted thorough quality control checks with follow-back to ensure that all data variables available were captured appropriately and accurately. In addition, all sampled cases were histologically confirmed, which reduced misclassification.

The major limitation of this study was that not all potential confounders were available in medical records and the dataset. Particularly, we would have liked to investigate obesity, personal income, personal education level, frequency of primary care checkups, ease and timeliness of scheduling primary care appointments, and number of local physicians or physician centers.[48] Also, the findings in these 3 states do not necessarily represent all women diagnosed with ovarian cancer in the United States. Finally, because our study was designed and powered to detect differences among women living in rural areas compared to others, our ability to look at other factors that may impact ovarian cancer diagnosis, such as race and ethnicity, was limited. Our sample size may have lacked power to detect all associations.

Conclusion

Rural ovarian cancer patients are more likely to be diagnosed with stage IV disease compared to their metropolitan counterparts. This may lead to fewer treatment options and higher mortality. The identification of the cause(s) of this disparity could lead to targeted public health efforts in the rural community to increase early stage ovarian cancer diagnoses. Further investigation of these findings is needed. In the meantime, tailored public health efforts in ovarian cancer education and patient navigation may help alleviate this disparity.

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Table 1

Demographic Characteristics of Study Sample

Characteristic	N (%)
Total	**1,000 (100)**
Rurality	
Metropolitan	668 (66.8)
Micropolitan	146 (14.6)
Rural	186 (18.6)
Age	
Age <65	510 (51.0)
Age ≥65	490 (49.0)
Insurance status	
Insured	962 (96.2)
Uninsured	38 (3.8)
Race White	939 (93.9)
Non-white	61 (6.1)

Table 2

Stages of Ovarian Cancer at Diagnosis

		Stage IV (N = 111)		Stages I-III (N = 889)		
		N	Percent	N	Percent	*P* value
Rurality	Metropolitan	68	61	600	68	.022
	Micropolitan	12	11	134	15	
	Rural	31	28	155	17	
Age	18–45 years	6	5	87	10	.048
	46–60 years	26	23	271	31	
	61–75 years	45	41	344	39	
	76–89 years	34	31	187	21	
Insured	Yes	-	-	-	-	.242
	No	-	-	-	-	
Race	White	103	93	869	94	.605
	Non-white	8	7	53	6	
Charlson score	0	74	67	691	78	.013
	1	21	19	133	15	
	2+	16	14	65	7	
Histology	Epithelial	104	94	864	97	.049
	Non-Epithelial	7	6	25	3	
Site of origin	Ovary	94	85	723	81	.388
	Fallopian tube or Peritoneum	17	15	166	19	
Distance to primary care physician	0–15 miles	64	60	475	55	.380
	16–30 miles	18	17	119	14	
	31–60 miles	10	9	133	15	
	60 miles or more	15	14	142	16	
	Unknown	4	4	22	3	
Census tract median income	$1-$39,999	26	23	202	23	.981
	$40,000-$50,999	30	27	241	27	
	$51,000-$65,999	31	28	239	27	
	$66,000+	24	22	207	23	

		Stage IV (N = 111)		Stages I-III (N = 889)		
		N	**Percent**	**N**	**Percent**	***P* value**
Census tract with less than a high school education	0%-10%	69	62	550	62	.293
	11%-20%	28	25	263	30	
	21% or greater	14	13	76	9	

Note. Missing values are because the cells contained fewer than 4 persons. Bolding of the *P* value indicates $P < .05$.

Table 3

Multivariable Analysis of the Odds of Having Metastatic Ovarian Cancer at the Diagnosis

		Odds Ratio	95% Confidence Interval
Rurality	Metropolitan	Reference	
	Micropolitan	0.90	0.45–1.78
	Rural	**2.41**	**1.33–4.39**
Age	18–45 years	Reference	
	46–60 years	1.46	0.56–3.81
	61–75 years	1.74	0.68–4.45
	76–89 years	2.01	0.76–5.33
Insured	Yes	Reference	
	No	0.51	0.12–2.24
Race	White	Reference	
	Non-white	1.25	0.53–2.91
Charlson score	0	Reference	
	1	1.35	0.78–2.10
	2+	1.86	0.97–3.56
Histology	Epithelial	Reference	
	Non-epithelial	2.24	0.85–5.87
Distance to	0–15 miles	Reference	
primary care	16–30 miles	0.96	0.53–1.76
physician	31–59 miles	**0.42**	**0.19–0.90**
	60 miles or more	0.60	0.30–1.20
	Unknown	1.14	0.36–3.65
Census tract	$1-$39,999	Reference	
median income	$40,000-$50,999	1.01	0.54–1.90
	$51,000-$65,999	1.19	0.61–2.31
	$66,000+	1.04	0.48–2.22
Census tract with	0%−10%	Reference	
less than a high	11%−20%	0.79	0.46–1.37
school	20% or greater	1.48	0.68–3.19
education			

Note. Bolding of the 95% confidence interval indicates the confidence interval does not cross 1 and is significant at $P < .05$.