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Rural-metropolitan disparities in ovarian cancer survival: A statewide population-based study

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Abstract

Purpose—To investigate rural-metropolitan disparities in ovarian cancer survival, we assessed ovarian cancer mortality, and differences in prognostic factors by rural-metropolitan residence.

Methods—The Utah Population Database was used to identify ovarian cancer cases diagnosed between 1997–2012. Residential location information at the time of cancer diagnosis was used to stratify rural-metropolitan residence. All-cause death and ovarian cancer death risks were estimated using Cox proportional hazard regression models.

Results—Among 1,661 patients diagnosed with ovarian cancer, 11.8% were living in rural counties of Utah. Although ovarian cancer patients residing in rural counties had different characteristics compared to metropolitan residents, we did not observe an association between rural residence and risk of all-cause nor ovarian cancer-specific death after adjusting for

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confounders. However, among rural residents, ovarian cancer mortality risk was very high in older age at diagnosis and for mucinous carcinoma, and low in overweight at baseline.

Conclusions—Rural residence was not significantly associated with the risk of ovarian cancer death. Nevertheless, patients residing in rural-metropolitan areas had different factors affecting the risk of all- cause mortality and cancer-specific death. Further research is needed to quantify how mortality risk can differ by residential location accounting for degree of healthcare access and lifestyle-related factors.

Keywords

ovarian cancer; rural; survivorship

INTRODUCTION

In the United States (US), ovarian cancer is the fifth most common cause of cancer-specific death among women(1). Annually in the US, nearly 22,440 women are diagnosed with ovarian cancer and approximately 14,000 of those patients die as a result of ovarian cancer(2). Over 70% of patients diagnosed with ovarian cancer present with advanced stage from metastasis, thus the prognosis of ovarian cancer is poor with an estimated 5-year survival rate of 46.5%(1,2). Although incidence and mortality rates of the disease have been decreasing over the last few decades(2), recent guidelines from the National Comprehensive Cancer Network suggest that addressing the consequences of cancer and its treatment is critical to improve survival(1).

Previous studies hypothesized that living in different locations is related to the exposure to different lifestyle, personal behaviors, and access to healthcare, which may expose population groups to different risks not only for developing cancer itself but also for timing of diagnosis, quality of treatment, and prognosis(3–5). However, to date, only few studies have explored ovarian cancer survival, and differences in prognostic factors by rural-metropolitan residence.

Limited evidence suggest that ovarian cancer patients living in rural areas are more likely to have advanced cancer stage and receive hospice care, and less likely to be seen by a gynecologic oncologist and receive adjuvant treatment compared to those living in metropolitan areas(6–9). In contrast, other studies have suggested that rural residents compared to metropolitan residents had neither higher risk of cancer mortality nor late cancer stage, and no differences were found in symptoms and quality of life among recurrent ovarian cancer patients(3,4,10–13).

To better understand the inconsistent evidence and address rural-metropolitan disparities in ovarian cancer survival, we examined differences in ovarian cancer survival among a population-based cohort in Utah. The objective of this study was to examine all-cause mortality and ovarian cancer specific mortality, and differences in demographic and prognostic factors by rural-metropolitan residence among ovarian cancer patients.

MATERIALS AND METHODS

Study Population

Data for the ovarian cancer cohort were identified by the Utah Population Data Base (UPDB). The UPDB is a database connecting between population-based information from numerous data sources including data from the Utah Cancer Registry (UCR) (one of the nine population-based Surveillance, Epidemiology, and End Results [SEER] Program registries), statewide vital records (birth and death certificates), inpatient discharge and ambulatory surgery data, family history records, and residential history records, and the electronic medical (EMR) records, held by the two of the largest healthcare providers in Utah (University of Utah Healthcare and Intermountain Healthcare). This study has been approved by the University of Utah's Resource for Genetic and Epidemiologic Research and its Institutional Review Board.

Patients primarily diagnosed with ovarian cancer were identified using International Classification of Diseases (ICD) codes according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3 code: C56.0). Based on the residential history records, women living in Utah at the time of ovarian cancer diagnosis with available information on last follow up date and known outcome were eligible for analysis. Among 1,803 identified ovarian cancer cases diagnosed between 1997–2012, we excluded patients with unknown or missing information on cancer stage, resulting in a cohort of 1,661 women.

Exposures of interest

Our exposures of interest were demographic factors including race, age/year at cancer diagnosis, baseline Body Mass Index (BMI), and baseline comorbidities as well as clinical risk factors including treatment type, cancer stage, histology grade, and histology subtype. Baseline comorbidity score was computed using Charlson Comorbidity Index (CCI)(14) to account for baseline health conditions. All medical record data before the date of ovarian cancer diagnosis were pooled and coded using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes to calculate the CCI score. County level education (% Bachelor's degree) and income (Median family Income and % Families below poverty in the past 12 month) variables from SEER*Stat, originating from US Census data (available data between 1997–2012), were used to account for factors associated with socioeconomic status. In order to identify rural-metropolitan residential status of each patient, we used each patient's residential location information at the time of cancer diagnosis. 29 counties in Utah were classified into metropolitan or rural area based on 2003 and 2013 rural-urban continuum code definition from SEER*Stat(15).

Outcomes of interest

Our primary outcomes of interest were all-cause mortality and ovarian cancer-specific mortality by residential location. To determine all-cause deaths as well as ovarian cancer-specific deaths, ICD-10 codes were used (ICD-10 code for ovarian cancer death: C56). Dates of death were assessed using death certificates from Utah Department of Health, and nationwide records of genealogy, Social Security Death index, and UCR. Time to outcome

was defined as the time from ovarian cancer diagnosis to death for those who confirmed to be dead. For women who were known to be alive, time to outcome was censored.

Statistical Analysis

Distributions of baseline demographics, health conditions prior to cancer diagnosis, cancer-related factors (stage, histology subtype, and histology grade), treatment received, and vital status with cause of death were compared by residential areas (metropolitan vs. rural) using descriptive statistics. Chi-square tests were used to assess the difference and P-values were calculated. Baseline BMI data was defined as the earliest BMI measurement at least a year prior to cancer diagnosis. Given that approximately 30% of our subjects had missing BMI values (30.1% and 29.6% for rural and metropolitan residents, respectively), we imputed BMI for the 30% who were missing it using age at diagnosis, race, and CCI score as predictors using multiple imputation. We compared Cox regression models including only subjects who had BMI in the data and with the full study population, including those who had imputed BMI, to assure that our inferences did not change due to the imputed BMI.

Survival time was calculated from ovarian cancer diagnosis date to death date or the last date known to be alive and living in Utah. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated to compare the risk of mortality between rural versus metropolitan residents. We conducted stratified analyses by rural-metropolitan location to evaluate an individual effect of each risk factor and prognostic factor on mortality by different environmental exposure. Potential confounders were determined using directed acyclic graphs(16) and included in the multivariable adjusted models, as appropriate. For the models that violated proportional hazards assumptions, we used Cox models with cubic splines to estimate the risk of mortality. SAS software version 9.4 (SAS Institute, Inc., Cary, North Carolina) and Stata software version 14.1 (Stata Corp, Texas) were used for statistical analyses.

RESULTS

Among 1,661 women diagnosed with ovarian cancer between 1997–2012, 1,465 (88.2 %) and 196 (11.8 %) were living in metropolitan and rural areas at the time of diagnosis, respectively. During the mean 4.7 years of follow up, 1,102 (66.4%) patients died and 761 (45.8%) died due to ovarian cancer. Ovarian cancer patients residing in rural counties were more likely to be obese (P=0.03), impoverished (P <0.0001), and have lower education level (P <0.0001) (Table 1).

With regard to cancer diagnosis and treatment, rural residents were more likely to be diagnosed with advanced cancer stage, and higher histology grade, histology subtype of Endometrioid/non-specific, and receive no treatment or surgery only, although the differences were not statistically significantly different (Table 2). BMI and stage were associated (P=0.02), with the highest proportion of localized cancer observed among underweight patients (50%) and the lowest proportion of localized cancer among the overweight patients (28.9%) (Table 3). However, when looking at the association stratified by rural-metropolitan residence, BMI and cancer stage were associated only among metropolitan residents P=0.01).

Overall, we did not observe an association between rural residence and risk of all-cause death nor ovarian cancer-specific death (HR= 1.09; 95% CI=0.90, 1.32 and HR=1.01; 95% CI=0.80, 1.27) after adjusting for age at diagnosis, year of diagnosis, BMI, CCI, race, stage, and treatment (Table 4). Survival curves for all-cause mortality and ovarian cancer-specific mortality are shown in Figure 1 for metropolitan and rural ovarian cancer patients.

When assessing an individual effect of each risk factor on mortality risk by rural-metropolitan residence, older age at cancer diagnosis was associated with an increased risk of all-cause death among metropolitan and rural residents (80+ years compared to 60–69 years; HR=2.70, 95% CI=2.02, 3.60 and HR=3.58, 95% CI=1.27, 10.14) (Table 5). However, for ovarian cancer-specific death, rural residents who were diagnosed at the age between 50–59 years had a higher risk than patients who were diagnosed at the age between 60–69 years. In addition, among rural residents, ovarian cancer mortality risk was relatively high in patients diagnosed at age ≥ 80 years (HR=5.94; 95% CI=1.64, 21.61) compared to metropolitan residents (HR=1.90; 95% CI=1.31, 2.74). While baseline BMI was not associated with mortality risk among patients living in metropolitan counties, we observed an inverse association between baseline BMI and risk of death in both all-cause mortality and ovarian cancer-specific mortality among rural ovarian cancer patients. With regards to baseline CCI score and mortality risk, whereas CCI score was not associated in rural counties, among metropolitan ovarian cancer patients, baseline CCI score was adversely associated with both all-cause and ovarian-cancer specific mortality risks. Education levels and poverty were not associated with risk of death among ovarian cancer patients.

Advanced cancer stage at diagnosis had significantly higher risks for all-cause death and ovarian cancer-specific death in both rural and metropolitan counties. Rural patients had increased risks of both all-cause and ovarian cancer-specific death when their histologies were mucinous (HR=18.49, 95%CI=3.68, 93.04 and HR=16.52, 95%CI=1.86, 146.41) or non-specific (HR=2.03, 95%CI=1.31, 3.15 and HR=1.85, 95%CI=1.07, 3.21). However, endometrioid histology subtype had almost 70% decreased risk of ovarian cancer-specific death (HR=0.31, 95%CI=0.11, 0.89) compared to patients with serous histology subtype in rural counties. Metropolitan patients had an increased risk of both all-cause death and ovarian cancer-specific death when they were diagnosed with higher histology grade and non173 specific histology subtype, and receive chemotherapy only (Table 6).

DISCUSSION

Although ovarian cancer patients residing in rural counties of Utah had different characteristics from patients residing in metropolitan counties, we did not observe an association between rural residence and risk of all-cause death nor ovarian cancer-specific death after adjusting for potential confounders. However, ovarian cancer patients had different mortality risks associated with prognostic factors by rural-metropolitan residence. Among rural residents, ovarian cancer mortality risk was very high in older age at diagnosis, late stage and for mucinous carcinoma, and low in overweight. Metropolitan residents had higher risk of death when they were diagnosed with higher histology grade and non-specific histology subtype, had low baseline CCI score, and received only chemotherapy for

treatment. Socioeconomic status was not associated with cancer survival among rural or metropolitan ovarian cancer patients.

Differences in ovarian cancer survival by place of residence have been shown in previous research, although results are conflicting. O'Malley *et al.* reported that adverse survival was influenced by rural location among women with ovarian cancer in California(8). Carney *et al.* reported in a study conducted among ovarian cancer patients in Utah that patient residing in rural regions were less likely to have been seen by a gynecologic oncologist in their course of treatment and were more likely to experience survival disadvantage when they were 70 years of age and older at diagnosis(7). However, in a recent study conducted in Poland, Szpurek *et al.* reported that there were no differences by residential location in cancer prognostic factors such as stage, histological grade/type, and tumor size/volume(3). Overall, in our study, rural residence was not significantly associated with ovarian cancer survival. Although we observed that several demographic and prognostic factors appear to contribute differently in ovarian cancer survival by location, our results should be interpreted with caution since our low number of patients in rural area were limiting the power to estimate the effect of risk factors on survival.

In our study, older age and advanced stage at diagnosis were associated with a decreased ovarian cancer survival regardless of rural residence, however we observed that rural patients who were diagnosed at age ≥ 80 years have relatively higher risk of ovarian cancer mortality than metropolitan patients. This may be because rural residents who were diagnosed ≥ 80 years are less likely to receive adjuvant treatment than metropolitan residents with same age group. Indeed, when we look at cancer treatment data for rural and metropolitan elderly (≥ 80 years), as we expected, rural patients were less likely to receive adjuvant treatment compared to metropolitan patients (16% in rural vs. 29.8% in metropolitan patients received different types of therapy other than receiving surgery only). For cancer stage at diagnosis, there were no differences in trend by rural-metropolitan counties. Previous studies have shown that ovarian cancer patients <40 years and >70 years of age were significantly less likely to be seen by a gynecologic oncologist and experience a significant survival disadvantage(7), and patients with advanced cancer stages had significantly reduced survival(8). However, given that no prior studies conducted in the US have explored the differences between rural-metropolitan areas regarding individual effect of age nor stage at diagnosis on ovarian cancer survival, comparison of findings between our study and previous research may be difficult.

Our finding of baseline BMI being associated with cancer stage among ovarian cancer patients supports the evidence from prior studies that obesity is associated with metastasis, poor prognosis, and worse survival among ovarian cancer patients(17–20). However, in rural ovarian cancer patients, baseline BMI was not associated with cancer stage (P=0.79), and overweight patients had significantly reduced risk of both all-cause and ovarian cancer-specific mortality. The associations between obesity and ovarian cancer survival may differ by cancer stage(21), with possible increased mortality for those with normal-weight, whereas those with overweight experienced reduced mortality. Unlike metropolitan residents, overweight rural patients had lower proportion of advanced stages at cancer diagnosis (69.4%) than rural normal weight patients (71.1%). Since we used normal weight

group as a reference group of the analysis, having lower proportion of advanced cancer stage in overweight patients might have contributed to reducing HRs for ovarian cancer mortality. Further studies should explore ovarian cancer survival differences by rural-metropolitan residence accounting for possible interactions between obesity and cancer stage.

We observed that an increase in CCI score at baseline was associated with a decrease in the risk of death. While baseline CCI score did not appear to increase the risk of all-cause death and ovarian cancer-specific death in rural areas, there was about a 30% reduced risk of death among patients with CCI score 2 or greater compared to patients with zero CCI score in metropolitan areas. One potential justification for this is that patients with comorbidities before ovarian cancer diagnosis may be more likely to visit healthcare providers, diagnosed earlier, and have increased chance of survival than patients without any comorbidities. Thus, in our cohort, higher CCI score may indirectly play a role on reducing the risk of mortality with early diagnosis, localized stage at diagnosis, and early clinical intervention. Given that the association between healthcare accessibility and cancer diagnosis, treatment, and prognosis by comorbidity clusters is still not fully explored, further work is warranted to understand the interplay between these factors.

Compared to serous histology subtype, mucinous and non-specific histologies were associated with an elevated risk, but endometrioid histology subtype was associated with a reduced risk of ovarian cancer-specific death in rural counties. Our results were consistent with findings from prior research reporting that compared to serous subtype, survival of mucinous ovarian cancer is worse than other histology subtypes since they are diagnosed in advanced stage, and endometrioid ovarian cancer has better survival as they are diagnosed with a younger age and earlier stage(22–24). A rigorous investigation is warranted to assess the mechanism behind survival differences between rural-metropolitan areas associated with histology subtypes.

Our study had many strengths such as the use of a large population-based data, including statewide cancer registry data, medical records, birth certificate/death records, and driver's license records. Our study cohort included approximately 1,600 ovarian cancer survivors with completed medical records ascertained from two biggest healthcare providers in Utah and hospital surgery, ambulatory, and discharge records collected from the Utah State Department of Health. This allowed us to successfully calculate Charlson Comorbidity Index and estimate the effect of baseline health conditions on cancer mortality. We also had baseline BMI to investigate a potential baseline factors. Further, by incorporating data on vital status as well as cause of death with the use of death certificates, our study had an advantage of minimizing recall bias over prior studies measured outcomes with self253 reported data.

A limitation in our study includes the use of ICD-9 codes and medical records for capturing the baseline comorbidities may have caused misclassification bias since there always is a possibility of coding or measurement errors. In addition, given that we used information on residential location at the time of diagnosis, we were not able to assess the amount of time and period that patients actually spent in rural area. We also had limited information on treatment such as type, dose, frequency and place that treatment was provided. In future

research, effect of treatment on survival disparities across rural-metropolitan population groups should be evaluated after taking into account differences in insurance status, options for treatment, and adherence to treatment guidelines. Lastly, the number of ovarian cancer patients residing in rural areas was small (n=196), limiting the power of some the smaller risk factor groups in the analysis.

In summary, among this cohort of women diagnosed with ovarian cancer, rural residence was not significantly associated with the risk of ovarian cancer death. Nevertheless, we found that patients residing in rural-metropolitan counties of Utah have different factors affecting the risk of all-cause mortality and cancer-specific death. The slightly higher proportions of obesity did not appear to contribute to higher risks of death among rural ovarian cancer patients. However, as the number of rural ovarian cancer patients was fairly low, our study results should be interpreted with caution. Further, more research is needed to quantify how mortality risk can differ by residential location accounting for degree of healthcare access and lifestyle-related factors.

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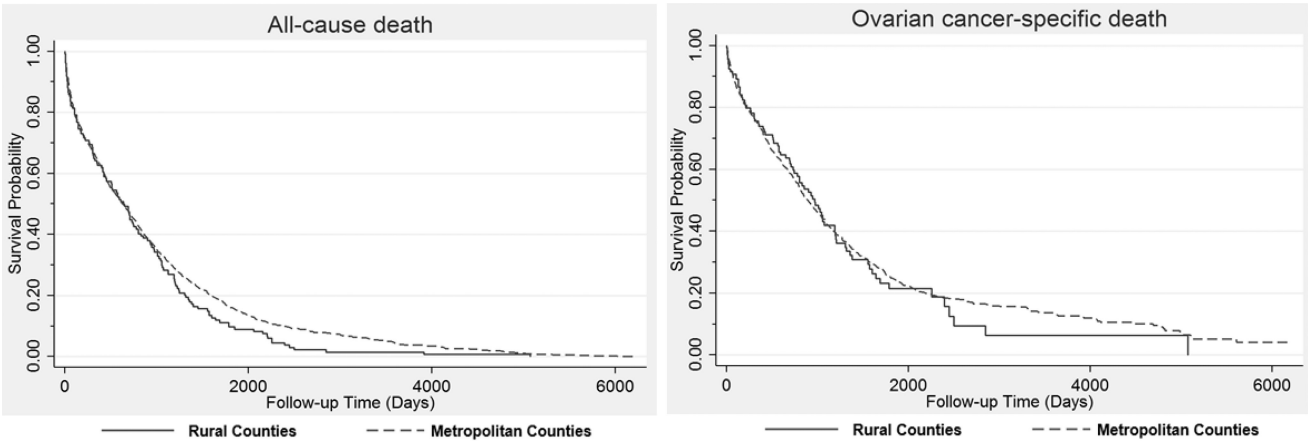

Figure 1.

Survival probability over time among ovarian cancer patients by rural-metropolitan residence, diagnosed between 1997–2012 (p-value for log-rank: all-cause death p=0.2391, ovarian cancer-specific death p=0.9691

Table 1

Baseline characteristics among ovarian cancer patients by rural-metropolitan residence, diagnosed between 1997–2012

	Total n=1,661		Metropolitan Counties n=1,465		Rural Counties n=196		χ^2 *P*-value
	n	%	n	%	n	%	
Age at cancer diagnosis							
< 40 years	157	9.5	146	10.0	11	5.6	0.43
40–49 years	227	13.7	200	13.7	27	13.8	
50–59 years	361	21.7	320	21.8	41	20.9	
60–69 years	359	21.6	316	21.6	43	21.9	
70–79 years	357	21.5	308	21.0	49	25.0	
80+ years	200	12.0	175	12.0	25	12.8	
Diagnosis year							
1997–2000	392	23.6	347	23.7	45	23.0	0.97
2001–2004	407	24.5	360	24.6	47	24.0	
2005–2008	413	24.9	365	24.9	48	24.5	
2009–2012	449	27.0	393	26.8	56	28.6	
BMI at baseline							
<18.5 kg/m^2	48	2.9	46	3.1	2	1.0	**0.03**
18.5–24.9 kg/m^2	809	48.7	726	49.6	83	42.4	
25–29.9 kg/m^2	488	29.4	426	29.1	62	31.6	
30+ kg/m^2	316	19.0	267	18.2	49	25.0	
Race							
Non-White	45	2.7	36	2.5	9	4.6	0.08
White	1,608	97.3	1422	97.5	186	95.4	
Unknown	8		7		7		
CCI score							
0	610	36.7	541	36.9	69	35.2	0.89
1	476	28.7	418	28.5	58	29.6	

	Total n=1,661		Metropolitan Counties n=1,465		Rural Counties n=196		χ^2 *P*-value
	n	%	n	%	n	%	
2+	575	34.6	506	34.5	69	35.2	
Vital Status							
Alive	559	33.7	497	33.9	62	31.6	0.52
Dead	1,102	66.4	968	66.1	134	68.4	
Cause of death (COD)							
Ovarian cancer COD	761	45.8	676	46.1	85	43.4	0.46
Cancer (not ovarian) COD	117	13.0	102	12.9	15	13.5	0.86
Non cancer COD	123	7.4	107	7.3	16	8.2	0.67
Unknown	660		580		80		
% Bachelor's degree *							
<15%	114	6.9	17	1.2	97	49.5	**<.0001**
15–24%	665	40.0	576	39.3	89	45.4	
>24%	882	53.1	872	59.5	10	5.1	
Median family Income ($) *							
<50,000	243	14.6	120	8.2	123	62.8	**<.0001**
≥50,000	1,418	85.4	1345	91.8	73	37.2	
% Families below poverty *							
<7%	950	57.2	892	60.9	58	29.6	**<.0001**
7–9%	518	31.2	483	33.0	35	17.9	
>9%	193	11.6	90	6.1	103	52.6	

* County level education (% Bachelor's degree) and income (Median family Income and % Families below poverty in the past 12 month) variables were from SEER*Stat, originating from US Census data (available data between 1997–2012).

Table 2

Family history of cancer and cancer prognostic factors among ovarian cancer patients by rural-metropolitan residence, diagnosed between 1997–2012

	Total n=1,661		Metropolitan Counties n=1,46		Rural Counties n=196		χ^2 *P*-value
	n	%	n	%	n	%	
Family history of any cancer							
First degree relative	642	38.7	565	38.6	77	39.3	0.85
Second degree relative	784	47.2	683	46.6	101	51.5	0.20
Third degree relative	756	45.5	655	44.7	101	51.5	0.07
Any relative	968	58.3	846	57.8	122	62.2	0.23
Family history of ovarian cancer							
First degree relative	58	3.5	51	3.5	7	3.6	0.95
Second degree relative	71	4.3	65	4.4	6	3.1	0.37
Third degree relative	75	4.5	66	4.5	9	4.6	0.96
Any relative	182	11.0	161	11.0	21	10.7	0.91
Cancer stage at diagnosis							
Local	285	17.2	257	17.5	28	14.3	0.44
Regional	252	15.2	224	15.3	28	14.3	
Advanced	1,124	67.7	984	67.2	140	71.4	
Histology grade							
Grade I (Well differentiated)	104	8.7	93	8.8	11	8.3	0.76
Grade II (Moderately differentiated)	274	23.0	245	23.2	29	21.8	
Grade III (Poorly differentiated)	660	55.4	588	55.6	72	54.1	
Grade IV (Undifferentiated)	153	12.9	132	12.5	21	15.8	
Unknown	470		407		63		
Histology subtype							
Serous	753	49.4	668	49.9	85	46.2	0.08
Mucinous	93	6.1	88	6.6	5	2.7	
Endometrioid	221	14.5	187	14.0	34	18.5	

	Total n=1,661		Metropolitan Counties n=1,46		Rural Counties n=196		χ^2 *P*-value
	n	%	n	%	n	%	
Clear cell	91	6.0	82	6.1	9	4.9	
Non-Specified	365	24.0	314	23.5	51	27.7	
Unknown	138		126		12		
Treatment							
None	170	10.8	148	10.6	22	12.1	
Surgery only	463	29.4	403	28.9	60	33.0	
Chemotherapy only	100	6.4	93	6.7	7	3.9	
Surgery and chemotherapy	824	52.3	733	52.6	91	50.0	
Other	18	1.1	16	1.2	2	1.1	
Unknown	86		72		14		

Table 3

Cancer stage at diagnosis stratified by baseline BMI among ovarian cancer patients, diagnosed between 1997–2012

	No. of Overall cohort	Baseline BMI								
		<18 kg/m^2		18–24.9 kg/m^2		25–29.9 kg/m^2		30+ kg/m^2		χ^2 *P*-value
		n	%	n	%	n	%	n	%	
Metropolitan + Rural residents										
Localized/Regional	537	24	50.0	270	33.4	141	28.9	102	32.3	**0.02**
Advanced	1,124	24	50.0	539	66.6	347	71.1	214	67.7	
Metropolitan residents										
Localized/Regional	481	24	52.2	246	33.9	122	28.6	89	33.3	**0.01**
Advanced	984	22	47.8	480	66.1	304	71.4	178	66.7	
Rural residents										
Localized/Regional	56	0	0	24	28.9	19	30.7	13	26.5	0.79
Advanced	140	2	100	59	71.1	43	69.4	36	73.5	

Table 4

Adjusted hazard ratios for all-cause and ovarian cancer-specific death among ovarian cancer patients residing in metropolitan vs. rural counties, diagnosed between 1997–2012

	No. of overall cohort	No. of death	Adjusted[a] HR (95% CI)	*P*-value
All-cause death				
Metropolitan	1,465	968	Reference	0.36
Rural	196	134	1.09 (0.90, 1.32)	
Ovarian cancer-specific death				
Metropolitan	1,465	676	Reference	0.93
Rural	196	85	1.01 (0.80, 1.27)	

[a]Adjusted for age at diagnosis, year of diagnosis, BMI, CCI, race, stage, and treatment

Table 5

Adjusted hazard ratios for baseline risk factors, and all-cause death and ovarian cancer-specific death by rural-metropolitan residence, diagnosed between 1997–2012

	All-cause death n=1,109				Ovarian cancer-specific death n=763			
	Metropolitan		Rural		Metropolitan		Rural	
	HR	95%	CI	HR	95%	CI	HR	95%
Age at cancer diagnosis[a]								
< 40 years	**0.50** *	**(0.33, 0.76)**	0.57	**(0.14, 2.28)**	0.81 *	(0.52, 1.26)	0.46	(0.05, 3.94)
40–49 years	**0.69** *	**(0.52, 0.91)**	0.52	(0.21, 1.26)	0.78 *	(0.57, 1.07)	0.78	(0.25, 2.43)
50–59 years	0.91 *	(0.73, 1.14)	0.97	(0.46, 2.03)	0.96 *	(0.74, 1.24)	**2.56**	**(1.02, 6.45)**
60–69 years	Reference		Reference		Reference		Reference	
70–79 years	**1.39** *	**(1.11, 1.74)**	1.42	(0.70, 2.91)	1.25 *	(0.95, 1.63)	1.47	(0.60, 3.57)
80+ years	**2.70** *	**(2.02, 3.60)**	**3.58**	**(1.27, 10.14)**	**1.90** *	**(1.31, 2.74)**	**5.94**	**(1.64, 21.61)**
P trend	**<.0001**		**<.0001**		**<.0001**		**<.0001**	
Diagnosis year[b]								
1997–2000	Reference		Reference		Reference		Reference	
2001–2004	1.15	(0.97, 1.36)	0.74	(0.45, 1.23)	**1.39** *	**(1.12, 1.71)**	1.24	(0.63, 2.44)
2005–2008	1.03	(0.86, 1.24)	0.80	(0.47, 1.35)	1.19 *	(0.95, 1.48)	1.33	(0.66, 2.66)
2009–2012	0.91	(0.75, 1.10)	0.84	(0.51, 1.39)	1.03 *	(0.82, 1.30)	1.48	(0.76, 2.89)
P trend	0.07		0.14		0.56		0.69	
Body Mass Index at baseline[c]								
<18 kg/m^2	0.86	(0.55, 1.34)	4.44 *	(0.97, 20.24)	0.82	(0.49, 1.39)	3.15	(0.38, 25.83)
18–24.9 kg/m^2	Reference		Reference		Reference		Reference	
25–29.9 kg/m^2	1.02	(0.88, 1.18)	**0.56** *	**(0.36, 0.87)**	0.98	(0.82, 1.17)	**0.48**	**(0.28, 0.83)**
30+ kg/m^2	0.91	(0.76, 1.08)	0.98 *	(0.64, 1.52)	0.90	(0.73, 1.12)	0.81	(0.47, 1.40)
P trend	0.06		0.79		0.24		0.56	

	All-cause death n=1,109				Ovarian cancer-specific death n=763			
	Metropolitan		Rural		Metropolitan		Rural	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Race[d]								
White	Reference		Reference		Reference		Reference	
Non-White	1.03	(0.67, 1.57)	0.91	(0.37, 2.22)	1.01	(0.61, 1.69)	0.57	(0.14, 2.30)
Charlson Comorbdity Index score[e]								
0	Reference		Reference		Reference		Reference	
1	0.92*	(0.79, 1.09)	1.29*	(0.81, 2.06)	0.89*	(0.74, 1.08)	1.17*	(0.67, 2.04)
2+	**0.72***	**(0.61, 0.84)**	0.87*	(0.55, 1.38)	**0.69***	**(0.58, 0.84)**	0.81*	(0.46, 1.43)
P trend	0.26		0.36		0.13		0.94	
% Bachelor's degree[f]								
<15%	Reference		Reference		Reference		Reference	
15–24%	0.95	(0.54, 1.67)	0.94	(0.66, 1.34)	1.60	(0.65, 3.92)	0.83	(0.53, 1.30)
>24%	0.94	(0.53, 1.65)	1.25	(0.59, 2.63)	1.72	(0.70, 4.19)	1.99	(0.92, 4.31)
P trend	0.46		0.74		0.36		0.47	
% Families below poverty[f]								
<7%	Reference		Reference		Reference		Reference	
7–9%	0.98	(0.84, 1.12)	0.71	(0.41, 1.23)	0.91	(0.77, 1.08)	0.86	(0.45, 1.65)
>9%	1.23	(0.95, 1.60)	0.84	(0.57, 1.24)	1.00	(0.72, 1.40)	0.87	(0.53, 1.42)
P trend	0.57		0.48		0.40		0.69	

*For the models that violated proportional hazards assumptions, we used Cox models with cubic splines

[a]adjusted for year of diagnosis, BMI, CCI, race, cancer stage, histology grade, education, and poverty

[b]adjusted for BMI, CCI, and age at diagnosis

[c]adjusted for age at diagnosis, race, education, and poverty

[d]not adjusted

[e] adjusted for age at diagnosis, race, education, and poverty

[f] adjusted for age at diagnosis and race

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Table 6

Adjusted hazard ratios for prognostic factors, and all-cause death and ovarian cancer-specific death by rural-metropolitan residence, diagnosed between 1997–2012

	All-cause death n=1,109				Ovarian cancer-specific death n=763			
	Metropolitan		Rural		Metropolitan		Rural	
	HR	95%	CI	HR	95%	CI	HR	95%
Treatment[a]								
Surgery only	Reference		Reference		Reference		Reference	
Chemotherapy only	**1.67** *	**(1.28, 2.20)**	1.87	(0.77, 4.55)	**1.76** *	**(1.28, 2.42)**	2.19	(0.74, 6.49)
Surgery and chemotherapy	**0.78** *	**(0.66, 0.93)**	0.99	(0.62, 1.57)	0.82 *	(0.67, 1.00)	1.19	(0.65, 2.17)
Other	1.29 *	(0.72, 2.32)	1.27	(0.15, 10.55)	1.52 *	(0.82, 2.83)	0	
Cancer stage at diagnosis[b]								
Local/Regional	Reference		Reference		Reference		Reference	
Advanced	**3.28** *	**(2.66, 4.04)**	**4.72** *	**(2.18, 10.23)**	**4.67**	**(3.54, 6.17)**	**7.15** *	**(2.63, 19.40)**
Histology grade[c]								
Grade I (Well differentiated)	Reference		Reference		Reference		Reference	
Grade II (Moderately differentiated)	1.52	(0.97, 2.35)	0.85	(0.20, 3.69)	**2.39**	**(1.19, 4.82)**	3.20	(0.32, 32.38)
Grade III (Poorly differentiated)	**1.89**	**(1.23, 2.90)**	1.27	(0.34, 4.76)	**3.26**	**(1.64, 6.49)**	3.98	(0.47, 33.75)
Grade IV (Undifferentiated)	**1.64**	**(1.02, 2.64)**	1.19	(0.30, 4.70)	**2.64**	**(1.27, 5.48)**	3.15	(0.36, 27.38)
Histology subtype[d]								
Serous	Reference		Reference		Reference		Reference	
Mucinous	1.14 *	(0.81, 1.60)	**18.49** *	**(3.68, 93.04)**	1.06 *	(0.68, 1.65)	**16.52** *	**(1.86, 146.41)**
Endometrioid	0.82 *	(0.63, 1.05)	0.51 *	(0.24, 1.12)	0.82 *	(0.59, 1.12)	**0.31** *	**(0.11, 0.89)**
Clear cell	1.25 *	(0.90, 1.75)	**4.42** *	**(1.49, 13.12)**	1.41 *	(0.95, 2.09)	3.21 *	(0.80, 12.85)
Non-Specified	**1.63** *	**(1.39, 1.91)**	**2.03** *	**(1.31, 3.15)**	**1.55** *	**(1.28, 1.88)**	**1.85** *	**(1.07, 3.21)**

* For the models that violated proportional hazards assumptions, we used Cox models with cubic splines

[a] adjusted for BMI, race, year of diagnosis, age at diagnosis, CCI, cancer stage, education, and poverty

[b] adjusted for histology grade, race, age at diagnosis, year of diagnosis, BMI, CCI, education, and poverty

[c] adjusted for cancer stage, race, age at diagnosis, year of diagnosis, BMI, and CCI

[d] adjusted for age at diagnosis, year of diagnosis, BMI, race, CCI, histology grade, and cancer stage