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Rural Residence Is Related to Shorter Survival in Epithelial Ovarian Cancer Patients

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Abstract

Objective: Rural residence has been related to health disparities and greater mortality risk in cancer patients, including gynecologic cancer patients. Lower survival rates for rural cancer survivors have been attributed to limited access to specialized healthcare, including surgery. Here, we examined whether a rural/urban survival gap existed in ovarian cancer patients receiving surgery at tertiary-care facilities, and potential causes for this gap, including educational attainment.

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Supplementary data

Supplementary material

Methods: Rural and urban patients with high grade invasive ovarian cancer (n=342) seeking treatment at two midwestern tertiary-care university hospitals were recruited pre-surgery and followed until death or censoring date. Rural/urban residence was categorized using the USDA Rural-Urban Continuum Codes. Stratified Cox proportional hazards regression analyses, with clinical site as strata, adjusting for clinical and demographic covariates, were used to examine the effect of rurality on survival.

Results: Despite specialized surgical care, rural cancer survivors showed a higher likelihood of death compared to their urban counterparts, HR=1.39 (95%CI: 1.04,1.85) p=0.026, adjusted for covariates. A rurality by education interaction was observed (p=0.027), indicating significantly poorer survival in rural vs. urban patients among those with trade school/some college education, adjusted HR=2.49 (95% CI: 1.44, 4.30), p=0.001; there was no rurality survival disparity for the other 2 levels of education.

Conclusions: Differences in ovarian cancer survival are impacted by rurality, which is moderated by educational attainment even in patients receiving initial care in tertiary settings. Clinicians should be aware of rurality and education as potential risk factors for adverse outcomes and develop approaches to address these possible risks.

Keywords

ovarian cancer; rurality; survival; education; disparities

Introduction

Rural residence has been related to health disparities and greater mortality risk in cancer patients [1, 2]. Compared to urban survivors, rural cancer survivors are more likely to have greater poverty, lower educational levels, poorer health screening and healthcare access, higher rates of risky health behaviors, and are more likely to be elderly [3, 4]. Additionally, rural cancer patients tend to have poorer health and quality of life [5, 6], poorer mental health [7–9], greater mortality (180/100,000 vs. 166/100,000) [3], and poorer outcomes from clinical trials than their urban counterparts [10]. Rural residents are more likely to be self-employed, lower-income, and uninsured or underinsured [11, 12] and to face debt from cancer treatment, which may lead to distress and reduced quality of life along with the need to forego medical treatment because of cost and decreased adherence to follow-up surveillance and treatment [12–15]. This could potentially result in delayed identification and treatment of recurrences or disease-related complications [16].

A 2017 Centers for Disease Control (CDC) report indicated that non-metropolitan rural areas had lower 5-year annual age-adjusted cancer incidence rates but higher average annual age-adjusted death rates for all cancer sites combined compared with non-metropolitan urban and metropolitan counties. Additionally, non-metropolitan areas showed slower rates of decrease in cancer deaths than in metropolitan areas, thus increasing disparities [8]. These rural-urban disparities in cancer prevention and control resulted in the National Cancer Institute declaring that addressing rural health disparities is a strategic priority.

With respect to gynecologic cancers, there is a rural-urban disparity in the density of gynecologic oncologists [17, 18]. Because of the need for access to multiple other specialties for gynecologic oncology surgery, such procedures cannot be safely provided in all hospital settings. As a consequence, rural gynecologic cancer survivors are more likely to be treated at low volume hospitals or at centers poorly equipped to provide the standard of care [19–21] and are less likely to receive guideline-adherent cancer care by specialists [18, 22, 23]. Moreover, they are less likely to receive care from a gynecologic oncologist despite a documented survival advantage for women when treated by gynecologic oncologists [19]. Thus, understanding rural-urban healthcare disparities in gynecologic oncology care are critical to addressing this issue. Whereas a recent study reported no differences in rural-urban survival in ovarian cancer [24], that study was a registry study and therefore the treatment paradigms and healthcare access were not always clear. Little is known about rural-urban survival disparities in ovarian cancer patients who have received initial treatment from gynecologic oncologists in a tertiary-care setting.

This study was designed to address that knowledge gap by investigating rural-urban survival disparities among ovarian cancer patients who received initial treatment at two large midwestern tertiary cancer centers catering to both urban and rural patients. Additionally, we examined the potential moderating role of educational attainment in explaining any observed survival disparities.

Methods

Participants

Participants were 342 women of at least 18 years of age with histologically confirmed high-grade primary epithelial ovarian, peritoneal or fallopian tube carcinoma. Women were recruited from two tertiary midwestern University hospitals as part of a larger biobehavioral study of ovarian cancer. Participants were excluded for low-grade cancer, history of previous cancer, comorbid condition with known immune system effects or systemic steroid use, current pregnancy, and inability to accurately answer questions (dementia). Included participants had surgery or initial treatment at least 2.5 years before the date of censoring. All procedures were approved by Institutional Review Boards of participating institutions. The earliest date of surgery was in 12/2003 and all survival information was censored on March 31, 2017 or on the date of the last recorded contact before March 2017. Of the 342 women meeting these conditions, 5 were excluded because of missing values for clinical covariates, leaving 337 included in the main Cox regression analyses. In total 137 patients were censored in this analysis. Data was not available for marital status in 6 and educational level in 13 subjects, leaving 318 in the Cox regression analyses that included marital status and education along with other covariates.

Procedure

Women were recruited during a pre-surgical clinic visit for pelvic masses suspected for ovarian cancer as part of a larger IRB-approved study on biobehavioral factors and tumor progression. Informed consent was obtained during the pre-surgical visit. Clinical

and demographic information was obtained pre-surgery and patient medical records were abstracted for survival every 6 months until death or March 31, 2017.

Demographic and Clinical Information

Demographic information was provided by self-report and included education, income, marital status (married/living with partner; single/divorced/widowed), residence zip-code and county. Education was coded as high school or less (≤ HS), trade school/some college (some college), and college graduate/advanced degree (≥ college degree). Because many patients did not report income, mean and median income for each zip-code was calculated by matching zip-codes to Zip designations used by the Census Bureau (ZCTA) codes. The relevant mean and median income for each ZCTA were then obtained from the Census Bureau Directory [25]. Clinical information derived from medical records included age, stage, grade, body mass index (BMI), extent of cytoreduction, histology, neoadjuvant treatment, follow-up visits, and survival. For analyses, stage was dichotomized into early (I to II) versus advanced (III to IV). The Charlson comorbidities index [26] was used to determine extent of comorbidities (non-cancer) and coded as 0, 1, 2 or more (2+). Follow-up visits were coded for the two years following the end of primary chemotherapy as at tertiary care, local, or both, and as compliant (3+ visits/year) or non-compliant (< 3 visits/year) according to National Comprehensive Cancer Network (NCCN) guidelines [27]. Although these guidelines recommend visits every 3 months for the first 2 years, a metric of at least 3 visits/year was utilized for compliance because of a variety of scheduling and confounding issues that emerged in the data. Information regarding follow-ups was abstracted for a subset of approximately 84.5% of patients. Date and cause of death were ascertained from patient medical records. Survival time was calculated as the number of days between date of tumor resection or initiation of neoadjuvant treatment and date of death or censoring at the date of last contact.

Rural/urban residence was categorized from patient counties using the USDA Rural-Urban Continuum Codes (RUCC) [28]. The RUCC differentiates metro counties by the population of the area and non-metropolitan counties by the degree of urbanization and adjacency to non-metropolitan areas, with codes 4–9 all considered non-metro counties. County level classification: Metropolitan counties (1= 1 million or more; 2= 250,000 to 1 million; 3 < 250,000), Non-metro counties (4= 20,000 or more adjacent; 5= 20,000 or more non-adjacent; 6= 2,500 to 19,999 adjacent; 7=2,500 to 19,999 nonadjacent; 8 < 2,500 adjacent; 9 < 2,500 nonadjacent).

Statistical Analyses—Version 25 of SPSS (IBM Armonk, NY) and version 9.4 of SAS (SAS/STAT 14.3) (SAS, Cary, NC) were used for data analysis. Distributions of the continuous variables were examined for outliers and checked for non-normality. Descriptive statistics were used to examine rurality, covariates, education, marital status, and follow-up visits. The Kaplan-Meier survival curve was constructed to initially describe the survival distribution (median survival time, 25^{th} and 75^{th} percentile) of ovarian cancer patients in our study population by rural or urban residence. The association of rurality with survival was then tested using stratified Cox proportional hazards regression, with clinical site as strata, adjusting for age and *a priori* defined clinical covariates that included disease

stage, cytoreduction (suboptimal vs. optimal), histology (serous vs non-serous), BMI, and comorbidities (none, 1, 2 or more). By applying the stratified analysis, we are able to aggregate the effects of rurality and covariates across the clinical sites and also account for a potential difference in baseline hazard between the sites. In a second set of analyses, socioenvironmental variables that might explain the rurality-survival association (education [≤ HS, some college, ≥ college degree] and marital status) were examined by expanding the previous model to include each factor as main effect, and including its interaction with rurality. By including the interaction effect, we are examining the role of education or marital status as effect moderators of rurality on survival. If a significant interaction was found, the interaction was retained in the model. Otherwise only the main effect of education and/or marital status was included. Standard diagnostics were used to evaluate model adequacy [29].

Results

Participant Characteristics

Among the 342 patients enrolled onto this study, the median follow-up time was 3.14 years (range, 1 day to 12.31 years). At diagnosis, 80.6% of patients had advanced-stage disease and all had high-grade tumor. Cause of death for the 200 patients who had died was persistent or recurrent ovarian cancer or complications associated with cancer disease and treatment (e.g., bowel obstruction, sepsis, pulmonary emboli). One hundred thirty-seven patients (40.6%) were still alive at the end of the observation period and were censored on March 31, 2017 or the date of last contact, for survival analyses. Of the censored patients, 112 (81.8%) were censored at date of last clinic visit, 15 (10.9%) were censored at the date of the last phone contact and one (0.7%) at her last mail contact, and 9 (6.6%) were lost to follow-up, defined as no contact, indication of death, or information from local provider in the last 3 years. As seen in Table 1, the mean age of participants was 60.7 (± 11.1, range 27–88) years. Respondents were predominantly white (96.8%), non-Hispanic (99.7%), and married or living with partner (78.0%). There was a wide distribution in educational status: 40.9% had not gone past high school, while 28.8% had completed college and/or graduate/professional school. The mean income was $65,000.

Rural patients comprised a significantly greater percentage of the Iowa sample (43.7%) compared to the Washington University sample (30.6%), p=0.02. There were no significant rural-urban differences in age, BMI, disease stage, race, ethnicity, marital status, or other clinical characteristics (all p values > 0.24). Rural patients had significantly lower levels of education (p=0.0002) and income ($p < 0.0001$). Whereas 75% of rural patients had zip-codes with a median income of $53,000 or less, only 50% of urban patients were in this category. Among urban patients, those with ≤ HS education had significantly lower incomes than either of the two higher education groups (some college: p=0.006; ≥ college degree: p=0.016). Among rural patients there was a similar but less pronounced pattern in average zip-code income according to education levels (p=0.079).

Rural patients tended to complete fewer follow-ups at tertiary care centers than their urban counterparts during the first two years following diagnosis (year 1: *rural*, 68.9% tertiary; 19.8 % combination of tertiary and local; 11.3% local; *urban* 82.3% tertiary; 14.3%

combination of tertiary and local, 3.4% local, p=0.039; proportions in year 2 were relatively similar and seen in Supplemental Table 1). Follow-up compliance for both years was high (≥ 95%) in patients from both rural and urban settings and from all educational levels and compliance did not differ appreciably by rurality (p's >0.27) or education (p's > 0.15). Urban patients (24.7%) were somewhat more likely to participate in clinical trials than rural patients (17.3%), but this difference was not significant; notably, both of these tertiary-care centers have high accrual rates for clinical trials. College-educated women were slightly more likely to be participating in clinical trials than the two other educational levels (≥ college: 26.3%; some college 21.7%; ≤ HS 19.4%), but this difference was not significant.

Survival Analysis

The Kaplan Meier curve describing the survival distribution for patients with high grade ovarian cancer residing in rural and urban areas is shown in Figure 1. Median survival was 3.5 (95% CI: 3.1, 4.6) years for rural patients and 4.3 (95% CI: 3.4, 5.2) years for urban patients. Survival 25th and 75th percentiles were 2.3 and 6.8 years for rural patients; and 2.2 and 8.2 years for urban patients. Assessing the effect of rurality on survival using Cox proportional hazards regression analysis adjusting for age, BMI, and clinical/medical covariates of disease (stage [early/advanced], cytoreduction [suboptimal/optimal], histology [serous/non-serous], comorbidities [1, 2+ vs. none]), showed a significantly higher likelihood of death among rural residents with HR=1.39 (95% CI:1.04,1.85), p = 0.026. (Table 2). To further understand what might be underlying a rurality effect, we examined the potential role of socioenvironmental characteristics in the model. We therefore expanded the model, including all clinical medical covariates as above as well as potential socioenvironmental characteristics (marital status and education). When marital status was included in this model as a potential effect moderator of rurality, there was no significant marital status by rurality interaction effect (p=0.94). Therefore, marital status was included only as a main effect.

We then examined the potential role of education in the model. When education was added to the adjusted model (including all covariates, marital status, the main effect of education and the rurality by education interaction), there was a rurality by education interaction (p=0.027) indicating that there was significantly poorer survival in rural vs. urban patients among those who had attended trade school or some college, with HR of 2.49 (95% CI: 1.44, 4.30), p=0.001. However, there was no difference in survival rates between rural and urban patients for the other 2 levels of education, with HR of 1.10 (95% CI: 0.71, 1.71; p=0.67) for high school or less, and HR of 0.86 (95% CI: 0.43, 1.75; p=0.69) for college/postgraduate (see Table 3; The fully parameterized model is shown in Supplemental Table 2). Figure 2 illustrates the survival distribution of high-grade ovarian cancer patients based on the fitted Cox proportional hazard regression model comparing urban vs. rural residence by education level (2A: high school or less; 2B: trade school/some college; 2C: college/postgraduate) with their clinical and demographic characteristics set to the most frequently occurring levels in the study population and age and BMI set at study mean values: stage=advanced, cytoreduction=optimal, histology=serous, comorbidities=none, age=61.0, BMI=29, site=Iowa, married/with partner. There was a 2-year difference in median survival time for rural (2.62 years) compared to urban (4.63 years) patients among those with trade

school/some college. In contrast, the difference in median survival between rural versus urban was much smaller among those with the highest level of education (4.90 vs. 4.53 years), and those with ≤ HS education (3.19 vs. 3.31 years). Additionally, this also shows that there is more than a one-year median survival difference between the highest and lowest educational strata for both rural and urban patients.

Discussion

The key findings of this study were that in a sample of high-grade ovarian cancer patients who received surgery in two large midwestern tertiary care centers, those living in rural areas had significantly poorer survival than those living in urban areas, adjusting for clinical covariates. Furthermore, the rural-urban difference appeared to be moderated by education levels, such that rural patients who had completed trade school/some college had poorer survival than their urban counterparts, again, adjusting for clinical covariates. In contrast, there were no rural-urban survival differences among those who had completed college or post-graduate education, or among those with high school education or less.

The observed rural-urban survival differences are consistent with reported rural-urban survival disparities in heterogeneous cancer patients [1]. Previous studies of rural-urban survival disparities among gynecological cancer patients highlighted differences in surgical setting and treatment by specialists as related to survival. Rural-urban differences in stage at diagnosis, likelihood of complete resection, and adherence to treatment guidelines have been thought to underlie such disparities [30–32]. In the present study, all patients received surgery from board certified gynecologic oncologists in a tertiary care setting where other specialists were available if needed, and thus had the highest level of surgical care available. There were no rural-urban differences in stage at the time of diagnosis; however, as the majority of ovarian cancer patients have stage III disease at diagnosis, there may not have been enough variability in stage to reflect rural-urban differences at diagnosis. It should be noted that during the time-frame of this study, maintenance therapy was not yet approved as standard of care and so is not captured in the analyses. With the small number of patients on clinical trials in our dataset it is unlikely that these would have affected survival. That a survival discrepancy still exists despite primary treatment in tertiary care settings suggests that other influences, such as education and associated health literacy, quality of follow-up care, and/or economic inequalities might be potential contributing factors.

Across all cancers, higher levels of educational attainment have been inversely associated with mortality, with one study reporting an estimated relative risk of 1.75 (95% CI=1.75–1.78) for white women and 1.43 (CI=1.41–1.46 for black women in the lowest (≤ 12 years) vs. the highest (> 12 years) education categories [33]. Interestingly, we did not observe rural-urban survival disparities at the highest level of educational attainment. It is possible that highly educated women, independent of rural/urban residence, may have had greater health literacy to guide them in their survivorship care, as health literacy has been shown to increase with level of education [34]. This may be particularly relevant as rural women tend to receive both poorer health education and primary care than their urban counterparts [12, 35]. It is possible that more educated women may have been more aware of positive health behaviors such as nutrition and exercise to support their survivorship care [36]. Although

the difference in clinical trial participation did not significantly differ according to education level, a slightly greater percentage of women in the highest education strata participated in clinical trials. Additionally, women with higher levels of education may have had the job flexibility to be able to take time off to seek follow-up care in a tertiary medical setting.

Interestingly, those with the lowest educational level did not show a rural-urban disparity in survival. Independent of rural-urban residence, the survival time of those with an education of ≤ 12 years was already substantially compromised compared to those with college/ postgraduate education; thus, it is possible that rural residence was not able to further compromise survival.

Our observation of rural/urban survival disparities in those attending trade school or with less than a 4-year college degree has not been previously reported. We had considered that for these women, follow-up care in a tertiary care center might have been more difficult because of occupations with less flexibility, transportation issues, and financial burdens. However, these women generally had high levels of follow-up compliance, and we did not see a consistent pattern of discrepancies in follow-up compliance between women of different educational levels. We did note that a non-significantly greater percentage of women with trade school/some college pursued their follow-ups locally, which may have influenced their quality of care. Individuals in this education bracket may be less able to financially afford the costs of missing work to complete a follow-up at a tertiary care center if it involved substantial travel.

In light of surprisingly high levels of general compliance with follow-up care in both rural and urban patients at all educational levels, other factors that might have accounted for the observed survival differences include health literacy-related issues and health behaviors, which were not assessed in this study [12, 35, 36]. Personal characteristics of rural cancer patients, such as exposure to a variety of practical and financial burdens, less available supportive care to assist with activities of daily living, and a tendency to be more stoical and less likely to ask for help have been reported [37]. All of these factors may have contributed to the current findings.

Limitations:

It is possible that rurality effects may vary in different rural locations, depending on extent of local resources and distance to care. For example, women in rural locations that are close to a metropolitan area of 20,000 or more (RUCC categories 4–6) may have had better access to care than those who live very far from metropolitan areas (RUCC categories 7–9). A major determinant of survival disparities may have been difference in adherence to NCCN guidelines for follow-up care. Although we attempted to collect data to assess compliance with guideline-based follow-up recommendations, limitations in available records, particularly for local follow-up, precluded formulating a detailed estimate of follow-up care that could reliably distinguish routine follow-up visits from those for chemotherapy, clinical trials, or complications, and precluded conclusions as to whether local care was NCCN guideline adherent. Further, it should be noted that up to 12.5% of data abstracted for follow-up visits was unavailable, leaving a lack of clarity whether missing data reflected non-compliance or non-availability of local records. Thus, our estimation of follow-up

compliance is quite approximate, other than to indicate that few gross discrepancies between groups were observed. As greater sharing of electronic records between institutions is now available, future research may be able to prospectively obtain a more accurate representation of follow-up care. Although we presented data on median income related to residential zip-code, information on personal income was not consistently available and not used in survival models; thus, educational status was utilized as an indicator of socioeconomic disparities. Lack of complete personal income data also precluded confirming interpretations that the survival differences seen in the “some college” group were based on economic disparities. Because of HIPAA and institutional constraints we were unable to obtain insurance/Medicare data on study participants. As rural patients are often under-insured or uninsured [11, 12], this might have contributed to delays in seeking either initial or follow-up care, and may have contributed to the disparities noted here. Surgical debulking during the time frame of the study (2003–2017) was categorized as < 1 cm (optimal) vs. suboptimal for many patients; further sub-characterization was not available for analyses. Because participants were initially recruited as part of a larger biobehavioral study of ovarian cancer, inclusion of those with a previous cancer history, previous treatment with steroids, or an immune system involvement were excluded as they could have potentially confounded the results of the larger study. It is possible that excluding these patients might have biased the population in some way. The sample was largely composed of non-Hispanic whites, and therefore does not address how ethnic and racial diversity may interact with rurality, education, and cancer survivorship. Future research should include greater diversity and a wider geographic area to increase the generalizability of these findings.

Clinical implications:

Clinicians should be aware of rurality as a potential risk factor for compromises to care and survival disparities. Future research should develop interventions to address health care disparities in rural ovarian cancer patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of interest disclosure statement:

Dr. Thaker has done consulting and/or speaking for Stryker, Iovance Biotherapeutics, Abbvie/Stemcentrx, Clovis Oncology, Unleash Immunolytics, Celsion, Merck, Aravive, and Glaxo Smith Kline and Astra Zeneca, has research funding from Merck and Glaxo Smith Kline, and is a Celsion shareholder; Dr. Sood has done consulting for Merck, Astra Zeneca and Kiyatec, has had research funding from M-Trap, and is a Biopath shareholder; Dr. Charlton has done consulting for Johnson and Johnson; other authors declare no potential conflicts of interest.

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Highlights

- Rural ovarian cancer patients have poorer survival than their urban counterparts even with access to specialized care.
- Rural patients with trade school/some college showed markedly poorer outcomes than urban patients with similar education.
- There was no rural-urban survival disparity for those completing college or those with high school or less education.
- Clinicians should be aware of rurality and education as potential risk factors for compromised care and survival disparities.

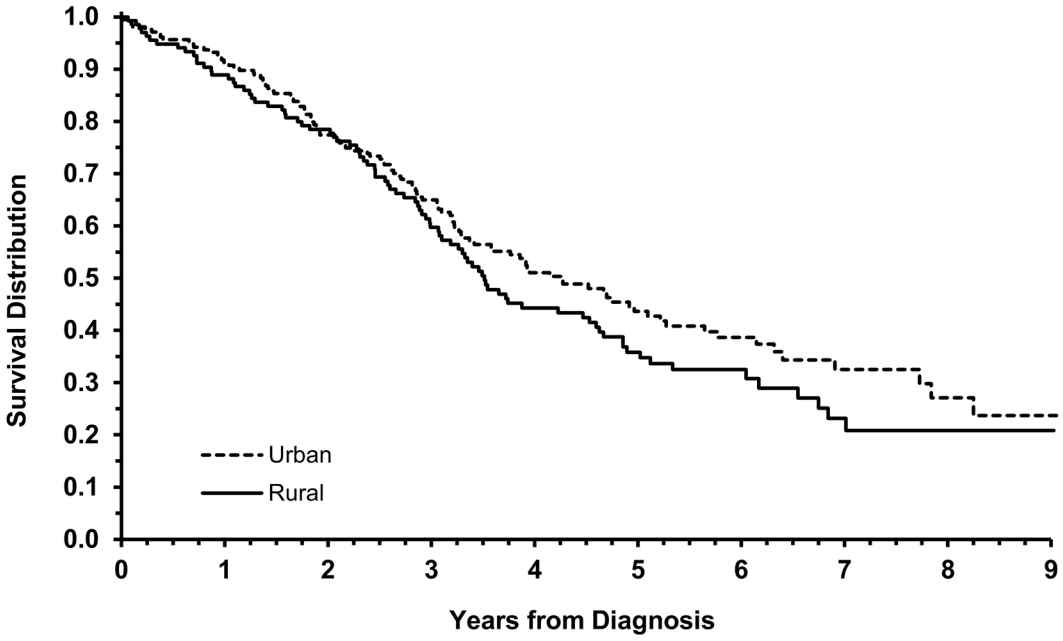

Figure 1:

Kaplan Meier curve describing the survival distribution of high-grade ovarian cancer patients comparing urban vs. rural survival.

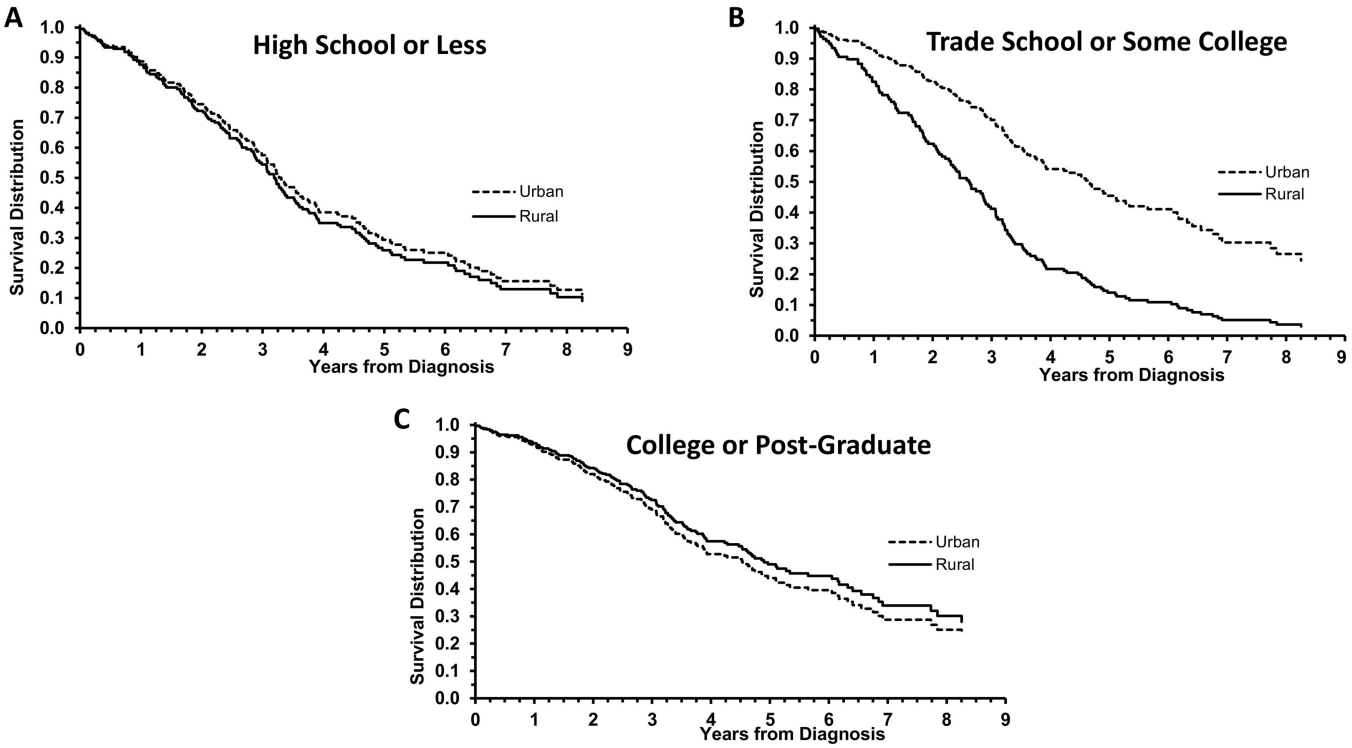

Figure 2:

Illustration of the survival distribution of high-grade ovarian cancer patients based on the fitted Cox proportional hazard regression model comparing urban vs. rural survival by education level (2A: high school or less; 2B: trade school/some college; 2C: college/ postgraduate) with their clinical and demographic characteristics set to the most frequently occurring levels in the study population and age and BMI set at study mean values: stage=advanced, cytoreduction=optimal, histology=serous, comorbidities=none, age=61.0, BMI=29, site=Iowa, married/with partner.

Table 1.

Demographics

	Entire Sample			
Variable	**Total n=342**	**Rural n=135**	**Urban n=207**	***p-value***
Site				
Iowa, count (%)	231 (60.5)	101 (74.8)	130 (62.8)	
Wash U	111 (39.5)	34 (25.2)	77 (37.2)	
Race				0.60
White	331 (96.8)	133 (98.5)	198 (96.6)	
Black	7 (2.1)	1 (0.7)	6 (2.9)	
Other race	4 (1.2)	1 (0.7)	3 (1.4)	
Ethnicity	(n=334)	(n=131)	(n=203)	
Non-Hispanic	333 (99.7)	131 (100)	202 (99.5)	1.0
Marital Status	(n=336)	(n=133)	(n=203)	
Married/with partner	262 (78.0)	108 (81.2)	154 (75.9)	0.25
Education	(n=330)	(n=132)	(n=198)	0.0002
High school or less	135 (40.9)	68 (51.5)	67 (33.8)	
Some college	100 (30.3)	42 (31.8)	58 (29.3)	
College grad/Postgraduate	95 (28.8)	22 (16.7)	73 (36.9)	
Average Income, in $1000	(n=334)	(n=133)	(n=201)	
Mean [SD]	65.0 [18.5]	58.4 [8.6]	69.4 [21.7]	<0.0001
Stage	(n=340)	(n=133)	(n=207)	0.44
I	47 (13.8)	19 (14.3)	28 (13.5)	
II	19 (5.6)	9 (6.8)	10 (4.8)	
III	236 (69.4)	92 (69.2)	144 (69.6)	
IV	38 (11.2)	13 (9.8)	25 (12.1)	
Cytoreduction	(n=341)	(n=135)	(n=206)	
Suboptimal	88 (25.8)	37 (27.4)	51 (24.8)	0.58
Serous	265 (77.5)	109 (80.7)	156 (75.4)	0.24
Neoadjuvant therapy	16 (4.7)	6 (4.4)	10 (4.8)	0.86
Smoking status	(n=338)	(n=108)	(n=144)	
Ever smoked	108 (32.0)	49 (36.3)	59 (29.1)	0.16
Comorbidities				0.76
0	249 (72.8)	97 (71.8)	152 (75.4)	
1	78 (22.8)	32 (23.7)	46 (22.2)	

	Entire Sample			
Variable	**Total n=342**	**Rural n=135**	**Urban n=207**	***p-value***
2+	15 (4.4)	6 (4.4)	9 (23.7)	
Age, mean [SD]	60.7 [11.1]	60.6 [11.2]	60.8 [11.1]	0.91
Body Mass Index, mean [SD]	(n=340) 29.0 [7.3]	(n=135) 28.8 [6.8]	(n=205) 29.1 [27.5]	0.68

Iowa patients are 43.7% rural; Wash U patients are 30.6% rural

Table 2.

Hazard ratio estimates of the effect of rurality on overall survival in ovarian cancer patients from Cox proportional hazard regression model stratified by site and adjusted for clinical covariates

	HR	95% CI	*P*-Value
Stage (advanced)	5.46	2.95, 10.08	<0.0001
Age/10 years	1.31	1.15, 1.49	<0.0001
Cytoreduction (suboptimal)	1.32	0.98, 1.79	0.069
Histology (serous)	1.04	0.68, 1.59	0.86
Comorbidities			
1 vs. none	1.12	0.79, 1.59	0.52
2 or more vs. none	0.67	0.32, 1.39	0.28
Body Mass Index/5 points	1.05	0.94, 1.17	0.37
Rural (vs. Urban) Residence	1.39	1.04, 1.85	0.026

n=337, 200 events, 137 censored (5 missing covariates; 2 in rural, 3 in urban)

Table 3.

Hazard ratio estimates on the effect of rurality on overall survival in ovarian cancer patients, from Cox proportional hazard regression model stratified by site, with education as effect modifier of rurality, and adjusted for other covariates

	HR	95% CI	P-Value
Stage (advanced)	5.75	3.07, 10.77	<0.0001
Age/10 years	1.36	1.18, 1.56	<0.0001
Cytoreduction (suboptimal)	1.33	0.96, 1.83	0.085
Histology (serous)	0.96	0.61, 1.51	0.85
Comorbidities			
1 vs. none	1.14	0.79, 1.66	0.48
2 or more vs. none	0.65	0.30, 1.40	0.27
Body Mass Index/5 points	1.04	0.92, 1.18	0.53
Marital status (married)	0.87	0.60, 1.25	0.44
Rural vs. Urban by Education Level			
For High school or less	1.10	0.71, 1.71	0.67
For Trade School or some college	2.49	1.44, 4.30	0.001
For College/postgraduate	0.86	0.43, 1.75	0.69

n=318, 187 events, 131 censored (missing covariates in 24; 5 clinical (2 rural, 3 urban) and 19 socio-environmental (5 rural, 14 urban)