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Socioeconomic disparities affect survival in malignant ovarian germ cell tumors in AYA population

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Abstract

Background—Malignant ovarian germ cell tumors (MOGCTs) are a rare form of ovarian malignancy. Socioeconomic status (SES) has been shown to affect survival in several gynecologic cancers. We examined whether SES impacted survival in adolescent and young adults (AYAs) with MOGCT.

Materials and Methods—The National Cancer Data Base was utilized to identify AYAs (aged 15–39 years) with MOGCT from 1998 to 2012. Three SES surrogate variables were identified: insurance type, income quartile, and education quartile. Pooled-variance t-tests and χ^2 were used to compare tumor characteristics, time from diagnosis to staging/treatment, and clinical outcome variables for each SES surrogate variable, while controlling for age and race/ethnicity in a multivariate model. Kaplan-Meier survival estimates were calculated using the log-rank test.

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Author Contributions:

Drs. Gow, Goldin, Goldfarb, Langer, Raval, Doski, Nuchtern, Vasudevan, and Beierle are all members of the CCDD, a collaborative group investigating the pediatric data available in the National Cancer Data Base. All authors reviewed and participated in the revision of the manuscript. Drs. Bownes, Stafman, and Maizlin participated in project conception, data evaluation, and writing of the manuscript. Dr. Maizlin performed statistical evaluation. Dr. Beierle assisted in project conception, manuscript writing, and editing.

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Results—3125 AYAs with MOGCT were identified. Subjects with lower SES measures had higher overall Stage and T-Stage MOGCTs at presentation. There was no significant difference in time to staging/treatment, extent of surgery, or use of chemotherapy by SES. Subjects from a lower education background, from a lower income quartile, and without insurance had decreased survival ($p = 0.02$ for all). Controlling for overall Stage and T-Stage, the difference in survival was no longer significant.

Conclusions—AYAs with MOGCT from lower SES backgrounds presented with more advanced stage disease. Further studies focused on the underlying reasons for this difference are needed to address these disparities.

Keywords

Socioeconomic; disparity; MOGCT; survival; stage

Introduction

Malignant ovarian germ cell tumors (MOGCTs) are rare, comprising 5% of all primary ovarian malignancies, and have a peak incidence from 16–20 years of age.^{1,2} MOGCTs are broadly divided into pure dysgerminomas and non-dysgerminomas, with the most common histologic subtypes being immature teratomas and yolk sac tumors.² Current treatment results in cure rates of approximately 95% and consists primarily of surgery and, if necessary, cisplatin-based combination chemotherapy.³ Fertility sparing surgery is commonly the goal, and reproductive outcomes are usually favorable.¹

Previous studies in adults have demonstrated a correlation between lower socioeconomic status (SES) and decreased cancer survival rates in a variety of cancer types.⁴ In gynecologic tumors specifically, investigators have shown an association between race and survival, with African Americans consistently having decreased survival from ovarian, uterine, and cervical cancers.^{5–7} Some of the suggested contributing issues include geographic access, biological factors, and hospital-based discrepancies.⁷ Others have investigated socio-demographic factors and survival among dysgerminoma versus non-dysgerminoma tumor histology and found that patients with non-dysgerminomas from lower SES have lower survival than patients from higher SES.⁸ A focused examination of the effects of SES on MOGCT survival in the adolescent and young adult population (AYA) has not been published. We focused our attention on the AYA population because the peak incidence of MOGCTs occurs in this population. We sought to determine if SES would affect survival in the AYA population.

Materials and Methods

Data source

The National Cancer Data Base (NCDB) is jointly maintained by the American Cancer Society and the American College of Surgeons Commission on Cancer. Database records are created by over 1500 accredited centers nationwide, using highly standardized methods and definitions, consistent with specifications by the North American Association of Central Cancer Registries. Records include patient characteristics, cancer properties, treatment

modality specifics, and basic outcome information. Data definitions are readily available online (<https://www.facs.org/quality-programs/cancer/ncdb/puf>). Approximately 70% of all cancer cases in the United States are captured in the database.^{9,10} Since its inception, data from the NCDB have been consistently verified for validity and have been used in over 350 articles over the last 25 years.¹¹

Study cohort

Institutional review board exemption was obtained from the University of Alabama, Birmingham IRB. The AYA age group was specified as ages 15–39 years old which has been defined by the Children’s Oncology Group guidelines.¹² All AYA women with the primary diagnosis of MOGCT were examined from the NCDB from 1998 to 2012. MOGCT diagnosis was determined based on the histological code designation of 9064, 9065, 9070–9073, 9081–9083, 9085, 9090 and 9091. Tumor stage was determined by the NCDB analytic stage, which uses pathologic staging when known. Otherwise clinical staging was used for the NCDB analytic stage. Three socioeconomic surrogate variables were identified: insurance type, median income in the patient’s ZIP code, and percent of people with no high school degree in the patient’s ZIP code. The median income and education by ZIP code was classified into quartiles from 2012 US Census data. Patient race was classified as White, Black, Asian, or other. The NCDB uses a second variable for ethnicity, and this was categorized as either Hispanic or non-Hispanic. The two variables were collated into a single variable (race/ethnicity). As a result, the White cohort was divided into Hispanic White and non-Hispanic White. The Hispanic Black and other populations were too small to be differentiated by ethnicity, and were therefore reported as Black, Asian, and other. Variables of interest included overall Stage at diagnosis, T-Stage at diagnosis, days from diagnosis to staging, days from diagnosis to treatment, and survival.

Statistical Analysis

Categorical variables were compared using chi-square in a univariate model. Continuous variables were evaluated with Student’s t-test. A multivariate analysis was then performed for variables of interest using a multivariate Cox proportional hazard model, with the lowest value in each independent variable (such as lowest quartile or lack of insurance) serving as the baseline value.

Kaplan-Meier survival estimates were calculated for each variable of interest using the log-rank test. This method was performed to allow use of time-dependent survival data from subjects whose overall survival status was censored.¹³ In addition, the Cox proportional hazards model was utilized to evaluate the effects of aforementioned three socioeconomic surrogate variables on overall survival in the form of hazard ratios.

Due to missing data, not all patients were included for every variable. Missing data points were deemed to meet all assumptions of missing at random (MAR).¹⁴ As such, pairwise deletion at variable level was performed, resulting in available case analysis. Entries lacking survival data were excluded in a list-wise deletion. Statistical analysis was performed using SAS software, version 9.3 (Cary, NC) and significance was defined as $p < 0.05$.

Results

The query resulted in 3337 females with a primary diagnosis of MOGCT. 3147 met AYA age criteria, of which 3125 had survival data available and thus comprised the study population. The mean age was 23.1 ± 5.56 years with a median age of 23 years. The majority of subjects were Non-Hispanic White (60.9%, Table 1). Regarding SES, the majority of patients had government insurance and were evenly distributed amongst all four education and income quartiles (Table 1). With regards to tumor characteristics, the majority of subjects presented with T-Stage I disease and overall Stage I disease (Table 2). Dysgerminoma was the most frequently encountered histologic subtype, followed by yolk sac tumor and mixed germ cell tumor. The remaining of subjects had one of the other histologic subtypes of MOGCT (Table 2).

An examination of survival in relation to stage revealed that AYA subjects with MOGCT who had a higher overall disease Stage and higher T-Stage had decreased survival when compared to patients with lower Stage disease (Supplementary Table 1, and Supplementary Figure 1). Additionally, we found that subjects from the lowest income and education quartiles and those without insurance had a higher T-Stage and higher overall disease Stage at presentation (Table 3).

Controlling for age and race/ethnicity, Cox regression of the resulting cohort of 2985 women demonstrated that uninsured subjects, those in the lowest income quartile, and those in the lowest education quartile had decreased survival compared to those with private or government insurance, those in higher income quartiles, and those in higher educated quartiles, respectively (Figure 1, Table 4). With the addition of controls for overall disease Stage and T-Stage, the previously observed survival differences by the three SES surrogate variables were no longer significant (Figure 2, Table 4), demonstrating that overall disease Stage and T-Stage were driving factors affecting survival.

Other variables known to affect survival were explored for a possible correlation with SES such as delay in staging/treatment or a difference in treatment ultimately received. Controlling for age and race/ethnicity, there was no significant difference in time between diagnosis and staging, time from diagnosis to definitive treatment, extent of surgery, rate of fertility versus non-fertility sparing procedures, and use of chemotherapy by insurance type, income quartile, or education quartile (Supplementary Tables 2–5).

Discussion

In this study, we found that AYA women from lower SES groups presented with higher overall Stage and T-Stage MOGCTs and had decreased survival compared to those from higher SES groups. However, taking into account the effects of higher overall Stage and T-Stage, the survival difference between SES groups was no longer significant. These findings indicated that the difference in survival was a result of those from lower SES groups presenting with more advanced disease. These data are consistent with others' findings that higher overall Stage of MOGCT was associated with decreased survival¹⁵ and that lower SES groups had decreased survival.⁸ However, the current study is the first to demonstrate

that a potential source of the survival difference by SES in the AYA population is the propensity for those from lower SES to present with more advanced disease.

The explanations for AYA patients from lower SES backgrounds presenting with higher stage MOGCT are unclear. In other cancers, researchers have suggested that the SES differences in Stage of disease at diagnosis are due to a delay in diagnosis in lower SES groups, but others have demonstrated no difference in time to diagnosis.¹⁶ This variable has not been examined in MOGCT and the variable regarding time from onset of disease to diagnosis was not available in the NCDB, making it impossible to assess whether this variable contributed to our findings. It is likely that a delay in diagnosis in lower SES groups does play some role in the survival disparity, and as such, we must focus interventions on early diagnosis across all SES groups. Since early stage MOGCTs tend to have few symptoms, increased awareness of the disease and access to care may lead to earlier diagnosis and decrease the survival gap revealed in this study.

We examined other potential explanations behind the survival difference observed. Although no such studies have been undertaken for MOGCTs, some researchers have demonstrated that SES is significantly associated with a delay in treatment for patients with other cancers.^{17,18} Martin *et al.* found that cancer type and insurance status, but not other surrogate measures of SES, were associated with a delay in treatment in leukemia, lymphoma, sarcoma, brain tumors, and thyroid cancer in subjects 15–29 years old.¹⁹ For AYAs with MOGCT, we found no difference in delays in staging or treatment based on SES. Additionally, there have been studies in various cancer types indicating that patients from different SES backgrounds receive a differing type or extent of treatment.^{16,20,21} Again, our data did not support that finding. In the current study, AYAs with MOGCT received similar treatment regardless of SES. It is encouraging that patients from different SES backgrounds are undergoing fertility-sparing surgery at similar rates given that fertility-sparing surgery is recommended when possible for MOGCT.²²

Aside from tumor stage and patient SES, other prognostic factors that have been implicated in survival for MOGCT including age, histology, and race. Solheim *et al.* found that patients with MOGCT over 40 years of age had lower survival than their younger counterparts.⁸ We accounted for this variable in the current study by including only women younger than 40 years of age and by controlling for age in the multivariate analysis. Regarding histology, patients with non-dysgerminoma had decreased survival compared to those with dysgerminoma. Additionally, those from a lower SES background with non-dysgerminoma, but not dysgerminoma, had lower survival than those from a higher SES background.⁸ The current study did not distinguish between histologic subtypes of MOGCT in the analysis and instead focused on all MOGCTs as a group. However, this study population had a similar distribution of dysgerminoma (43.5%) and non-dysgerminoma (56.5%) histology. Race has also been shown to affect survival in MOGCTs. Hinchcliff *et al.* found that African Americans had decreased survival compared to Whites despite similar Stage at presentation, histologic subtype, and treatment in each racial group.² Similar to our findings based upon SES, African Americans have also been shown to have higher Stage MOGCTs at presentation than Whites.²³ We accounted for this difference in survival and tumor stage by controlling for race/ethnicity in the statistical analysis.

A potential weakness of this study is that NCDB data regarding survival are only reported as overall survival; the NCDB does not provide disease-specific survival. However, the study population only included women with MOGCT aged 15–39 years, a population not likely to have significant comorbidities. An examination of AYA subjects with a variety of cancers found that less than 15% had ≥ 2 comorbidities,²⁴ making it likely that the mortality we observed was due to MOGCT. Another possible weakness may be the grouping of MOGCTs as one entity, when each histologic subtype behaves in a different manner clinically. Dysgerminomas have a better prognosis and improved survival compared to non-dysgerminomas.⁸ The study population included similar frequencies of dysgerminomas (43.5%) and non-dysgerminomas (56.5%), but subtypes were not separated out for analysis.

Conclusions

This examination of survival based on SES in AYAs with MOGCT revealed decreased survival rates in patients from a lower SES background. The driver of this survival difference was more extensive disease at presentation, such that those from lower SES groups presented with higher overall Stage and T-Stage tumors. Further efforts should focus on examining why lower SES groups present with more extensive MOGCTs so that interventions may be undertaken to eliminate this disparity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Kaplan-Meier survival curves by (A) insurance type, (B) income quartile, and (C) education quartile for AYAs with MOGCT controlling for age and race/ethnicity. Survival was determined by last contact or death and reported in months from diagnosis. $p < 0.05$ statistically significant.

Figure 2.

Kaplan-Meier survival curves by (A) insurance type, (B) income quartile, and (C) education quartile for AYAs with MOGCT controlling for age, race/ethnicity, overall Stage, and T-Stage. Survival was determined by last contact or death and reported in months from diagnosis. $p < 0.05$ statistically significant.

Table 1

Descriptive and socioeconomic characteristics of AYA women with MOGCT in the NCDB from 1998–2012.

Variable		N	Percent
Mean Age Years (SD)		23.10 (± 5.56)	
Race/ethnicity	Non-Hispanic White	1906	60.9%
	Hispanic White	599	19.2%
	Black	338	10.8%
	Asian	21	0.6%
	Other	263	8.5%
Insurance	None	302	10.1%
	Government	2017	67.9%
	Private	653	22.0%
Percent without High School Degree	21%	739	24.2%
	13.0–20.9%	745	24.3%
	7.0–12.9%	909	29.7%
	<7.0%	667	21.8%
Income quartile	< \$38,000	639	20.9%
	\$38,000–47,999	727	23.8%
	\$48,000–62,999	796	26.0%
	>\$63,000	898	29.3%

Table 2

Tumor characteristics of AYA women with MOGCT in the NCDB from 1998–2012.

Variable		N	Percent
T-Stage	I	1838	58.8%
	II	269	8.6%
	III	503	16.1%
	Unknown	515	16.5%
Overall Stage	I	1756	56.2%
	II	272	8.7%
	III	705	22.5%
	IV	146	4.7%
	Unknown	246	7.9%
Tumor Type	Dysgerminoma	1360	43.5%
	Yolk Sac Tumor	759	24.3%
	Mixed Germ Cell Tumor	633	20.3%
	Other	373	11.9%

Table 3

Local tumor extension (T-Stage) and overall disease Stage at presentation by socioeconomic surrogate variables for AYAs with MOGCT. 95% CI refers to 95% confidence interval.

	Local Tumor Extension (T-Stage)				
	I	II	III	p-value	Hazard Ratio (95% CI)
Insurance Type				0.006*	Ref
None	153 (62.2%)	29 (11.8%)	64 (26.0%)		0.62 (0.61–0.82)
Government	383 (67.8%)	55 (9.7%)	127 (22.5%)		0.55 (0.43–0.67)
Private	1250 (71.8%)	185 (10.6%)	305 (17.5%)		
Median Income Quartile				0.001*	Ref
<\$38,000	362 (65.8%)	43 (7.8%)	145 (26.4%)		0.53 (0.46–0.66)
\$38,000–\$47,999	433 (70.2%)	60 (9.7%)	124 (20.1%)		0.31 (0.29–0.50)
\$48,000–\$62,999	481 (72.1%)	73 (10.9%)	113 (16.9%)		0.25 (0.22–0.43)
\$63,000+	562 (72.5%)	92 (11.9%)	121 (15.6%)		
% Without High School Degree				<0.001*	Ref
21%	400 (63.6%)	59 (9.4%)	170 (27.0%)		0.76 (0.68–0.83)
13.0–20.9%	482 (74.7%)	51 (7.9%)	112 (17.4%)		0.65 (0.62–0.84)
7.0–12.9%	527 (69.6%)	94 (12.4%)	136 (18.0%)		0.24 (0.13–0.44)
<7.0%	429 (74.2%)	64 (11.1%)	85 (14.7%)		
Neoplasm Stage					
	I	II	III	IV	Hazard Ratio (95% CI)
Insurance Type					
None	152 (56.1%)	27 (10.0%)	70 (25.8%)	22 (8.1%)	Ref
Government	358 (59.2%)	34 (5.6%)	166 (27.4%)	47 (7.8%)	0.64 (0.51–0.77)
Private	1186 (63.8%)	156 (8.4%)	453 (24.4%)	65 (3.5%)	0.46 (0.34–0.58)
Median Income Quartile					
<\$38,000	349 (58.0%)	38 (6.3%)	172 (28.6%)	43 (7.1%)	Ref

	Local Tumor Extension (T-Stage)					
	I	II	III	p-value	Hazard Ratio (95% CI)	
\$38,000–\$47,999	416 (62.1%)	42 (6.3%)	168 (25.1%)	44 (6.6%)	0.54 (0.44–0.62)	
\$48,000–\$62,999	462 (64.8%)	57 (8.0%)	160 (22.4%)	34 (4.8%)	0.39 (0.26–0.51)	
\$63,000+	529 (63.1%)	80 (9.5%)	205 (25.0%)	25 (3.0%)	0.34 (0.21–0.47)	
% Without High School Degree					0.001*	
21%	398 (57.4%)	48 (6.9%)	200 (28.9%)	47 (6.8%)	Ref	
13.0–20.9%	449 (64.6%)	38 (5.5%)	162 (23.3%)	46 (6.6%)	0.87 (0.73–0.89)	
7.0–12.9%	499 (61.5%)	75 (9.2%)	204 (25.2%)	33 (4.1%)	0.52 (0.41–0.61)	
<7.0%	410 (65.6%)	56 (9.0%)	139 (22.2%)	20 (3.2%)	0.39 (0.27–0.42)	

* p < 0.05 statistically significant.

Table 4

Proportional Cox regression of survival as a function of socioeconomic surrogate variables in AYAs with MOGCT. Analysis was performed while controlling for age and race/ethnicity or while controlling for age, race/ethnicity, T-stage, and overall stage.

	Controlling for age and race/ethnicity				Controlling for age, race/ethnicity, T-stage, and overall stage			
	Hazard Ratio	95% Confidence Interval	p-value		Hazard Ratio	95% Confidence Interval	p-value	
Insurance Type								
None	Ref	Ref			Ref	Ref		
Government	0.65	0.58–0.71	0.019 *		0.82	0.41–1.01		0.543
Private	0.57	0.45–0.68			0.70	0.33–1.18		
Median Income Quartile								
<\$38,000	Ref	Ref			Ref	Ref		
\$38,000–\$47,999	0.80	0.73–0.90	0.039 *		0.97	0.48–1.11		0.705
\$48,000–\$62,999	0.66	0.48–0.77			0.69	0.53–1.05		
\$63,000+	0.41	0.30–0.53			0.58	0.26–1.64		
% Without High School Degree								
21%	Ref	Ref			Ref	Ref		
13.0–20.9%	0.85	0.72–0.88	0.022 *		0.96	0.89–1.07		0.677
7.0–12.9%	0.73	0.69–0.77			0.70	0.64–1.15		
<7.0%	0.65	0.61–0.70			0.78	0.54–0.99		

* p 0.05 statistically significant.