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Histological Tumor Type is Associated with One-Year Cause-Specific Survival in Women with Stage III–IV Epithelial Ovarian Cancer: A Surveillance, Epidemiology, and End Results (SEER) Database Population Study, 2004–2014

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Data Interpretation D
Manuscript Preparation E
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Background: The prognosis of epithelial ovarian cancer (EOC) remains poor. Cause-specific survival (CSS) is an overall survival measure of cancer survival that excludes other causes of death. This retrospective population study used the Surveillance, Epidemiology, and End Results (SEER) database to evaluate prognostic factors associated with one-year CSS in women with stage III–IV EOC between 2004–2014.





Material/Methods: Data from the SEER program included a cohort of patients with stage III–IV EOC between 2004–2014. Binomial logistic regression analysis, Kaplan-Meier survival curves, and multivariate Cox proportional hazards models were used for analysis of patient outcome, including the one-year CSS.

Results: There were 14,798 patients with stage III–IV EOC identified from SEER between 2004–2014, including 13,134 (88.8%), 892 (6.0%), 448 (3.0%), and 324 (2.2%) patients with serous, endometrioid, clear cell, and mucinous ovarian cancer, respectively. The overall one-year CSS was 91.2%. One-year CSS was 92.5%, 92.2%, 74.0%, and 62.5% in patients with serous, endometrioid, clear cell, and mucinous ovarian cancer, respectively ($P < 0.001$). Histological tumor type was an independent prognostic factor of one-year CSS. Patients with mucinous EOC (HR, 8.807; 95% CI, 6.563–9.965; $P < 0.001$) and clear cell EOC (HR, 4.581; 95% CI, 3.774–5.560; $P < 0.001$) had a significantly lower one-year CSS compared with patients with endometrioid and serous EOC who had comparable one-year CSS (HR, 1.247; 95% CI, 0.978–1.590; $P = 0.075$).

Conclusions: A retrospective population study of the SEER database between 2004–2014 identified that histological tumor type was associated with one-year CSS in women with stage III–IV EOC.

MeSH Keywords: **Histology • Mortality • Ovarian Neoplasms • Prognosis**

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Background

Worldwide, epithelial ovarian cancer (EOC) is associated with a high mortality rate due to the late presentation [1]. Approximately 85–90% of patients with primary ovarian cancer are diagnosed with a histological epithelial subtype that includes serous, endometrioid, clear cell, and mucinous EOC [2]. According to the ovarian cancer statistics from the United States (US), in 2018, 80% of patients were diagnosed with advanced stage, or stage III–IV, EOC [3]. In recent decades, there has been some improvement in the prognosis of EOC due to advances in ovarian cancer treatment [4–6]. However, the improvements achieved for patient survival from late-stage EOC have been significantly less than that for other solid tumors, and patients with stage II–IV EOC often die soon after diagnosis [7].

In 2014, the World Health Organisation (WHO) classified tumors of the female reproductive tract [8]. EOC is classified histologically as high-grade or low-grade, serous, endometrioid, clear cell, and mucinous ovarian cancer [8]. In 2015, Cress et al. reported the findings from a population study that analyzed data from a cancer registry and showed that non-serous histology was associated with increased long-term survival in patients with EOC [9]. Although previous studies have shown that histology is a prognostic factor for advanced EOC [10–12], little information is available on the effect of histology on early death in this patient subset, particularly for those treated outside the setting of a clinical trial. Further insight into the potentially intrinsic tumor-related factors that impact the risk of early death could help to optimize the approach to treatment and supportive care of patients with EOC.

Cause-specific survival (CSS) is an overall survival measure of cancer survival that excludes other causes of death. The advantage of using CSS in population studies of cancer survival is that it does not depend on the ability to find a control population without EOC for data analysis. Therefore, this retrospective population study aimed to use the Surveillance, Epidemiology, and End Results (SEER) database to evaluate prognostic factors associated with one-year CSS in women with stage III–IV EOC between 2004–2014, including the evaluation of histological tumor type.

Material and Methods

Surveillance, Epidemiology, and End Results (SEER) database 2004–2014 and patients with advanced-stage epithelial ovarian cancer (EOC)

Data were extracted from the Surveillance, Epidemiology, and End Results (SEER) database [13]. The SEER program includes 18 population-based cancer registries which collect cancer demographic,

clinical, treatment, and outcome information on approximately 28% of the US population [13]. Patients diagnosed with advanced-stage EOC (stage III–IV) between 2004–2014 were identified. The selection criteria in this study included patients with stage III–IV EOC, including serous, endometrioid, clear cell, and mucinous histological subtypes; patients treated with surgery and chemotherapy; and patients with available data on race/ethnicity, tumor grade, and their marital status. Patients with no histological diagnostic details, who had early-stage serous subtype, and incomplete clinical data were excluded. This study used retrospective and anonymized data from the SEER program, and was exempt from institutional review board (IRB) approval.

Clinical variables

The following demographic, clinicopathological, and survival variables for each patient were recorded: the diagnosis period, age at diagnosis, race/ethnicity, tumor grade, histological tumor type, American Joint Committee on Cancer (AJCC) stage, and marital status. The staging system definitions were based on the sixth edition of the AJCC staging system. The year of diagnosis were divided into four cohorts: 2004–2006, 2007–2009, 2010–2012, and 2013–2014. Marital status was classified as married, single (never married), divorced (divorced or separated), and widowed. Cause-specific death was defined as the death from ovarian cancer.

Statistical analysis

Patients with EOC were divided into two study cohorts for data analysis, patients who survived for ≤ 1 year and patients who survived for > 1 year. The chi-squared (χ^2) test was used to compare the frequencies of the patient variables. The predictors of patients who survived ≤ 1 year were identified using binomial logistic regression analysis. Kaplan-Meier survival curves and the Cox proportional hazards models were used to determine indicators associated with variation in one-year cause-specific survival (CSS). CSS was the overall survival measure of survival from EOC that excluded other causes of death. All models included the diagnosis period, age, race/ethnicity, AJCC stage, histology, grade, and marital status. Statistical analysis was performed using SPSS version 22.0 software (IBM Corporation, Armonk, NY, USA). A P-value < 0.05 was considered to be statistically significant.

Results

Characteristics of patients with advanced-stage epithelial ovarian cancer (EOC) from the Surveillance, Epidemiology, and End Results (SEER) database, 2004–2014

A total of 14,798 patients were identified from SEER, including 88.8% ($n=13,134$) with the serous subtype of EOC, and 6.0%

Table 1. Patient demographic and clinical characteristics.

Variables	n	Survival ≤1 year (%)	Survival >1 year (%)	P-value
Diagnosis period				
2004–2006	3873	410 (32.1)	3463 (25.6)	<0.001
2007–2009	4065	338 (26.5)	3727 (27.6)	
2010–2012	4143	336 (26.3)	3807 (28.2)	
2013–2014	2717	192 (15.0)	2525 (18.7)	
Age (years)				
<50	2609	172 (13.5)	2437 (18.0)	<0.001
50–64	6420	444 (34.8)	5976 (44.2)	
≥60	5769	660 (51.7)	5109 (37.8)	
Race/ethnicity				
Non-Hispanic white	11183	952 (74.6)	10231 (75.7)	0.055
Non-Hispanic black	933	103 (8.1)	830 (6.1)	
Hispanic	1530	127 (10.0)	1403 (10.4)	
Other	1152	94 (7.4)	1058 (7.8)	
Tumor grade				
Well-differentiated	503	37 (2.9)	466 (3.4)	0.281
Moderately-differentiated	1961	184 (14.4)	1777 (13.1)	
Poorly/undifferentiated	12334	1055 (82.7)	11279 (83.4)	
AJCC stage				
III	10381	741 (58.1)	9640 (71.3)	<0.001
IV	4417	535 (41.9)	3882 (28.7)	
Histological subtypes				
Serous	13134	978 (76.6)	12156 (89.9)	<0.001
Endometrioid	892	68 (5.3)	824 (6.1)	
Mucinous	324	116 (9.1)	208 (1.5)	
Clear cell	448	114 (8.9)	334 (2.5)	
Marital status				
Married	8715	662 (51.9)	8053 (59.6)	<0.001
Divorced	1835	158 (12.4)	1677 (12.4)	
Single	2368	202 (15.8)	2166 (16.0)	
Widowed	1880	254 (19.9)	1626 (12.0)	

AJCC – American Joint Committee on Cancer.

(n=892), 3.0% (n=448), and 2.2% (n=324) with endometrioid, clear cell, and mucinous EOC, respectively. Most patients were aged >50 years (82.4%) and were non-Hispanic white (75.6%), with poorly differentiated or undifferentiated EOC (83.3%), and stage III (70.2%) EOC. Concerning marital status, 58.9%, 16.0%, 12.4%, and 12.7% of patients were married, single, divorced, and widowed, respectively. The demographic and clinicopathological characteristics of the patients included in the study are shown in Table 1.

Time trends for ovarian cancer-related death and one-year cause-specific survival (CSS)

A total of 8,936 (60.4%) patients died during follow-up, including 7,809 (52.8%) patients who died of ovarian cancer. Also, 1,510 patients died within one year of diagnosis, and 84.5% (n=1,276) of these patients died of ovarian cancer. The one-year CSS was 91.2% in the overall cohort, including 92.5%, 92.2%, 74.0%, and 62.5% with serous, endometrioid, clear cell, and mucinous tumors, respectively (P<0.001) (Figure 1).

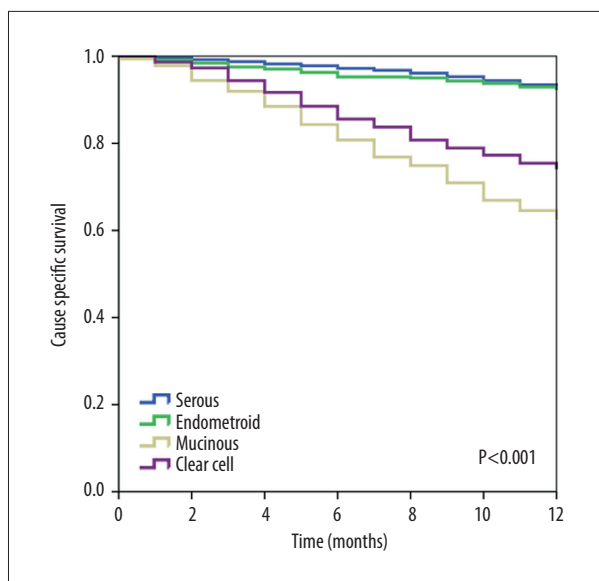


Figure 1. The one-year cause-specific survival (CSS) according to the histology in epithelial ovarian cancer (EOC).

The time trends for ovarian cancer-related death were evaluated in each year of diagnosis from 2004–2014 (Figure 2). The effects on one-year CSS from serous and endometrioid tumors were not affected by the year of diagnosis (all $P < 0.001$). When stratified by histological subtype, only serous tumors had a survival benefit from the year of diagnosis in terms of the one-year CSS. Patients who were diagnosed with EOC in the later years (2007–2014) had an improved one-year CSS compared with those diagnosed in earlier years (2004–2006) ($P < 0.001$). However, the year of diagnosis did not affect the

one-year CSS in endometrioid ($P = 0.202$), clear cell ($P = 0.120$), and mucinous ($P = 0.916$) ovarian tumors.

Analysis of the distribution of ovarian cancer-related death within the five years after diagnosis was undertaken (Figure 3). There were 16.0% and 22.5% of cases with serous and endometrioid tumors, respectively, who died within the first year from diagnosis. However, approximately two-thirds (64.1%) of cases with mucinous tumors died within the first year of diagnosis, and 43.8% of cases with clear cell tumors died within the first year of diagnosis.

Independent predictive factors associated with one-year CSS

Patients who survived ≤ 1 year and > 1 year showed significant differences in several parameters (Table 1). In particular, patients diagnosed in the earlier years ($P < 0.001$), patients with older age ($P < 0.001$), advanced-stage disease (stage IV) ($P < 0.001$), clear cell and mucinous tumors ($P < 0.001$), and widowed status ($P < 0.001$) were more likely to die within one year of diagnosis (Table 1). Binomial regression analysis confirmed that diagnosis in the early years of the study, older age, non-Hispanic black ethnicity, higher tumor grade, advanced stage, mucinous and clear cell tumors, and widowed status were independently associated with a higher risk of cancer-related mortality within one year after diagnosis (Table 2).

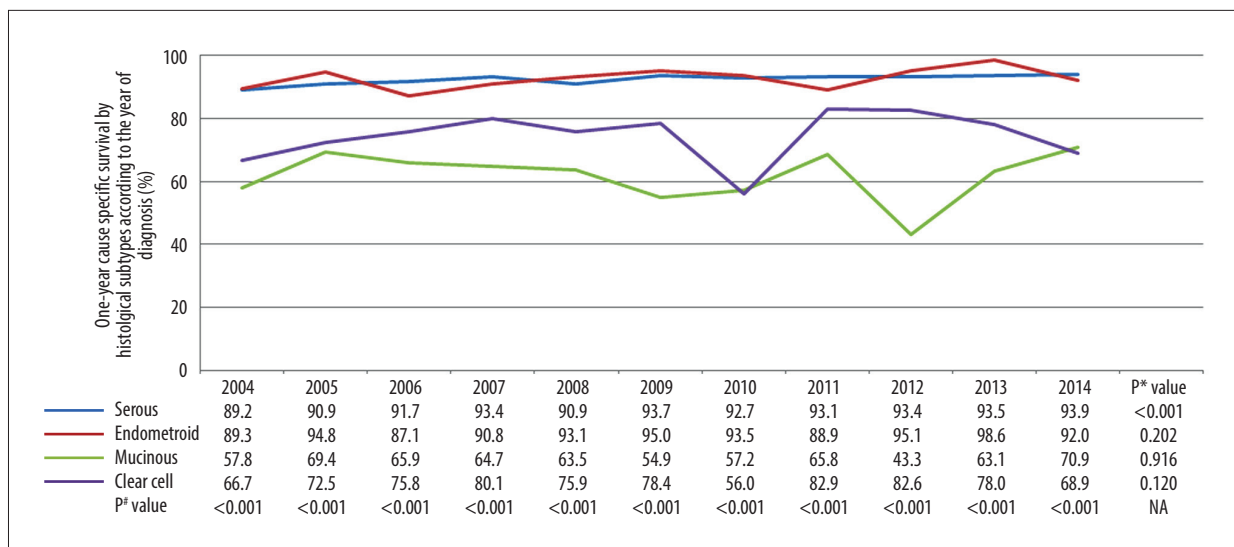


Figure 2. The trends for the one-year cause-specific survival (CSS) over time for women with epithelial ovarian cancer (EOC).

* Indicates the Kaplan-Meier analysis of the one-year cause-specific survival (CSS), and comparison between the periods of diagnosis using the log-rank test. # Indicates the Kaplan-Meier analysis of one-year CSS, and comparison between the four histological subtypes using the log-rank test.

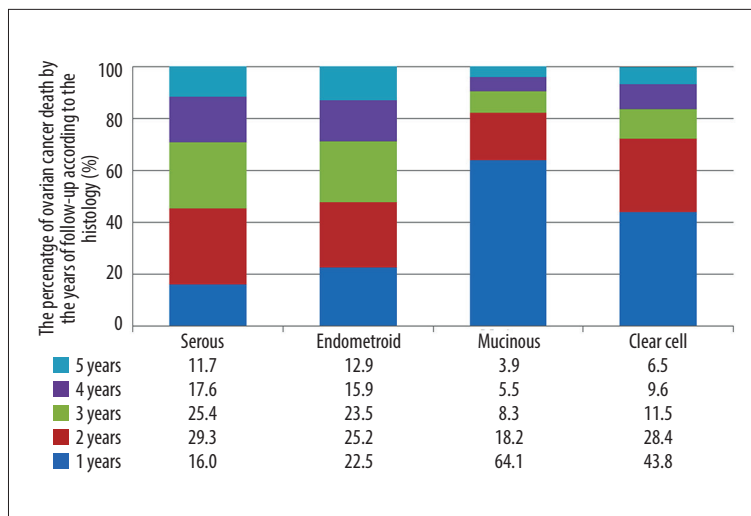


Figure 3. The distribution of ovarian cancer-related death within the five years from diagnosis of epithelial ovarian cancer (EOC).

Independent prognostic factor associated with one-year CSS

Multivariate Cox proportional analysis was performed to assess the independent prognostic factors associated with one-year CSS (Table 3). After adjusting for the period of diagnosis, age, race/ethnicity, grade, AJCC stage, and marital status, the findings showed that histological tumor type was an independent prognostic factor associated with one-year CSS. Patients with mucinous EOC (HR, 8.807; 95% CI, 6.563–9.965; $P < 0.001$) and clear cell EOC (HR, 4.581; 95% CI, 3.774–5.560; $P < 0.001$) had a significantly lower one-year CSS compared with patients with serous tumors. The one-year CSS was comparable between endometrioid and serous tumors (HR, 1.247; 95% CI, 0.978–1.590; $P = 0.075$). Using clear cell tumors as reference, serous carcinoma (HR, 0.218; 95% CI, 0.180–0.266; $P < 0.001$), and endometrioid carcinoma (HR: 0.260; 95% CI, 0.192–0.353; $P < 0.001$) had a significantly better CSS, while patients with mucinous tumors had a significantly reduced CSS (HR, 1.745; 95% CI, 1.329–2.291; $P < 0.001$) compared with patients with clear cell tumors. Also, the interval of diagnosis, patient age, race/ethnicity, tumor grade, AJCC stage, and patient marital status were also independent prognostic factors associated with one-year CSS. Similar trends were observed after stratification by the interval of diagnosis, age, race/ethnicity, tumor grade, tumor stage, and patient marital status.

Discussion

In this large retrospective cohort population study, the Surveillance, Epidemiology, and End Results (SEER) database was used to evaluate the one-year cause-specific survival (CSS) in women with stage III–IV epithelial ovarian cancer (EOC) between 2004–2014. Approximately 10% of patients died within one year from diagnosis, and when the cases were stratified

by histological tumor type, most of the deaths occurred in patients with clear cell and mucinous EOC, whereas those with serous and endometrioid EOC had a significantly better one-year CSS. These findings have implications for future studies, as patients with clear cell and mucinous EOC may die too early to benefit from the therapeutic advances, including those studied in new clinical trials.

Patients with early-stage clear cell and mucinous EOC have improved outcomes when compared with patients with serous tumors [14–17]. However, in patients with advanced-stage clear cell and mucinous tumors, aggressive tumor behavior and progressively poor prognosis are observed, relative to patients with endometrioid and serous tumors [10–12]. Within the first year of diagnosis, the proportion of cases with ovarian cancer-related death was significantly higher in those with clear cell and mucinous tumors, with a one-year CSS of 62.5%, and 74.0%, respectively, compared with patients with serous and endometrioid tumors, with a one-year CSS of 92.5%, and 92.2%, respectively. Histological subtype remained an independent prognostic indicator, even after adjusting for other significant factors. In current clinical practice, the optimal treatment for advanced-stage EOC remains unclear due to the rare occurrence of mucinous and clear cell ovarian tumors. Therefore, only a few institutions have sufficient numbers of patients to perform studies to develop treatment recommendations. In the present study, mucinous and clear cell EOC has a significantly lower one-year CSS compared with other EOC subtypes. Therefore, both preoperative work-up and intensive follow-up after surgery should be performed to detect disease progression in these specific subtypes.

In the past 20 years, there has been progress in the treatment of EOC [18–21]. However, whether the therapeutic advances translate into survival benefits remains unclear. A study from Korea showed that outcomes have improved for patients with

Table 2. Multivariate logistic analysis of factors associated with one-year ovarian cancer-related death.

Variables	OR	95% CI	P-value
Diagnosis period			
2004–2006	1		
2007–20096	0.798	0.691–0.922	0.002
2010–2012	0.778	0.673–0.900	0.001
2013–2014	0.682	0.572–0.808	<0.001
Age (years)			
<50	1		
50–64	1.166	0.974–1.397	0.094
≥60	2.011	1.675–2.414	<0.001
Race/ethnicity			
Non-Hispanic white	1		
Non-Hispanic black	1.302	1.059–1.600	0.012
Hispanic	1.112	0.921–1.342	0.269
Other	0.955	0.771–1.183	0.674
Grade			
Well-differentiated	1		
Moderately-differentiated	1.66	1.159–2.379	0.006
Poorly/undifferentiated	1.766	1.250–2.495	0.001
AJCC stage			
III	1		
IV	1.749	1.565–1.956	<0.001
Histological subtypes			
Serous	1		
Endometrioid	1.190	0.928–1.528	0.171
Mucinous	7.985	6.469–9.856	<0.001
Clear cell	4.577	3.761–5.570	<0.001
Marital status			
Married	1		
Divorced	1.145	0.961–1.363	0.129
Single	1.136	0.965–1.337	0.124
Widowed	1.503	1.291–1.751	<0.001

AJCC – American Joint Committee on Cancer; CI – confidence interval; OR – odds ratio.

serous (P<0.001) and endometrioid (P<0.001) tumors in the last 20 years (1995–2014). However, no improvement in survival outcomes has been observed for patients with mucinous (P=0.1894) and clear cell (P=0.2926) tumors [4]. Therefore, the various histological subtypes in EOC exhibit different survival outcomes. In the present study, patients with serous tumors diagnosed in later years of the study had improved outcomes, whereas the year of diagnosis did not affect outcomes in patients with non-serous EOC histology. The limited impact of the years from diagnosis on the outcome of endometrioid

tumors may be due to the higher one-year CSS in these patients. However, in patients with advanced mucinous and clear cell tumors, the current use of anticancer agents has limited ability to improve the poor outcomes [22,23]. Therefore, the findings from the present study highlight the need for continued research on the treatment of mucinous and clear cell EOC.

In a previously published study from the SEER-Medicare database that included 9,491 patients with advanced EOC, approximately 39.2% of patients died of ovarian cancer within one

Table 3. Multivariate Cox regression analyses of factors associated with one-year ovarian cancer-related death.

Variables	HR	95% CI	P-value
Diagnosis period			
2004–2006	1		
2007–20096	0.799	0.692–0.923	0.002
2010–2012	0.779	0.673–0.901	0.001
2013–2014	0.663	0.562–0.783	<0.001
Age (years)			
<50	1		
50–64	1.169	0.979–1.396	0.085
≥60	1.999	1.669–2.394	<0.001
Race/ethnicity			
Non-Hispanic white	1		
Non-Hispanic black	1.310	1.069–1.606	0.009
Hispanic	1.126	0.937–1.353	0.206
Other	0.968	0.785–1.194	0.761
Grade			
Well-differentiated	1		
Moderately-differentiated	1.647	1.154–2.349	0.006
Poorly/undifferentiated	1.755	1.248–2.468	0.001
AJCC stage			
III	1		
IV	1.781	1.595–1.989	<0.001
Histological subtypes			
Serous	1		
Endometrioid	1.247	0.978–1.590	0.075
Mucinous	8.807	6.563–9.965	<0.001
Clear cell	4.581	3.774–5.56	<0.001
Marital status			
Married	1		
Divorced	1.147	0.965–1.364	0.120
Single	1.160	0.989–1.361	0.069
Widowed	1.538	1.323–1.788	<0.001

AJCC – American Joint Committee on Cancer; CI – confidence interval; HR – hazard ratio.

year of diagnosis [24]. However, 17.8% of patients had other EOC subtypes, and 24.4% did not receive any initial treatment, which limited the interpretation of the relevance of the study findings [24]. In the SEER cohort in the present study, all patients received surgical treatment and chemotherapy, and the incidence of one-year ovarian cancer-related death was 8.8%, which was significantly lower when compared with the results from the SEER-Medicare study [24]. Therefore, the difference in the included population and treatment patterns could contribute to the difference in one-year mortality in EOC. Another

previously published prospective nationwide cohort study of Danish women showed that residual tumor tissue and the International Federation of Gynecology and Obstetrics (FIGO) stage were important predictors of mortality within one year in patients with ovarian cancer [25], although histological tumor subtype was not included in this previous study.

In the present study, the findings showed that, unlike serous EOC (16.0%) and endometrioid EOC (22.5%), 64.1% and 43.8% of the ovarian cancer-related deaths in mucinous and clear cell

EOC, respectively, developed within the first year after diagnosis. However, although there were no significant difference in one-year CSS between clear cell and mucinous tumors over time, there was a sharp drop in one-year CSS for clear cell EOC (from 2009 to 2010) and mucinous EOC (from 2011 to 2012). In both cases, there was recovery during the following year, and a steady increase in one-year CSS up to 2011 for clear cell tumors, and then it fell back to the same rate as in 2004 (Figure 1). The underlying causes of this phenomenon remain unclear. The heterogeneity in tumors and response to different chemotherapy regimens may be the potential reasons for this finding [26,27].

The heterogeneity of response to chemotherapy and outcomes based on histology has not been considered in previous clinical trials that included patients with EOC [28–31]. Despite the availability of current treatments that can potentially prolong survival time and palliate symptoms, many women with mucinous and clear cell EOC die within one year of diagnosis, and may not have the opportunity to receive appropriate therapy. The available data suggest that the process of evaluation of patients for enrollment in early clinical trials should involve stratification based on histological subtypes to avoid bias resulting from the wrong attribution of cause of early death, which may be associated with histological tumor subtype.

The findings from the present study showed that baseline clinicopathological indicators associated with an increased risk of early mortality included diagnosis of EOC in the early years of the study, older patient age, non-Hispanic black ethnicity, higher tumor grade, advanced tumor stage, and widowed status. The demographic, clinicopathological, and biological background in various EOC histological subtypes may be related to different prognosis. However, this study showed that mucinous and clear cell EOC had a lower one-year CSS compared with endometrioid and serous tumors. These data indicate that gynecologic oncologists may be able to provide valuable histological support for treatment decisions made at the time of the initial consultation with patients with EOC who have a histological diagnosis. The findings from the present study may have clinical implications for gynecologic oncologists to inform their patients and counsel them regarding the risk of early mortality from EOC, particularly for those with mucinous and clear cell tumors who are at an increased risk of early death.

This study had several limitations. This study was retrospective and was based on the available data from the SEER program database. There was a lack of available data on several clinical variables, including performance status, comorbidity, socioeconomic status, patient environment, treatment decisions, and compliance with and completeness of treatment regimens. Also, central pathology reviews of the histology were not available for patients with EOC who were registered in the SEER program. The detailed surgery and chemotherapy information, including surgeon's specialty, the extent of debulking procedures, the presence of residual tumors, the sequence of chemotherapy and surgery, and the specific treatment regimens, were also lacking in the SEER database. The response to chemotherapy and the patterns of disease recurrence after treatment were also not recorded in the SEER program database. However, the findings of this study are particularly important because the study involved a relatively large, representative, national cohort, and high-quality population-based design. Also, the study findings highlight the importance of histology-based research for follow-up and treatment selection, which also warrants further studies on histological subtype and tissue biomarker expression and prognosis in patients with EOC.

Conclusions

This retrospective population study used the Surveillance, Epidemiology, and End Results (SEER) database to evaluate the one-year cause-specific survival (CSS) in women with stage III–IV EOC between 2004–2014 based on the tumor histopathology. The findings showed that histological tumor subtype was an independent prognostic indicator for one-year CSS and that most of the early patient deaths occurred in patients with mucinous and clear cell EOC. The study findings highlight that patients with EOC should receive individualized treatment and follow-up based on the tumor histology as well as the tumor stage and early clinical trials should include histological subtype as a factor when evaluating clinical outcomes. However, further prospective clinical studies are needed to validate the findings from this retrospective population study.

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