Chapter 6

Demographic and Clinical Characteristics of Mucinous Epithelial Ovarian Cancer, and Survival Following a Mucinous Epithelial Ovarian Cancer Diagnosis

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http://dx.doi.org/10.5772/53740

1. Introduction

Ovarian cancer is the fifth leading cause of cancer death in the United States, and contributes significantly to the worldwide cancer burden [1]. The lack of gynecologic-specific symptoms and effective early detection methods for ovarian cancer leads to a preponderance of late-stage diagnoses. Ovarian cancer is a surgically-staged and treated disease, and the application of appropriate, guidelines-based treatment is currently the only option to reduce ovarian cancer mortality [2].

The National Comprehensive Cancer Network (NCCN) [3] and the National Institutes of Health (NIH) [4] publish widely used treatment guidelines for ovarian cancer cases in the United States. Both NCCN and NIH's Physician Data Query (PDQ) incorporate tumor histology into treatment guidelines. While the NCCN publishes guidelines for the three main types of ovarian cancer, epithelial, sex cord-stromal, and germ cell tumors [5]; the PDQ offers guidelines only for the most common epithelial tumors. While epithelial tumors account for about 90% of all ovarian neoplasms, they are not a homogenous group [5]. The four main epithelial subtypes (serous, mucinous, clear cell, and endometrioid) can have very different clinical and pathologic patterns.

Among epithelial ovarian cancer subtypes is mucinous epithelial ovarian cancer (mEOC), a relatively rare subtype accounting for approximately 14% of invasive ovarian

cancer cases [6]. mEOC has a distinct natural history compared to other epithelial subtypes, especially the most common serous subtype. mEOCs are more often diagnosed in younger women [6] than other epithelial tumors, and epidemiologic studies have shown a lack of protective effect from parity and oral contraceptive use [7-11]. Pathologic studies have determined that mutations in the K-ras oncogene are more common in mEOC compared to other subtypes [12], while mutations in the BRCA1 tumor suppressor gene are less common [13]. Despite their distinctive nature, mEOCs are included in overall epithelial ovarian cancer treatment guidelines, as standard care for all epithelial subtypes is defined in the same manner [3,4].

Because of the differences in risk factors and presentation, a few studies have examined differences in outcomes of mEOC compared to other epithelial subtypes. Many have found lower response rates to chemotherapy and inferior outcomes compared to other subtypes [14-16]. Based on these results, it has been suggested that mEOC be treated as a different entity and not grouped along with epithelial tumors in standard treatment and also in clinical trials for epithelial ovarian cancer [17]; however, these suggestions have yet to be widely adopted or implemented. While the existing evidence seems consistent, studies producing this evidence have contained small numbers and generally represent the experience of individual institutions.

1.1. Objectives

The objective of this chapter is to fully characterize mEOC using a population-based approach. We add to the paucity of existing literature on mEOC with an analysis that utilizes ovarian cancer medical record data from two large populations in the United States, New York and Northern California. We comprehensively examine demographics, pathologic characteristics, and the outcomes of treatment for mEOC. We compare these characteristics to other epithelial subtypes in order to determine whether clinical presentation or outcomes differ among epithelial subtypes. Finally, we discuss the results of this research in the context of published studies on mEOC.

2. Study design

2.1. Setting and population

The data presented and analyzed here are from the Ovarian Cancer Treatment Patterns and Outcomes (OCTPO) study, funded by the Centers for Disease Control and Prevention (CDC), and conducted by the New York State and the California Cancer Registries [18-20]. The New York State Cancer Registry (NYSCR) conducts surveillance on all 19 million New York state residents, and the two components of the California Cancer Registry (CCR) that were funded for this study serve the contiguous geographical area of Greater San Francisco-San Jose and Sacramento regions, providing surveillance for a population of 9 million residents in California. Both the NYSCR and the CCR conduct high quality, population-based cancer surveillance, and routinely review medical records to abstract demographics, tumor

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characteristics and treatment data as part of state-mandated cancer surveillance. For this retrospective study, additional detailed patient, tumor, and treatment data were collected by these registries from multiple sources including hospital, outpatient facility and physician records. Vital status was determined by linkage with the National Death Index http://www.cdc.gov/nchs/ndi.htm. The study population included patients with invasive epithelial ovarian cancer diagnosed between 1998 and 2000. Only invasive cases of epithelial ovarian cancer were included; benign and low malignant potential tumors were excluded. Primary peritoneal cancers and fallopian tube cancers were also excluded. Subjects diagnosed at autopsy or by death certificate were ineligible. All cases included were histologically confirmed. Cases were followed up for six years for vital status information.

2.2. Data classification

Histology was collected according to World Health Organization International Classification of Diseases for Oncology, third edition (ICD-O-3) morphology codes [21]. All epithelial histologies collected were collapsed into categories for analysis according to Table 1.

Epithelial Ovarian Cancer (EOC) Subtype	ICD-O-3 Codes
Mucinous (mEOC)	8470, 8471, 8480, 8481
Serous	8441,8442,8460,8461,8462
Other (includes endometrioid, clear cell, Brenner, mixed, undifferentiated, and unspecified or other epithelial tumors)	8380,8940,8950,8951,8310,9000,8323,8020,8050,8052, 8070,8120,8130,8140,8260, 8330,8340,8440,8450,8490,8560,8570,8980,8981

Table 1. Histologic definitions by epithelial ovarian cancer subtype

Race and ethnicity was categorized as white non-Hispanic, black non-Hispanic, Asian non-Hispanic, and Hispanic. A total of 34 cases were excluded from the analysis on the basis of race or ethnicity data. Three of the 34 cases were classified as American Indian/Alaska Native race; these were excluded because of the inability to draw any conclusions from this race because of the very small number. The remaining 31 cases were excluded because race or ethnicity information was unspecified or missing. Stage was defined using the International Federation of Gynecology and Obstetrics (FIGO) system, with categories I, II, III IV, or unknown. Grade was collapsed into four categories defined as Grade I (well differentiated tumors), Grade II (moderately differentiated tumors), Grade III/IV (poorly differentiated and undifferentiated tumors) and unknown grade. Laterality was collapsed into unilateral (single ovary involved at diagnosis: right, left, or unspecified), or bilateral (both ovaries involved at diagnosis) categories. Comorbidity was defined using the Deyo-Charlson Comorbidity Index [22, 23], a commonly used measure of disease burden. Comorbidity information was collected via linkage with state hospital discharge data. Any comorbidity present in the 12 months prior to or 4 months following an ovarian cancer diagnosis was included. Type of treatment was defined to distinguish patients who received various com-

binations of surgery and chemotherapy. In descriptive analyses, chemotherapy was further categorized by receipt of specific agents. These categories consisted of surgery and platinum agent (cisplatin or carboplatin) receipt, surgery and platinum agent and paclitaxel receipt (standard treatment for EOC) [24], and surgery and any chemotherapy agent or combination of agents other than cisplatin, carboplatin, or paclitaxel.

2.3. Analyses

Statistical testing was performed using the likelihood ratio chi-square test for discrete variables. The Kruskal-Wallis test was used to test for differences among continuous variables. A generalized logits model was fit to determine the characteristics associated with epithelial subtype. Variables included in the model were age, race/ethnicity, stage, grade, and laterality. Age was transformed in all models using restricted cubic spline functions to allow for nonlinearity [25]. Due to the lack of availability of grade and stage information for some cases (31% for grade; 15% for stage), missing indicator variables were included for each variable in all models. Because of potential issues with using missing indicator variables, separate models that imputed missing data were fit (data not shown) [26,27]. These models yielded consistent results with the un-imputed models. Six-year survival curves are presented as Kaplan-Meier estimates. Statistical testing for differences in unadjusted survival rates across epithelial subtypes was performed using the log-rank test. For adjusted survival, a time-dependent Cox model was used to determine the predictors of six-year survival. Age, race/ethnicity, stage, grade, epithelial subtype, comorbidity, laterality, surgery, and chemotherapy were included as covariates in the survival model. Time-dependent covariates for surgery and chemotherapy were used to prevent an artificial inflation of the association between treatment and survival. Cases were considered as not receiving treatment until the date of the procedure; they were considered as having received treatment after the date of the procedure. Interactions between epithelial subtype and treatment were included to determine if the effects of surgery and chemotherapy varied across subtypes. The proportional hazards assumption was assessed using time-dependent covariates and the Schoenfeld residual correlation test. Laterality was found to violate the proportional hazards (PH) assumption. Stratified log[-log S(t)] plots were used to help determine time intervals within which the PH assumption held. An interaction between laterality and time was included in the final model to satisfy the PH assumption.

3. Results

3.1. Demographic and clinical characteristics of mucinous epithelial ovarian cancer

The characteristics of ovarian cancer cases in New York and Northern California are presented by epithelial subtype in Table 2. Overall, 230 (8.7%) tumors were mEOC, 1195 (45.3%) tumors were serous EOC, and 1211 (45.9%) were other EOC. mEOCs were diagnosed at younger ages (57 years) compared to other subtypes (62 years for serous, 63 years for other EOCs). Relatively higher percentages of mEOCs were found among black non-Hispanic

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(8.0% vs. 5.9 and 6.7%) and Asian non-Hispanic (14.2% vs. 5.4 and 9.8%) populations compared to serous and other EOCs. Lower percentages of mEOCs (5.8%) were found among Hispanics compared to serous and mEOCs (7.5 and 7.7%). mEOCS were more likely to be diagnosed at FIGO stage I (45.2%) compared to serous (10.0%) and other mEOCs (24.9%). Higher percentages of low grade tumors and unilateral ovarian involvement at diagnosis were also present with mEOCs compared to other EOC types. A little under half of mEOC patients (46.3%) were treated with surgery only and 39.0% were treated with surgery plus a platinum agent and paclitaxel.

Characteristic	Mucinous (n=230)	Serous (n=1195)	Other Epithelial (n=1211)	**P-value**
Age at diagnosis*	57 (45, 72)	62 (52, 72)	63 (51, 75)	<0.001
Race/Ethnicity				<0.001
White Non-Hispanic	162 (72.0%)	956 (81.3%)	910 (75.8%)	
Black Non-Hispanic	18 (8.0%)	69 (5.9%)	80 (6.7%)	
Asian Non-Hispanic	32 (14.2%)	63 (5.4%)	118 (9.8%)	
Hispanic	13 (5.8%)	88 (7.5%)	93 (7.7%)	
FIGO Stage				<0.001
I	104 (45.2%)	119 (10.0%)	302 (24.9%)	
II	26 (11.3%)	66 (5.5%)	125 (10.3%)	
III	62 (27.0%)	747 (62.5%)	380 (31.4%)	
IV	19 (8.3%)	153 (12.8%)	225 (18.6%)	
Unknown	19 (8.3%)	110 (9.2%)	179 (14.8%)	
Grade				<0.001
I	73 (31.7%)	80 (6.7%)	92 (7.6%)	
II	69 (30.0%)	223 (18.7%)	193 (15.9%)	
III/IV	30 (13.0%)	730 (61.1%)	493 (40.7%)	
Unknown	58 (25.2%)	162 (13.6%)	433 (35.8%)	
Laterality				<0.001
Unilateral	167 (77.7%)	410 (36.7%)	634 (67.7%)	
Bilateral	48 (22.3%)	707 (63.3%)	302 (32.3%)	
Comorbidity				0.0257
None	161 (74.5%)	847 (77.6%)	814 (74.9%)	
1	38 (17.6%)	181 (16.6%)	170 (15.6%)	
2 or more	17 (7.9%)	63 (5.8%)	103 (9.5%)	

Characteristic	Mucinous (n=230)	Serous (n=1195)	Other Epithelial (n=1211)	P-value
Treatment				<0.001
Surgery only	95 (46.3%)	132 (12.2%)	196 (17.9%)	
Surgery+Platinum	7 (3.4%)	46 (4.3%)	28 (2.6%)	
Surgery+Platinum+ Paclitaxel	80 (39.0%)	826 (76.5%)	565 (51.6%)	
Surgery+other chemotherapy	2 (1.0%)	21 (1.9%)	12 (1.1%)	
Chemotherapy only	12 (5.9%)	32 (3.0%)	169 (15.4%)	
No surgery/no chemotherapy	9 (4.4%)	23 (2.1%)	124 (11.3%)	

Table 2. Demographic and clinical characteristics of invasive epithelial ovarian cancer cases by subtype, New York and Northern California. * Continuous variable presented as median (25th percentile, 75th percentile).

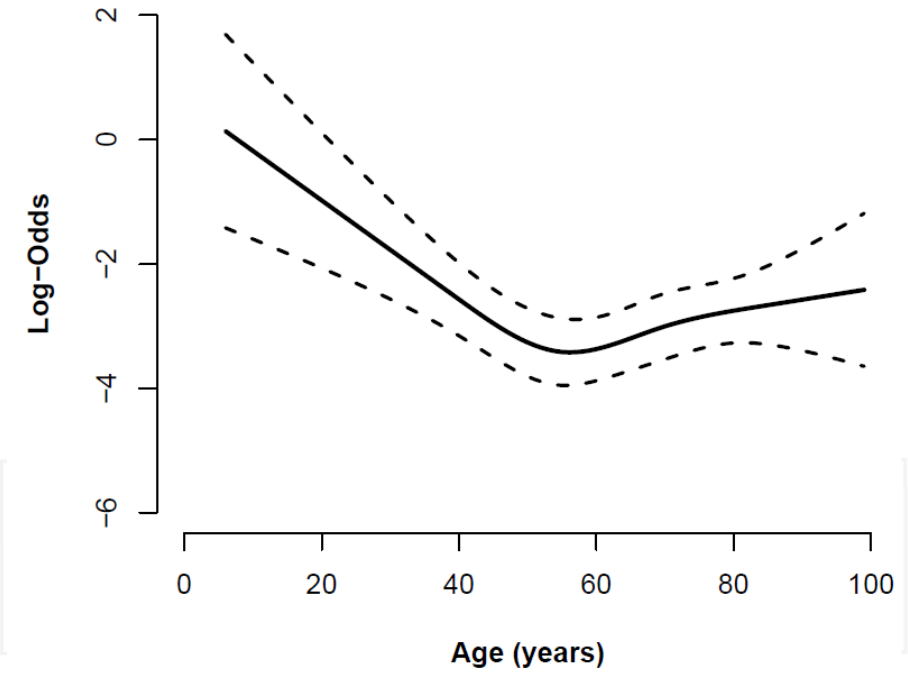

Figure 1. Adjusted relationship between age and risk of mucinous epithelial compared to serous epithelial ovarian cancer. Solid line indicates log-odds ratio, dotted lines indicated confidence intervals.

Table 3, Figure 1 and Figure 2 show the demographic and clinical characteristics significantly associated with mEOCs compared to other epithelial ovarian cancers, after adjusting for other factors. mEOCs were more often associated with Asian non-Hispanic race/ethnicity

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compared to serous tumors (odds ratio [OR] 1.94, 95% confidence interval [CI] 1.13-3.35). The relationship between age and epithelial subtype was nonlinear; ages 55 years and younger were more often associated with mEOC compared to both serous and other EOCs (Figures 1 and 2). Less advanced stage was associated with mEOCs compared to serous EOC (OR 0.29, 95% CI 0.18-0.47 for stage III and 0.39, 0.19-0.78 for stage IV). mEOCs were less likely to be grade III/IV compared to serous (OR 0.11, 95% CI 0.07-0.20) and other EOC (OR 0.10, 95% CI 0.06-0.16). Bilateral ovarian cancer at diagnosis was less often associated with mEOCs compared to serous EOC (OR = 0.32, 95% CI 0.22-0.49).

Characteristic	P-value	Mucinous vs. Serous Odds Ratio 95% CI	Mucinous vs. Other Epithelial Odds Ratio 95% CI
Age at diagnosis*	0.0008	Nonlinear	Nonlinear
Nonlinear	0.0002		
Race/Ethnicity	0.0723		
White non-Hispanic		1.00	1.00
Black non-Hispanic		1.36 (0.73-2.54)	1.52 (0.82-2.80)
Asian non-Hispanic		1.94 (1.13-3.35)	1.17 (0.72-1.90)
Hispanic		0.77 (0.40-1.50)	0.76 (0.40-1.44)
FIGO Stage	<.0001		
I		1.00	1.00
II		0.89 (0.50-1.60)	0.96 (0.57-1.63)
III		0.29 (0.18-0.47)	1.10 (0.70-1.72)
IV		0.39 (0.19-0.78)	0.68 (0.35-1.32)
Unknown		0.41 (0.21-0.83)	0.80 (0.41-1.57)
Grade	<.0001		
I		1.00	1.00
II		0.62 (0.38-1.00)	0.49 (0.31-0.77)
III/IV		0.11 (0.07-0.20)	0.10 (0.06-0.16)
Unknown		0.92 (0.55-1.55)	0.31 (0.19-0.49)
Laterality	<.0001		
Unilateral		1.00	1.00
Bilateral		0.32 (0.22-0.49)	0.80 (0.53-1.21)

Table 3. Adjusted odds ratios and 95% confidence intervals for demographic and clinical characteristics of invasive epithelial ovarian cases by subtype, New York and Northern California. *The relationship between age and histologic subtype is shown in Figures 1 and 2.CI=confidence interval

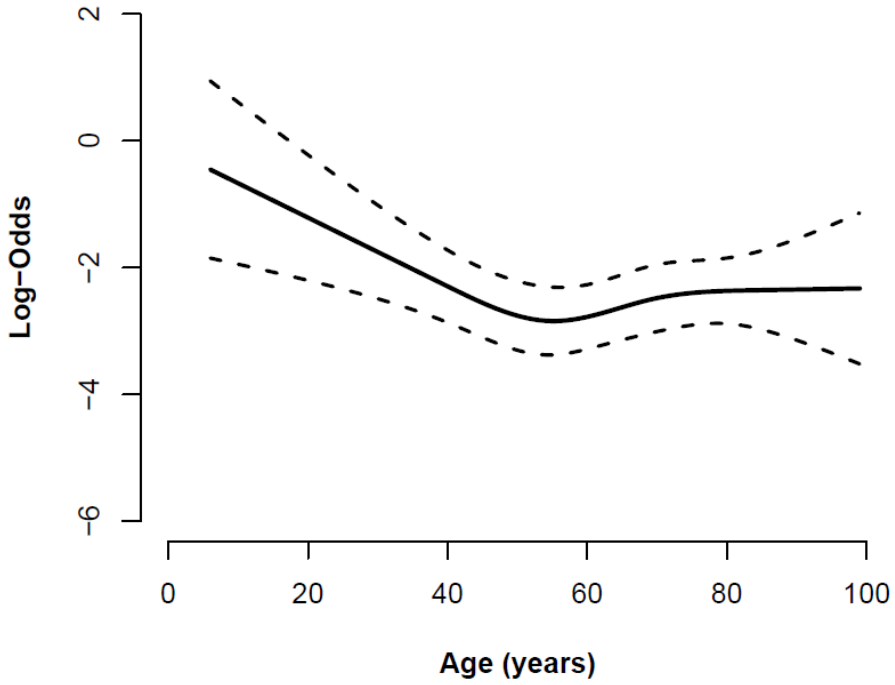

Figure 2. Adjusted relationship between age and risk of and mucinous epithelial ovarian cancer compared to other epithelial ovarian cancer. Solid line indicates log-odds ratio, dotted lines indicated confidence intervals.

3.2. Survival following a mucinous ovarian cancer diagnosis

Unadjusted Kaplan-Meier estimates showed that survival following an epithelial ovarian cancer diagnosis was initially worse for mEOC and other EOC compared to serous EOC (Figure 3). At approximately 38-40 months post-diagnosis, mEOC and other EOC tumor survival rates stabilized, whereas survival from serous EOC continually decreased. At the end of the 6 year follow-up period, survival was significantly different among the epithelial subtypes (log rank $p<0.001$). Unadjusted survival was 49.8% among women with mEOC, 39.0% among women with other EOC, and 30.8% among women serous EOC.

The results of the multivariable Cox model predicting 6-year survival are shown in Table 4 and Figure 4. After adjustment, black race, advanced stage, higher grade, and the presence of comorbidities were all associated with increased mortality from EOC (Table 4), as was increasing age (especially age > 60, Figure 4). By epithelial subtype, mEOC conferred a worse prognosis and was associated with increased mortality compared to both serous EOC (Hazard ratio [HR] 0.51, 95% CI 0.40-0.65), and other EOC (HR 0.56, 95% CI 0.44-0.72). Significant interactions were found between epithelial subtype and both surgery ($p=0.0064$) and chemotherapy ($p=0.0340$). In all cases, mEOC was associated with increased mortality. Significant

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associations occurred among those who received both surgery and chemotherapy; women with serous EOC and other EOC had better survival than those with mEOC in this group (serous HR 0.45, 05% CI 0.33-0.62; other EOC HR 0.44, 95% CI 0.32-0.61). This was also the case for women who were treated with chemotherapy alone (serous EOC HR 0.16, 95% CI 0.07-0.38; other EOC HR 0.40, 95% CI 0.20-0.81). In women who received only surgery or did not receive treatment, those with serous EOC had better survival than those with mEOC (HR 0.65, 95% CI 0.42-1.00, HR 0.23, 95% CI 0.10-0.53, respectively).

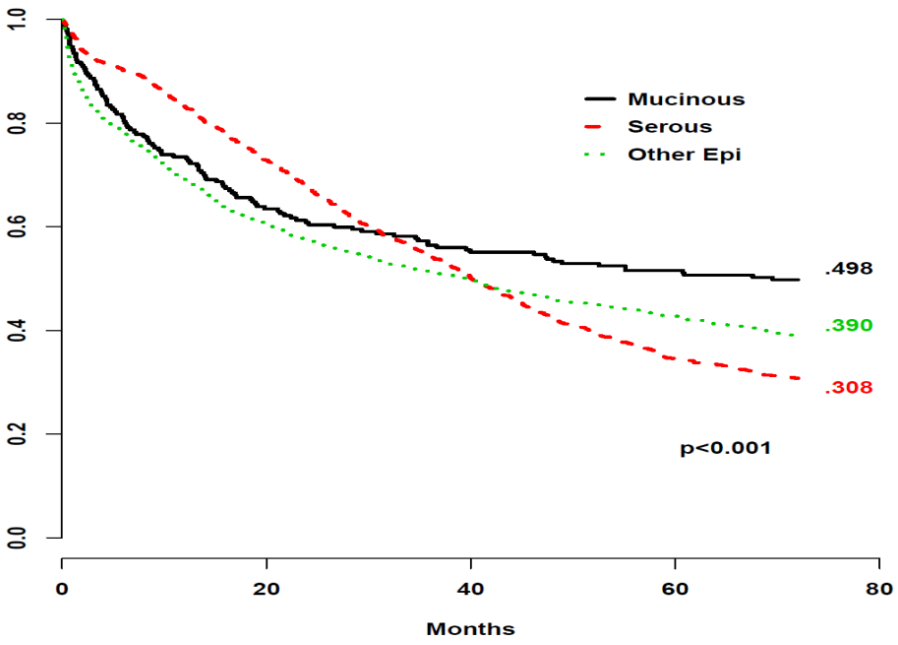

Figure 3. Six-year survival following an invasive epithelial ovarian cancer diagnosis by subtype, New York and Northern California

Characteristic	Wald χ^2	DF*	P-value	Hazard Ratio (95% CI)
Age at diagnosis*	99.68	2	<0.0001	
Nonlinear	10.75	1	0.0010	
Race/Ethnicity	26.63	3	<0.0001	
White non-Hispanic				1.00
Black non-Hispanic				1.47 (1.17-1.86)

Characteristic	**Wald χ^2**	**DF***	**P-value**	Hazard Ratio (95% CI)
Asian non-Hispanic				0.62 (0.45-0.84)
Hispanic				0.76 (0.59-0.98)
FIGO Stage	239.24	4	<0.0001	
I				1.00
II				1.40 (0.96- 2.04)
III				4.96 (3.77- 6.51)
IV				8.02 (5.93-10.84)
Unknown				5.36 (3.93- 7.31)
Grade	12.83	3	0.0050	
I				1.00
II				1.36 (1.01-1.84)
III/IV				1.50 (1.13-2.00)
Unknown				1.69 (1.25-2.29)
Laterality	38.41	2	<0.0001	
0 – 2 years				
Bilateral vs. Unilateral				1.04 (0.87-1.23)
"/>2 years – 6 years				
Bilateral vs. Unilateral				1.86 (1.53-2.27)
Comorbidity	20.04	2	<0.0001	
0				1.00
1				1.26 (1.08-1.48)
2 or more				1.59 (1.26-2.01)
Epithelial subtype**	48.68	6	<0.0001	
Mucinous				1.0
Serous				0.51 (0.40-0.65)
Other Epithelial				0.56 (0.44-0.72)
Surgery+Chemotherapy				

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Characteristic	Wald χ^2	DF*	P-value	Hazard Ratio (95% CI)
Mucinous				1.0
Serous				0.45 (0.33-0.62)
Other Epithelial				0.44 (0.32-0.61)
Surgery/No chemotherapy				
Mucinous				1.0
Serous				0.65 (0.42-1.00)
Other Epithelial				0.83 (0.55-1.26)
Chemotherapy/No Surgery				
Mucinous				1.0
Serous				0.16 (0.07-0.38)
Other Epithelial				0.40 (0.20-0.81)
No Surgery/ No Chemotherapy				
Mucinous				1.0
Serous				0.23 (0.10-0.53)
Other Epithelial				0.75 (0.38-1.49)
Surgery (Yes vs. No)	34.93	3	<0.0001	
Mucinous				0.38 (0.20-0.75)
Serous				1.06 (0.63-1.79)
Other Epithelial				0.42 (0.31-0.58)
Chemotherapy (Yes vs. No) 11.05 3 0.0115				
Mucinous				1.25 (0.79-1.97)
Serous				0.88 (0.68-1.14)
Other Epithelial				0.67 (0.51-0.87)

Table 4. Multivariate proportional hazards results of invasive epithelial ovarian cancer cases, New York and Northern California. *The relationship between age and risk of death is shown in Figure 4. **The overall epithelial subtype comparisons are from a model excluding the subtype and treatment interactions. These are presented to show the "average" effect across treatments. All other hazard ratios in the model are calculated from the model including the interactions.

4. Discussion

This large, population-based study adds further, definitive evidence for demographic and clinical characteristics previously associated with mEOC: Asian race, early stage, low grade, and unilateral ovarian involvement at diagnosis [9,16,28]. Regardless of the large proportion of stage I diagnoses (about 45%), mEOC appears to be a particularly deadly subtype of ovarian cancer. These patterns seen in mEOC are consistent with clear cell EOC, which also tends to be diagnosed at early stages [29], and has poor overall survival compared to other EOCs [29,30]. Patterns of other epithelial subtypes vary: endometrioid EOC is often diagnosed at early stages, but generally has better overall survival compared to other EOCs [31]; serous EOC is most often diagnosed at late stages (stage III and IV), and survival from these tumors appears to be significantly associated with grade [32]. These divergent patterns suggest that EOC is an extremely heterogeneous group, and histologic subtype should be considered in addition to stage before and during treatment.

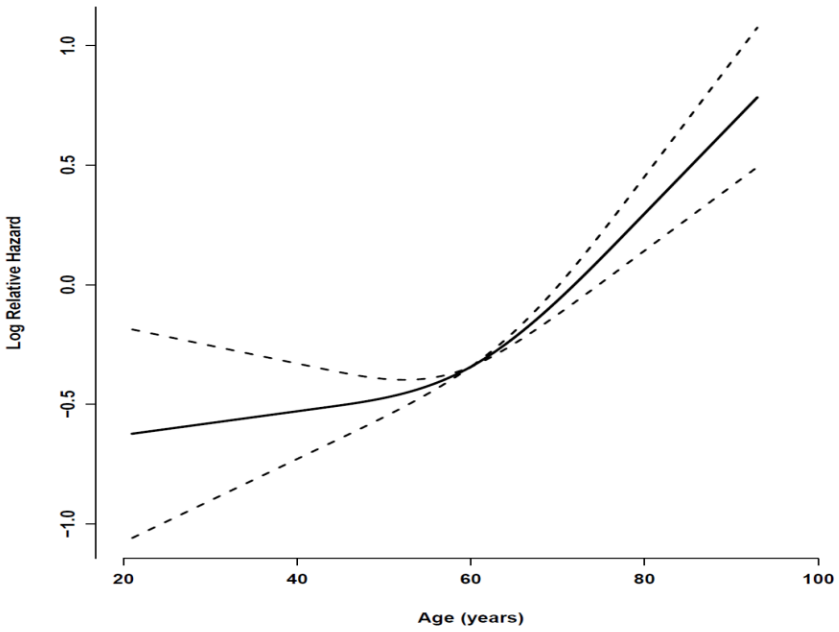

Figure 4. Adjusted relationship between age and risk of death within six years following an epithelial ovarian cancer diagnosis. Solid line indicates log-hazard ratio, dotted lines indicate 95% confidence intervals.

The poor survival from mEOC shown here is consistent with other studies [14,16,33] and may be due to a decreased response to chemotherapy. Our study results are consis-

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tent with these findings, in that chemotherapy did not appear to have a beneficial effect in women with mEOC. Evidence suggests that mEOC response rates to platinum-based chemotherapy are low overall (13-26%) [14,34]. This decreased response could be related to a lack of sensitivity of mEOCs to standard platinum-containing chemotherapy regimens [17]. It is well-established that platinum sensitivity varies by pathologic and clinical characteristics including tumor type [34,35]. Relatively recently, some groups in the United States have suggested that different treatment strategies should be considered for mEOC, and that future clinical trials should be redesigned to 1) exclude women with mEOC and other rare EOC types [36], and 2) assist with the development of novel agents more targeted to mEOC that can be used in the front-line and recurrent settings [17, 37]. Several barriers exist to such clinical trials, including decreased availability of funding [38], as well as potential lack of enrollment and participation due to the rarity and deadly nature of mEOC. Despite these limitations however, a phase III clinical trial comparing standard carboplatin and paclitaxel regimen (with and without bevacizumab) to oxalitlatin and capecitabine (with and without bevacizumab) in women with stages II-IV or recurrent untreated stage I primary mEOC was recently announced [39].

Some groups have suggested additional chemotherapeutic agents that may be more effective in the treatment of mEOC. Based on studies with mEOC cell lines, combination chemotherapy consisting of oxaliplatin and 5-fluorouracil may be beneficial for mEOCs [40]. The suggested use of fluorouracil, a chemotherapy agent used in the treatment of colon cancer [41], has gained additional support because of the similarities between mEOC and mucinous tumors of the colon [16,42]. A recent review comparing characteristics of these two tumor types concluded that there are multiple similarities with respect to mutational patterns, clinical presentation, therapy response, and outcomes [43]. The review further proposes that the search for new and more effective chemotherapeutic agents for mucinous tumors might be more successful if comparisons are made across organs [43]. However, there are clear differences in the cellular localization of mucin in these two types, and further research is needed to substantiate the usefulness of this approach.

Regardless of the availability of and evidence for alternative treatment regimens, the results presented here underscore the need for precise pathologic assessment of all EOCs with respect to site of tumor origin, histologic type and subtype, behavior and grade. The vast majority of histologic-specific analyses using medical record data (including this one) are limited by the fact that there is no central pathology review of included cases. Because of this, a few studies have retrospectively reviewed stored specimens and medical records to examine concordance of pathologic characteristics of ovarian cancer. In a population-based study using Surveillance Epidemiology and End Results (SEER) data, there was 98% concordance on site of origin, and 97% concordance on overall epithelial histologic type [44]. Concordance varied by histologic subtype; it was 100% for clear cell EOC, 87% for mEOC, 80% for serous EOC, and 73% for endometrioid EOC. For tumor behavior, there was 85% concordance for invasive ovarian tumors. In most cases (90%), tumors originally diagnosed as invasive were thought to be low malignant potential upon review. Another study examining pathology in the Gilda Radner Familial Ovarian Cancer Tumor Registry reported

95.3% concordance on primary site [45]. The agreement by histologic subtype was lower, with disagreement on 38.3% of cases. The vast majority of differences were related to differences in classification of serous EOC, either by the initial or reviewing pathologist. Concordance by grade was slightly better than that by histologic subtype, with disagreement on 31.2% of cases. The majority of differences centered on the differential assignment of grade II versus grade III. Few cases (a total of 7.6%) were upgraded or downgraded in a way that would have potential implications for treatment. While these pathologic review findings are encouraging overall and provide support for analyses of mEOC such as this one, they may not be exact enough to support the prescription of alternative treatment regimens based solely on histologic subtype.

5. Conclusions

The results presented here provide definitive evidence that mEOC is associated with different demographic and clinical characteristics than other EOC subtypes, and women diagnosed with mEOC have worse adjusted survival compared to those with other EOC subtypes. A particular strength of this study is the population-based approach, which reflects the experience of two U.S. populations of women with ovarian cancer, as opposed to that of a single institution or those participating in clinical research. This study yields several implications for future research. First and foremost, the continued characterization of the heterogeneity of ovarian cancer through basic, clinical, and population research is necessary. Second, the need for precision in pathologic assessments is paramount, and pathologists, oncologists and scientists all have a role in assisting with this through research and education. Finally, assessment of provider knowledge and awareness regarding treatment recommendations, and proposed or enacted changes to these recommendations, would be beneficial for ensuring appropriate use of evidence-based practices in the treatment of ovarian cancer.

Acknowledgments

This work was supported by cooperative agreements (U58/CCU920352 and U58/CCU220322) with the Centers of Disease Control and Prevention. The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract N01-PC-35136 awarded to the Northern California Cancer Center and contract N01-PC-45025 awarded to the Public Health Institute; the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement #U58/DP00080 awarded to the Public Health Institute, and agreement #U58/DP000783 awarded to the New York State Department of Health; and the New York State Department of Health as part of the statewide cancer reporting mandate specified in New York State Public Health Law Section 2401. The findings and conclusions in this report are

those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, the State of California Department of Public Health, and the New York State Department of Health.

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