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Predictors of survival trajectories among women with epithelial ovarian cancer

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Abstract

Objective.—Although ovarian cancer is a deadly disease, approximately a third of women survive ≥9 years after diagnosis. The factors associated with achieving long-term survival are not well understood. In this study, data from the Surveillance, Epidemiology, and End Results (SEER) program were used to determine predictors of survival trajectories among women with epithelial ovarian cancer and across histotype (high-grade serous carcinoma (HGSC) and non-HGSC).

Methods.—Data on 35,868 women diagnosed with epithelial ovarian cancer in 2004–2016 were extracted from SEER. Extended Cox proportional hazards regression was used to estimate overall

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Author contributions

Drs. Peres and Tworoger developed the original concept and study design. Dr. Peres completed all data analyses. Drs. Peres and Ms. Sinha generated the initial draft of the manuscript. All authors contributed to the interpretation of the findings, critically reviewed and edited the manuscript, and approved the final manuscript version.

Declaration of competing interest

Dr. Sood has received research funding from M-Trap, has consulted for Merck and Kiyatec, and is a shareholder in BioPath. All other co-authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

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and histotype-specific associations between patient and tumor characteristics and all-cause mortality within each survival time (t) interval ($t < 3$, $3 \leq t < 6$, $6 \leq t < 9$, and $9 \leq t < 13$ years).

Results.—Age at diagnosis, marital status, race/ethnicity, stage, and surgery were more strongly associated with mortality in the short-term survival period, and these associations waned with increasing survival time. Exceptions to this pattern were age >70 years at diagnosis, where a high risk of mortality was observed in both the $t < 3$ and $t \geq 9$ year time periods, and non-Hispanic Asian/Pacific Islanders, where a more pronounced inverse association with mortality was observed in $t \geq 9$ years after diagnosis. Similar associations were observed for HGSC, although the waning effect was not apparent for most characteristics. Mortality associations for non-HGSC were more pronounced for stage and race/ethnicity, primarily for non-Hispanic Asian/Pacific Islanders.

Conclusions.—Most patient and tumor characteristics were more strongly associated with mortality in the years following diagnosis, but have declining impact with increasing survival time. Given this waning effect, it is critical to identify factors impacting risk of mortality as ovarian cancer patients advance through the survival trajectory.

Keywords

Ovarian cancer; Long-term survivors; Mortality; Histotype

1. Introduction

Ovarian cancer is the deadliest gynecologic malignancy in the U.S., accounting for 5% of all cancer deaths among women [1]. The majority of ovarian cancer patients are diagnosed with late stage disease, which is associated with a poor prognosis and a lower 5-year survival (29%) compared to localized disease (92%) [1]. In addition, 70–90% of women with advanced stage disease recur within 18 months of diagnosis [2,3]. Together, these factors account for a five-year relative survival of only 47% [1].

Despite the overall poor survival of women with ovarian cancer, outcomes are heterogeneous, with approximately a third of women achieving long-term survival (≥9 years after diagnosis) [4]. These long-term survivors also include a proportion of women with poor clinical characteristics at diagnosis, such as late stage disease or suboptimal debulking status. The predictors of long-term survival are not well understood, and it remains unknown whether associations between patient characteristics and risk of mortality differ across the survival trajectory and whether these associations vary according to histotype. Our study objective was to use high-quality, nationally-representative cancer registry data from the Surveillance, Epidemiology, and End Results (SEER) program to examine predictors of survival throughout the disease course, and to assess whether there are differences in these associations by histotype.

2. Methods

2.1. Study population

Ovarian cancer cases were identified and extracted from the most recent submission of the National Cancer Institute's SEER program (SEER 18 registries, November 2018 data

submission) [5] based on the following criteria: incident diagnosis of ovarian cancer (International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) [6] primary site, C56.9: ovary) between 2004 and 2016, malignant behavior, microscopically confirmed, aged 20–84 years at diagnosis, and no prior cancer diagnosis. Any case identified through an autopsy or death certificate was excluded as follow-up time was unavailable.

2.2. Histotype classification

As described in Peres et al. [7], histotype was classified using a combination of the ICD-O-3 [6] morphology codes and tumor grade into one of the five major epithelial histotypes according to the 2014 World Health Organization guidelines for female reproductive tumors [8]: high-grade serous, low-grade serous, endometrioid, clear cell, and mucinous carcinoma. Approximately 22% of serous carcinomas did not have tumor grade information (n = 5446) but were classified as high-grade serous carcinoma (HGSC) as the majority of serous carcinomas are high-grade [9]. We further grouped the histotypes into two categories, HGSC and non-HGSC (low-grade serous, endometrioid, clear cell, and mucinous carcinoma), for subsequent analyses.

2.3. Vital status and follow-up information

Survival time (t) was defined as the time from diagnosis until death or last follow-up. Four survival time intervals were considered: $t < 3$, $3 \leq t < 6$, $6 \leq t < 9$, and $9 \leq t < 13$ years. The $t < 3$ year interval represents a “short-term” survival period characterized by women with rapidly fatal disease, while the $9 \leq t < 13$ year interval represents “long-term” survival as 9 years after diagnosis is the time point where mortality becomes stable and parallel to that of the general age-matched population [4]. For deceased patients, cause of death, as determined by a cancer-registry derived algorithm that assigns a single cause of death from the death certificate [10], was extracted from SEER.

2.4. Statistical analysis

The distribution of patient and tumor characteristics was compared across survival time intervals. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for the association between each patient and tumor characteristic with risk of all-cause mortality within each survival time interval using extended Cox regression models [11]. The risk of mortality for each characteristic was estimated within the survival time intervals using heaveside functions [11], which allow the hazard for each characteristic to vary by the survival time intervals. All models included the following factors assessed at diagnosis: age (<50, 50–59, 60–69, ≥70 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic of any race, non-Hispanic Asian/Pacific Islander, non-Hispanic American Indian/Alaskan Native), region of residence (Northeast: Michigan, Iowa, New Jersey, and Connecticut; Northwest: Washington and Alaska; Southeast: Georgia, Kentucky, and Louisiana; Southwest: California, Hawaii, New Mexico, and Utah), stage [12] (localized, regional, distant), marital status (married, never married, widowed, divorced/separated), surgery of primary site (yes, no), and histotype (HGSC, low-grade serous, endometrioid, clear cell, and mucinous carcinoma). To test whether there was a trend in the HRs across the survival time intervals, we used the meta-regression method with a survival time interval-specific random effects term [13]. Associations were also examined separately by histotype

(HGSC, non-HGSC). As a sensitivity analysis, we repeated the analyses for HGSC excluding any unknown grade serous carcinoma.

In addition to all-cause mortality, we repeated all analyses with ovarian cancer-specific mortality as the outcome. For these analyses, any cause of death not due to the ovarian cancer diagnosis was censored at the time of death.

An additional patient characteristic, insurance status, was not available in SEER until 2007. A separate analysis was completed among women diagnosed ≥2007 to assess the association between insurance status (insured, uninsured, Medicaid) and risk of all-cause and ovarian-cancer specific mortality using three survival time intervals ($t < 3$, $3 \leq t < 6$, $6 \leq t < 10$ years), adjusting for the covariates described above.

All analyses were completed using SAS, Version 9.4 (SAS Institute; Cary, North Carolina).

3. Results

A total of 35,868 women were included in the analyses (Table 1). The majority of women were aged ≥60 years, non-Hispanic white, married, residents of the Southwest U.S., insured, diagnosed with HGSC, had distant stage disease, and had surgery. Compared to short-term survivors ($t < 3$ years), long-term survivors ($9 \leq t < 13$ years) were more likely to be diagnosed at a younger age, non-Hispanic white, insured, diagnosed with localized or regional stage disease, diagnosed with non-HGSC, and had surgery.

3.1. Risk of all-cause mortality among women with epithelial ovarian cancer

In comparison to women aged 50–59 years at diagnosis, women aged <50 years had a lower risk of mortality in the first 6 years after diagnosis ($HR_{t<3}$ = 0.82, 95% CI = 0.76, 0.89 and $HR_{3\leq t<6}$ = 0.87, 95% CI = 0.79, 0.95; Table 2). Although women aged ≥70 years had worse survival throughout the entire time period, the greatest risks of mortality were observed for the $t < 3$ and $9 \leq t < 13$ year intervals. In the first 3 years after diagnosis, an increased risk of mortality was observed for women who were widowed (HR = 1.35, 95% CI = 1.28, 1.42), separated/divorced (HR = 1.22, 95% CI = 1.15, 1.30), or never married (HR = 1.18, 95% CI = 1.12, 1.25) compared to married women. The increased risk of mortality persisted throughout the survival time period for women who were widowed or separated/divorced, although not statistically significant for every time interval. However, for women who were never married, the risk of mortality declined over time (p-trend ≤ 0.0001). Non-Hispanic black women had a greater risk of mortality than non-Hispanic white women for the first six years after diagnosis ($HR_{t<3}$ = 1.25, 95% CI = 1.17, 1.34 and $HR_{3\leq t<6}$ = 1.18, 95% CI = 1.05, 1.33), but this association declined over time and no difference in mortality was present in the later survival time intervals (p-trend = 0.08). Non-Hispanic Asian/Pacific Islander and Hispanic women had a suggestively lower risk of mortality compared to non-Hispanic white women throughout the survival trajectory, with the lowest risk of mortality observed in the $9 \leq t < 13$ year interval for non-Hispanic Asian/Pacific Islanders (HR = 0.55, 95% CI = 0.34, 0.91; p-trend = 0.04). Across the entire survival period, women diagnosed with regional or distant versus localized stage disease had a greater risk of mortality. This positive association with mortality was the most pronounced in the first six years after

diagnosis and waned over time (p-trend$_{Regional}$ = 0.0004 and p-trend$_{Distant}$ = 0.0002). Women who did not have surgery had an increased risk of mortality right after diagnosis, but this association waned across the rest of the survival period (p-trend < 0.0001). A visual assessment of the patterns in the HRs is provided for patient characteristics in Fig. 1 and for tumor and clinical characteristics in Fig. 2.

3.2. Risk of all-cause mortality by histotype

When evaluating these associations by histotype (Table 3), we noted similar patterns to the overall findings for age at diagnosis for HGSC, but not for non-HGSC, where women ≥70 versus 50–59 years at diagnosis showed a statistically significant trend of increasing risk of mortality as the survival time interval increased (p-trend = 0.004). Likewise, the pattern for marital status among women with HGSC was similar to the results for the overall cohort; however, among women diagnosed with non-HGSC, an increased risk of mortality was observed only in widowed women and this association remained until the 9 year survival interval, where an increased risk was still present but not statistically significant. Regardless of histotype, the increased risk of mortality among non-Hispanic Black women in the time period right after diagnosis was observed, but the decreased risk of mortality for Hispanic women in the first 3 years after diagnosis was only observed in HGSC. In contrast to the overall findings, among non-Hispanic Asian/Pacific Islanders, a decreased risk of mortality was not present among women with HGSC, but was observed among women with non-HGSC ($HR_{9\leq t<13}$ = 0.28, 95% CI = 0.11, 0.70). The increased risk of mortality for regional and distant stage disease was present in both HGSC and non-HGSC; however, a waning trend in the association with higher stage was only observed for non-HGSC (p-trend ≤ 0.0001). Additionally, the association for distant stage disease during the $t < 3$ year time period was the most pronounced for non-HGSC (HR = 12.47, 95% CI = 10.79, 14.41). The associations between surgery and risk of mortality by histotype were similar to the overall findings, although for HGSC, there was a suggestive increased risk of mortality during the $9 \leq t < 13$year time interval for women who did not have surgery (HR = 2.05, 95% CI = 0.94, 4.49). The findings among women with HGSC were consistent after serous cases with unknown grade were excluded from the analyses (Supplemental Table 1).

3.3. Risk of cause-specific mortality among women with epithelial ovarian cancer and by histotype

Although we observed that most women died due to their disease (90%), the proportion of deaths due to other causes increased over time (7% for $t < 3$, 33% for $9 \leq t < 13$; Table 1). After excluding women with an unknown cause of death (n = 205), associations for ovarian cancer-specific mortality were similar to those for all-cause mortality except for age at diagnosis and stage (Supplemental Table 2). Specifically, older age at diagnosis was no longer positively associated with mortality in the long-term survival period, and the associations with stage were more pronounced. Also, unlike the pattern observed for all-cause mortality, women with distant stage disease had the highest risk of cancer-specific mortality during the $3 \leq t < 6$ year (HR = 14.54, 95% CI = 12.17, 17.36) and $6 \leq t < 9$ year (HR = 14.87, 95% CI = 10.97, 20.16) intervals. The differences in associations with age at diagnosis and stage were also apparent in analyses of ovarian cancer-specific mortality by histotype (Supplemental Table 3).

3.4. Risk of all-cause and cause-specific mortality for insurance status and by histotype

Among women with available data on insurance status (n = 27,827), women who were uninsured or on Medicaid had an increased risk of all-cause mortality in the $t < 3$ year interval compared to insured women ($HR_{Uninsured} = 1.22$, 95% CI = 1.08, 1.37 and $HR_{Medicaid} = 1.24$, 95% CI = 1.16, 1.33; Supplemental Table 4). The increased risk for women on Medicaid was also present in the $3 \leq t < 6$ year interval, but not long-term, while the risk of mortality for uninsured women declined over time (p-trend = 0.0006). These associations were fairly similar by histotype and for ovarian cancer-specific mortality (Supplemental Tables 4 and 5).

4. Discussion

Research investigating the unique factors contributing to long-term survival for a proportion of ovarian cancer patients has been hindered by the rarity of the disease and having sufficient follow-up time to identify such cases. Further, few studies have examined the associations of predictors of survival across the survivorship trajectory in ovarian cancer patients, which tends to feature a high mortality rate in the years shortly after diagnosis, but reduced mortality the longer patients survive [4]. In the present study, we leveraged nationally representative cancer registry data and observed that while tumor and clinical characteristics (e.g., stage and surgery) are strongly associated with survival throughout the entire survival trajectory, these factors are the most influential on prognosis in the time periods initially following diagnosis. Likewise, other patient characteristics, such as race/ethnicity, marital status, and age at diagnosis were also important predictors of mortality, typically within the short-term survival period.

Previous studies [14–16] characterizing long-term ovarian cancer survivors identified younger age, early stage disease, low-grade tumors, non-serous histology, no gross residual disease after cytoreductive surgery, absence of ascites, and lower CA-125 levels as predictors. Germline *BRCA1* or *BRCA2* mutations are associated with better survival overall; but, after five years of survival, *BRCA1* carriers have a higher risk of dying compared to non-carriers [17–19]. In the present study, we show that many tumor and patient characteristics are most strongly associated with mortality in the first 6 years after diagnosis, but can wane with increasing survival time, although remaining significantly associated for some variables (e.g., stage). Our findings suggest that other factors, such as lifestyle factors or medication use, could be particularly important in determining risk of mortality as women advance through the survival trajectory. An exception to this pattern was an age at diagnosis >70 years, where a high risk of mortality was noted in the first 3 years after diagnosis and then again ≥9 years after diagnosis. This may be due, in part, to the majority of these women aging to >80 years after 9 years of follow-up, with increasing mortality in that period. Similarly, non-Hispanic Asian/Pacific Islanders and to a lesser extent, Hispanic women, had a lower risk of mortality compared to non-Hispanic white women as they advanced in the survivorship continuum. Although the reasons for this are unclear, Asian/Pacific Islander women are more commonly diagnosed with non-HGSC (particularly clear cell carcinoma) [20–22], which has a better prognosis than HGSC if diagnosed at an early stage [7].

Similar patterns were generally observed by histotype, although associations of tumor and clinical characteristics did not wane significantly with increasing time since diagnosis for HGSC tumors, perhaps because of the aggressive nature of this histotype. Prior studies [23–27] focusing exclusively on long-term survivors of HGSC or advanced stage serous carcinoma noted similar patient and clinical characteristics associated with long-term survival as in overall ovarian cancer. Two studies [25,26] evaluated the molecular landscape of short- versus long-term survivors of HGSC, noting that long-term survivors had a greater somatic mutation burden, an enrichment of tumor-infiltrating lymphocytes, and distinct gene expression profiles compared to short-term survivors. Less work has focused on non-HGSC histotypes, but should be evaluated as our results suggest unique prognostic determinants and patterns of associations across the survivorship trajectory.

Many studies have shown that non-Hispanic black women with ovarian cancer have the worst survival of all racial/ethnic groups [22,28,29]. In the present study, this racial/ethnic outcome disparity was present but only within the first six years after diagnosis. One potential reason is that that there are certain factors that differentially impact short-term survival in non-Hispanic black women, such as access to care and adherence to treatment guidelines, which are notably worse among black women with ovarian cancer compared to other racial/ethnic groups [30–35]. Additional factors that may be important in short-term survival and may differ by race/ethnicity include tumor biology, comorbid conditions, or other epidemiologic characteristics. Future research should confirm our findings and leverage large-scale studies, such as the recently established Ovarian Cancer in Women of African Ancestry (OCWAA) consortium [36] that has a variety of patient characteristics usually absent in large national cancer databases or medical claims data (e.g., comorbidities, obesity), to elucidate key factors explaining this disparity.

Stage was the most important predictor of mortality across the survival trajectory. However, the magnitude of association waned over time. The association with all-cause mortality was the most pronounced in magnitude for non-HGSC during the first three years after diagnosis. This is likely reflective of distant stage mucinous and clear cell carcinoma, which have a markedly higher rate of mortality during the first two years after diagnosis [7]. We also observed more pronounced associations between stage and cause-specific mortality than for all-cause mortality, which is unsurprising given that stage will be more influential for deaths due to the ovarian cancer diagnosis versus deaths due to other causes.

Marital status was an important predictor of survival in this study, where in general, unmarried women had an increased risk of mortality compared to married women. The increased risk of mortality was more pronounced for women who were widowed or separated/divorced and persisted throughout the survival trajectory, although not statistically significant in all time intervals. Our findings are consistent with the work of others [37–39], although these studies also used data from the SEER program. Marital status likely impacts survival through social support, although other beneficial consequences of marriage, such as an increase in financial resources and assistance in attending physician visits and receipt of cancer treatment, may also contribute. The role of social support in outcomes of ovarian cancer patients has been some-what mixed [40–42], although higher levels of emotional support or social attachment have been linked to better survival [41]. Additionally, studies

have shown that in ovarian cancer patients, social support was associated with key biological pathways that have implications for outcomes, including the circulating and intratumoral immune response [43,44] as well as the stress response through an increase in tumor norepinephrine levels [45,46].

As cancer patients age, the likelihood of being diagnosed with other chronic diseases (e.g., cardiometabolic conditions) increases, and consequently, it is more likely that the patient will have a competing risk event [47], which in this case, is a death due to causes unrelated to their cancer diagnosis. This is evident in our findings as we observed an increased risk of all-cause mortality for an older age at diagnosis throughout the entire survival trajectory, but for cancer-specific mortality, the increased risk for women of older ages was concentrated in the short-term survival period. We also noted that the percentage of deaths due to other causes shifted from 7% to 33% across the survival period.

Data from the SEER program provides a unique opportunity to study a rare disease given the large, nationally-representative sample of cancer patients, extensive follow-up information, and availability of detailed histomorphologic data. Despite the notable strengths of SEER, there are also limitations to these data. Non-HGSC histotypes could not be examined separately given their rarity and the small number of deaths occurring during the long-term survival period. SEER provides data on patient characteristics at baseline, but some of these characteristics have the potential to change over time (marital status, insurance status, and region of residence). For these characteristics, the baseline measurement is more likely to accurately reflect the characteristics of the patient right after diagnosis than in the long-term survival period. Data on treatment (e.g., chemotherapy, residual disease after cytoreductive surgery) and other potential important prognostic characteristics (e.g., comorbidities, quality of life) were not available in SEER. Large consortia that have pooled and harmonized extensive epidemiologic data on ovarian cancer patients, such as the Ovarian Cancer Association Consortium [48] or the Ovarian Cancer Cohort Consortium [49], will be particularly useful in investigating a wide array of characteristics associated with short versus long-term survival.

The present study identified a variety of characteristics that are associated with risk of mortality during different survival time intervals, and suggest that tumor characteristics, while important throughout the survival trajectory, are more predictive of short-term survival. Given this waning effect of tumor characteristics on mortality, it is critical to work toward identifying other modifiable or treatable factors that can be targeted to reduce mortality and improve survival. Our work is particularly useful for generating hypotheses and can be a primer for future research dedicated to filling in the gaps in our understanding of long-term survivors, such as examining differences in tumor biology, biobehavioral factors, epidemiologic characteristics, and both pre- and post-diagnostic exposures, as well as changes in these exposures across the survival trajectory, in short versus long-term survivors. A more comprehensive examination of long- and short-term survivors of ovarian cancer holds the greatest promise to improve outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Though an important predictor of survival overall, stage had a declining impact on mortality with increasing survival time.
- Increased risk of mortality for non-Hispanic black women was restricted to the first six years after diagnosis.
- Only stage, non-Hispanic Asian/Pacific Islander race, and an age of >70 years were associated with long-term survival.

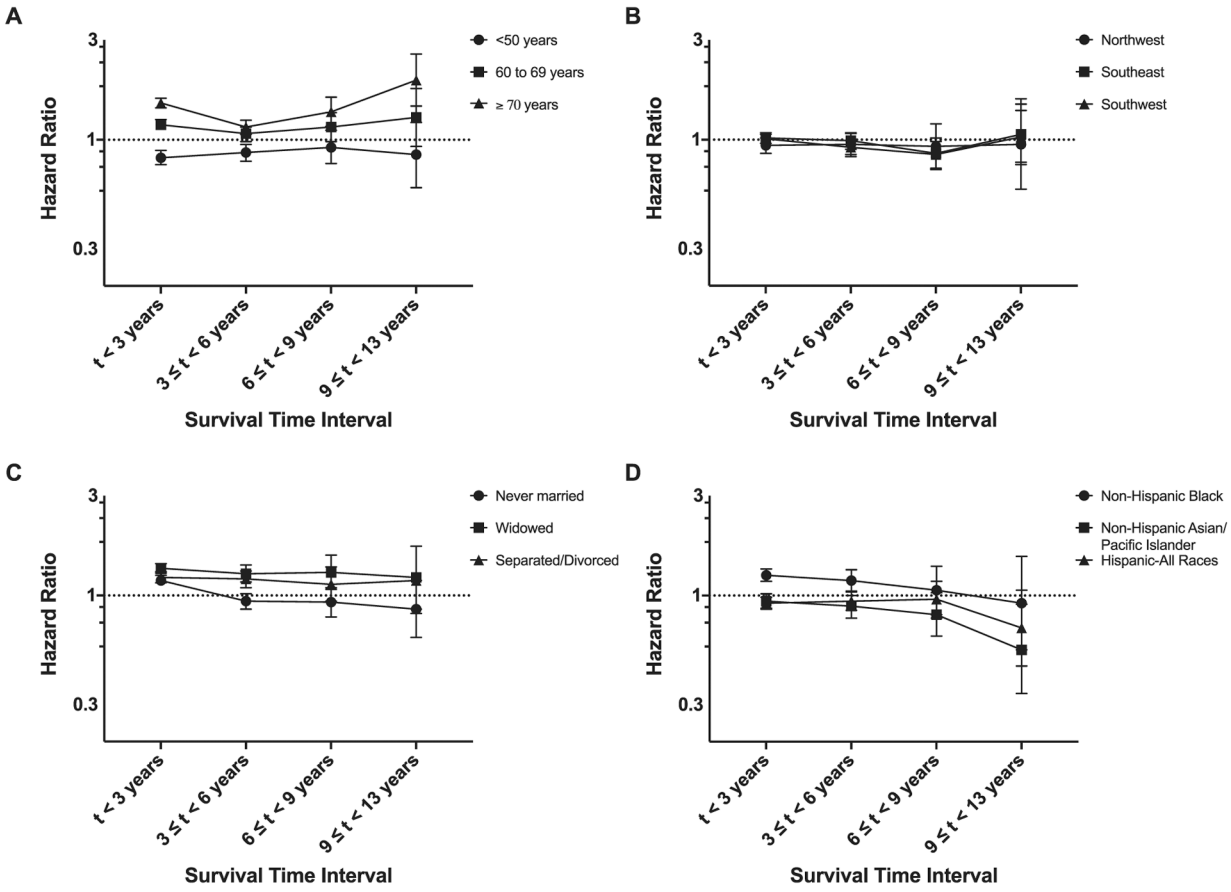

Fig. 1.

Estimated HRs and 95% CIs for the association between patient characteristics and risk of all-cause mortality by survival time interval among women diagnosed with invasive epithelial ovarian cancer, 2004–2016, SEER 18 Registries (N = 35,868). Panel A provides the association with age at diagnosis (referent is women aged 50 to 59 years), Panel B provides the association with region of residence (referent is women residing in the Northeast region of the U.S.), Panel C provides the association with marital status (referent is women who were married at the time of diagnosis), and Panel D provides the association with race/ethnicity (referent is Non-Hispanic White women). Models are adjusted for age at diagnosis, region of residence, marital status, race/ethnicity, stage, surgery, and histotype.

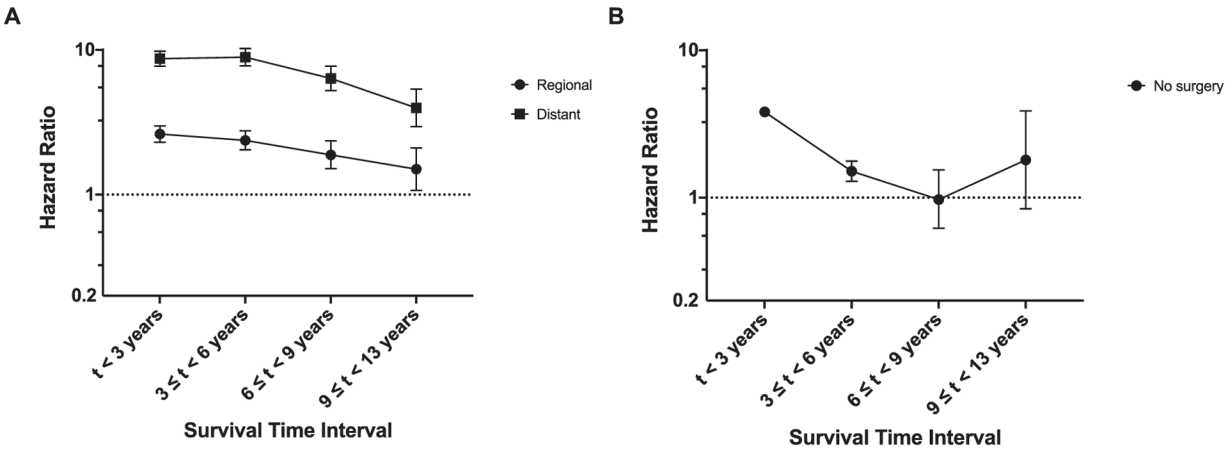

Fig. 2.

Estimated HRs and 95% CIs for the association between tumor and clinical characteristics and risk of all-cause mortality by survival time interval among women diagnosed with invasive epithelial ovarian cancer, 2004–2016, SEER 18 Registries (N = 35,868). Panel A provides the association with stage (referent is localized stage) and Panel B provides the association with surgery of primary site (referent is women who had surgery). Models are adjusted for age at diagnosis, region of residence, marital status, race/ethnicity, stage, surgery, and histotype.

Table 1

Characteristics of patients diagnosed with epithelial ovarian cancer overall and by categories of survival time, 2004–2016, SEER 18 Registries (N = 35,868).

Patient characteristics	**Total**	**Survival time**			
		***t* < 3 years**	**3 ≤ *t* < 6 years**	**6 ≤ *t* < 9 years**	**9 ≤ *t* < 13 years**
		(N = 18,667)	**(N = 9121)**	**(N = 4515)**	**(N = 3565)**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Age at diagnosis					
<50 years	5577 (16)	2252 (12)	1567 (17)	934 (21)	824 (23)
50–59 years	9956 (28)	4657 (25)	2746 (30)	1370 (30)	1182 (33)
60–69 years	9678 (27)	5316 (28)	2488 (27)	1127 (25)	747 (21)
≥70 years	10,657 (30)	6441 (35)	2320 (25)	1084 (24)	812 (23)
Region of residence at diagnosis[a]					
Northeast	8767 (24)	4449 (24)	2313 (25)	1139 (25)	866 (24)
Northwest	2373 (7)	1209 (6)	631 (7)	307 (7)	226 (6)
Southeast	7081 (20)	3829 (21)	1759 (19)	834 (18)	659 (18)
Southwest	17,647 (49)	9180 (49)	4418 (48)	2235 (50)	1814 (51)
Race/ethnicity					
Non-Hispanic White	25,430 (71)	12,921 (69)	6567 (72)	3275 (73)	2667 (75)
Non-Hispanic Black	2542 (7)	1581 (8)	565 (6)	231 (5)	165 (5)
Non-Hispanic Asian/Pacific Islander	3190 (9)	1612 (8)	800 (9)	433 (10)	345 (10)
Non-Hispanic American Indian/Alaskan Native	229 (1)	122 (1)	54 (1)	28 (1)	25 (1)
Hispanic - all races	4477 (12)	2431 (13)	1135 (12)	548 (12)	363 (10)
Stage					
Localized	5764 (16)	1936 (10)	1400 (15)	1174 (26)	1254 (35)
Regional	7802 (22)	3088 (17)	2114 (23)	1395 (31)	1205 (34)
Distant	22,302 (62)	13,643 (73)	5607 (61)	1946 (43)	1106 (31)
Histotype					
High-grade serous	24,004 (67)	13,683 (73)	6281 (69)	2495 (55)	1545 (43)
Low-grade serous	768 (2)	245 (1)	230 (3)	160 (4)	133 (4)
Endometrioid	5015 (14)	1779 (10)	1294 (14)	982 (22)	960 (27)

Patient characteristics	Total	Survival time			
		t < 3 years (N = 18,667)	3 ≤ *t* < 6 years (N = 9121)	6 ≤ *t* < 9 years (N = 4515)	9 ≤ *t* < 13 years (N = 3565)
	n (%)	n (%)	n (%)	n (%)	n (%)
Clear cell	3098 (9)	1506 (8)	713 (8)	428 (9)	451 (13)
Mutinous	2983 (8)	1454 (8)	603 (7)	450 (10)	476 (13)
Marital status at diagnosis					
Married	19,950 (56)	9765 (52)	5332 (58)	2700 (60)	2153 (60)
Never married	7129 (20)	3738 (20)	1727 (19)	917 (20)	747 (21)
Widowed	4448 (12)	2776 (15)	963 (11)	417 (9)	292 (8)
Separated/divorced	4341 (12)	2388 (13)	1099 (12)	481 (11)	373 (11)
Surgery of primary site					
No	2945 (8)	2631 (14)	222 (2)	61 (1)	31 (1)
Yes	32,923 (92)	16,036 (86)	8899 (98)	4454 (99)	3534 (99)
Insurance status at diagnosis[b]					
Insured	23,427 (83)	12,850 (82)	6504 (85)	3351 (87)	722 (87)
Uninsured	1040 (4)	535 (3)	317 (4)	153 (4)	35 (4)
Medicaid	3360 (12)	2183 (14)	799 (10)	314 (8)	64 (8)
Unknown	279 (1)	170 (1)	65 (1)	35 (1)	9 (1)
Cause of death[c]					
Death due to ovarian cancer	14,906 (90)	9928 (92)	3887 (89)	884 (78)	207 (65)
Death due to other causes	1524 (9)	778 (7)	414 (10)	226 (20)	106 (33)
Unknown	205 (1)	120 (1)	58 (1)	22 (2)	5 (2)

SEER: Surveillance, Epidemiology, and End Results.

[a]Northeast includes Michigan, Iowa, New Jersey, and Connecticut; Northwest includes Washington and Alaska; Southeast includes Georgia, Kentucky, and Louisiana; Southwest includes California, Hawaii, New Mexico, and Utah.

[b]Insurance status was available for cases diagnosed in 2007 and later. Statistics provided for cases diagnosed in 2007 and later (n = 28,106).

[c]Restricted to women who died during the follow-up period (n = 16,635).

Table 2

Estimated HRs and 95% CIs for the association between each patient characteristic and risk of all-cause mortality by survival time interval among women diagnosed with invasive epithelial ovarian cancer, 2004–2016, SEER 18 Registries (N = 35,868).

		Survival time							p-Trend
		$t < 3$ years		$3 \le t < 6$ years		$6 \le t < 9$ years		$9 \le t < 13$ years	
Patient characteristics	**Cases**	**Deaths**	**HR (95% CI)**	**Deaths**	**HR (95% CI)**	**Deaths**	**HR (95% CI)**	**Deaths**	**HR (95% CI)**	
Age at diagnosis										
<50 years	5577	1009	0.82 (0.76, 0.89)	647	0.87 (0.79,0.95)	186	0.92 (0.77, 1.11)	47	0.85 (0.59,1.21)	0.27
50 to 59 years	9956	2426	1.00 (Referent)	1253	1.00 (Referent)	317	1.00 (Referent)	84	1.00 (Referent)	
60 to 69 years	9678	3080	1.18 (1.12,1.25)	1246	1.07 (0.98,1.15)	301	1.15 (0.98,1.35)	73	1.28 (0.93,1.76)	0.35
≥70 years	10,657	4311	1.50 (1.42,1.58)	1213	1.15 (1.06,1.24)	328	1.36 (1.16,1.60)	114	1.93 (1.45,2.57)	0.41
Region of residence[a]										
Northeast	8767	2656	1.00 (Referent)	1123	1.00 (Referent)	295	1.00 (Referent)	72	1.00 (Referent)	
Northwest	2373	706	0.94 (0.86,1.02)	304	0.95 (0.83,1.07)	81	0.93 (0.73, 1.19)	20	0.95 (0.58,1.57)	0.98
Southeast	7081	2336	1.02 (0.97,1.08)	884	0.99 (0.90,1.08)	210	0.86 (0.72,1.02)	68	1.06 (0.76,1.48)	0.18
Southwest	17,647	5128	1.01 (0.96,1.06)	2048	0.92 (0.85, 0.99)	546	0.85 (0.73, 0.98)	158	1.03 (0.78,1.38)	0.03
Marital status										
Married	19,950	5347	1.00 (Referent)	2536	1.00 (Referent)	672	1.00 (Referent)	192	1.00 (Referent)	
Never married	7129	1965	1.18 (1.12,1.25)	684	0.94 (0.86,1.02)	193	0.93 (0.79,1.09)	52	0.86 (0.63,1.18)	<0.0001
Widowed	4448	2049	1.35 (1.28,1.42)	574	1.27 (1.16,1.40)	139	1.29 (1.07, 1.56)	41	1.22 (0.86,1.72)	0.31
Separated/divorced	4341	1465	1.22 (1.15,1.30)	565	1.20 (1.09,1.31)	128	1.13 (0.94,1.37)	33	1.18 (0.82,1.72)	0.49
Race/ethnicity[b]										
Non-Hispanic White	25,430	7832	1.00 (Referent)	3272	1.00 (Referent)	868	1.00 (Referent)	260	1.00 (Referent)	
Non-Hispanic Black	2542	1032	1.25 (1.17,1.34)	303	1.18 (1.05,1.33)	61	1.06 (0.81,1.38)	16	0.92 (0.55,1.54)	0.08
Non-Hispanic Asian/Pacific Islander	3190	728	0.94 (0.87,1.02)	295	0.89 (0.78,1.00)	78	0.81 (0.64,1.03)	17	0.55 (0.34,0.91)	0.04
Hispanic - all races	4477	1163	0.92 (0.86, 0.98)	459	0.94 (0.85,1.04)	118	0.96 (0.78, 1.17)	25	0.70 (0.46,1.06)	0.85
Stage at diagnosis										
Localized	5764	301	1.00 (Referent)	231	1.00 (Referent)	122	1.00 (Referent)	59	1.00 (Referent)	
Regional	7802	1007	2.62 (2.30, 2.98)	599	2.37 (2.04,2.76)	218	1.88 (1.51,2.35)	79	1.50 (1.07,2.10)	0.0004
Distant	22,302	9518	8.70 (7.72,9,80)	3529	8.90 (7.76,10.22)	792	6.36 (5.24, 7.72)	180	3.97 (2.95, 5.36)	0.0002
Surgery of primary site										

		Survival time								p-Trend
		t < 3 years		3 ≤ *t* < 6 years		6 ≤ *t* < 9 years		9 ≤ *t* < 13 years		
Patient characteristics	**Cases**	**Deaths**	**HR (95% CI)**	**Deaths**	**HR (95% CI)**	**Deaths**	**HR (95% CI)**	**Deaths**	**HR (95% CI)**	
No	2945	2224	3.82 (3.64,4.01)	160	1.51 (1.29,1.77)	19	0.97 (0.62, 1.54)	7	1.80 (0.84,3.88)	<0.0001
Yes	32,923	8602	1.00 (Referent)	4199	1.00 (Referent)	1113	1.00 (Referent)	311	1.00 (Referent)	

SEER: Surveillance, Epidemiology, and End Results; HR: hazard ratio; CI: confidence interval.

Adjusted for age at diagnosis, region of residence, race/ethnicity, primary surgery, stage, and histotype.

[a]Northeast includes Michigan, Iowa, New Jersey, and Connecticut; Northwest includes Washington and Alaska; Southeast includes Georgia, Kentucky, and Louisiana; Southwest includes California, Hawaii, New Mexico, and Utah.

[b]HRs for American Indian/Alaskan Native not shown due to low numbers of cases and unstable estimates.

Table 3

Estimated HRs and 95% CIs for the association between each patient characteristic and risk of all-cause mortality by survival time interval and by histotype (HGSC and non-HGSC), 2004–2016, SEER 18 Registries (N = 35,868).

		Survival time								p-Trend
		t < 3 years		3 ≤ *t* < 6 years		6 ≤ *t* < 9 years		9 ≤ *t* < 13 years		
Patient characteristics	**Cases**	**Deaths**	**HR (95% CI)**	**Deaths**	**HR (95% CI)**	**Deaths**	**HR (95%CI)**	**Deaths**	**HR (95%CI)**	
HGSC										
Age at diagnosis										
<50 years	2950	657	0.79 (0.72,0.86)	513	0.90 (0.81,1.00)	136	0.97 (0.78,1.19)	31	0.98 (0.63,1.52)	0.02
50 to 59 years	6195	1803	1.00 (Referent)	1038	1.00 (Referent)	243	1.00 (Referent)	54	1.00 (Referent)	
60 to 69 years	7193	2595	1.24 (1.17,1.32)	1073	1.02 (0.94,1.11)	244	1.07 (0.89,1.28)	47	1.06 (0.72,1.58)	0.01
≥70 years	7666	3614	1.59 (1.50,1.69)	989	1.09 (1.00,1.20)	227	1.20 (1.00,1.45)	74	1.77 (1.23,2.54)	0.99
Region of residence[a]										
Northeast	5918	2166	1.00 (Referent)	934	1.00 (Referent)	207	1.00 (Referent)	44	1.00 (Referent)	
Northwest	1692	597	0.93 (0.85,1.02)	270	0.94 (0.82,1.07)	71	1.05 (0.80,1.37)	17	1.13 (0.64,2.00)	0.40
Southeast	4905	1891	1.00 (0.94,1.06)	728	0.96 (0.87,1.06)	163	0.92 (0.75,1.13)	46	1.14 (0.75,1.74)	0.66
Southwest	11,489	4015	0.98 (0.93,1.03)	1681	0.91 (0.83, 0.98)	409	0.89 (0.75,1.06)	99	0.93 (0.65,1.35)	0.13
Marital status										
Married	13,501	4307	1.00 (Referent)	2151	1.00 (Referent)	517	1.00 (Referent)	130	1.00 (Referent)	
Never married	4052	1417	1.20 (1.13,1.27)	507	0.93 (0.85,1.03)	137	1.01 (0.84,1.23)	31	0.93 (0.63,1.39)	0.04
Widowed	3410	1749	1.35 (1.27,1.43)	472	1.24 (1.12,1.38)	94	1.15 (0.92,1.45)	27	1.12 (0.73,1.72)	0.05
Separated/divorced	3041	1196	1.25 (1.17,1.33)	483	1.25 (1.17,1.33)	102	1.25 (1.13,1.38)	18	1.09 (0.66,1.80)	0.83
Race/ethnicity[b]										
Non-Hispanic White	17,483	6438	1.00 (Referent)	2732	1.00 (Referent)	662	1.00 (Referent)	164	1.00 (Referent)	
Non-Hispanic Black	1828	806	1.21 (1.12,1.30)	249	1.13 (0.99,1.29)	45	0.93 (0.68,1.26)	11	0.91 (0.49,1.70)	0.07
Non-Hispanic Asian/Pacific Islander	1696	498	0.93 (0.85,1.02)	228	1.00 (0.87,1.14)	44	0.80 (0.59,1.10)	12	0.95 (0.52,1.74)	0.96
Hispanic - all races	2839	870	0.88 (0.81,0.94)	376	0.92 (0.82,1.03)	94	0.98 (0.79,1.23)	19	0.85 (0.52,1.39)	0.37
Stage at diagnosis										
Localized	1127	78	1.00 (Referent)	58	1.00 (Referent)	33	1.00 (Referent)	10	1.00 (Referent)	
Regional	3639	548	2.21 (1.75,2.81)	361	2.40 (1.82,3.17)	128	1.80 (1.23,2.64)	48	2.52 (1.27,4.98)	0.76
Distant	19,238	8043	6.12 (4.90, 7.66)	3194	6.98 (5.38, 9.05)	689	4.62 (3.25,6.55)	148	4.61 (2.42,8.78)	0.21

		Survival time								p-Trend
		t < 3 years		3 ≤ *t* < 6 years		6 ≤ *t* < 9 years		9 ≤ *t* < 13 years		
Patient characteristics	**Cases**	**Deaths**	**HR (95% CI)**	**Deaths**	**HR (95% CI)**	**Deaths**	**HR (95%CI)**	**Deaths**	**HR (95%CI)**	
Surgery of primary site										
No	2541	1905	3.86 (3.66,4.07)	144	1.46 (1.23,1.72)	16	0.96 (0.58,1.58)	7	2.05 (0.94,4.49)	0.07
Yes	21,463	6764	1.00 (Referent)	3469	1.00 (Referent)	834	1.00 (Referent)	199	1.00 (Referent)	
				Non-HGSC[c]						
Age at diagnosis										
<50 years	2627	352	0.84 (0.74,0.96)	134	0.84 (0.67,1.04)	50	0.90 (0.63,1.28)	16	0.69 (0.38,1.28)	0.86
50 to 59 years	3761	623	1.00 (Referent)	215	1.00 (Referent)	74	1.00 (Referent)	30	1.00 (Referent)	
60 to 69 years	2485	485	1.02 (0.90,1.15)	173	1.20 (0.98,1.48)	57	1.25 (0.88,1.78)	26	1.71 (1.00,2.92)	0.02
≥70 years	2991	697	1.27 (1.14,1.43)	224	1.39 (1.15,1.69)	101	1.90 (1.40,2.58)	40	2.12 (1.31,3.42)	0.004
Region of residence[a]										
Northeast	2849	490	1.00 (Referent)	189	1.00 (Referent)	88	1.00 (Referent)	28	1.00 (Referent)	
Northwest	681	109	1.01 (0.82,1.24)	34	0.91 (0.63,1.32)	10	0.52 (0.27,1.00)	3	0.47 (0.14,1.53)	0.04
Southeast	2176	445	1.14 (1.00,1.30)	156	1.13 (0.91,1.40)	47	0.71 (0.49,1.01)	22	0.97 (0.55,1.71)	0.08
Southwest	6158	1113	1.14 (1.02,1.27)	367	1.01 (0.84,1.21)	137	0.76 (0.57,1.01)	59	1.23 (0.78,1.95)	0.08
Marital status										
Married	6449	1040	1.00 (Referent)	385	1.00 (Referent)	155	1.00 (Referent)	62	1.00 (Referent)	
Never married	3077	548	1.07 (0.96,1.19)	177	1.07 (0.90,1.29)	56	0.82 (0.60,1.11)	21	0.84 (0.51,1.40)	0.14
Widowed	1038	300	1.32 (1.16,1.52)	102	1.50 (1.20,1.88)	45	1.78 (1.26,2.50)	14	1.41 (0.78,2.54)	0.16
Separated/divorced	1300	269	1.13 (0.98,1.29)	82	1.03 (0.81,1.31)	26	0.86 (0.57,1.30)	15	1.46 (0.83,2.58)	0.76
Race/ethnicity[b]										
Non-Hispanic White	7947	1394	1.00 (Referent)	540	1.00 (Referent)	206	1.00 (Referent)	96	1.00 (Referent)	
Non-Hispanic Black	714	226	1.45 (1.25,1.67)	54	1.38 (1.04,1.83)	16	1.32 (0.79,2.19)	5	0.94 (0.38,2.31)	0.79
Non-Hispanic Asian/Pacific Islander	1494	230	0.93 (0.80,1.07)	67	0.73 (0.56, 0.95)	34	0.97 (0.66,1.42)	5	0.28 (0.11,0.70)	0.11
Hispanic - all races	1638	293	1.04 (0.92,1.19)	83	0.96 (0.75,1.22)	24	0.83 (0.54,1.29)	6	0.45 (0.20,1.05)	0.06
Stage at diagnosis										
Localized	4637	223	1.00 (Referent)	173	1.00 (Referent)	89	1.00 (Referent)	49	1.00 (Referent)	
Regional	4163	459	2.45 (2.09, 2.88)	238	1.85 (1.52,2.25)	90	1.54 (1.15,2.06)	31	0.94 (0.60,1.49)	<0.0001
Distant	3064	1475	12.47 (10.79,14.41)	335	7.02 (5.82, 8.45)	103	5.35 (4.02,7.12)	32	3.25 (2.07, 5.09)	<0.0001

		Survival time								p-Trend
		t < 3 years		3 ≤ *t* < 6 years		6 ≤ *t* < 9 years		9 ≤ *t* < 13 years		
Patient characteristics	**Cases**	**Deaths**	**HR (95% CI)**	**Deaths**	**HR (95% CI)**	**Deaths**	**HR (95%CI)**	**Deaths**	**HR (95%CI)**	
Surgery of primary site										
No	404	319	3.78 (3.31,4.32)	16	2.13 (1.29,3.53)	3	1.25 (0.40,3.95)	0	N/A	0.005
Yes	11,460	1838	1.00 (Referent)	730	1.00 (Referent)	279	1.00 (Referent)	112	1.00 (Referent)	

SEER: Surveillance, Epidemiology, and End Results; HR: hazard ratio; CI: confidence interval; HGSC: high-grade serous carcinoma. Adjusted for age at diagnosis, region of residence, race/ethnicity, primary surgery, and stage.

N/A: HR could not be calculated because no deaths occurred during this time period.

[a]Northeast includes Michigan, Iowa, New Jersey, and Connecticut; Northwest includes Washington and Alaska; Southeast includes Georgia, Kentucky, and Louisiana; Southwest includes California, Hawaii, New Mexico, and Utah.

[b]HRs for American Indian/Alaskan Native not shown due to low numbers of cases and unstable estimates.

[c]Models additionally adjusted for histotype (endometrioid, low-grade serous, clear cell and mucinous carcinoma).