

Original Article



Cause-specific mortality rate of ovarian cancer in the presence of competing risks of death: a nationwide population-based cohort study

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ABSTRACT

Objective: This nationwide cohort study aimed to evaluate the cause-specific mortality (probability of death by ovarian cancer, probability of death by other causes) under the competing risks of death in women with ovarian cancer.

Methods: The Korea Central Cancer Registry was searched to identify women with primary ovarian cancer diagnosed between 2006 and 2016. Epithelial ovarian cancer cases were identified using the International Classification of Diseases for Oncology 3rd edition. We estimated the cause-specific mortality according to age (<65 years, ≥65 years), stage (local, regional, and distant), and histology (serous, mucinous, endometrioid, clear cell, and others) under the competing risks framework; moreover, cumulative incidences were estimated.

Results: We included 21,446 cases. Cause-specific mortality continuously increased throughout 10 year follow-up. Compared with women aged <65 years, ovarian cancer-specific mortality (5-year, 28.9% vs. 61.9%; 10-year, 39.0% vs. 68.6%, $p<0.001$) and other cause mortality (5-year, 1.7% vs. 4.8%; 10-year, 2.8% vs. 8.2%, $p<0.001$) increased in women aged ≥65 years. This trend was consistent across all the stages and histological types. There was a substantial increase in competing risks from 1.1% in women aged <65 years to 8.0% in women aged ≥65 years in patients with early-stage ($p<0.001$) non-serous ovarian cancer ($p<0.001$).

Conclusion: Older age at diagnosis is associated with increasing ovarian cancer-specific mortality and competing risks. Given the substantial effect of competing risks on elderly patients, there is a need for assessment tools to balance the beneficial and harmful effects to provide optimal treatment.

Keywords: Ovarian Cancer; Survival; Mortality; Elderly; Cause of Death

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Data statement

Data that support this study's findings can be requested from the Korea Central Cancer Registry (https://ncc.re.kr/main.ncc?uri=manage02_4) and Statistics Korea (<https://mdis.kostat.go.kr/index.do>). The data are not publicly available due to privacy or ethical restrictions.

Authors Contributions

Conceptualization: S.S.H., L.M.C., C.H.; Data curation: L.D., W.Y.J.; Formal analysis: S.S.H., L.M.C., L.D., C.H.; Investigation: L.D., W.Y.J., C.H.; Methodology: L.D., C.H.; Supervision: L.M.C., C.H.; Validation: W.Y.J., H.H.I., C.H.K.; Writing - original draft: S.S.H., L.M.C., C.H.; Writing - review & editing: L.D., W.Y.J., H.H.I., C.H.K.

Synopsis

This nationwide cohort study analyzed 21,446 women with primary ovarian cancer to evaluate survival and cause-specific competing mortality. Older age was associated with increasing both ovarian cancer-specific mortality and competing risks. Increased awareness of competing mortality is required for the optimal treatment decisions in the elderly.

INTRODUCTION

Worldwide, there are 313,959 new cases of ovarian cancer; moreover, in 2020, the estimated number of deaths was 207,252 [1]. This represents approximately 3% of all diagnosed cancer cases and makes it the eighth most prevalent cancer among women. In Korea, there were 2,898 new cases of ovarian cancer in 2018, which made it the third most common gynecological cancer and age-standardized incidence rate and mortality rate in 2018 was 7.1 and 2.4, respectively [2]. Although ovarian cancer is not common, it is considered the most fatal gynecologic cancer. Ovarian cancer symptoms are generally vague, with the initial diagnosis in most patients being in the advanced stage. This results in a worse prognosis and the need for more complex treatment. Nonetheless, over the decades, there have been improved survival rates among patients with ovarian cancer attributable to maximal cytoreductive surgery with platinum-based cytotoxic chemotherapy, which is the standard treatment for ovarian cancer. With the improved survival rate and increased number of ovarian cancer survivors, there has been increased interest in competing risks from other mortality causes as well as ovarian cancer mortality. The competing risks from other mortality causes are the probability of death due to causes other than ovarian cancer. Comorbidities, treatment-related morbidities, frailty and old age are often related to non-cancer competing mortalities in cancer patients, leading to the increased interest in competing risks from other mortality causes, particularly in the elderly.

Ovarian cancer mainly develops in older women. According to the 2019 Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review, the median age at diagnosis of ovarian cancer in the United States is 63 years [3]. Although the risk of developing ovarian cancer increases with age, there is a concomitant increase in the risk of developing other comorbidities. When evaluating cancer-specific mortality, it is important to consider that the mortality risk from causes other than the specific cancer type is generally much higher in older women than in younger women. This can be explained by competing risk, which is defined as “an event whose occurrence precludes the occurrence of the primary event of interest” [4]. Selective reporting without considering the competing mortality risk from other causes can result in biased conclusions. Moreover, information regarding the competing risk of death is particularly relevant when selecting treatment strategies for older patients with ovarian cancer to balance overtreatment and undertreatment. Given the recent emphasis on this concept, there are increasing studies on the competing risk for survival (or mortality) in patients with several types of solid cancer [5-10]. However, there have been no studies on this topic in patients with ovarian cancer [11]. Recently, a survival prediction nomogram in primary fallopian tube cancer patients using SEER database considering competing risk has been reported, but the study did not include cohort with ovarian cancer and did not report competing risk according to age [12]. Therefore, this study aimed to evaluate the cancer-specific mortality rate (probability of death by ovarian cancer) and competing risk of death (probability of death by other causes) in women with ovarian cancer stratified according to age, cancer stage, and histological type.

MATERIALS AND METHODS

1. Dataset

We obtained data from the Korea Central Cancer Registry (KCCR). The KCCR is a nationwide, population-based cancer registry that covers the entire South Korean population, collects information on approximately 98% of cancer cases in Korea, and publishes annual cancer statistics [13]. The completeness of the cancer incidence data for 2016 was estimated as 98.2% based on the method proposed by Ajiki et al. [14]. Detailed information regarding the KCCR is provided elsewhere [15,16]. Patients diagnosed with ovarian cancer from January 1, 2006, to December 31, 2016, were included and followed up until December 31, 2017. We only included cases of epithelial ovarian cancer and excluded all cases of non-epithelial ovarian cancer. Primary ovarian cancer (C56) was defined following the International Classification of Diseases for Oncology 3rd edition. Moreover, tumors of the peritoneum (C48.1) and other unspecified female genital organs (C57) were included. We excluded sex cord stromal tumors (ICD-O-3 Mcode=8590) and germ cell tumors (ICD-O-3 Mcode=9050-9055, 9060, 9070-9071, 9082, 9100). The mortality cases were registered with the cause of death following the International Classification of Diseases, 10th edition (ICD-10). KCCR data are linked to the mortality statistics provided by Statistics Korea, which collects data regarding mortality, including the cause of death, and annually reports the official cause of death statistics. For this study, we utilized available underlying cause of death information from the data.

2. Variables and statistical analyses

The KCCR provides individual patient-level data. Therefore, we extracted accurate clinicodemographic variables, including age at diagnosis, date of diagnosis, histological type, stage, date of death, and cause of death. Age at diagnosis was classified into two categories (<65 years and ≥65 years), because most studies and guidelines suggest the age of 65 as the threshold to define the geriatric patients [17,18]. Histological types were classified as serous, mucinous, endometrioid, clear, and others. Staging information was based on the SEER summary staging [19], which categorizes cancer spread from its origin (localized, regional, and distant). All-cause survival was estimated and compared using the Kaplan–Meier method and log-rank test, respectively. Relative survival, which is defined as a ratio of the observed survival rate among women with cancer to the expected survival rate among age- and sex-matched individuals in the general population, was estimated using the Ederer II method [20] and compared using the log-rank type test [21,22]. Cause-specific mortality was defined as death resulting from ovarian cancer. In the analyses, death resulting from causes other than ovarian cancer was considered as a competing risk. The cumulative incidence function (CIF) was used to estimate the cause-specific probability of death under the competing risks framework [23], with CIF comparisons being performed using Gray's test [24]. The effect of age at diagnosis on cause-specific mortality was assessed in patients with serous histology. All statistical tests were two-sided. Statistical significance was set at an alpha level of 0.05. Statistical analyses were performed using Statistics Analysis Systems 9.4 (SAS Institute Inc, Cary, NC, USA).

3. Ethics approval

The study protocol was approved by the institutional review board of the National Cancer Center (NCC2016-0041). This study used secondary de-identified data.

Table 1. Patients' characteristics of women with epithelial ovarian cancer, Korea Central Cancer Registry 2006–2016

Variables	Values
Age at diagnosis (yr)	54.1±15.5*
<65	15,946 (74.4*)
≥65	5,500 (25.7*)
Stage	
Localized	6,006 (28*)
Regional	3,723 (17.4*)
Distant	9,743 (45.4*)
Unknown	1,855 (9*)
Histology	
Serous	9,284 (43.3*)
Endometrioid	1,509 (7.0*)
Clear	1,784 (8.3*)
Mucinous	2,310 (10.8*)
Others	6,559 (30.6*)
Alive	12,999 (60.6*)
Death	8,447 (39.4*)
Ovarian cancer death	7,863 (36.7*)
Non-ovarian cancer death	227 (1.1*)
Other causes death	357 (1.7*)
Heart diseases (I20-I51)	65 (18.2 [†])
Intentional self-harm (X60-X84) [†]	52 (14.6 [†])
Cerebrovascular diseases (I60-I69) [†]	49 (13.7 [†])
Diabetes mellitus (E10-E14) [†]	15 (4.2 [†])
Diseases of liver (K70-K76)	14 (3.9 [†])
Pneumonia (J12-J18)	12 (3.4 [†])
Other non-cancer causes	191 (53.5 [†])

Values are presented as number (%) or mean±standard deviation.

*Percentage of total patients (n=21,446); [†]Percentage of other causes death (n=357).

RESULTS

1. Characteristics of the study population

This study included 21,446 women; average age was 54.1 (standard deviation=15.5). Among study population, 15,946 (74.4%) and 5,500 (25.7%) were aged <65 years and ≥65 years at diagnosis, respectively. **Table 1** shows the baseline characteristics. Serous histology (43.3%) was the most common cancer type, followed by mucinous (10.8%), clear cell (8.3%), and endometrioid (7.0%). Distant disease (45.4%) was the most common finding at diagnosis. Patient characteristics for the age groups subdivided more precisely (≤34, 35–49, 50–64, 65–79, ≥80) were provided in **Table S1**.

2. All-cause survival, cause-specific competing risks mortality according to age group and stage

All-cause survival decreased from 60.2% at 5 years after diagnosis to 49.3% at 10 years after diagnosis (**Fig. 1A**). The 5-year all-cause survival was significantly lower in women aged ≥65 years (33.4%) than in women aged <65 years (69.4%) ($p<0.001$, log-rank test) (**Fig. 1B**). **Table 2** shows the 5-year and 10-year all-cause survival and cause-specific mortality according to age, stage, and histology. The cause-specific mortality rate continued to increase at 10 follow-up years. Specifically, the 5-year cause-specific mortality was lower in women aged <65 years (28.9%) than in women aged ≥65 years (61.9%) ($p<0.001$). Moreover, the 10-year ovarian cancer mortality was lower in women aged <65 years (39.0%) than in women aged ≥65 years (68.6%) ($p<0.001$). Further, the 5-year and 10-year other-cause competing mortality risks were lower in women aged <65 years (1.7% and 2.8%, respectively) than in women aged ≥65 years (4.8% and 8.2%, respectively; $p<0.001$) (**Fig. 2**).

Cause-specific mortality rate of ovarian cancer

Table 2. Survival and competing risks probability of death by ovarian cancer and other-causes, Korea Central Cancer Registry 2006–2016

Characteristics	All cause survival* (95% CI)			Probability of death (95% CI)					
			p-value [‡]	Ovarian cancer [†]			Other causes [†]		
	5-year	10-year		5-year	10-year	p-value [§]	5-year	10-year	p-value [§]
Total	60.2 (59.5–61.0)	49.3 (48.4–50.3)		37.3 (36.6–38.0)	46.6 (45.7–47.4)		2.4 (2.2–2.7)	4.1 (3.7–4.5)	
Age at diagnosis			<0.001			<0.001			<0.001
<65	69.4 (68.6–70.2)	58.2 (57.2–59.3)		28.9 (28.1–29.7)	39.0 (38.0–40.0)		1.7 (1.5–1.9)	2.8 (2.4–3.1)	
≥65	33.4 (32.0–34.8)	23.2 (21.6–24.8)		61.9 (60.4–63.3)	68.6 (67.1–70.2)		4.8 (4.2–5.4)	8.2 (7.1–9.3)	
Histology			<0.001			<0.001			<0.001
Serous	57.3 (56.1–58.5)	40.0 (38.4–41.5)		41.1 (39.9–42.3)	57.0 (55.4–58.5)		1.6 (1.3–1.9)	3.0 (2.5–3.7)	
Endometrioid	80.9 (78.5–83.0)	71.0 (67.6–74.1)		17.3 (15.2–19.5)	25.2 (22.2–28.3)		1.8 (1.2–2.7)	3.8 (2.6–5.4)	
Clear	75.6 (73.3–77.7)	71.2 (68.4–73.8)		23.6 (21.4–25.8)	27.0 (24.5–29.6)		0.9 (0.5–1.5)	1.8 (1.0–3.0)	
Mucinous	75.9 (74.0–77.8)	69.2 (66.7–71.5)		21.8 (20.0–23.6)	26.1 (24–28.3)		2.3 (1.7–3.1)	4.7 (3.5–6.1)	
Stage			<0.001			<0.001			<0.001
Localized	88.2 (87.3–89.1)	82.5 (81.2–83.8)		9.8 (9.0–10.6)	12.9 (11.8–14.0)		2.0 (1.6–2.4)	4.6 (3.8–5.5)	
Regional	72.2 (70.5–73.7)	61.5 (59.2–63.7)		25.8 (24.3–27.4)	35.3 (33.2–37.4)		2.0 (1.5–2.5)	3.2 (2.5–4.2)	
Distant	39.6 (38.5–40.7)	24.4 (23.1–25.7)		58.0 (56.9–59.1)	72.1 (70.7–73.4)		2.4 (2.1–2.7)	3.5 (3.0–4.1)	

CI, confidence interval.

*All cause survival was estimated by Kaplan-Meier estimator; †Probability of death under competing risks was estimated based on Surveillance, Epidemiology, and End Results cause-specific death classification variable and by Cumulative Incidence Competing Risk Methods; ‡Log-rank test; §Gray's test.

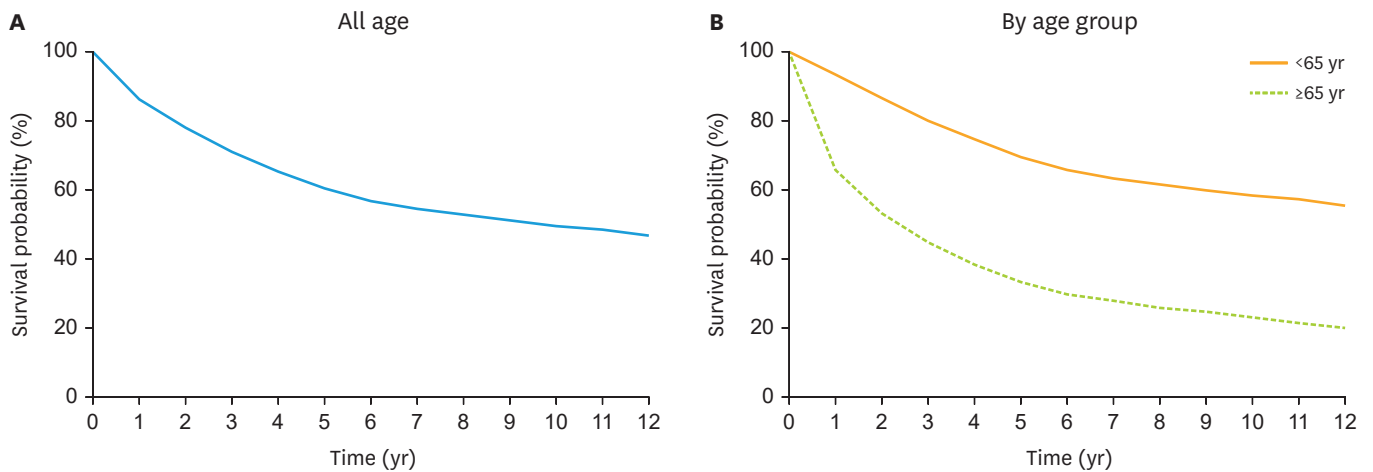


Fig. 1. Observed survival of patients with epithelial ovarian cancer, Korea Central Cancer Registry 2006–2016. (A) All ages, (B) By age group

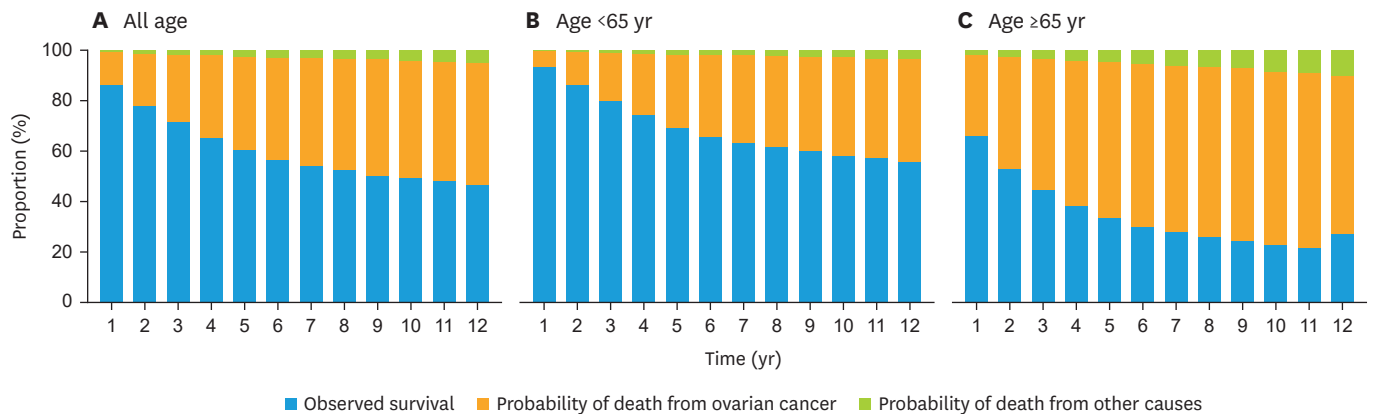


Fig. 2. Survival and competing risks probability of death according to age group, Korea Central Cancer Registry 2006–2016. (A) All ages, (B) Age <65 years, and (C) Age ≥65 years. Probabilities of death were estimated by the cumulative incidence function.

Cause-specific mortality rate of ovarian cancer
Table 3. Survival and competing risks probability of death by ovarian cancer and other causes according to age group, Korea Central Cancer Registry 2006–2016

Characteristics	All cause survival* (95% CI)			Probability of death† (95% CI)					
			p-value‡	By ovarian cancer			By other causes		
	5-year	10-year		5-year	10-year	p-value§	5-year	10-year	p-value§
Age <65									
Stage			<0.001			<0.001			<0.001
Localized	91.8 (90.9–92.6)	87.4 (86.0–88.6)		7.1 (6.3–7.9)	10.0 (8.9–11.1)		1.1 (0.8–1.5)	2.6 (2.0–3.4)	
Regional	78.5 (76.8–80.2)	68.1 (65.6–70.5)		20.4 (18.7–22.0)	30.1 (27.7–32.5)		1.1 (0.7–1.6)	1.8 (1.2–2.6)	
Distant	47.7 (46.3–49.0)	30.0 (28.3–31.6)		50.4 (49.0–51.7)	67.1 (65.4–68.7)		2.0 (1.6–2.3)	3.0 (2.4–3.6)	
Histology			<0.001			<0.001			<0.001
Serous	63.4 (62.1–64.7)	45.3 (43.5–47.0)		35.2 (33.9–36.5)	52.4 (50.6–54.1)		1.3 (1.1–1.7)	2.4 (1.9–3.0)	
Endometrioid	84.1 (81.7–86.1)	75.1 (71.6–78.2)		15.1 (13.0–17.3)	22.8 (19.7–26.0)		0.9 (0.5–1.6)	2.1 (1.2–3.4)	
Clear	76.6 (74.3–78.8)	72.3 (69.4–75.0)		22.8 (20.6–25)	26.2 (23.6–28.9)		0.7 (0.3–1.3)	1.5 (0.7–2.8)	
Mucinous	79.7 (77.6–81.5)	74.3 (71.7–76.6)		18.8 (17–20.7)	22.8 (20.6–25.1)		1.5 (1.0–2.3)	2.9 (1.9–4.3)	
Age ≥65									
Stage			<0.001			<0.001			<0.001
Localized	67.8 (64.4–71.0)	55.0 (50.3–59.4)		25.0 (22.1–28.1)	29.2 (25.8–32.6)		7.1 (5.4–9.1)	15.8 (12.3–19.8)	
Regional	46.9 (42.9–50.8)	35.3 (30.6–40.0)		47.7 (43.7–51.5)	55.9 (51.2–60.3)		5.5 (3.8–7.5)	8.9 (6.3–12.0)	
Distant	21.8 (20.1–23.5)	11.8 (9.9–13.9)		68.9 (67.0–70.6)	82.7 (80.7–84.4)		3.1 (2.5–3.8)	4.2 (3.4–5.2)	
Histology			<0.001			<0.001			<0.001
Serous	38.9 (36.5–41.3)	24.6 (21.7–27.6)		57.9 (55.5–60.3)	68.8 (66.0–71.5)		3.2 (2.4–4.1)	6.6 (4.9–8.7)	
Endometrioid	62.8 (55.1–69.6)	49.8 (40.7–58.4)		30.2 (23.5–37.1)	36.7 (29.2–44.3)		7.0 (3.8–11.5)	13.4 (7.5–21.0)	
Clear	61.4 (50.4–70.6)	49.3 (36.8–60.7)		34.9 (25.1–44.8)	45.2 (32.9–56.8)		3.8 (1.2–8.8)	5.4 (1.9–11.8)	
Mucinous	55.6 (49.9–60.9)	42.6 (35.7–49.3)		38.2 (32.9–43.5)	44.3 (38.2–50.1)		6.2 (3.8–9.4)	13.2 (8.5–18.8)	

p-values from Log-rank test and Gray's test comparing age groups (Age <65 vs. Age ≥ 5) were less than 0.0001 except histology type clear (Log-rank test p=0.001, Gray's test of ovarian cancer death probability p=0.001).

CI, confidence interval.

*All cause survival was estimated by Kaplan-Meier estimator; †Probability of death under competing risks was estimated based on SEER cause-specific death classification variable and by Cumulative Incidence Competing Risk Methods; ‡Log-rank test; §Gray's test.

Among all groups according to stage, compared with women aged <65 years, women aged ≥65 years showed a significantly higher 5-year cause-specific mortality of ovarian cancer (25.0% vs. 7.1% for localized, p<0.001; 47.7% vs. 20.4% for regional, p<0.001; 68.9% vs. 50.4% for distant, p<0.001, Gray's test) and 5-year other cause mortality (7.1% vs 1.1% for localized, p<0.001; 5.5% vs. 1.1% for regional, p<0.001; 3.1% vs 2.0% for distant; p<0.001, Gray's test) (**Table 3**). We provided all cause-survival, probability of death from ovarian cancer and other causes by the age groups (≤34, 35–49, 50–64, 65–79, ≥80) in **Table S2** (which is an expansion of **Table 3** to the more precise age groups).

3. Cause-specific competing risks mortality according to histology

Among all groups according to histology, compared with women aged <65 years, women aged ≥65 years showed a significantly higher 5-year cause-specific mortality of ovarian cancer (serous: 57.9% vs. 35.2%, p<0.001; mucinous: 38.2% vs 18.8%, p<0.001; endometrioid: 30.2% vs. 15.1%, p<0.001; clear cell: 34.9% vs 22.8%, p=0.001) and 5-year other cause mortality (serous: 3.2% vs. 1.3%, p<0.001; mucinous: 6.2% vs. 1.5%, p<0.001; endometrioid: 7.0% vs. 0.9%, p<0.001; clear cell: 3.8% vs. 0.7%, p<0.001) (**Table 3**). This trend was consistent after adjustment for the general life expectancy of each age group (relative survival) (**Table S3**).

Table S4 shows additional age-grouped analyses stratified according to serous and non-serous histology and stage. Compared with women aged <65 years, women aged ≥65 years showed the most significant increase in the competing risk in the group with local stage non-serous ovarian cancer (8.0% vs. 1.0%, p<0.001), with this increase being less prominent in the group with distant stage serous ovarian cancer (2.1% vs. 1.4%, p=0.010).

DISCUSSION

This nationwide population-based cohort study on 21,446 women with ovarian cancer showed a continuous increase in the cause-specific mortality at 10 follow-up years. Women aged ≥ 65 years at diagnosis showed an increase in cause-specific and other-cause mortality. The effect of increasing age at diagnosis on observed survival was consistent across the stages and histologies. Specifically, there was a more prominent effect size in endometrioid and mucinous histologies as well as the localized stage. Our results indicate the need for developing assessment tools for predicting both ovarian cancer-specific mortality and competing risk to balance the harms and benefits of standard treatment.

Well-designed clinical trials yield crucial reference-standard findings regarding the relative effect size in etiologic research. However, they are limited in terms of the inclusion criteria and exclusion of older or comorbid patients, who comprise a substantial proportion in real-world clinical practice [25]. Moreover, few studies have reported disease-related endpoints and performed competing risk analyses for appropriate estimation of cause-specific mortality. A recent systematic review of geriatric oncology trials reported that only 15 (36.6%) out of 41 trials used disease-related endpoints to account for death from other causes; moreover, only one study employed statistical analysis addressing competing risks [11]. Contrastingly, large population-based cohort studies are much more representative of the real-world clinical practice given that they include patients generally excluded from clinical trials. In addition to these characteristics, this nationwide population-based cohort study ensured completeness of mortality data, including the mortality cause. Therefore, it is suitable to estimate cause-specific mortality (or survival) while accounting for competing risk.

In this study, analysis using the CIF method revealed that the 5-year other causes (competing risk) mortality in women aged ≥ 65 years was 4.8%. This is lower than the values reported for patients with breast cancer (4.9% and 14.6% for patients aged 65–74 years and ≥ 75 years, respectively) in a previous Dutch study [26]; however, it was still non-negligible in the analysis of cause-specific mortality. Furthermore, the 5-year competing risk increased by 7% in patients with endometrioid and mucinous histologies. Additionally, this value increased to 7.1% in women aged ≥ 65 years with localized stage tumors with a relatively good prognosis while the 10-year other causes mortality increased to 15.8%. Similar to most solid cancers, there is an increased risk of developing ovarian cancer in elderly women, who also are at a high risk of comorbid diseases, which results in an increased competing risk. When estimating the cause-specific failure in patients with cancer, there is a need to use an appropriate statistical method that addresses competing risks to yield unskewed results. The Kaplan–Meier method is commonly used to assess the probability of failure in time-to-event data [27]. However, it censors patients who experienced competing events and generally leads to an overestimation of the absolute risk of the event of interest in case of existing competing risks. Contrastingly, the CIF assumes that patients with competing events are no longer at risk of the event of interest and provides appropriate estimates for the cumulative probability of cause-specific failure in the presence of competing risk [23,28]. Therefore, researchers should consider estimating the CIF under the competing risks framework.

The competing risk would be prominent in indolent cancer types, which involve a low probability of death from cancer. Additionally, it should be highlighted in populations with numerous concomitant diseases or older age where competing events are more frequent [6]. In this study, there was a substantial increase in competing risks in patients aged ≥ 65 years

with non-serous ovarian cancer. This might be explained by that non-serous histology such as mucinous or endometrioid is associated with long-term survival because they are typically also low-grade and low stage [29,30]. Moreover, for the advanced stage, the competing risks of patients ≥ 65 years and < 65 years were similarly low (5-year CIF: 3.1% vs. 2.0%). This suggests that in older patients, the disease course of the advanced stage is not indolent and the cause-specific mortality is not outweighed by other-cause mortality. Similar to other metastatic diseases with a high probability of death from cancer itself, the issue of competing risk is not significantly involved in older populations with advanced-stage ovarian cancer.

In this study, older women had a higher ovarian cancer-specific mortality than younger women across the stages and histologies. This trend remained even after adjustment for the general life expectancy of each age group. These findings are consistent with those of a recently published cohort study using the SEER database on 49,932 women with ovarian cancer diagnosed from 1975 to 2011. In this previous study, survival decreased with increasing age across all stages; further, there was a more pronounced decrease in relative survival among women with advanced-stage tumors [31]. It remains unclear why older patients are at a higher risk of ovarian cancer mortality; however, there are several possible explanations. First, older women are more likely to be in advanced stages at diagnosis with adverse tumor biology [32]. Second, older women receive less definitive treatment, including the combination of surgery and chemotherapy, due to geriatric health conditions [33]. Third, there is scarce data regarding the tolerability and efficacy of emerging target therapy and immunotherapy in the elderly population, which impedes the provision of specific recommendations [34]. Based on the result from our study, the competing risk varies from individual to individual according to clinicopathologic characteristics including age, stage and histology. If the individual competing risk is expected to be low, same aggressive treatment strategy as in the younger patients including definitive and novel therapy should be considered in elderly patients. Therefore, to improve survival outcomes in older patients, future studies should develop a geriatric assessment tool for identifying elderly patients who could benefit from optimal treatment.

A strength of this nationwide population-based study is the inclusion of a large number of women with ovarian cancer and the availability of information regarding the cause of mortality. However, this study has several important limitations. First, there was limited clinical information, including weight, genetic tests for BRCA mutations, and postoperative residual tumor status. Although this did not considerably affect our analysis, this is an intrinsic limitation of using cohort data in the cancer registry database, KCCR. Moreover, we did not perform multivariable analysis with adjustment of relevant covariates to estimate the effect of prognostic factors for cause-specific mortality and remained as a future study. Second, there might have been misclassification of the cause of death based on death certificates, which might have led to the underestimation of non-cancer deaths. However, we used cause-of-death information from Statistics Korea, where the official causes of death statistics are annually reported in South Korea [35]. Further, we applied the SEER cause-specific death classification algorithm for enhanced accuracy [36].

In conclusion, this nationwide population-based study comprises 21,446 women with ovarian cancer and the availability of information regarding the cause of mortality. Our findings showed that older age at diagnosis is associated with increasing cause-specific mortality and competing risks across the stages and histologies. Although there will be several limitations, this highlights that clinicians need to better understand biological

differences in tumors of older patients and develop better decision aids to discriminate those patients with prominent competing risk. Given the substantial effect of competing risk on older patients, there is a need for geriatric assessment tools for predicting both ovarian cancer-specific mortality and other cause mortality. These tools can be used to identify subgroups who could benefit from optimal treatment that balances the harms and benefits, and consequently improves survival in older patients.

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SUPPLEMENTARY MATERIALS

Table S1

Patients' characteristics of women with epithelial ovarian cancer by age group, Korea Central Cancer Registry 2006–2016

[Click here to view](#)

Table S2

Survival and competing risks probability of death by ovarian cancer and other-causes according to age group, Korea Central Cancer Registry 2006–2016

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Table S3

Relative survival probability according to age (Age <65, Age ≥65), tumor stage, and histology, Korea Central Cancer Registry 2006–2016

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Table S4

Survival and competing risks probability of death by ovarian cancer and other-cause stratified according to age (Age <65, Age ≥65), histology (serous, non-serous) and tumor stage

[Click here to view](#)

REFERENCES

1. Ferlay JE, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, et al. Global cancer observatory: cancer today. December 2020. Lyon: International Agency for Research on Cancer; 2020.
2. Hong S, Won YJ, Lee JJ, Jung KW, Kong HJ, Im JS, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2018. *Cancer Res Treat* 2021;53:301-15.
[PUBMED](#) | [CROSSREF](#)
3. Howlader NN, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, et al. SEER cancer statistics review, 1975–2017. April 15, 2020. Bethesda, MD: National Cancer Institute; 2020.

4. Austin PC, Fine JP. Accounting for competing risks in randomized controlled trials: a review and recommendations for improvement. *Stat Med* 2017;36:1203-9.
[PUBMED](#) | [CROSSREF](#)
5. Chapman JA, Pritchard KI, Goss PE, Ingle JN, Muss HB, Dent SF, et al. Competing risks of death in younger and older postmenopausal breast cancer patients. *World J Clin Oncol* 2014;5:1088-96.
[PUBMED](#) | [CROSSREF](#)
6. de Glas NA, Kiderlen M, Vandenbroucke JP, de Craen AJ, Portielje JE, van de Velde CJ, et al. Performing survival analyses in the presence of competing risks: a clinical example in older breast cancer patients. *J Natl Cancer Inst* 2015;108:108.
[PUBMED](#)
7. Hoag JR, Hegde U, Zweifler R, Berwick M, Swede H. Competing risks survival of older patients with metastatic cutaneous melanoma: a SEER population-based study. *Melanoma Res* 2016;26:505-12.
[PUBMED](#) | [CROSSREF](#)
8. Jørgensen TL, Hallas J, Friis S, Herrstedt J. Comorbidity in elderly cancer patients in relation to overall and cancer-specific mortality. *Br J Cancer* 2012;106:1353-60.
[PUBMED](#) | [CROSSREF](#)
9. Patel HD, Kates M, Pierorazio PM, Allaf ME. Race and sex disparities in the treatment of older patients with T1a renal cell carcinoma: a comorbidity-controlled competing-risks model. *Urol Oncol* 2014;32:576-83.
[PUBMED](#) | [CROSSREF](#)
10. Zaorsky NG, Churilla TM, Egleston BL, Fisher SG, Ridge JA, Horwitz EM, et al. Causes of death among cancer patients. *Ann Oncol* 2017;28:400-7.
[PUBMED](#) | [CROSSREF](#)
11. Burdett N, Vincent AD, O'Callaghan M, Kichenadasse G. Competing risks in older patients with cancer: a systematic review of geriatric oncology trials. *J Natl Cancer Inst* 2018;110:825-30.
[PUBMED](#) | [CROSSREF](#)
12. Li C, Li J, Huang Q, Feng X, Zhao F, Xu F, et al. Developing and validating a novel nomogram used a competing-risks model for predicting the prognosis of primary fallopian tube carcinoma: a retrospective study based on the SEER database. *Ann Transl Med* 2021;9:378.
[PUBMED](#) | [CROSSREF](#)
13. Hong S, Won YJ, Park YR, Jung KW, Kong HJ, Lee ES, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2017. *Cancer Res Treat* 2020;52:335-50.
[PUBMED](#) | [CROSSREF](#)
14. Ajiki W, Tsukuma H, Oshima A. Index for evaluating completeness of registration in population-based cancer registries and estimation of registration rate at the Osaka Cancer Registry between 1966 and 1992 using this index. *Nippon Koshu Eisei Zasshi* 1998;45:1011-7.
[PUBMED](#)
15. Jung KW, Won YJ, Oh CM, Kong HJ, Lee DH, Lee KH, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2014. *Cancer Res Treat* 2017;49:292-305.
[PUBMED](#) | [CROSSREF](#)
16. Shin HR, Won YJ, Jung KW, Kong HJ, Yim SH, Lee JK, et al. Nationwide cancer incidence in Korea, 1999–2001; first result using the national cancer incidence database. *Cancer Res Treat* 2005;37:325-31.
[PUBMED](#) | [CROSSREF](#)
17. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol* 2014;32:2595-603.
[PUBMED](#) | [CROSSREF](#)
18. Kim J, Chang Y, Kim TJ, Lee JW, Kim BG, Bae DS, et al. Optimal cutoff age for predicting prognosis associated with serous epithelial ovarian cancer: what is the best age cutoff? *J Gynecol Oncol* 2019;30:e11.
[PUBMED](#) | [CROSSREF](#)
19. Young JL. SEER summary staging manual 2000: codes and coding instructions. Bethesda, MD: National Cancer Institute, National Institutes of Health; 2001.
20. Ederer F, Heise H. Instructions to IBM 650 programmers in processing survival computations. Methodological note. Bethesda, MD: National Cancer Institute; 1959.
21. Pavlič K, Perme MP. On comparison of net survival curves. *BMC Med Res Methodol* 2017;17:79.
[PUBMED](#) | [CROSSREF](#)
22. Grafféo N, Castelf F, Belot A, Giorgi R. A log-rank-type test to compare net survival distributions. *Biometrics* 2016;72:760-9.
[PUBMED](#) | [CROSSREF](#)

23. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Stat Med* 2007;26:2389-430.
[PUBMED](#) | [CROSSREF](#)
24. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988;16:1141-54.
[CROSSREF](#)
25. Camm AJ, Fox KA. Strengths and weaknesses of 'real-world' studies involving non-vitamin K antagonist oral anticoagulants. *Open Heart* 2018;5:e000788.
[PUBMED](#) | [CROSSREF](#)
26. Derks MG, Bastiaannet E, van de Water W, de Glas NA, Seynaeve C, Putter H, et al. Impact of age on breast cancer mortality and competing causes of death at 10 years follow-up in the adjuvant TEAM trial. *Eur J Cancer* 2018;99:1-8.
[PUBMED](#) | [CROSSREF](#)
27. Dinse GE, Lagakos SW. Nonparametric estimation of lifetime and disease onset distributions from incomplete observations. *Biometrics* 1982;38:921-32.
[PUBMED](#) | [CROSSREF](#)
28. Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. *Int J Epidemiol* 2012;41:861-70.
[PUBMED](#) | [CROSSREF](#)
29. Cress RD, Chen YS, Morris CR, Petersen M, Leiserowitz GS. Characteristics of long-term survivors of epithelial ovarian cancer. *Obstet Gynecol* 2015;126:491-7.
[PUBMED](#) | [CROSSREF](#)
30. McCluggage WG. Morphological subtypes of ovarian carcinoma: a review with emphasis on new developments and pathogenesis. *Pathology* 2011;43:420-32.
[PUBMED](#) | [CROSSREF](#)
31. Wright JD, Chen L, Tergas AI, Patankar S, Burke WM, Hou JY, et al. Trends in relative survival for ovarian cancer from 1975 to 2011. *Obstet Gynecol* 2015;125:1345-52.
[PUBMED](#) | [CROSSREF](#)
32. Creasman WT, Di Saia PJ, Mannell RS, McMeekin S, Mutch DG. *Clinical gynecologic oncology*. Philadelphia, PA: Elsevier Inc.; 2018.
33. Ries LA. Ovarian cancer. Survival and treatment differences by age. *Cancer* 1993;71 Suppl:524-9.
[PUBMED](#) | [CROSSREF](#)
34. Tortorella L, Vizzielli G, Fusco D, Cho WC, Bernabei R, Scambia G, et al. Ovarian cancer management in the oldest old: improving outcomes and tailoring treatments. *Aging Dis* 2017;8:677-84.
[PUBMED](#) | [CROSSREF](#)
35. Shin HY, Lee JY, Song J, Lee S, Lee J, Lim B, et al. Cause-of-death statistics in the Republic of Korea, 2014. *J Korean Med Assoc* 2016;59:221-32.
[CROSSREF](#)
36. Howlader N, Ries LA, Mariotto AB, Reichman ME, Ruhl J, Cronin KA. Improved estimates of cancer-specific survival rates from population-based data. *J Natl Cancer Inst* 2010;102:1584-98.
[PUBMED](#) | [CROSSREF](#)