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Long-Term Mortality Among Women with Epithelial Ovarian Cancer

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Abstract

Objectives—Patients with solid tumors are at greatest risk for dying from their cancers in the five years following diagnosis. For most malignancies, deaths from other chronic diseases begin to exceed those from cancer at some point. As little is known about the causes of death among long-term survivors of ovarian cancer, we examined causes of death by years from diagnosis.

Methods—The Surveillance, Epidemiology, and End Results (SEER) database was used to identify women diagnosed with ovarian cancer between 1988 and 2012. We compared causes of death by stage, age, and interval time after diagnosis.

Results—A total of 67,385 women were identified. For stage I neoplasms, 13.6% (CI, 13.0-14.2%) died from ovarian cancer, 4.2% (CI, 3.8-4.5%) from cardiovascular disease, 3.6% (CI, 3.3-3.9%) from other causes and 2.6% (CI, 2.4-2.9%) from other tumors; ovarian cancer was the leading cause of death until 7 years after diagnosis after which time deaths are more frequently due to other causes. For those with stage III-IV tumors, 67.8% (CI, 67.3-68.2%) died from ovarian cancer, 2.8% (CI, 2.6-2.9%) from other causes, 2.3% (CI, 2.2-2.4%) from cardiovascular disease and 1.9% (CI, 1.7-2.0%) from other cancers; ovarian cancer was the most frequent cause of death in years 1-15 after which time deaths were more commonly due to other causes.

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Conclusions—The probability of dying from ovarian cancer decreases with time. Ovarian cancer remains the most common cause of death for 15 years after diagnosis in women with stage III-IV tumors.

Introduction

There will be an estimated 21,290 cases of ovarian cancer diagnosed in the United States in 2015, which will result in approximately 14,180 deaths. Ovarian cancer has the lowest five year survival rate among gynecologic cancers at 46%.¹ Ovarian cancer typically remains asymptomatic in its early stages, and over 70% of patients present with advanced stage disease.²⁻⁵ Women with early stage tumors typically respond well to treatment and some sub-groups have greater than 90% five-year survival rates. In contrast, five-year survival is less than 50% for patients with advanced stage disease.⁶

For most solid tumors, the most common cause of death in the first five years after a diagnosis of cancer is due to cancer itself. As the duration from diagnosis increases, other causes of death become more common⁷⁻⁹. These findings have been reported for cancers of the prostate^{10,11}, kidney⁷, central nervous system^{7,12-15}, lung^{11,16}, head and neck⁸, and colon.^{11,17} In a study 217,573 patients with breast, colorectal, lung, and prostate cancer, the probability of long-term survival increased significantly after patients survived a critical time period following diagnosis. The median conditional survival, or likelihood of survival after a specified time from initial diagnosis, increased from initial diagnosis to five years after diagnosis from 18.5 to 42.5 months for breast, 7.5 to 71.5 months for colorectal, 4.5 to 52.5 months for lung, and 24.5 to 34.5 months for prostate cancer.¹¹

Mortality estimates and the specific causes of death are of clinical importance to patients and physicians and can be used for counseling and prognostication as well as to help design more tailored surveillance and survivorship strategies.^{7,12,13,15,18,19} In contrast to other solid tumors, little is known about the causes of death among long-term survivors of ovarian cancer. We therefore examined survival and cause of death among ovarian cancer patients and estimated the risk of death from various causes based on the duration since diagnosis.

Materials and Methods

Data Source

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database was utilized for this analysis.^{20,21} SEER is a population-based cancer registry that includes data on approximately 28% of the United States population and captures patient demographics, cancer site and stage, and survival. Exemption from the Columbia University Institutional Review Board was obtained.

Patient Characteristics

Women diagnosed with epithelial ovarian cancer between January 1988 and December 2012 were analyzed. The cohort was limited to women with epithelial ovarian tumors based on the World Health Organization (WHO) criteria including serous, mucinous, endometrioid, clear cell, transitional cell carcinomas, and epithelial tumors not otherwise specified.²² Age

at diagnosis was categorized into 10-year intervals, race recorded as white, black, and other, and diagnosis stratified by year. The SEER marital status variable was recorded as married, single, and unknown. The SEER registries were categorized as Eastern (Connecticut, New Jersey, Atlanta, rural Georgia, greater Georgia), Central (Detroit, Iowa, Kentucky, Louisiana, Utah), and Western (Alaska, California, Hawaii, Los Angeles, New Mexico, San Francisco, San Jose, Seattle). Tumor grade was grouped as well, moderately, or poorly differentiated, or unknown. Stage was determined based on the American Joint Cancer Committee and FIGO staging criteria as classified by SEER.

Outcomes

The primary outcome of the analysis was death. SEER records cause of death based on death certificate data. Patients were considered to have died from ovarian cancer if the cause of death was reported as ovarian cancer or cancer-related death likely due to ovarian cancer (miscellaneous malignant cancer, female genital tract cancer, cancer of the peritoneum, mesentery or omentum). Additional categories for cause of death included cardiovascular disease (disease of heart, hypertension without heart disease, cerebrovascular diseases, atherosclerosis, aortic aneurysm and dissection), other chronic disease (diabetes mellitus, alzheimers diseaeas, chronic obstructive pulmonary disease and allied conditions, chronic liver disease and cirrhosis, nephritis, nephrotic syndrome and nephrosis), and other cancer (“all malignant cancers” with the exception of ovarian cancer). A category of other was included for patients with codes that did not meet criteria for the above categories.

Statistical Analysis

Data for the cohort is reported descriptively. Causes of death were calculated and reported as rates with 95% confidence intervals (95% CI). Cause of death was further stratified by stage groupings (stage I, stage II, stage III/IV). A sensitivity analysis was performed in which the cohort was stratified by both stage and age (<60 or >60 years of age). Kaplan-Meier curves were developed to examine stage-specific cumulative mortality rates. All statistical tests were two-sided. All analyses were performed with SAS version 9.4 (SAS Institute Inc, Cary, North Carolina).

Results

We identified 67,385 women with epithelial ovarian cancer diagnosed between 1988 and 2012. The cohort included 14,190 stage I, 5302 stage II, 25,194 stage III, and 19,465 patients with stage IV tumors. The clinical and demographic characteristics of the epithelial ovarian cancer patients are displayed (Table 1). Overall, 85.2% of the women were white and serous histology was most common accounting for 50.2% of the tumors. Median follow-up was 6.5 years (IQR, 2.7-11.7 years) for women with stage I neoplasms, 4.3 years (IQR, 1.5-8.8 years) for those with stage II tumors and 1.8 years (IQR, 0.6-3.9) for patients with stage III-IV neoplasms.

At last follow-up, 37.5% (95% CI, 37.1-37.9%) of the cohort was alive while 53.6% (95% CI, 53.2-54.0%) had died from ovarian cancer (Table 2). For the remainder of the cohort, 3.0% (95% CI, 2.8-3.1%) had died from cardiovascular disease, 2.0% (95% CI, 1.9-2.1%)

had died from other cancers, 0.9% (95% CI, 0.8-0.9) had died from other chronic diseases and 3.0% (95% CI, 2.9-3.2%) had died from other causes.

When stratified by stage, 74.5% (95% CI, 73.8-75.2%) of stage I patients, 54.5% (95% CI, 53.1-55.8%) of stage II patients and 24.7% (95% CI, 24.3-25.1%) of those with stage III-IV neoplasms were alive at last follow-up (Table 2). Overall, ovarian cancer was the most common cause of death for each of the individual stage groups. For women with stage I neoplasms, 13.6% (95% CI, 13.0-14.2%) died from ovarian cancer, 4.2% (95% CI, 3.8-4.5%) from cardiovascular disease, 3.6% (95% CI, 3.3-3.9%) from other causes and 2.6% (95% CI, 2.4-2.9%) from other tumors. Figure 1A displays the cumulative frequency of death from ovarian cancer and other causes based on years from diagnosis. Figure 2 displays the annual frequency and percentage of deaths from ovarian cancer and other causes based on the number of years since diagnosis. For women with stage I tumors, ovarian cancer is the leading cause of death until 7 years after diagnosis after which time death is more frequently due to other causes than ovarian cancer. Similarly, among women with stage II tumors, ovarian cancer was the leading cause of death until 10 years after diagnosis (Figure 3).

Among women with stage III-IV tumors, 67.8% (95% CI, 67.3-68.2%) had died from ovarian cancer, 2.8% (95% CI, 2.6-2.9%) from other causes, 2.3% (95% CI, 2.2-2.4%) from cardiovascular disease and 1.9% (95% CI, 1.7-2.0%) from other cancers. Compared to early-stage disease, the cumulative death rate for women with advanced stage disease shows a sharper peak (Figure 1B). When the annual percentage of deaths is stratified by cause for women with stage III-IV tumors, ovarian cancer is the most frequent cause of death in years 1 through 15 after diagnosis after which time deaths that occur are more commonly due to reasons other than ovarian cancer (Figure 4).

A sensitivity analysis in which patients were stratified by age is displayed in Table 3. For each stage group a higher number of younger compared to older women survived. Among women >60 years of age death from ovarian cancer and death from cardiovascular disease was more common compared to younger women.

Discussion

Our findings suggest that women with ovarian cancer remain at substantial risk of cancer-related death for many years after initial diagnosis. For women with early stage ovarian cancer, the leading cause of death remains ovarian cancer for seven years after diagnosis. In patients diagnosed with advanced stage tumors, the most likely cause of death remains ovarian cancer until sixteen years after diagnosis. Cardiovascular mortality and other causes of death are responsible for only a fraction of deaths in women with ovarian cancer within a decade after diagnosis.

For women with ovarian cancer diagnosed at any stage, the probability of dying from ovarian cancer decreases with time and the probability of dying from other causes increases. The concept of conditional survival, or the chance of survival after achieving a set amount of time without recurrence or death from cancer, has been examined for a number of solid

tumors including ovarian cancer.^{23,24} An analysis of the Hormones and Ovarian Cancer Prediction case-control study noted that the probability of surviving an 3 additional years without recurrence in women who had already survived to 1, 3, and 5 years after remission was 64%, 90% and 98%.²⁴ Similar findings of improved conditional survival over time were noted in a population-based cohort in the U.S.²³ Our data is in accord with prior studies; although the absolute number of women with ovarian cancer who die decreases with time since diagnosis, ovarian cancer remains the leading cause of mortality for those women who do die for many years after treatment.

Unlike other gynecologic cancers that are associated with higher cure rates, we noted that women with ovarian cancer remained at substantial risk of cancer-related death for more than a decade after diagnosis. Ward and colleagues analyzed cause of death in a cohort of over 44,000 endometrial cancer patients derived from the SEER database. The investigators noted that women with low grade, localized disease were 6 times more likely to die from cardiovascular disease than endometrial cancer. In this report endometrial cancer was the most common cause of death in the first 5-year interval after diagnosis but thereafter cardiovascular mortality predominated.²⁵ The high mortality and risk of ovarian cancer specific mortality we noted reflects the aggressive nature of these neoplasms. Like endometrial cancer, we noted a higher rate of cardiovascular-related death among older women.

These findings have important implications for ovarian cancer patients and clinicians. First, these data help inform discussions surrounding survival. Survival estimates are often conveyed in the form of five year survival and long-term cure rates. Our findings allow clinicians to address the dynamic aspects of prognosis and individualize discussions about outcomes and how they change over time. Particularly for women with early-stage tumors these data provide reassurance that after six years mortality risks from other causes outweigh the risk from ovarian cancer. These data can help promote age appropriate screening and utilization of preventive health services.

Second, and more controversial, these data can be used to help guide surveillance for women with ovarian cancer receiving follow-up care. Surveillance guidelines for patients with ovarian cancer typically rely on periodic physical examination, serum tumor marker testing (CA125) and often imaging.^{26,27} To date early intervention based on CA125 and imaging has not been shown to impact survival, however these tests are commonly used in clinical practice.²⁸ Our data suggest that it may be reasonable to prospectively evaluate surveillance regimens that become appropriately less intensive further out from the time of diagnosis, particularly for women with early stage neoplasms.

We recognize a number of important limitations. First, utilization of death certificate data and algorithms to determine cause of death is subject to some degree of misclassification.²⁹⁻³¹ Prior work examining cancer specific mortality using registry data has reported acceptable validity.³¹ In addition to misclassification of cancer-related death there may be misclassification of other causes of death. To limit this bias our primary analysis compared ovarian cancer specific mortality to all other causes of death. Second, SEER lacks a number of important factors that likely were associated with mortality

including comorbidity, performance status and cardiovascular and other risk factors. Further work examining specific patterns of survival in women with specific comorbidities would be of great interest. Lastly, because the analysis spans a twenty-four year time period, changing treatment practices over time likely influenced the allocation of treatments and outcomes.

In summary, our findings show that women diagnosed with early stage epithelial ovarian cancer have a less prolonged risk of death from ovarian cancer than women diagnosed with stage III or IV ovarian cancer. These data suggest that it may be appropriate to utilize stratified surveillance strategies for early stage versus advanced stage ovarian cancer patients. Additionally, we hope that this information may benefit practitioners in counseling and expectation setting among ovarian cancer survivors.

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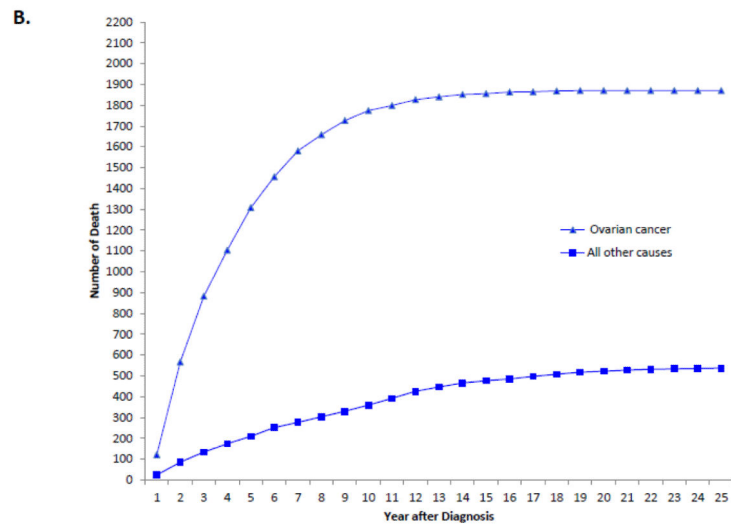
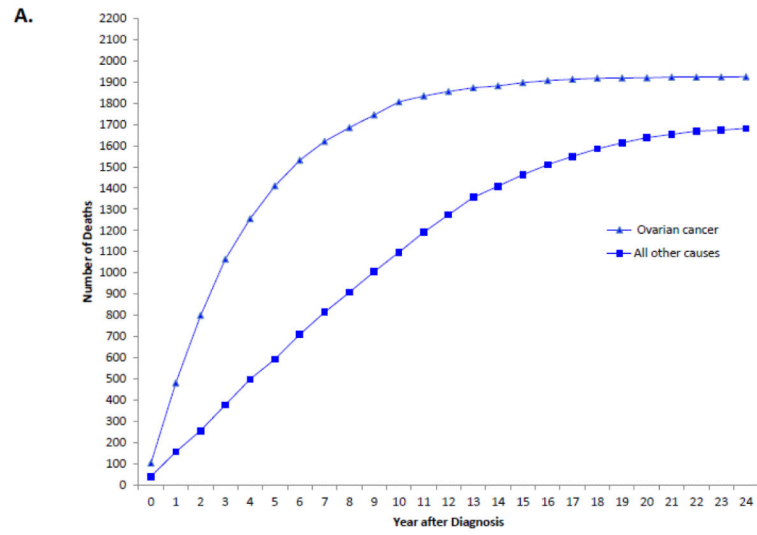
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Research Highlights

- The probability of dying from ovarian cancer decreases with time.
- Ovarian cancer remains the most common cause of death for 15 years after diagnosis in women with stage III-IV tumors.
- For stage I tumors, ovarian cancer remains the most common cause of death for 6 years after diagnosis.



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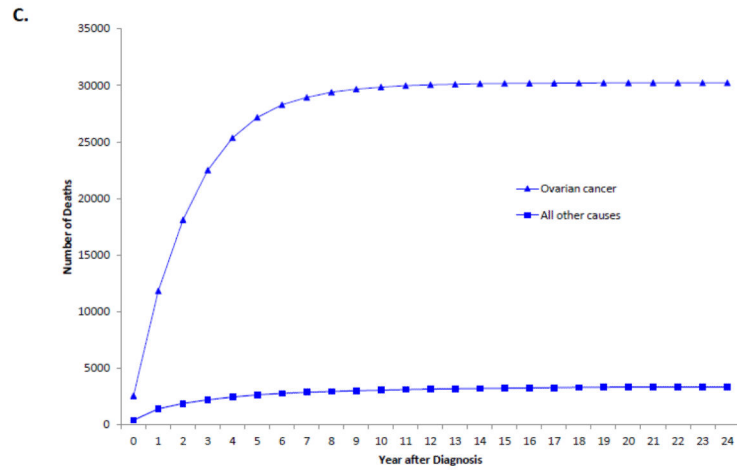


Figure 1.

A. Cumulative frequency of death from ovarian cancer and other causes among patients with stage I tumors. 1B. Cumulative frequency of death from ovarian cancer and other causes among patients with stage II tumors. 1C. Cumulative frequency of death from ovarian cancer and other causes among patients with stages III-IV tumors.

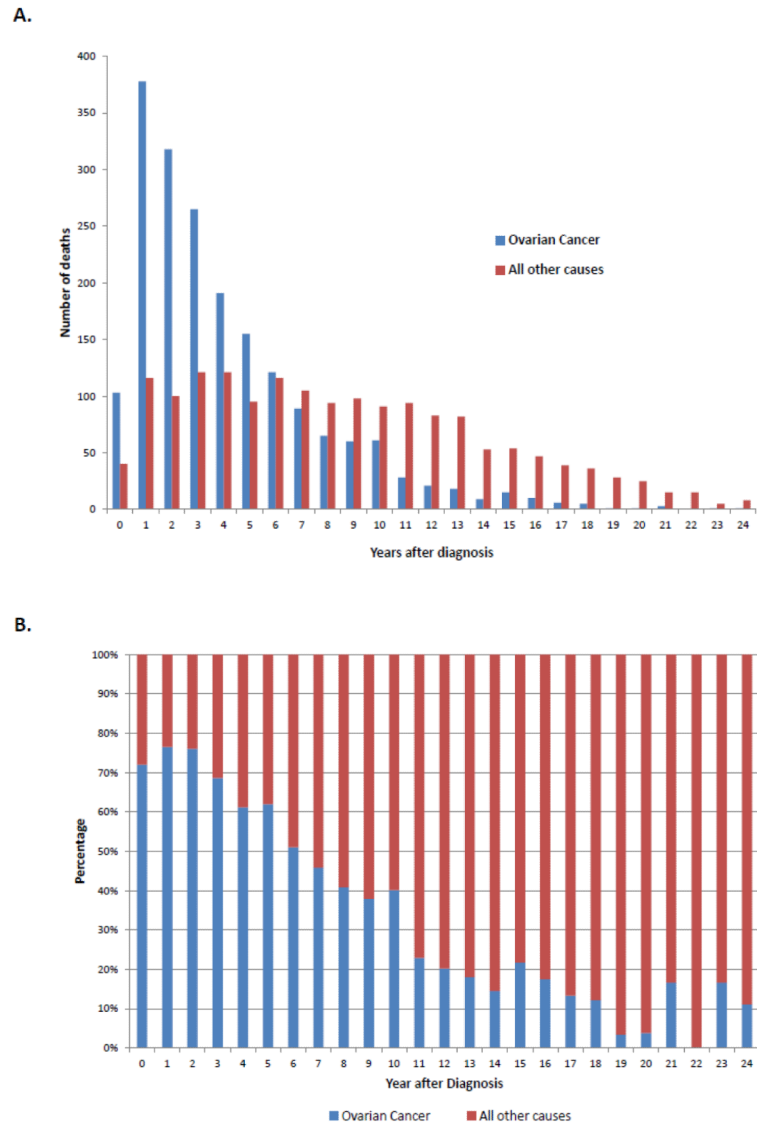


Figure 2.
 A. Annual frequency of death from ovarian cancer and other causes among patients with stage I tumors. 2B. Annual percentage of deaths from ovarian cancer and other causes among patients with stage I tumors.

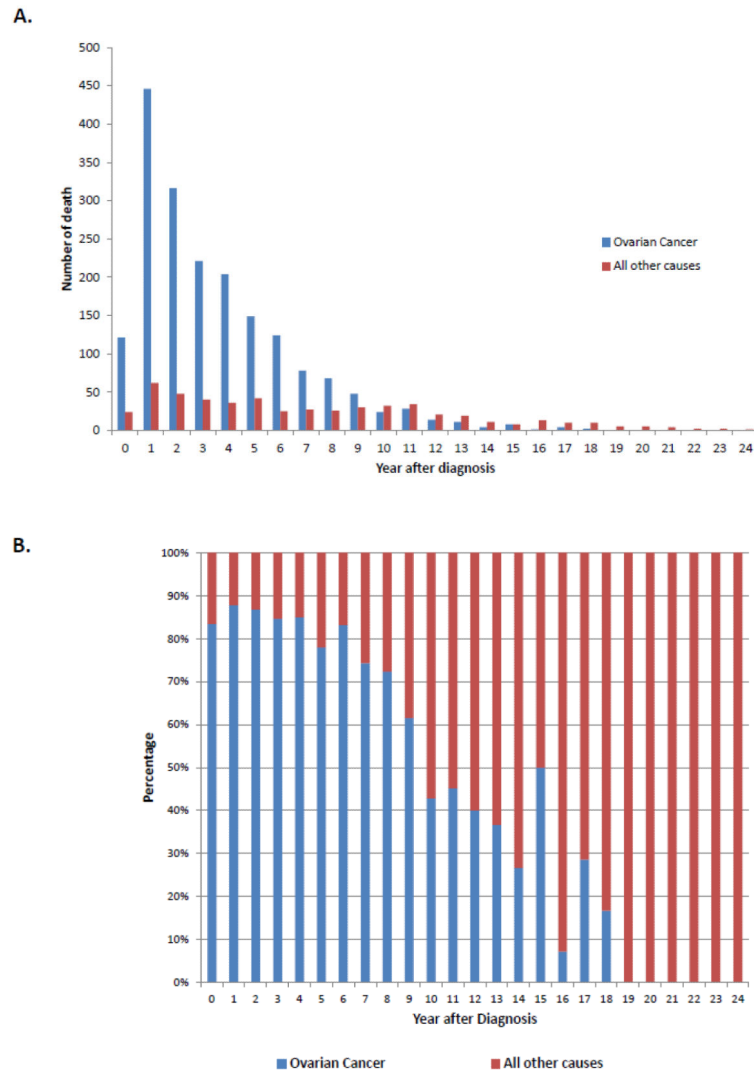


Figure 3. A. Annual frequency of death from ovarian cancer and other causes among patients with stage II tumors. 3B. Annual percentage of deaths from ovarian cancer and other causes among patients with stage II tumors.

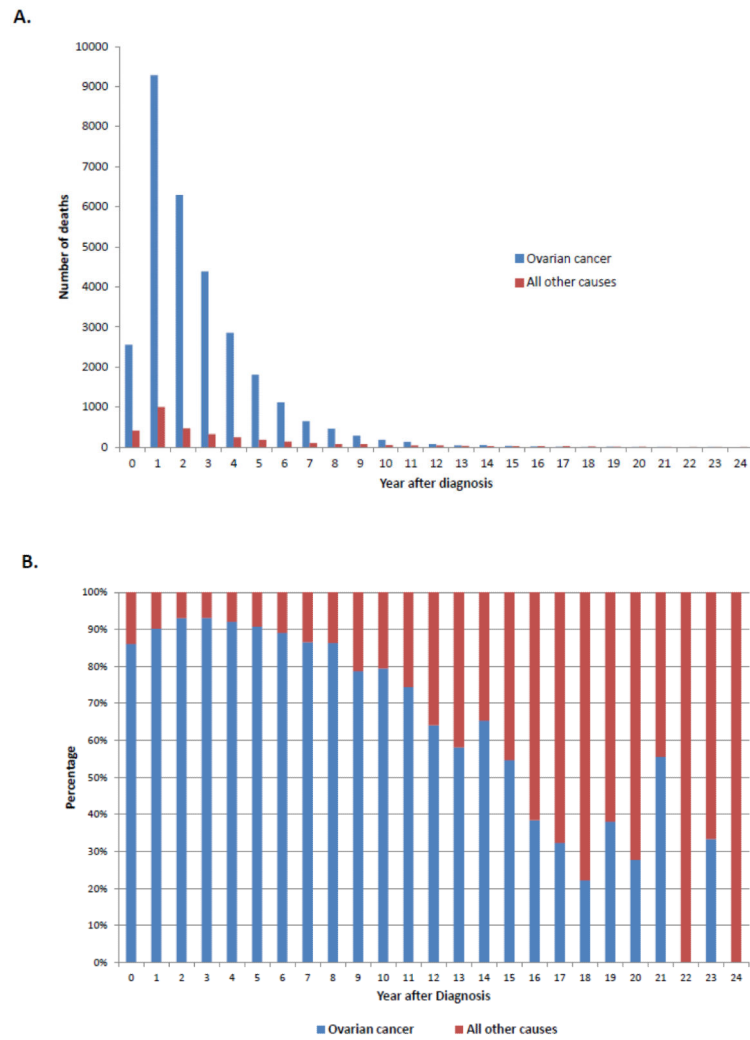


Figure 4. A. Annual frequency of death from ovarian cancer and other causes among patients with stage III-IV tumors. 4B. Annual percentage of deaths from ovarian cancer and other causes among patients with stage III-IV tumors.

Table 1

Clinical and demographic characteristics of the cohort.

	N	(%)
<i>Year of diagnosis</i>		
1988	1295	(1.9)
1989	1293	(1.9)
1990	1294	(1.9)
1991	1340	(2.0)
1992	1820	(2.7)
1993	1858	(2.8)
1994	1745	(2.6)
1995	1773	(2.6)
1996	1758	(2.6)
1997	1811	(2.7)
1998	1833	(2.7)
1999	1859	(2.8)
2000	3871	(5.7)
2001	3900	(5.8)
2002	3730	(5.5)
2003	3681	(5.5)
2004	3636	(5.4)
2005	3544	(5.3)
2006	3663	(5.4)
2007	3589	(5.3)
2008	3645	(5.4)
2009	3606	(5.4)
2010	3643	(5.4)
2011	3568	(5.3)
2012	3630	(5.4)
<i>Age</i>		
<40	3991	(5.9)
40-49	9663	(14.3)
50-59	15489	(23.0)
60-69	16248	(24.1)
70-79	13934	(20.7)
80	8060	(12.0)
<i>Race</i>		
White	57387	(85.2)
Black	4689	(7.0)
Other	5173	(7.7)
Unknown	136	(0.2)
<i>Marital status</i>		

	N	(%)
Married	34469	(51.2)
Single	30587	(45.4)
Unknown	2329	(3.5)
<i>Histology</i>		
Serous	33848	(50.2)
Mucinous	5729	(8.5)
Endometrioid	8280	(12.3)
Clear cell	4166	(6.2)
Transitional cell	264	(0.4)
Not otherwise specified	15098	(22.4)
<i>Grade</i>		
Well differentiated	5270	(7.8)
Moderately differentiated	10884	(16.2)
Poorly differentiated	30929	(45.9)
Unknown	20302	(30.1)
<i>Region</i>		
West	34292	(50.9)
Central	16029	(23.8)
East	17064	(25.3)
<i>Stage</i>		
IA	8100	(12.0)
IB	764	(1.1)
IC	4871	(7.2)
INOS	455	(0.7)
II	5302	(7.9)
IIIA	1205	(1.8)
IIIB	1791	(2.7)
IIIC	16275	(24.2)
IIINOS	5923	(8.8)
IV	19465	(28.9)
Unknown	3234	(4.8)

Table 2

Cause of death stratified by stage.

	All Patients		Stage I		Stage II		Stage III/IV	
	N	Rate (95% CI)	N	Rate (95% CI)	N	Rate (95% CI)	N	Rate (95% CI)
Alive	25274	37.5 (37.1, 37.9)	10,567	74.5 (73.8, 75.2)	2889	54.5 (53.1, 55.8)	11,036	24.7 (24.3, 25.1)
Ovarian cancer	36125	53.6 (53.2, 54.0)	1928	13.6 (13.0, 14.2)	1872	35.3 (34.0, 36.6)	30,262	67.8 (67.3, 68.2)
Other cancer	1373	2.0 (1.9, 2.1)	372	2.6 (2.4, 2.9)	97	1.8 (1.5, 2.2)	827	1.9 (1.7, 2.0)
Cardiovascular disease	1985	3.0 (2.8, 3.1)	591	4.2 (3.8, 4.5)	223	4.2 (3.7, 4.8)	1030	2.3 (2.2, 2.4)
Other chronic disease	580	0.9 (0.8, 0.9)	225	1.6 (1.4, 1.8)	49	0.9 (0.7, 1.2)	274	0.6 (0.5, 0.7)
Death from other	2048	3.0 (2.9, 3.2)	507	3.6 (3.3, 3.9)	172	3.2 (2.8, 3.7)	1230	2.8 (2.6, 2.9)

Rate expressed as percentage.

Table 3

Cause of death stratified by stage and age.

	<60 years of age	60 years of age
	Rate (95% CI)	Rate (95% CI)
<i>Stage I</i>		
Alive	85.0 (84.3, 85.7)	56.2 (54.9, 57.5)
Ovarian cancer	9.9 (9.3, 10.5)	20.0 (18.9, 21.1)
Other cancer	1.8 (1.5, 2.1)	4.1 (3.6, 4.6)
Cardiovascular disease	1.0 (0.8, 1.2)	9.7 (8.9, 10.5)
Other chronic disease	0.5 (0.4, 0.6)	3.4 (2.9, 3.9)
Death from other	1.9 (1.6, 2.2)	6.6 (5.9, 7.3)
<i>Stage II</i>		
Alive	68.6 (66.8, 70.4)	40.9 (39.0, 42.8)
Ovarian cancer	26.4 (24.7, 28.1)	43.9 (42.0, 45.8)
Other cancer	1.4 (0.9, 1.9)	2.3 (1.7, 2.9)
Cardiovascular disease	1.2 (0.8, 1.6)	7.1 (6.1, 8.1)
Other chronic disease	0.4 (0.2, 0.6)	1.4 (1.0, 1.8)
Death from other	2.0 (1.5, 2.5)	4.5 (3.7, 5.3)
<i>Stage III/IV</i>		
Alive	34.3 (33.6, 35.0)	19.0 (18.5, 19.5)
Ovarian cancer	60.6 (60.0, 61.3)	72.0 (71.5, 72.5)
Other cancer	1.5 (1.3, 1.7)	2.1 (1.9, 2.3)
Cardiovascular disease	0.9 (0.8, 1.0)	3.2 (3.0, 3.4)
Other chronic disease	0.3 (0.2, 0.4)	0.8 (0.7, 0.9)
Death from other	2.5 (2.3, 2.7)	2.9 (2.7, 3.1)