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Characteristics of Long-Term Survivors of Epithelial Ovarian Cancer

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Abstract

Objective—To identify characteristics associated with long-term survival forepithelial ovarian cancer patients using the California Cancer Registry.

Methods—A descriptive analysis of survival of all California residents diagnosed with epithelial ovarian cancer between 1994 and 2001 was conducted using patients identified through the cancer registry with follow up through 2011. Characteristics of the patients who survived more than 10 years (long-term survivors) were compared to three other cohorts: patients who survived less than 2 years, those who survived at least 2 but no more than 5 years, and those who survived at least 5 but no more than 10 years.

Results—A total of 3,582 out of 11,541 (31% CI=30.2%, 31.8%) of the patients survived more than 10 years. Younger age, early stage, low-grade, and non-serous histology were significant predictors of long-term survival, but long-term survivors also included women with high-risk cancer.

Conclusion—Long-term survival is not unusual in patients with epithelial ovarian cancer, even in those with high-risk disease. Many of the prognostic factors are well known, but it remains to be determined why some patients with advanced stage high-grade cancers survive longer than others with the same histology. These findings are important for patient counseling.

Introduction

Patients and physicians commonly perceive ovarian cancer as a highly fatal disease. Since most patients present with advanced stage disease, the prognosis is often poor. Ovarian

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cancer five-year survival varies significantly by stage, but, for women diagnosed 2004 through 2010, ranged from 92% for localized disease to 27% for distant.[1]

Although most women diagnosed with advanced stage ovarian cancer will succumb to the disease, the biological behavior of ovarian cancer is quite variable. Even some of those patients with high-risk, advanced stage ovarian cancer survive well beyond 5 years. With an increased focus on survivorship, understanding of this information becomes important for patient counseling. There is a paucity of data about long-term ovarian cancer survivors since very few clinical series or population-based database studies extend beyond 5 years of survival. The purpose of this study was to identify characteristics associated with long-term survival from epithelial ovarian cancer, using the California Cancer Registry.

Materials and Methods

This was a retrospective, cross sectional descriptive analysis of patients diagnosed through the California Cancer Registry. This registry is the single largest population-based cancer registry in the U.S. and contains demographic, diagnostic, treatment and outcome information extracted from medical records for every reportable cancer diagnosed among residents of the state since 1988. California law requires that physicians and hospitals report all cancer cases, and information is collected from diagnostic and treatment facilities. To ensure current follow up for vital status and cause of death, the cancer registry database is linked annually to death certificates, hospital discharge data, Medicare files, the Department of Motor Vehicles, Social Security, and other administrative databases. Linkage to the National Death Index ensures capture of deaths occurring outside California as well as cause of death, and follow up is over 96% for patients diagnosed since 2000. The California Cancer Registry is part of both the Centers for Disease Control National Program of Cancer Registries and the National Cancer Institute Surveillance Epidemiology and End Results program and meets or exceeds the standards of both groups for data quality and completeness. This study was determined by the Institutional Review Board at the University of California Davis to be exempt because only existing, de-identified data were included.

For this analysis we identified all patients residing in California and diagnosed with ovarian cancer between 1994 and 2001. We collected data on patient demographics (age, race–ethnicity, socioeconomic status, insurance status), year of diagnosis, cancer characteristics (stage at diagnosis, tumor grade, histology), and hospital. Patients were followed through December 31, 2011, thus allowing us at least 10 years of follow-up for all surviving patients. Characteristics of the patients who survived more than 10 years (long-term survivors) were compared to three other cohorts: patients who survived less than 2 years, those who survived at least 2 but no more than 5 years, and those who survived at least 5 but no more than 10 years. Only patients for whom ovarian cancer was the first or only cancer diagnosis were included. Patients diagnosed at autopsy were excluded from analysis.

Race–ethnicity in the cancer registry is based on information collected from medical records supplemented with linkage to algorithms to better identify Hispanics and Asian/Pacific Islanders. We categorized race/ethnicity as Hispanic, non-Hispanic white, non-Hispanic

black, and non-Hispanic Asian–Pacific Islander. Neighborhood level socioeconomic status (SES) was based on U.S. Census characteristics linked to the address at diagnosis combined into the summary Yost index.[2] To measure urban/rural differences, we used the census-based rural/urban commuting codes, which combine population density, urbanization, and commuting times, to categorize residence at diagnosis as urban, small town, or rural (www.ers.usda.gov/Data/RuralUrbanCommutingAreaCodes). Insurance coverage was defined as private/government (including managed care and Medicare with supplement), Medicaid/low income, Medicare, Insured NOS, and uninsured. Volume of treatment facilities was categorized according to how many ovarian cancer patients received initial treatment at each facility during the study period.

Stage at diagnosis was defined based on a modification of American Joint Committee on Cancer staging system. Only invasive epithelial cancers were included. Tumors with ICD-O-3 morphology codes 8010-8570 (excluding 8240-8255), were considered epithelial tumors. Tumors were further categorized as serous (codes 8050, 8052, 8260, 8441, 8450, 8460, 8461), mucinous (codes 8471, 8481, 8480), clear cell (codes 8005, 8310, 8313), endometrioid (codes 8380, 8381, 8382), or adenocarcinoma not otherwise specified (NOS, codes, 8010, 8020, 8021, 8140, 8141, 8323, 8440, 8570). TNM staging was not included in the registry prior to 2004, thus subset analysis could not be done on this factor. Early stage patients may have included patients understaged because of inadequate surgical staging. The grading system included four grades, with IV being classified as undifferentiated, using the International Classification of Disease-Oncology/World Health Organization system. Tumor grades were grouped into grades I and II versus III and IV.

Patient demographic, hospital, and tumor characteristics were summarized using descriptive statistics. Associations between these factors and survival category were evaluated using chi-square tests. Multivariable logistic regression was done to estimate the odds of surviving more than 10 years while simultaneously controlling for demographic, clinical, and hospital characteristics. Statistical significance was defined by a P value <0.05. Statistical computing was performed with SAS software, Version 6.12.

Results

A total of 11,541 women residing in California were diagnosed with invasive epithelial ovarian cancer during the period of 1994 to 2001. Patient demographics, cancer characteristics, insurance status and hospital volume are described in Table 1. About one quarter of the patients were under the age of 50. A majority of the patients were non-Hispanic whites, with smaller numbers of Hispanics, Asian/Pacific Islanders, and non-Hispanic blacks. Almost all patients resided in an urban area (97%). There were nearly twice as many cases categorized as grade III and IV as grade I and II, but grade information was missing in 27% of cases. 67% of ovarian cancers were stages III and IV, and only about one fifth were stage I. Serous was the predominant histologic type, followed by endometrioid, clear cell, and mucinous types. The majority of ovarian cancer patients received their treatment at high volume hospitals.

Patients were divided into four cohorts based on length of survival (Table 2). Most patients survived less than 5 years, however, 31.0% (CI=30.2%, 31.8%) of all patients survived more than 10 years (long-term survivors). Nearly half of long-term survivors were 18-50 years old compared to 13% among those who survived less than 2 years. Hispanic and Asian/Pacific Islander patients made up a higher proportion of long-term survivors than other groups. A slightly higher proportion of patients who survived more than 10 years had private insurance. A higher percentage of patients who survived for at least two years resided in high SES neighborhoods and a larger proportion were cared for in hospitals that treated more than 40 cases during the study period.

Although the majority of long-term survivors had stage I cancer, 32.4% (CI=30.9%, 33.9%) had stage III and IV disease at diagnosis. Tumor grade also varied significantly, with a predominance of low-grade cancers in the women surviving more than 10 years. If the patients with unknown grade are removed, then about 58% of the long-term survivors had grade I and II cancers. Long-term survival favored those with endometrioid, clear cell, and mucinous types. However, 62.3% of stage I/II patients with grade 3/4 tumor survived 10+ years, and 66.2% of stage I/II patients with serous histology survived more than 10 years.

Odds ratios that favored survival greater than 10 years over shorter survival periods are shown in Table 3. Patients missing information on SES, race/ethnicity, insurance, stage, grade, or cause of death were excluded from the multivariable analysis. Women with stage I cancer had very high odds of survival more than 10 years. Similar, but less marked associations were detected for stages II and III compared to stage IV disease. Patients with low-grade tumors were more likely to be long-term survivors. The favorable prognoses persisted for mucinous, clear cell, and endometrioid histologies compared to serous after adjustment for other factors. Younger age also remained as a significantly positive prognostic factor. However, race, SES, insurance, and hospital volume were no longer statistically significant. Results were similar when odds ratios were calculated separately for patients with stage I/II and those with stage III/IV (results not shown).

After patients with missing values were excluded from analysis, there were 954 stage III and IV epithelial ovarian cancer patients (17.2% of a total of 5536 patients) who survived more than 10 years (Table 4). 26% of women under age 50 survived more than 10 years, and although the majority of women over age 75 with late stage ovarian cancer survived less than two years, 6% survived more than 10. A higher proportion of Hispanic and Asian/PI patients survived more than 10 years. Although there were higher proportions of long-term survivors among patients with endometrioid tumors, 16% of patients with late stage serous cancer survived more than 10 years.

Discussion

This study provided a unique opportunity to examine the characteristics of women who are long-term survivors of epithelial ovarian cancer, commonly thought to be a highly fatal disease. There has been limited information about women surviving greater than 10 years, many of who are cured. Using cancer registry data not only allowed us to collect long-term survival data beyond 10 years (most studies are limited to five years of survival,[3-5]) but the

cohort was far larger than seen in other studies.[6] Most surprising was that nearly one third of ovarian cancer patients were long-term survivors, which is very important for counseling about prognosis.

Tumor biology (cancer stage, grade, and histology) had the strongest associations with survival. Although long-term survival did vary based on race–ethnicity, socioeconomic status, and insurance status, none of these remained statistically significant after adjustments for the other covariates. As expected, patients with Stage I cancers had the greatest likelihood of long-term survival, probably reflecting that many are actually cured of their disease.[7,8] Chan identified four independent risk factors that were associated with survival in early stage ovarian cancer: age, stage, tumor grade, and peritoneal cytology Low-risk patients (none or 1 risk factor) had a 5-year survival of 88%, compared to the high-risk group 75% (3 or 4 risk factors), but all of these patients received adjuvant chemotherapy.[7]

Low-grade cancers had improved survival over high-grade cancers, consistent with earlier studies,[5,9]. Patients with grade 1 or 2 epithelial cancers were twice as likely to survive more than 10 years compared to those with grade 3 or 4 cancers in multivariate analysis. As noted above, grade is often not independent of stage, since the majority of Stage IA cancers are also grade 1. Grade also is not independent of histology in epithelial cancers, since several histological types, including mucinous and endometrioid, are usually low-grade, have a more indolent behavior, and are more likely to be confined to one ovary.[10,11]

Histology is also closely tied to both stage and grade, as noted above.[12] The histologies most commonly associated with long-term survival are endometrioid, clear cell, and mucinous; consistent with previous reports.[5] It is not surprising that endometrioid and mucinous cancers should have a generally favorable prognosis, since they are typically also low-grade and low stage.[10-12] Clear cell cancers are a distinct entity that appears to have two different behaviors. Many clear cell cancers are early stage and often associated with endometriosis, and therefore have a better prognosis than high-grade serous cancers.[10,13] In contrast, advanced stage clear cell cancers tend to have a poorer survival compared to high-grade serous cancers, probably due to relative chemotherapy resistance[10,13,14].

One of the most surprising findings was that nearly a third of all long-term survivors had Stages III and IV epithelial cancer, including serous cancers. The explanation for this is unclear, but there are several possibilities. Improved surgical techniques that result in high percentage of patients with no or minimal residual disease have improved outcomes.[15] The use of concomitant intraperitoneal and intravenous adjuvant chemotherapy has been associated with prolonged survival with a median overall survival of 110 months in patients debulked to no residual disease.[16] Advanced stage ovarian cancer patients who are BRCA 1 or 2 mutation carriers have an improved survival compared to those without these mutations.[17,18] It may be that there are somatic (as opposed to germline) genomic alterations that may account for long-term survival in patients with the same histology,[19]. Unfortunately, the cancer registry does not have information on the completeness of surgical debulking, use of intraperitoneal chemotherapy, BRCA mutation status, or genomic data, so these should be topics of future investigation.

Consistent with earlier studies, [5,6,20-24] age had a great impact on overall survival in epithelial ovarian cancer and long-term survivors were more likely to be women under age 50. Young women are more likely to have low stage and low-grade epithelial cancers[21] which points to a more favorable biological behavior, however the better prognosis for younger women persisted after adjustment for stage, grade, and histology and was also seen in patients with advanced stage disease similar to prior studies.[24,25] Better performance status may allow younger women to tolerate more aggressive surgery and chemotherapy.

Long-term survival may bring its own challenges beyond worry about recurrence. Studies have shown that ovarian cancer patients are challenged with problems of anxiety, fatigue, sexual, social, and financial problems,[26] which should be amenable to appropriate interventions. These studies highlight that physicians, especially those who provide primary care, should be prepared to address cancer survivorship needs in this group of patients.

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Table 1

Characteristics of patients with epithelial ovarian cancer diagnosed 1994-2001, California

Variables	Frequency (%) (N = 11,541)
Age (years)	
18-50	2938 (25.46)
51-64	3382 (29.30)
65-74	2707 (23.46)
75+	2514 (21.78)
Race	
Non-Hispanic White	8464 (73.34)
Non-Hispanic Black	496 (4.30)
Hispanic	1534 (13.29)
Asian/Pacific Islander	967 (8.38)
Other/Unknown	80 (0.69)
Socioeconomic status	
Low	3665 (31.76)
Medium	3957 (34.29)
High	3919 (33.96)
Rural urban residence	
Urban	11207 (97.11)
Small town	184 (1.59)
Rural	150 (1.30)
Tumor grade	
Grade I and II	3104 (26.90)
Grade III and IV	5295 (45.88)
Grade and differentiation not stated	3142 (27.22)
Stage categories	
Stage I	2228 (19.31)
Stage II	951 (8.24)
Stage III	5173 (44.82)
Stage IV	2559 (22.17)
Unknown	630 (5.46)
Histology types	
Serous	5547 (48.06)
Mucinous	541 (4.69)
Clear Cell	612 (5.30)
Endometrioid	1392 (12.06)
Carcinoma, not otherwise specified	2679 (23.21)
Other	770 (6.67)
Insurance types	
Private/Government	4929 (42.71)

Variables	**Frequency (%) (N = 11,541)**
Medicaid/Low income	733 (6.35)
Medicare	2878 (24.94)
Insured, NOS	1035 (8.97)
Not insured	256 (2.22)
Unknown	1710 (14.82)
Volume of treatment hospital	
Low (0-10 cases)	548 (4.77)
Medium (11-40 cases)	2965 (25.79)
High (> 40 cases)	7982 (69.44)

Table 2

Characteristics of patients with epithelial ovarian cancer diagnosed 1994-2001, California, by length of survival.

	< 2 years (N=4343, 37.6%)	2-5 years (N=2534, 22.0%)	5-10 years (N=1082, 9.4%)	>10 years (N=3582, 31.0%)
	N (%)	N (%)	N (%)	N (%)
Age (years)				
18-50	576 (13.26)	544 (21.47)	284 (26.25)	1534 (42.83)
51-64	942 (21.69)	839 (33.11)	379 (35.03)	1222 (34.12)
65-74	1134 (26.11)	706 (27.86)	281 (25.97)	586 (16.36)
75+	1691 (38.94)	445 (17.56)	138 (12.75)	240 (6.70)
Race				
Non-Hispanic White	3263 (75.13)	1933 (76.28)	812 (75.05)	2456 (68.57)
Non-Hispanic Black	249 (5.73)	100 (3.95)	28 (2.59)	119 (3.32)
Hispanic	522 (12.02)	319 (12.59)	150 (13.86)	543 (15.16)
Asian/Pacific Islander	282 (6.49)	168 (6.63)	88 (8.13)	429 (11.98)
Socioeconomic status				
Low	1552 (35.74)	708 (27.94)	329 (30.41)	1076 (30.04)
Medium	1516 (34.91)	860 (33.94)	369 (34.10)	1212 (33.84)
High	1275 (29.36)	966 (38.12)	384 (35.49)	1294 (36.13)
Rural/urban residence				
Urban	4231 (97.42)	2454 (96.84)	1038 (95.93)	3484 (97.26)
Small town	60 (1.38)	49 (1.93)	21 (1.94)	54 (1.51)
Rural	52 (1.20)	31 (1.22)	23 (2.13)	44 (1.23)
Tumor grade				
Grade I and II	647 (14.90)	532 (20.99)	302 (27.91)	1623 (45.31)
Grade III and IV	1965 (45.25)	1522 (60.06)	610 (56.38)	1198 (33.45)
Grade not stated	1731 (39.86)	480 (18.94)	170 (15.71)	761 (21.25)
Stage categories				
Stage I	161 (3.71)	120 (4.74)	110 (10.17)	1837 (51.28)
Stage II	206 (4.74)	141 (5.56)	111 (10.26)	493 (13.76)
Stage III	2028 (46.70)	1523 (60.10)	642 (59.33)	980 (27.36)
Stage IV	1541 (35.48)	657 (25.93)	180 (16.64)	181 (5.05)
Unknown	407 (9.37)	93 (3.67)	39 (3.60)	91 (2.54)
Histology types				
Serous	1823 (41.98)	1673 (66.02)	699 (64.60)	1352 (37.74)
Mucinous	213 (4.90)	56 (2.21)	23 (2.13)	249 (6.95)
Clear Cell	163 (3.75)	60 (2.37)	30 (2.77)	359 (10.02)
Endometrioid	210 (4.84)	217 (8.56)	134 (12.38)	831 (23.20)
Carcinoma, not otherwise specified	1709 (39.35)	464 (18.31)	147 (13.59)	359 (10.02)
Other	225 (5.18)	64 (2.53)	49 (4.53)	432 (12.06)
Insurance types				

	< 2 years (N=4343, 37.6%)	2-5 years (N=2534, 22.0%)	5-10 years (N=1082, 9.4%)	>10 years (N=3582, 31.0%)
	N (%)	N (%)	N (%)	N (%)
Private/Government	1557 (35.85)	1155 (45.58)	489 (45.19)	1728 (48.24)
Medicaid/Low income	251 (5.78)	157 (6.20)	73 (6.75)	252 (7.04)
Medicare	1389 (31.98)	667 (26.32)	301 (27.82)	521 (14.54)
Insured, not otherwise specified	273 (6.29)	229 (9.04)	82 (7.58)	451 (12.59)
Not insured	88 (2.03)	50 (1.97)	16 (1.48)	102 (2.85)
Unknown	785 (18.08)	276 (10.89)	121 (11.18)	528 (14.74)
Volume of hospital				
Low	256 (5.93)	92 (3.64)	35 (3.25)	165 (4.62)
Medium	1279 (29.64)	591 (23.38)	229 (21.26)	866 (24.22)
High	2780 (64.43)	1845 (72.98)	813 (75.49)	2544 (71.16)

Table 3

Predictors of long-term survival for patients with epithelial ovarian cancer diagnosed 1994-2001, California

Variables	Crude ORs	Adjusted* ORs
Age (years)		
18-50	4.5 (3.5, 5.8)	4.1 (2.9, 5.8)
51-64	2.7 (2.1, 3.5)	3.5 (2.5, 4.9)
65-74	1.7 (1.3, 2.1)	2.1 (1.5, 2.9)
75+	Ref	Ref
Race		
Non-Hispanic White	Ref	Ref
Non-Hispanic Black	1.0 (0.7, 1.5)	1.3 (0.8, 2.1)
Hispanic	1.4 (1.1, 1.7)	1.2 (0.9, 1.5)
Asian/Pacific Islander	1.9 (1.5, 2.5)	1.3 (1.0, 1.8)
Socioeconomic status		
High	0.9 (0.8, 1.1)	1.0 (0.8, 1.3)
Medium	0.9 (0.8, 1.1)	1.0 (0.8, 1.2)
Low	Ref	Ref
Tumor grade		
Grade I and II	3.4 (3.0, 4.0)	1.6 (1.4, 2.0)
Grade III and IV	Ref	Ref
Stage categories		
Stage I	50.3 (35.9, 70.5)	30.9 (22.3, 45.7)
Stage II	13.0 (9.3, 18.1)	10.7 (7.5, 12.3)
Stage III	2.2 (1.7, 2.8)	2.2 (1.7, 2.9)
Stage IV	Ref	Ref
Histology types		
Serous	Ref	Ref
Mucinous	6.2 (4.3, 9.0)	2.1 (1.4, 3.3)
Clear Cell	6.3 (4.2, 9.5)	1.9 (1.2, 3.2)
Endometrioid	4.9 (4.1, 5.9)	1.8 (1.4, 2.3)
Insurance types		
Private/Government	Ref	Ref
Medicaid/Low income	1.1 (0.9, 1.5)	1.0 (0.7, 1.4)
Medicare	0.6 (0.5, 0.7)	1.2 (0.9, 1.5)
Insured, not otherwise specified	1.3 (1.0, 1.6)	1.1 (0.8, 1.4)
Not insured	1.3 (0.8, 2.0)	0.9 (0.5, 1.6)
Volume of hospital	0.999 (0.998, 1.000)	1.0 (0.999, 1.001)

* Each variable adjusted for all other predictors

Table 4

Characteristics of patients diagnosed with Stage III and IV epithelial ovarian cancer 1994-2001 in California by length of survival

Variables	< 2 years (N=2141)	2-5 years (N=1752)	5- 10 years (N=689)	>10 years (N=954)	Chi-square test
	N (%)	N (%)	N (%)	N (%)	p-value
Age (years)					<.001
18-50	337 (27.33)	390 (31.63)	182 (14.76)	324 (26.28)	
51-64	551 (31.06)	598 (33.71)	251 (14.15)	374 (21.08)	
65-74	584 (40.19)	500 (34.41)	182 (12.53)	187 (12.87)	
75+	669 (62.17)	264 (24.54)	74 (6.88)	69 (6.41)	
Race					<.001
Non-Hispanic White	1616 (38.60)	1366 (32.62)	527 (12.59)	678 (16.19)	
Non-Hispanic Black	122 (51.48)	61 (25.74)	14 (5.91)	40 (16.88)	
Hispanic	244 (34.96)	210 (30.09)	99 (14.18)	145 (20.77)	
Asian/Pacific Islander	147 (38.18)	105 (27.27)	48 (12.47)	85 (22.08)	
Tumor grade					
Grade I and II	428 (31.42)	416 (30.54)	194 (14.24)	324 (23.79)	
Grade III and IV	1237 (38.11)	1104 (34.01)	410 (12.63)	495 (15.25)	<.001
Grade and differentiation not stated	476 (51.29)	232 (25.00)	85 (9.16)	135 (14.55)	
Histology types					
Serous	1675 (37.12)	1526 (33.81)	588 (13.03)	724 (16.04)	
Mucinous	182 (63.86)	42 (14.74)	18 (6.32)	43 (15.09)	<.001
Clear Cell	124 (61.39)	23 (11.39)	9 (4.46)	46 (22.77)	
Endometrioid	160 (29.85)	161 (30.04)	74 (13.81)	141 (26.31)	