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CLINICAL RESEARCH



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ollection G	BC 3	Yixian Yu	
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Ва	ckground:	Patients with primary breast cancer following primary or reports of the survival outcomes of this cohort are rare. search was to investigate the survival outcomes of pat cancer.	varian cancer do not comprise a large clinical entity, and The purpose of this retrospective population-based re- tients with primary breast cancer after primary ovarian
Material	/Methods:	A cohort of patients diagnosed with primary breast can 2014 was drawn from the National Cancer Institute's S base. Cox proportional hazards survival regression ana all survival (OS), cancer-specific survival (CSS), and inde	cer following primary ovarian cancer between 1973 and Gurveillance Epidemiology and End Results (SEER) data- Ilysis and Kaplan-Meier were applied to calculate over- ependent predictors of CSS.
	Results:	A total of 1455 patients with primary breast cancer follo and 10-year OS rates for the entire cohort were 81.7% ar were 84.2% and 74.3% for ovarian cancer, and 76.0% analysis revealed that independent predictors of ovaria and histological subtype.	wing primary ovarian cancer were identified. The 5-year nd 67.4%, respectively. The 5-year and 10-year CSS rates and 67.8% for breast cancer, respectively. Multivariate In cancer CSS include age, cancer stage, diagnosis time,
Co	nclusions:	Patients diagnosed with breast cancer following ovaria ian cancer stage, ovarian cancer histological type, and	n cancer have better survival rates. Patients age, ovar- time of diagnose affect the survival rate.
MeSH H	Keywords:	Ovarian Neoplasms • SEER Program • Triple Negativ	ve Breast Neoplasms
Ful	l-text PDF:	https://www.medscimonit.com/abstract/index/idArt/9	914163
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Survival Outcomes of Patients with Primary Breast Cancer Following Primary Ovarian Cancer



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Authors' Contribution:

Study Design A

Data Collection B

Statistical Analysis C

Data Interpretation D

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Background

Ovarian cancer and breast cancer are the most common malignancies in women. Ovarian cancer is the fifth major cause of cancer mortality among women with 22 440 new cases and 14 080 deaths in the United States (US) during 2017 [1]. In addition, approximately 252 710 new cases and 40 610 deaths due to invasive breast cancer are expected to occur among US women in 2017 [2]. Women with breast cancer have a higher incidence of second primary cancers, particularly ovarian and endometrial cancer [3,4]. Similarly, patients diagnosed with ovarian cancer have an increased incidence of breast cancer. The actuarial risk of developing breast cancer is 7.8% in the 10-year period following ovarian cancer [5]. Most ovarian cancer patients have advanced disease at the time of diagnosis, resulting in poor long-term survival [6], and the 5-year survival (OS) for those with ovarian cancer is only 45.6% [7]. However, improved OS and cancer-specific survival (CSS) have been reported for patients with breast cancer following an ovarian cancer diagnosis [8,9].

Unfortunately, most studies have small sample sizes, and no population-based statistics exist regarding the survival outcomes of women with primary breast cancer following primary ovarian cancer. The main aim of this retrospective populationbased analysis was to estimate the survival outcomes and clinical characteristics of patients with primary breast cancer after primary ovarian cancer from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database.

Material and Methods

Data source

A cohort of patients diagnosed with primary breast cancer following primary ovarian cancer from 1973 to 2014 was drawn from the National Cancer Institute's SEER database. The patient data in the present study were derived from 18 population-based cancer registries, as released in November 2016. Patient data are de-identified and made available to the public for research purposes. Because the SEER program is an openaccess resource and patients are de-identified, this study was exempt from ethical review and does not contain any personally identifiable information. The SEER program statistical analysis software package (SEER*Stat version 8.3.4) was used to extract the data.

Clinical information

Demographic variables (marital status, year of diagnosis, race, registration area, age at diagnosis, and follow-up of patient status), and clinicopathological variables (tumor grade,

American Joint Committee on Cancer (AJCC) stage, histological subtype, survival and cause of death, and associated treatment) were extracted using the "case-listing" option. Primary breast cancer cases and primary ovarian cancer cases were eligible for the study, and cases of metastatic tumors to the breast and ovary from other origins were excluded. Thus, only primary breast cancer and primary ovarian cancer patients were included, and patients with a clinical history of other cancers were excluded. Finally, 1455 patients with breast cancer following ovarian cancer were identified (Figure 1).

The ICD-0-3 site/histology validation list and the World Health Organization histological classification were used to identify ovarian cancer and breast cancer. The cancer stage was based on the AJCC staging system. Ovarian cancer staging between 1988 and 2003 was defined by the 3rd edition of the AJCC TNM categories. Ovarian cancer staging between 2004 and 2014 was derived from the 6th edition of AJCC TNM categories. Breast cancer staging between 1988 and 2014 was determined by an adjusted version of the categories of the 6th edition of the AJCC TNM system. In the SEER database, the cause of death is linked to the National Death Index and state mortality records for validation.

Statistical analysis

The diagnosis time interval from ovarian cancer to breast cancer was calculated. The CSS and OS were analyzed as the principal outcomes using the Kaplan-Meier method. The magnitudes of statistical significance were expressed as the hazard ratio (HR) and 95% confidence interval (CI). Univariate and multivariate Cox hazard regression analyses were also applied to determine independent predictors of CSS in patients with breast cancer and ovarian cancer. All statistical analyses were conducted using IBM SPSS 24.0 and Graph Pad Prism 7.0. P<0.05 was considered statistically significant.

Results

Over the past 41 years, 1455 patients were identified who had primary breast cancer following primary ovarian cancer in the SEER database. There were 1.05% of ovarian cancer patients with chemotherapies who developed breast cancers, while 1.03% of patients developed breast cancers who were reported without chemotherapies. The demographic and clinicopathological characteristics are presented in Table 1.

The median diagnosis time from ovarian cancer to breast cancer was 60 months (range, 1–453 months). The median age at ovarian cancer diagnosis was 58 years (range, 10–94 years).



Figure 1. Screening flow chart of patients diagnosed with breast cancer following ovarian cancer.

The majority of the population were white (87.1%), and 69.0% were younger than 65 years. The median age at breast cancer diagnosis was 65 years (range, 22–97 years), and 47.7% were younger than 65 years of age. Of the 1455 patients, 94.8% underwent ovarian cancer-related surgeries, 87.9% underwent breast cancer-related surgeries, 50.7% received ovarian cancer-related chemotherapies, 27.9% received breast cancer-related chemotherapies, 6.1% had ovarian cancer-related radiation therapies, but the detailed surgical approaches, the specific chemotherapy regimens, and the concrete radiation therapies were not known.

The multivariate survival analysis showed that independent predictors of ovarian cancer CSS were age at diagnosis (P<0.001), cancer stage (P<0.001), diagnosis time (P=0.005), and histological types (P=0.001), while age at diagnosis (P<0.001), tumor grade (P=0.044), cancer stage (P<0.001), and diagnosis time (P<0.001) were independent predictors of breast cancer CSS after adjusting for age at diagnosis, marital status, tumor grade, year of diagnosis, stage, chemotherapy, radiation, and histological types. However, chemotherapy was negatively associated with ovarian cancer CSS (P<0.001) and breast cancer CSS (P=0.019) (Table 2). The differences in these adjusted variables were statistically significant in univariate analysis of CSS (Table 3).

Of the 1455 patients, 257 patients (26.7%) died of ovarian cancer, 212 patients (23.1%) died of breast cancer, and 272 patients (18.7%) died of other causes. Kaplan-Meier survival analysis showed that a higher survival benefit was observed in patients with breast cancer following ovary cancer than ovary cancer patients without secondary or more malignant tumors (P<0.001). The 5-year and the 10-year OS rates for the entire cohort of 1455 patients were 81.7% and 67.4%, 17.0% and 6.5% for 110 639 ovary cancer patients, respectively (Figure 2). Survival analysis showed that the 5-year and the 10-year CSS rates of ovarian cancer were 84.2% and 74.3% (Figure 3), and those of breast cancer were 76.0% and 67.8% (Figure 4), respectively.

The median diagnosis time intervals from ovarian cancer to breast cancer were 63 months (range 1~453 months); the mean interval was 87.91 months. As shown in Figure 5, in the entire

 Table 1. Demographic and clinicopathological characteristics of ovarian cancer and breast cancer patients.

Characteristic	n (%)		Characteristic	n (%)	
Race			Ovarian cancer		
White	1268	(87.1%)	Age at diagnosis		
Black	94	(6.5%)	<50	374	(25.7%)
Other/unknown	93	(6.4%)	50–64	630	(43.3%)
Marital status			65–74	304	(20.9)
Married	842	(57.9%)	≥75	147	(10.1%)
Divorced	114	(7.8%)	Tumor grade		
Separated	23	(1.6%)	Grade I	161	(11.1%)
Single	238	(16.4%)	Grade II	248	(17.0%)
Widowed	195	(13.4%)	Grade III	460	(31.6%)
Unknown	43	(3.0%)	Grade IV	138	(9.5%)
Breast cancer			Unknown	448	(30.8%)
Age at diagnosis			Histology		
<50	163	(11.2%)	Serous	556	(38.2%)
50–64	531	(36.5%)	Mucinous	162	(11.1%)
65–74	400	(27.5%)	Endometrioid	224	(15.4%)
≥75	361	(24.8%)	Clear cell	88	(6.0%)
Tumor grade			Germ cell	29	(2.0%)
Grade I	231	(15.9%)	Sex cord/stromal	45	(3.1%)
Grade II	456	(31.3%)	Others	351	(24.1%)
Grade III	457	(31.4%)	Stage (AJCC3) [#]		
Grade IV	20	(1.4%)	I	214	(14.7%)
Unknown	291	(20.0%)	II	88	(6.0%)
Histology			III	136	(9.3%)
Infiltrating duct carcinoma	1029	(70.7%)	IV	89	(6.1%)
Others	426	(29.3%)	Others	928	(63.8%)
Stage (AJCC6)*			Stage (AJCC6)##		
1	635	(43.6%)	1	124	(8.5%)
II	347	(23.8%)	II	50	(3.4%)
III	116	(8.0%)	III	133	(9.1%)
IV	64	(4.4%)	IV	80	(5.5%)
Others	293	(20.1%)	Others	1068	(73.4%)

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Table 1 continued. Demographic and clinicopathological characteristics of ovarian cancer and breast cancer patients.

Characteristic	n (%)		Characteristic	n (%)	
Year of diagnosis		Year of diagnosis			
1973–1982	68	(4.7%)	1973–1982	257 (17.7%)	
1983–1992	185	(12.7%)	1983–1992	289 (19.9%)	
1993–2002	326	(22.4%)	1993–2002	442 (30.4%)	
2003–2014	876	(60.2%)	2003–2014	467 (32.1%)	
Surgery			Surgery		
Yes	1279	(87.9%)	Yes	1379 (94.8%)	
Others	176	(12.1%)	Others	76 (5.2%)	
Chemotherapy			Chemotherapy		
Yes	406	(27.9%)	Yes	869 (50.7%)	
No/Unknown	1049	(72.1%)	No/Unknown	586 (40.3%)	
Radiation			Radiation		
Yes	481	(33.1%)	Yes	89 (6.1%)	
No	972	(66.9%)	No	1366 (93.9%)	

* Breast cancer stage adjusted from AJCC 6th Stage (1988+); [#] ovarian cancer stage derived from AJCC 3th Stage (1998–2003); ^{##} ovarian cancer stage derived from AJCC 6th Stage (2004+).

Table 2. Multivariate survival analysis of ovarian cancer and breast cancer patients.

Verichies	0	varian cancer CS	S	Breast cancer CSS		
variables	HR	95%CI	<i>p</i> -Value	HR	95%CI	<i>p</i> -Value
Marital status			0.051			0.111
Married	Reference			Reference		
Divorced	0.91	0.56-1.48		1.11	0.58–2.09	
Separated	1.78	0.65–4.85		1.85	0.73–4.70	
Single	0.75	0.51-1.11		0.69	0.45-1.07	
Widowed	1.47	1.03-2.10		1.43	0.96–2.14	
Unknown	1.45	0.72–2.91		1.20	0.37–3.84	
Age at diagnosis			<0.001			<0.001
<50	Reference			Reference		
50–64	1.17	0.82–1.68		0.60	0.39–0.93	
65–74	2.52	1.68-3.76		0.94	0.56-1.51	
≥75	4.40	2.76-7.02		2.17	1.33–3.52	
Tumor grade			0.092			0.044
Grade I	Reference			Reference		
Grade II	2.21	0.97–5.03		2.20	1.18–4.13	

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Variables	Ovarian cancer CSS			Breast cancer CSS			
Vallables	HR	95%CI	p-Value	HR	95%CI	<i>p</i> -Value	
Grade III	2.14	0.97–4.71		2.63	1.43–4.83		
Grade IV	2.16	0.92–5.07		1.98	0.61–6.39		
Unknown	2.81	1.27–6.19		2.38	1.21–4.68		
Stage (AJCC)*			<0.001			<0.001	
I	Reference			Reference			
II	1.87	0.92–3.80		2.10	1.34–3.32		
	5.10	2.85–9.11		6.62	3.94–11.12		
IV	6.88	3.78–12.53		23.45	13.44–40.93		
Others	4.09	2.20–7.61		3.38	1.20–5.71		
Year of diagnosis			0.005			<0.001	
1973–1982	Reference			Reference			
1983–1992	0.46	0.28–0.75		0.75	0.40-1.41		
1993–2002	0.47	0.28–0.77		0.65	0.33–1.29		
2003–2014	0.39	0.22–0.67		0.27	0.13–0.55		
Histology			0.001				
Serous	Reference						
Mucinous	0.46	0.25–0.86					
Endometrioid	0.53	0.32–0.88					
Clear cell	0.46	0.20–1.08					
Germ cell	0.00	0.00-6.508E+95					
Sex cord/stromal	0.53	0.21–1.34					
Others	1.27	0.95–1.69					
Histology						0.498	
Infiltrating duct carcinoma				Reference			
Others				1.11	0.82–1.52		
Chemotherapy							
Yes	Reference		<0.001	Reference		0.019	
No/unknown	0.50	0.36–0.69		0.67	0.48–0.94		
Radiation						0.284	
Yes				Reference			
No				1.20	0.86-1.68		

Table 2 continued. Multivariate survival analysis of ovarian cancer and breast cancer patients.

* American Joint Committee on Cancer stage,

Table 3. Univariate survival analysis of ovarian cancer and breast cancer patients.

ValuationHR95%CIp-ValueHR95%CIp-ValueRace0.1340.120.120.12WhiteReferenceReference0.120.350.87-2.41Black1.440.89-2.331.450.87-2.410.0010.001Marital Status-0.001-0.0010.0010.0010.001MaritedReference0.0010.40-1.360.0010.001Separated1.260.47-3.411.820.75-4.460.01Single0.730.50-1.060.670.45-1.000.01Widowed2.561.89-3.581.891.30-2.75-0.001Widowed2.561.89-3.580.690.16-1.53-0.00150-641.300.93-1.830.670.44-1.01-0.00150-641.300.93-1.830.670.44-1.01-0.00150-641.300.93-1.830.670.44-1.01-0.00150-641.300.93-1.830.670.44-1.01-0.00150-641.300.87-8.710.6710.46-1.13-0.00150-641.300.87-8.710.6710.46-1.13-0.00167-742.551.78-3.710.710.46-1.13-0.00167-641.322.48-11.444.172.33-4.47-0.001Grade II5.222.311.25-4.262.311.25-4.26Grade IV4.531.89-1.90-0.001-0.001IReference <td< th=""><th>Variables</th><th>0</th><th>varian cancer CS</th><th>S</th><th colspan="4">Breast cancer CSS</th></td<>	Variables	0	varian cancer CS	S	Breast cancer CSS			
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Separated 1.26 0.47-3.41 1.82 0.75-4.46 Single 0.73 0.50-1.06 0.67 0.45-1.00 Widowed 2.56 1.89-3.58 1.89 1.30-2.75 Unknown 1.15 0.58-2.26 0.49 0.16-1.53 Age at diagnosis - <0.001	Divorced	0.92	0.57-1.49		0.74	0.40-1.36		
Single0.730.50-1.060.670.45-1.00Widowed2.561.89-3.581.891.30-2.75Unknown1.150.58-2.260.490.16-1.53Age at diagnosis0.001-50ReferenceReference-0.730.44-1.0150-641.300.93-1.830.670.44-1.01-65-742.561.76-3.710.710.46-1.11-65-742.561.78-3.710.710.46-1.11-7755.803.87-8.711.641.07-2.52-Grade IReferenceGrade I2.761.22-6.222.311.25-4.26-Grade III5.322.48-11.444.172.33-4.47-Grade III5.322.48-11.444.172.33-4.47-Grade IV4.672.15-10.116.853.76-12.49-Unknown4.672.15-10.116.853.76-12.49-I2.871.43-5.742.721.77-4.17-II8.454.89-14.7010.136.46-15.88-V1.4097.97-24.9230.541.87-4.97-IP37-1982Ster0.723.70-11973-1982Reference1983-19920.570.37-0.880.780.43-1.32-1973-1982Reference1	Separated	1.26	0.47-3.41		1.82	0.75–4.46		
Widowed2.561.89–3.581.891.30–2.75Unknown1.150.58–2.260.490.16–1.53Age at diagnosis < 0.001 < 0.001 < 0.001 550ReferenceReference < 0.007 0.44–1.0155–742.561.78–3.710.710.46–1.1165–742.563.87–8.711.641.07–2.5275.803.87–8.711.641.07–2.52Grade IReference < 0.001 < 0.001 Grade I2.761.22–6.222.311.25–4.26Grade III5.322.48–11.444.172.33–4.47Grade III5.322.48–11.444.172.33–4.47Grade IV4.531.98–10.344.441.45–13.63Unknown4.672.15–10.116.853.76–12.49II2.871.43–5.742.721.77–4.17III8.454.89–14.7010.136.46–15.88IV14.099.72-4.923.05.418.73–49.79Others5.903.49–10.27.204.75–10.92II9.499.49–10.29.00.47.1973–1982Reference < 0.001 1983–19920.570.37–0.880.780.43–1.321993–20020.620.43–0.900.490.28–0.871993–20240.680.46–1.000.180.10–0.32	Single	0.73	0.50–1.06		0.67	0.45-1.00		
Unknown 1.15 0.58-2.26 0.49 0.16-1.53 Age at diagnosis (0.001 (0.001 C50 Reference Reference Reference Reference Reference Reference Reference C0.001 55-64 1.30 0.93-1.83 0.67 0.44-1.01 Colspan="2">(0.44-1.01 65-74 2.56 1.78-3.71 0.71 0.46-1.11 275 5.80 3.87-8.71 0.61 0.17-2.52 Tumor grade 2.56 1.78-3.71 0.61 0.17-2.52 Grade II 2.76 1.22-6.22 2.31 1.25-4.26 Grade III 5.32 2.48-11.44 4.17 2.33-447 Grade III 5.32 2.48-11.41 4.44 1.45-13.63 Unknown 4.67 2.15-10.11 6.85 3.76-12.49 JUnknown 4.67 2.15-10.11 6.85 3.76-12.49 I 2.87 1.43-5.74 2.72 1.77-4.17 III 8.45 4.89-14.70 10.13 6.46-15.88 IV 14.09 <th< td=""><td>Widowed</td><td>2.56</td><td>1.89–3.58</td><td></td><td>1.89</td><td>1.30–2.75</td><td></td></th<>	Widowed	2.56	1.89–3.58		1.89	1.30–2.75		
Age at diagnosis .0.001 .0.001 <50	Unknown	1.15	0.58–2.26		0.49	0.16–1.53		
<50 Reference Reference 50-64 1.30 0.93-1.83 0.67 0.44-1.01 65-74 2.56 1.78-3.71 0.71 0.46-1.11 ≥75 5.80 3.87-8.71 1.64 1.07-2.52 Tumor grade Grade I Reference Reference Grade II 2.76 1.22-6.22 2.31 1.25-4.26 Grade II 5.32 2.48-11.44 4.17 2.33-4.47 Grade IV 4.53 1.98-10.34 4.44 1.45-13.63 Unknown 4.67 2.15-10.11 6.85 3.76-12.49 II 2.87 1.43-5.74 2.72 1.77-4.17 III 2.87 1.43-5.74 2.72 1.77-4.17 IV 14.09 7.97-24.92 3.054 1.87.3-49.79 Others 5.90 3.49-10.2 7.20 4.75-10.92 Others 5.90 3.49-10.2 7.00	Age at diagnosis			<0.001			<0.001	
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≥755.803.87-8.711.641.07-2.52Tumor grade < 0.001 < 0.001 < 0.001 Grade IReferenceReferenceGrade II2.761.22-6.222.311.25-4.26Grade III5.322.48-11.444.172.33-4.47Grade IV4.531.98-10.344.441.45-13.63Unknown4.672.15-10.116.853.76-12.49Stage (AJCC)* < 0.001 < 0.001 < 0.001 IReference < 0.001 < 0.001 IReference < 0.001 < 0.001 IReference < 0.001 < 0.001 II2.871.43-5.742.721.77-4.17III2.871.43-5.742.721.77-4.17Others5.903.49-10.27.204.75-10.92Ver of diagnosis 0.047 < 0.001 < 0.001 1973-1982Reference < 0.001 < 0.78 $0.43-1.32$ 1993-20020.620.43-0.900.490.28-0.872003-20140.680.46-1.000.180.10-0.32	65–74	2.56	1.78–3.71		0.71	0.46–1.11		
Tumor grade < (0.001 Grade I Reference Reference Grade II 2.76 1.22-6.22 2.31 1.25-4.26 Grade II 5.32 2.48-11.44 4.17 2.33-4.47 Grade IV 4.53 1.98-10.34 4.44 1.45-13.63 Unknown 4.67 2.15-10.11 6.85 3.76-12.49 Unknown 4.67 2.15-10.11 6.85 3.76-12.49 I Reference <0.001	≥75	5.80	3.87-8.71		1.64	1.07–2.52		
Grade I Reference Grade II 2.76 1.22-6.22 2.31 1.25-4.26 Grade II 5.32 2.48-11.44 4.17 2.33-4.47 Grade IV 4.53 1.98-10.34 4.44 1.45-13.63 Unknown 4.67 2.15-10.11 6.85 3.76-12.49 Stage (AJCC)* < I Reference Reference	Tumor grade			<0.001			<0.001	
Grade II 2.76 1.22-6.22 2.31 1.25-4.26 Grade III 5.32 2.48-11.44 4.17 2.33-4.47 Grade IV 4.53 1.98-10.34 4.44 1.45-13.63 Unknown 4.67 2.15-10.11 6.85 3.76-12.49 Stage (AJCC)*	Grade I	Reference			Reference			
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Grade IV 4.53 1.98–10.34 4.44 1.45–13.63 Unknown 4.67 2.15–10.11 6.85 3.76–12.49 Stage (AJCC)* <0.001 <0.001 <0.001 I Reference Reference <0.001 II 2.87 1.43–5.74 2.72 1.77–4.17 III 8.45 4.89–14.70 10.13 6.46–15.88 IV 14.09 7.97–24.92 30.54 18.73–49.79 Others 5.90 3.49–10.2 7.20 4.75–10.92 V 14.09 7.97–24.92 30.54 18.73–49.79 Others 5.90 3.49–10.2 7.20 4.75–10.92 IP73–1982 Reference <0.001 <0.001 1973–1982 0.57 0.37–0.88 0.78 0.43–1.32 1993–2002 0.62 0.43–0.90 0.49 0.28–0.87 2003–2014 0.68 0.46–1.00 0.18 0.10–0.32	Grade III	5.32	2.48-11.44		4.17	2.33–4.47		
Unknown 4.67 2.15–10.11 6.85 3.76–12.49 Stage (AJCC)* <0.001 <0.001 I Reference Reference <0.001 II 2.87 1.43–5.74 2.72 1.77–4.17 III 8.45 4.89–14.70 10.13 6.46–15.88 IV 14.09 7.97–24.92 30.54 18.73–49.79 Others 5.90 3.49–10.2 7.20 4.75–10.92 Vear of diagnosis 0.047 <0.001 <0.001 1973–1982 Reference <0.001 <0.001 1983–1992 0.57 0.37–0.88 0.78 0.43–1.32 1993–2002 0.62 0.43–0.90 0.49 0.28–0.87 2003–2014 0.68 0.46–1.00 0.18 0.10–0.32	Grade IV	4.53	1.98–10.34		4.44	1.45-13.63		
Stage (AJCC)* < < 0.001 I Reference Reference II 2.87 1.43-5.74 2.72 1.77-4.17 III 8.45 4.89-14.70 10.13 6.46-15.88 IV 14.09 7.97-24.92 30.54 18.73-49.79 Others 5.90 3.49-10.2 7.20 4.75-10.92 Vear of diagnosis 0.047 <	Unknown	4.67	2.15-10.11		6.85	3.76-12.49		
I Reference Reference II 2.87 1.43–5.74 2.72 1.77–4.17 III 8.45 4.89–14.70 10.13 6.46–15.88 IV 14.09 7.97–24.92 30.54 18.73–49.79 Others 5.90 3.49–10.2 7.20 4.75–10.92 Vear of diagnosis 0.047 <0.001	Stage (AJCC)*			<0.001			<0.001	
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III 8.45 4.89–14.70 10.13 6.46–15.88 IV 14.09 7.97–24.92 30.54 18.73–49.79 Others 5.90 3.49–10.2 7.20 4.75–10.92 Year of diagnosis 0.047 <0.001	II	2.87	1.43–5.74		2.72	1.77–4.17		
IV 14.09 7.97-24.92 30.54 18.73-49.79 Others 5.90 3.49-10.2 7.20 4.75-10.92 Year of diagnosis 0.047 <0.001 1973-1982 Reference <0.001	III	8.45	4.89-14.70		10.13	6.46-15.88		
Others 5.90 3.49–10.2 7.20 4.75–10.92 Year of diagnosis 0.047 <0.001 1973–1982 Reference Reference 1983–1992 0.57 0.37–0.88 0.78 0.43–1.32 1993–2002 0.62 0.43–0.90 0.49 0.28–0.87 2003–2014 0.68 0.46–1.00 0.18 0.10–0.32	IV	14.09	7.97–24.92		30.54	18.73–49.79		
Year of diagnosis 0.047 <0.001 1973-1982 Reference Reference 1983-1992 0.57 0.37-0.88 0.78 0.43-1.32 1993-2002 0.62 0.43-0.90 0.49 0.28-0.87 2003-2014 0.68 0.46-1.00 0.18 0.10-0.32	Others	5.90	3.49–10.2		7.20	4.75-10.92		
1973–1982 Reference Reference 1983–1992 0.57 0.37–0.88 0.78 0.43–1.32 1993–2002 0.62 0.43–0.90 0.49 0.28–0.87 2003–2014 0.68 0.46–1.00 0.18 0.10–0.32	Year of diagnosis			0.047			<0.001	
1983-19920.570.37-0.880.780.43-1.321993-20020.620.43-0.900.490.28-0.872003-20140.680.46-1.000.180.10-0.32	1973–1982	Reference			Reference			
1993-20020.620.43-0.900.490.28-0.872003-20140.680.46-1.000.180.10-0.32	1983–1992	0.57	0.37–0.88		0.78	0.43–1.32		
2003–2014 0.68 0.46–1.00 0.18 0.10–0.32	1993–2002	0.62	0.43-0.90		0.49	0.28–0.87		
	2003–2014	0.68	0.46-1.00		0.18	0.10-0.32		

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Table 3 continued. Univariate survival analysis of ovarian cancer and breast cancer patients.

Wastablas		Ovarian cancer CSS		Breast cancer CSS			
variables	HR	95%CI	p-Value	HR	95%CI	p-Value	
Histology			<0.001				
Serous	Reference						
Mucinous	0.30	0.17-0.55					
Endometrioid	0.31	0.19–0.50					
Clear cell	0.22	0.10-0.49					
Germ cell	0.00	0.00-3.17E+123					
Sex cord/stromal	0.50	0.20-1.21					
Others	1.21	0.92–1.58					
Histology						0.001	
Infiltrating duct carcinoma				Reference			
Others				1.61	1.22-2.14		
Chemotherapy			<0.001			<0.001	
Yes	Reference			Reference			
No/unknown	0.46	0.34–0.61		0.57	0.43–0.75		
Radiation			0.709			<0.001	
Yes	Reference						
No	0.90	0.51–1.57		1.96	1.44–2.67		

* American Joint Committee on Cancer stage.





group, 50.7% of the patients were diagnosed with breast cancer within 5 years after being diagnosed with ovarian cancer and 74.6% were diagnosed within 10 years. As the time after diagnosis increased, the number of patients diagnosed with breast cancer following ovarian cancer decreased.



Figure 3. Kaplan-Meier survival curves for cancer-specific survival according to the survival state of patients with ovarian cancer.

Discussion

To the best of our knowledge, few studies have evaluated the survival outcomes of patients with breast cancer after



Figure 4. Kaplan-Meier survival curves for cancer-specific survival according to survival state of patients with breast cancer.

a diagnosis of ovarian cancer. A previous study demonstrated that the 5-year OS rate of ovarian cancer was only 45.6% [7]. However, the survival rates of women with breast cancer following ovarian cancer differ from those of women with ovarian cancer who do not develop breast cancer. A recent study revealed that the 5-year and 10-year OS rates were 58.3% and 50% for BRCA mutation-associated ovarian cancer patients who developed breast cancer but 30.9% and 13.8% for BRCA mutation-associated ovarian cancer patients who did not develop breast cancer [8]. Our study showed that the 5-year and 10-year OS rates for the entire cohort were 81.7% and 67.4%, while the corresponding OS rates of ovarian cancer patients without secondary or more malignant tumors were 17.0% and 6.5%. Our results showed that patients diagnosed with breast cancer following ovarian cancer survived longer than ovarian cancer patients who do not develop breast cancer.

Younger patient age, early cancer stage, and newly diagnosed nonserous ovarian cancer were significantly associated with better CSS of ovarian cancer in our study. Choi et al. [10] also showed that advanced stage, older patient age, poor grade, and serous epithelial ovarian cancer may result in poor survival. Cancer staging is an important factor in determining the survival outcomes and prognosis of women with ovarian cancer. Most patients with advanced-stage cancer have a worse prognosis and die as a result of the disease [11]. Heintz et al. [12] found that the 5-year survival rates were 85%, 70%, 32%, and 18.6% for patients with stage I, IIA, IIIC, and IV disease respectively. Thus, 32.7% of women with ovarian cancer classified as early-stage (stage I, 23.2%; stage II, 9.5%) lived an extended period of time after developing breast cancer.

In addition, the inclusion of fewer serous (38.2%) and younger (<65 years, 69%) ovarian cancer patients may partially contribute to the improved survival. Most studies have reported



Figure 5. Distribution of time intervals between primary breast cancer and primary ovarian.

a low prognostic value for histological type, probably because of bias in analysis due to difficulties in diagnosis and/or small samples. However, in some studies, the serous type of ovarian cancer was an independent prognostic factor and tended to decrease survival [13,14]. Younger patients with epithelial ovarian cancer have been reported to have a better survival rate than older patients [11,15,16]. Moreover, from 1975-2004 to 2005-2011 the 5-year OS rate of ovarian cancer increased from 36.0% to 45.9% and from 74.8% to 90.7% for breast cancer [7]. Our study also found that diagnosis time was associated with better survival, which may be largely attributable to improvements in treatment. However, chemotherapy was negatively linked to ovarian cancer CSS. This may be because there had been more early-stage cases (132 stage I patients account for 38.9% in all kinds of stages) and less serous ovarian cancers cases (97 patients account for 28.6% in histology) in patients without chemotherapy, there had been had less early-stage cases (130 stage I patients account for 20.9% in all kinds of stages) and more serous ovarian cancers cases (297 patients account for 47.7% in histology) in patients with chemotherap.

Several studies have reported that approximately 15% of ovarian cancer patients, irrespective of family history, have BRCA1 or BRCA2 mutations [17], and that BRCA1/2-associated ovarian cancer is related to improved OS and progression-free survival (PFS) regardless of tumor stage, grade, or histological subtype [18–20]. BRCA1 or BRCA2 carrier status can be considered a factor influencing the survival rate. Whether BRCA has any effect on survival in this study remains unknown because of a lack of data regarding BRCA carriers. Although the SEER database lacks information on BRCA carriers, the aforementioned results suggest

that younger patient age, early cancer stage, newly diagnosed, and nonserous ovarian cancer can partly explain the good survival of women with breast cancer after ovarian cancer.

Available studies have shown that the median diagnosis time from ovarian cancer to breast cancer was 50.5–108 months [8,9]. McGee et al. [5] reported that the average diagnosis interval from ovarian cancer to breast cancer was 3.5 years. The aforementioned studies were all based on small sample sizes. The present population-based study showed that 50.7% of the patients were diagnosed with breast cancer within 5 years after a diagnosis of ovarian cancer and 74.6% were diagnosed within 10 years. A greater number of ovarian cancer patients were diagnosed at shorter the time interval, but as the time interval progressed, the ovarian cancer incidence gradually decreased. In our study, most breast cancer diagnoses occurred in the first several years after a diagnosis of ovarian cancer. Thus, breast cancer surveillance may need to be advocated during the first few years after a diagnosis of ovarian cancer. However, Gangi et al. [8] reported that 8.9% of BRCA1/2 mutation carriers who have a history of ovarian cancer developed breast cancer, and Vencken et al. [21] showed a 6% 5-year risk of primary breast cancer in 79 women with BRCA-associated ovarian cancer. Domchek et al. [9] reported 5-year and 10-year breast cancer-free survival rates after ovarian cancer diagnosis 97% and 91%, respectively and that all deaths in this cohort were owing to ovarian cancer. These data support the use of less aggressive risk-reduction strategies of breast cancer during the first few years after a diagnosis of ovarian cancer. Peters et al. [22] considered that appropriate breast cancer screening and prevention are necessary for ovarian cancer patients with less favorable advanced-stage disease who achieve sustained remission (>2 years), or with early-stage disease or more favorable advanced disease. In addition, the benefits of early diagnosis of breast cancer need to be balanced the risks of additional testing, including the potential risks/limitations of false-positive test results, overdiagnosis, and patient anxiety. Additionally, decisions need to incorporate the patient's life expectancy from the ovarian cancer itself [23].

Although multivariate survival analysis revealed that age, histological grade, cancer stage, and diagnosis time were independent predictors of breast cancer CSS, the 5-year CSS

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rate for breast cancer was only 76.0%, in contrast to 89.4% to 90.3% in other studies [7,24]. Some studies have suggested that OS and the prognosis of patients diagnosed with breast cancer following ovarian cancer was determined by ovarian cancer [8,9]. However, 212 patients (23.1%) died of breast cancer, 257 patients (26.7%) died of ovarian cancer and 272 patients (18.7%) died of other causes in this study; thus, both cancers had serious impacts on overall health. Neither ovarian cancer nor breast cancer obviously can determine the mortality rate of patients with breast cancer following ovarian cancer.

This was the first population-based study examining the survival rate of patients with breast cancer following ovarian cancer. The major advantage of our study was that we reported the survival rates of a large number of patients with ovarian cancer and breast cancer using the well-established SEER cancer registry, which was set up to reflect the general populationbased data. In addition, our study contained only patients diagnosed between 1973 and 2014 with the majority diagnosed between 1993 and 2014. Therefore, the management of patients might have been more current and uniform in our study.

The main limitation of our study was that information on the concrete surgical types, detailed chemotherapy, and radiotherapy regimens, and the proportion of BRCA1/2-associated ovarian cancers were not available. As a result, we could not confirm the effects of surgery, chemotherapy, radiotherapy, or BRCA1/2 on the survival of patients with ovarian cancer and breast cancer. Moreover, selection bias may have been introduced due to the retrospective nature of the study.

Conclusions

Our study evaluated the survival of a sub-cohort of patients with breast cancer following ovarian cancer whose demographic and clinicopathological characteristics were obtained from the SEER database of the United States. Patients with breast cancer following ovarian cancer survive longer and have other well-described prognostic factors for improved survival rates including an early cancer stage, nonserous ovarian cancer, a younger patient age, and a new diagnosis.

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