Original Article

Clinical characteristics and prognostic factors analysis of patients stricken with double primary breast and ovarian cancer based on the SEER database

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Background: Dual primary breast cancer (BC) and ovarian cancer (OC) represent a distinct subset of patients with diverse survival situation compared to those with a single primary BC or OC. Nonetheless, comprehensive research on their clinical characteristics and prognosis is lacking. This study conducted a retrospective analysis of clinical characteristics, survival outcomes, and prognostic factors of dual primary BC and OC patients.

Methods: We applied the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database to identify patients with dual primary BC and primary OC (DPBOC) from 2000 to 2019, and divided patients into two groups: the BC-first group (BO group) and the OC-first group (OB group). Moreover, we employed Kaplan-Meier method to assess overall survival (OS), breast cancer-specific survival (BCSS), and ovarian cancer-specific survival (OCSS), and the Cox proportional hazards model to analyze prognostic factors.

Results: There were 1,074 patients enrolled, 665 in the BO group and 409 in the OB group. The median time interval was for 48 (range, 0–228) months. There were significant differences in serous carcinoma and OC tumor stage between the two groups (P<0.001; P<0.001). There was no significant difference in BCSS between the two groups (Log-rank P=0.67), but the BO group had inferior OS and OCSS than the OB group (Log-rank P<0.001). Patients with an interval of ≥48 months had a significantly lower risk of death [hazard ratio (HR) =0.323, 95% confidence interval (CI): 0.264–0.395, P<0.001; HR =0.527, 95% CI: 0.305–0.908, P=0.02; HR =0.709, 95% CI: 0.560–0.897, P=0.004].

Conclusions: OC primarily determines the survival outcomes of DPBOC. Patients with BC as the first primary cancer (FPC) have a worse prognosis than patients with OC as FPC. After a diagnosis of BC or OC, we should pay close attention to another site, particularly after BC diagnosis, and monitor screening for ovarian lesions as early as feasible, as well as strengthening the treatment for OC.

Keywords: Double primary cancer; breast cancer (BC); ovarian cancer (OC); clinical features; survival

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Introduction

Breast cancer (BC) is the most common female cancer worldwide and the primary trigger of cancer-related deaths among women (1). In recent years, the incidence of BC has consistently increased by 0.5% per year (2). Coincidentally, another prevalent female malignancy—ovarian cancer (OC), has a poorer prognosis (3). In 2022, OC-related deaths were projected to take up a proportion of 4% of all female cancer-related mortality in the United States (4).

Multiple primary malignant neoplasms (MPMNs) are defined as at least two independent primary malignant tumors which occur on a patient (5). Over the last few years, the incidence of MPMNs has fluctuated between 0.73 and 11.7% (6-8). Numerous malignancies exhibit canonical correlations with genetics. In recent years, susceptibility genes commonly associated with both BC and OC have been reported, including but not limited to *BRCA*, *KRAS*, *RAD51D* (9-11). These susceptibility gene mutations amplify the risk of being afflicted by the diseases, making BC patients more prone to OC and OC patients are similarly susceptible to BC (9,12,13), forming the dual primary BC and primary OC (DPBOC) subset. Currently, studies targeting on hereditary breast cancer and ovarian cancer syndrome (HBOC) in this subset comparatively delve into depth, with the majority of HBOC cases attributed to *BRCA1* and *BRCA2* mutations (14). A study by John *et al.* found that 10% of *BRCA*-related epithelial ovarian cancer (EOC) patients were diagnosed with BC within an average of 3.3 years after the OC diagnosis (15). Metcalfe *et al.* revealed that *BRCA1* carriers among BC patients have a 12.7% 10-year cumulative risk of developing OC, whereas *BRCA2* carriers have a risk of 6.8% (12).

DPBOC entails a relatively higher risk, and the health and economic effects of MPMNs on patients are substantial. The primary objective of this article is to lay a solid foundation for early monitoring and treatment of this patient population, by means of employing the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database and conducting a retrospective analysis directing at the clinical characteristics, survival situations, and prognostic factors of DPBOC. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-480/rc).

Highlight box

Key findings

- Time interval is an independent influence factor of dual primary breast cancer and primary ovarian cancer (DPBOC). The longer the time after being diagnosed the first primary cancer (FPC), the lower the risk for patients to develop the second primary cancer (SPC) and with better prognosis.
- The survival outcome of DPBOC is mainly determined by ovarian cancer (OC), and the prognosis of patients with breast cancer (BC) as FPC is worse than that of patients with OC as FPC.

What is known and what is new?

- Prognostic factors for BC and OC have been widely studied, and it is well-established that survival rates and clinical characteristics of patients with these cancers have a clear impact in those with single primary breast or ovarian cancers.
- The survival outcome of DPBOC is mainly determined by OC, and the prognosis of patients with BC as FPC is worse than that of patients with OC as FPC. Additionally, the study reveals the critical role of the time interval between the diagnoses of BC and OC, with a longer time interval associated with a lower risk of developing SPC and better prognosis.

What is the implication, and what should change now?

- The study emphasizes the decisive role of OC in the survival outcomes of DPBOC patients. Clinicians should prioritize monitoring for OC in patients with BC, especially those with a shorter interval between diagnoses, to facilitate early detection and treatment of OC. Moreover, for patients with BC as the FPC, treatment strategies should be adjusted to address the poorer prognosis, with a focus on enhancing OC management. Early intervention and personalized treatment plans can help improve survival outcomes.

Methods

Data collection

SEER Stat software (version 8.4.1.2) was employed to query the SEER databases of 17 registries. We extracted data of patients diagnosed with BC between 2000 and 2019, and selected DPBOC cases. These cases were divided into two groups: the BO group (BC diagnosed before OC) and the OB group (OC diagnosed before BC). Cases following the criteria below are excluded: (I) accompanied by missing molecular subtype information of BC; (II) accompanied by missing tumor stage information; (III) classified as human epidermal growth factor receptor 2 (HER2) positive or triple-negative breast cancer (TNBC) in BC; (IV) with the age of <18 or >80 years old. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Research indicators

Demographic information

Age at diagnosis, time interval [time between the first primary cancer (FPC) and the second primary tumor (SPC) diagnosis], race (non-Hispanic White, non-Hispanic Black, non-Hispanic Asian/Pacific Islander, non-Hispanic American Indian/Alaska Native, Hispanic), and marital status (single, married, divorced/separated/widowed, other).

Pathological information

Pathological types (BC: invasive ductal carcinoma, invasive lobular carcinoma, other; OC: serous carcinoma, endometrioid carcinoma, clear cell carcinoma, mucinous carcinoma, other), tumor stage [criteria: American Joint Committee on Cancer Staging Manual, 8th edition (16,17)], T stage, N stage, M stage, estrogen receptor (ER) status, progesterone receptor (PR) status, and HER2 status.

Survival information

Survival status, overall survival (OS), breast cancer-specific survival (BCSS), ovarian cancer-specific survival (OCSS), cause of death.

Statistical analysis

SPSS 25.0 software (SPSS, Chicago, IL, USA) was utilized for statistical analysis. The optimal cutoff values for age and time interval subgroups were determined by using X-tile 3.6.1 software. We expressed categorical data as counts (percentages), as well as applying Pearson's Chi-squared test to assess intergroup differences, with Fisher's exact probability test applied when necessary. Owing to adopting the Kaplan-Meier method, we plotted survival curves. By applying the Log-rank test, the differences in the survival curves were compared. The Cox proportional hazards model was utilized for univariate and multivariate analyses. The level of statistical significance was set at P<0.05.

Data availability

The data of the current study are available in the SEER database (https://seer.cancer.gov/).

Results

Demographic characteristics

From 2000 to 2019, the SEER database collected 1,157,106 primary BC patients, among which there were 3,095 (0.27%) DPBOC patients. After excluding patients with insufficient information, HER2-positive or TNBC, and those aged under 18 or over 80, we bring 1,074 samples in this investigation. These patients were categorized into two groups: the BO group (665, 61.9%) and the OB group (409, 38.1%) (*Figure 1*).

The respective median age at diagnosis for FPC and SPC was 60 (range, 29–80) and 65 (range, 33–80) years. The median interval for all patients was 48 (range, 0–228) months. The majority of patients were married white women. There were no statistically significant differences between the two groups in age at FPC diagnosis (P=0.50), age at SPC diagnosis (P=0.23), time interval (P=0.10), or marital status (P=0.64). Nonetheless, there exist statistically significant variation in race (P=0.005) (*Table 1*).

Pathological characteristics

Table 1 outlines the pathological characteristics. It is evident that the primary pathological characteristics, tumor stage, T stage, N stage, and M stage for BC were infiltrating ductal carcinoma (834, 77.7%), stage I (603, 56.1%), T1 (721, 67.1%), N0 (750, 69.8%), and M0 (1,031, 96.0%). Regarding OC, the predominant pathological type, tumor stage, T stage, N stage, and M stage respectively correspond to serous carcinoma (526, 49.0%), stage III (411, 38.3%), T3 (526, 49.0%), N0 (795, 74.0%), and M0 (839, 78.1%).

A comparison between the two groups reveals that there were no statistically significant differences between the two groups in BC-related aspects (P>0.05). However, significant differences were observed in the pathological characteristics of OC. Specifically, the BO group had a higher proportion of serous carcinoma (52.8% *vs.* 42.8%, P<0.001), stages III and IV (68.6% *vs.* 46.7%, P<0.001), T3 (56.2% *vs.* 37.2%, P<0.001), N1 (17.7% *vs.* 14.2%, P=0.009), and M1 (25.9% *vs.* 15.4%, P<0.001) compared to the OB group.

Survival analysis

The Kaplan-Meier survival curves presented in *Figure 2* illustrate that the BO group did not reach the median BCSS, while the OB group failed to reach the median OS, BCSS, or OCSS. There were statistically noticeable differences in OS and OCSS between the two groups (Log-rank P<0.001; Log-rank P<0.001), but basically identical in BCSS (Log-rank P=0.67).

All enrolled patients had cumulative 3-, 5-, and 10-year

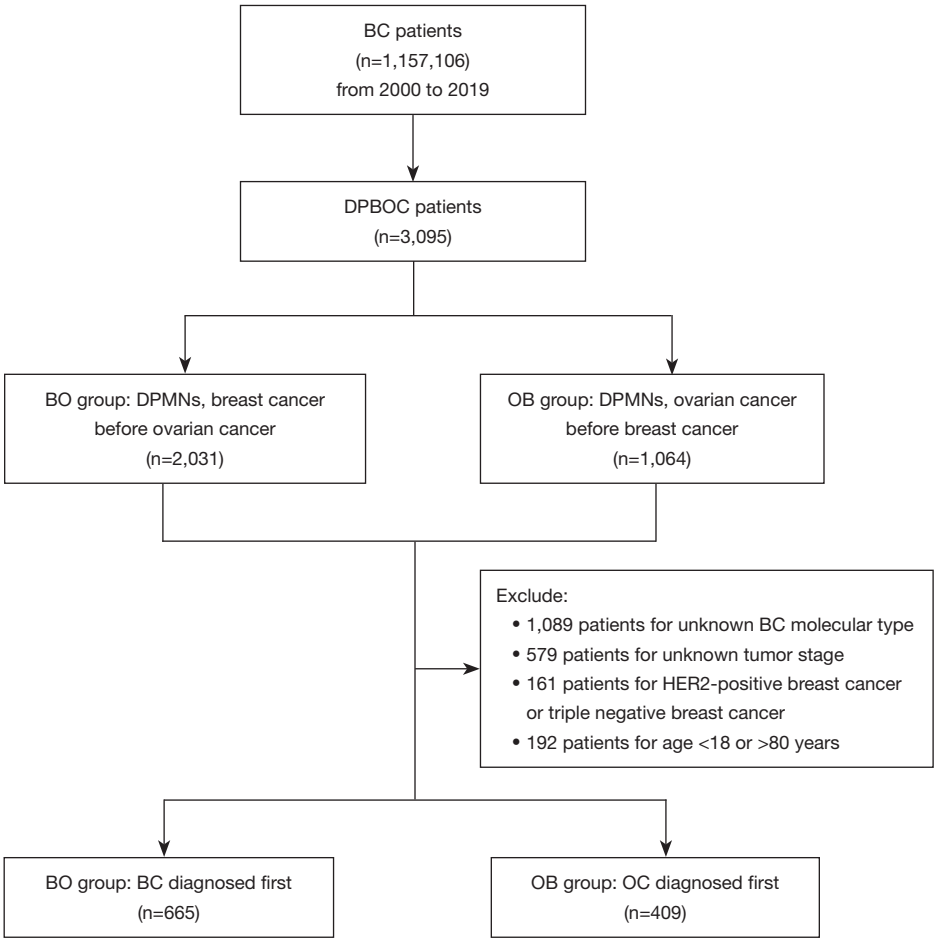

Figure 1 Screening flow chart for patients with primary breast cancer and primary ovarian cancer. BO group: BC diagnosed before OC; OB group: OC diagnosed before BC. BC, breast cancer; DPBOC, dual primary BC and primary OC; DPMNs, double primary malignant neoplasms; HER2, human epidermal growth factor receptor 2; OC, ovarian cancer.

survival rates of 89.5%, 79.0%, and 55.6%, respectively. Statistically significant differences were observed between the BO group and the OB group in the 5-year OS rate (76.0%±1.7% *vs.* 83.8%±1.8%, Log-rank P=0.004) and the 5-year OCSS (53.5%±2.3% *vs.* 89.8%±1.5%, Log-rank P<0.001). However, there was no statistically significant difference in the 5-year BCSS between the two groups (96.0%±0.8% *vs.* 96.4%±1.1%, Log-rank P=0.99). Patients in the OB group had significantly superior survival outcomes than those in the BO group, with the differences primarily reflected in OS and OCSS.

Table 2 provides survival data of all patients. The overall median OS for all patients was 143 months [95% confidence interval (CI): 130.2–155.8], with a median OS of 115 months (95% CI: 107.7–122.3) for the BO group. Among the patients, 51.1% passed away, with significantly more deaths attributed to OC than to BC (33.1% *vs.* 6.1%). The BO group experienced a significantly higher mortality rate compared to the OB group (62.0% *vs.* 33.5%, P<0.001). Additionally, both BC-specific mortality rate (7.5% *vs.* 3.9%, P=0.02) and OC-specific mortality rate (42.9% *vs.* 17.1%, P<0.001) were higher in the BO group compared to the OB group.

Univariate and multivariate analyses

The T stage and N stage of BC were excluded from the Cox regression analysis for BCSS because certain subgroups within these stages had not experienced BC-related deaths. *Table 3* displays the results of the univariate Cox analysis. We selected factors with statistically significant results (P<0.05). A collinearity diagnosis was performed using

Table 1 Comparison of demographic and clinicopathological characteristics between the BO group and the OB group

Variables	BO group, n (%)	OB group, n (%)	P	Overall, n (%)
Total	665 (61.9)	409 (38.1)		1074
Age at diagnosis of the first tumor (years)			0.50	
≥18 to <57	257 (38.6)	168 (41.1)		425 (39.6)
≥57 to <72	322 (48.4)	197 (48.2)		519 (48.3)
≥72 to ≤80	86 (12.9)	44 (10.8)		130 (12.1)
Age at diagnosis of the second tumor (years)			0.23	
≥18 to <66	346 (52.0)	225 (55.0)		571 (53.2)
≥66 to <76	218 (32.8)	137 (33.5)		335 (33.1)
≥76 to ≤80	101 (15.2)	47 (11.5)		148 (13.8)
Interval between two tumors (months)			0.10	
<48	334 (50.2)	184 (45.0)		518 (48.2)
≥48	331 (49.8)	225 (55.0)		556 (51.8)
Race			0.005	
White	537 (80.8)	360 (88.0)		360 (88.0)
Black	48 (7.2)	22 (5.4)		22 (5.4)
Other	80 (12.0)	27 (6.6)		27 (6.6)
Marital status			0.64	
Never married	105 (15.8)	73 (17.8)		178 (16.6)
Married	402 (60.5)	233 (57.0)		635 (59.1)
Divorced/separated/widowed	140 (21.1)	89 (21.8)		229 (21.3)
Other	18 (2.7)	14 (3.4)		32 (3.0)
BC histologic type			0.16	
Infiltrating duct carcinoma	506 (76.1)	328 (80.2)		834 (77.7)
Infiltrating lobular carcinoma	111 (16.7)	62 (15.2)		173 (16.1)
Other	48 (7.2)	19 (4.6)		67 (6.2)
OC histologic type			<0.001	
Serous carcinoma	351 (52.8)	175 (42.8)		526 (49.0)
Endometrioid carcinoma	47 (7.1)	50 (12.2)		97 (9.0)
Clear cell carcinoma	49 (7.4)	35 (8.6)		84 (7.8)
Mucinous carcinoma	26 (3.9)	33 (8.1)		59 (5.5)
Other	192 (28.9)	116 (28.4)		308 (28.7)
BC stage			0.26	
I	360 (54.1)	243 (59.4)		603 (56.1)
II	229 (34.4)	124 (30.3)		353 (32.9)
III	51 (7.7)	24 (5.9)		75 (7.0)
IV	25 (3.8)	18 (4.4)		43 (4.0)

Table 1 (*continued*)

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Variables	BO group, n (%)	OB group, n (%)	P	Overall, n (%)
OC stage			<0.001	
I	151 (22.7)	160 (39.1)		311 (29.0)
II	58 (8.7)	58 (14.2)		116 (10.8)
III	283 (42.6)	128 (31.3)		411 (38.3)
IV	173 (26.0)	63 (15.4)		236 (22.0)
T stage of BC			0.50	
T0	1 (0.2)	0		1 (0.1)
T1	439 (66.0)	282 (68.9)		721 (67.1)
T2	172 (25.9)	104 (25.4)		276 (25.7)
T3	33 (5.0)	11 (2.7)		44 (4.1)
T4	13 (2.0)	7 (1.7)		20 (1.9)
TX	7 (1.1)	5 (1.2)		12 (1.1)
T stage of OC			<0.001	
T0	3 (0.5)	1 (0.2)		4 (0.4)
T1	166 (25.0)	172 (42.1)		338 (31.5)
T2	80 (12.0)	63 (15.4)		143 (13.3)
T3	374 (56.2)	152 (37.2)		526 (49.0)
TX	42 (6.3)	21 (5.1)		63 (5.9)
N stage of BC			0.06	
N0	451 (67.8)	299 (73.1)		750 (69.8)
N1mi	17 (2.6)	18 (4.4)		35 (3.3)
N1	156 (23.5)	68 (16.6)		224 (20.9)
N2	25 (3.8)	12 (2.9)		37 (3.4)
N3	10 (1.5)	9 (2.2)		19 (1.8)
NX	6 (0.9)	3 (0.7)		9 (0.8)
N stage of OC			0.009	
N0	472 (71.0)	323 (79.0)		795 (74.0)
N1	118 (17.7)	58 (14.2)		176 (16.4)
NX	75 (11.3)	28 (6.8)		103 (9.6)
M stage of BC			0.60	
M0	640 (96.2)	391 (95.6)		1031 (96.0)
M1	25 (3.8)	18 (4.4)		43 (4.0)
M stage of OC			<0.001	
M0	493 (74.1)	346 (84.6)		839 (78.1)
M1	172 (25.9)	63 (15.4)		235 (21.9)

BO group: BC diagnosed before OC; OB group: OC diagnosed before BC. BC, breast cancer; OC, ovarian cancer.

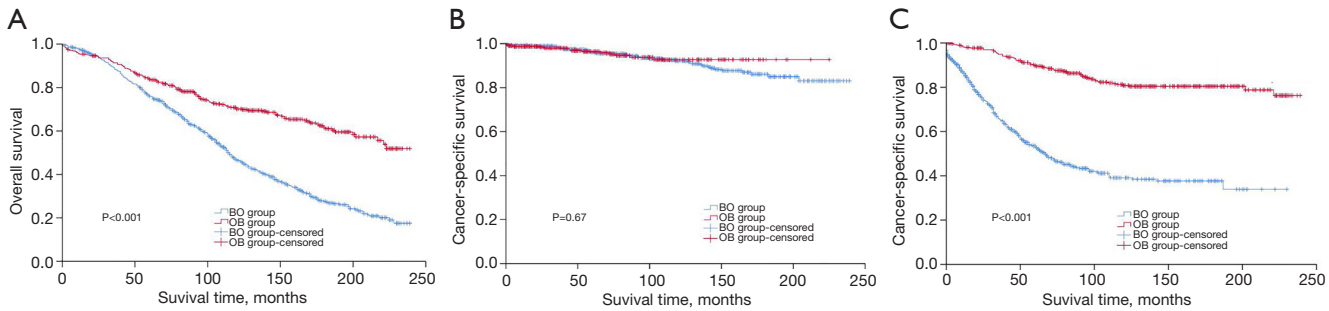

Figure 2 Survival for the two groups. (A) Overall survival for the two groups after the first malignant tumor. (B) Breast cancer-specific survival for the two groups. (C) Ovarian cancer-specific survival for the two groups. BO group: BC diagnosed before OC; OB group: OC diagnosed before BC. BC, breast cancer; OC, ovarian cancer.

Table 2 Survival outcome

Variables	BO group	OB group	P	Overall
Total, n (%)	665 (61.9)	409 (38.1)		1074
OS (months), median (95% CI)	115 (107.7–122.3)	Not reached	<0.001	143 (130.2–155.8)
Deceased, n (%)	412 (62.0)	137 (33.5)	<0.001	549 (51.1)
Died of BC	50 (7.5)	16 (3.9)	0.02	66 (6.1)
Died of OC	285 (42.9)	70 (17.1)	<0.001	355 (33.1)
Died of other	77 (11.6)	51 (12.5)	0.66	128 (11.9)
Alive, n (%)	253 (38.0)	272 (66.5)	<0.001	525 (48.9)

BO group: BC diagnosed before OC; OB group: OC diagnosed before BC. BC, breast cancer; OC, ovarian cancer; OS, overall survival.

the variance inflation factor (VIF), with a threshold of 5. Variables with VIF values exceeding 5 were excluded from the multivariate Cox analysis, while the remaining variables were incorporated into the final model (the M1 stage of BC is equivalent to the stage IV of BC, so the M stage of BC is excluded from the multivariate Cox analysis due to variable collinearity).

The results of the multivariable Cox analysis are presented in *Table 4*. Age at FPC diagnosis, time interval, tumor stage of BC, N stage of BC, pathological type of OC, T stage of OC, N stage of OC, and M stage of OC served as all independent factors of OS (P<0.05). Age at FPC diagnosis, time interval, tumor stage of BC, and N stage of OC were independent contributors to BCSS (P<0.05). Age at SPC diagnosis, time interval, pathological type of OC, T stage of OC, and M stage of OC were independently determinate OCSS (P<0.05).

The risk of death of patients was basically positively correlated with the age of diagnosis, and the age of FPC diagnosis had a greater impact on survival compared to age of SPC diagnosis. For OS, the death risk of patients diagnosed with FPC at the age range between 57–72 and 72–80 years was 1.596 times (95% CI: 1.245–2.047, P<0.001) and 3.458 times (95% CI: 2.252–5.311, P<0.001) higher than those diagnosed at the age of 18–57 respectively. For BCSS, the death risk of patients diagnosed with FPC at the age range between 72–80 years was 2.651 times (95% CI: 1.167–6.024, P=0.02) higher than those diagnosed at the age of 18–57 years.

The longer the interval, the better survival for patients. For OS, BCSS, and OCSS, the risk of death with an interval of ≥48 months was significantly lower than that of patients with an interval of <48 months [hazard ratio (HR) =0.323, 95% CI: 0.264–0.395, P<0.001; HR =0.527, 95% CI: 0.305–0.908, P=0.02; HR =0.709, 95% CI: 0.560–0.897, P=0.004].

The survival for patients with higher BC tumor stages is worse. For OS, the death risk of stage III and stage IV in BC was both higher than stage I (HR =1.837, 95% CI: 1.068–3.158, P=0.03; HR =2.373, 95% CI: 1.383–4.073,

Table 3 Univariate analysis of risk factors influencing OS, BCSS and OCSS

Variables	OS		BCSS		OCSS	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age at diagnosis of the first tumor (years)						
≥18 to <57	1		1		1	
≥57 to <72	1.931 (1.591–2.344)	<0.001	1.468 (0.860–2.507)	0.16	1.651 (1.304–2.089)	<0.001
≥72 to ≤80	5.318 (1.591–2.344)	<0.001	3.009 (1.413–6.409)	0.004	2.721 (1.980–3.739)	<0.001
Age at diagnosis of the second tumor (years)						
≥18 to <66	1		1		1	
≥66 to <76	1.422 (1.177–1.717)	<0.001	0.686 (0.372–1.264)	0.23	1.663 (1.322–2.094)	<0.001
≥76 to ≤80	2.164 (1.729–2.709)	<0.001	1.570 (0.837–2.944)	0.16	2.178 (1.623–2.923)	<0.001
Interval time (months)						
<48	1		1		1	
≥48	0.339 (0.286–0.403)	<0.001	0.487 (0.299–0.795)	0.004	0.673 (0.545–0.831)	<0.001
Race						
White	1		1		1	
Black	1.383 (1.000–1.911)	0.05	0.814 (0.254–2.606)	0.73	1.324 (0.880–1.992)	0.18
Other	0.985 (0.739–1.312)	0.92	1.141 (0.543–2.397)	0.73	1.015 (0.708–1.454)	0.94
Marital status						
Never married	1		1		1	
Married	1.015 (0.796–1.293)	0.91	0.622 (0.339–1.139)	0.12	1.479 (1.066–2.052)	0.02
Divorced/separated/widowed	1.438 (1.095–1.888)	0.009	0.912 (0.451–1.844)	0.80	1.676 (1.160–2.423)	0.006
Other	1.223 (0.725–2.061)	0.45	0.000 (0.000–2.707E+274)	0.97	1.745 (0.920–3.310)	0.09
BC histologic type						
Infiltrating duct carcinoma	1		1		1	
Infiltrating lobular carcinoma	0.949 (0.755–1.193)	0.66	1.798 (1.037–3.119)	0.04	0.927 (0.693–1.241)	0.61
Other	1.223 (0.887–1.686)	0.22	1.265 (0.501–3.196)	0.62	1.170 (0.771–1.776)	0.46
OC histologic type						
Serous carcinoma	1		1		1	
Endometrioid carcinoma	0.390 (0.267–0.568)	<0.001	0.568 (0.201–1.601)	0.28	0.280 (0.166–0.473)	<0.001
Clear cell carcinoma	0.495 (0.340–0.722)	<0.001	0.160 (0.022–1.171)	0.07	0.499 (0.316–0.790)	0.003
Mucinous carcinoma	0.483 (0.303–0.768)	0.002	1.482 (0.579–3.791)	0.41	0.258 (0.127–0.522)	<0.001
Other	0.991 (0.822–1.195)	0.93	1.173 (0.686–2.006)	0.56	0.885 (0.698–1.122)	0.31
BC stage						
I	1		1		1	
II	1.089 (0.906–1.308)	0.36	2.109 (1.186–3.750)	0.01	0.980 (0.779–1.233)	0.87
III	1.244 (0.891–1.738)	0.20	4.152 (1.955–8.819)	<0.001	1.076 (0.705–1.641)	0.74
IV	2.456 (1.654–3.647)	<0.001	11.008 (5.014–24.167)	<0.001	0.740 (0.380–1.442)	0.38

Table 3 (*continued*)

Table 3 (*continued*)

Variables	OS		BCSS		OCSS	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
OC stage						
I	1		1		1	
II	1.577 (1.069–2.326)	0.02	1.032 (0.400–2.661)	0.95	2.478 (1.389–4.419)	0.002
III	3.741 (2.859–4.895)	<0.001	1.169 (0.602–2.268)	0.64	8.671 (5.670–13.260)	<0.001
IV	6.450 (4.866–8.551)	<0.001	2.893 (1.515–5.526)	0.001	14.346 (9.207–22.354)	<0.001
T stage of BC						
T0	1				1	
T1	0.216 (0.030–1.544)	0.13			0.155(0.022–1.111)	0.06
T2	0.264 (0.037–1.888)	0.26			0.155 (0.021–1.115)	0.06
T3	0.251 (0.034–1.865)	0.25			0.217 (0.029–1.644)	0.14
T4	0.356 (0.046–2.765)	0.36			0.123 (0.014–1.101)	0.06
TX	0.639 (0.081–5.051)	0.64			0.139 (0.014–1.337)	0.09
T stage of OC						
T0	1		1		1	
T1	0.064 (0.024–0.177)	<0.001	0.078 (0.010–0.593)	0.01	0.042 (0.010–0.176)	<0.001
T2	0.119 (0.043–0.329)	<0.001	0.080 (0.010–0.655)	0.02	0.122 (0.029–0.512)	0.004
T3	0.265 (0.099–0.711)	0.008	0.121 (0.016–0.888)	0.04	0.375 (0.093–1.513)	0.17
TX	0.454 (0.164–1.256)	0.13	0.350 (0.044–2.778)	0.32	0.489 (0.116–2.065)	0.33
N stage of BC						
N0	1				1	
N1mi	0.776 (0.463–1.300)	0.34			0.948 (0.531–1.692)	0.86
N1	0.988 (0.801–1.219)	0.91			0.904 (0.691–1.183)	0.46
N2	0.894 (0.542–1.476)	0.66			0.672 (0.346–1.306)	0.24
N3	1.931 (1.087–3.433)	0.02			0.963 (0.397–2.334)	0.93
NX	8.516 (4.364–16.620)	<0.001			1.725 (0.552–5.389)	0.35
N stage of OC						
N0	1		1		1	
N1	1.466 (1.178–1.823)	0.001	1.168 (0.585–2.333)	0.66	1.752 (1.353–2.268)	<0.001
NX	2.633 (2.075–3.340)	<0.001	3.782 (2.089–6.847)	<0.001	2.640 (1.920–3.630)	<0.001
M stage of BC						
M0	1		1		1	
M1	2.348 (1.593–3.461)	<0.001	6.894 (3.392–14.014)	<0.001	0.741 (0.382–1.436)	0.37
M stage of OC						
M0	1		1		1	
M1	2.857 (2.387–3.420)	<0.001	2.706 (1.635–4.477)	<0.001	3.219 (2.566–4.039)	<0.001

BC, breast cancer; BCSS, breast cancer-specific survival; CI, confidence interval; HR, hazard ratio; OC, ovarian cancer; OS, overall survival; OCSS, ovarian cancer-specific survival.

Table 4 Multivariate analysis of risk factors influencing OS, BCSS and OCSS

Variables	OS		BCSS		OCSS	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age at diagnosis of the first tumor (years)						
≥18 to <57	1		1		1	
≥57 to <72	1.596 (1.245–2.047)	<0.001	1.566 (0.889–2.758)	0.12	1.071 (0.788–1.456)	0.66
≥72 to ≤80	3.458 (2.252–5.311)	<0.001	2.651 (1.167–6.024)	0.02	1.101 (0.644–1.885)	0.72
Age at diagnosis of the second tumor (years)						
≥18 to <66	1				1	
≥66 to <76	1.019 (0.799–1.301)	0.88			1.393 (1.034–1.877)	0.03
≥76 to ≤80	0.838 (0.575–1.220)	0.36			1.520 (0.941–2.454)	0.09
Interval time (months)						
<48	1		1		1	
≥48	0.323 (0.264–0.395)	<0.001	0.527 (0.305–0.908)	0.02	0.709 (0.560–0.897)	0.004
Race						
White	1					
Black	1.116 (0.789–1.577)	0.54				
Other	0.958 (0.714–1.285)	0.77				
Marital status						
Never married	1				1	
Married	0.873 (0.676–1.127)	0.30			1.141 (0.819–1.589)	0.43
Divorced/separated/widowed	1.081 (0.811–1.440)	0.59			1.202 (0.822–1.757)	0.34
Other	0.929 (0.531–1.624)	0.80			1.339 (0.692–2.594)	0.39
BC histologic type						
Infiltrating duct carcinoma			1			
Infiltrating lobular carcinoma			1.586 (0.900–2.795)	0.11		
Other			0.853 (0.318–2.286)	0.75		
OC histologic type						
Serous carcinoma	1				1	
Endometrioid carcinoma	1.280 (0.851–1.926)	0.24			0.934 (0.539–1.618)	0.81
Clear cell carcinoma	1.556 (1.028–2.356)	0.04			2.052 (1.238–3.400)	0.005
Mucinous carcinoma	1.138 (0.697–1.857)	0.60			0.828 (0.400–1.712)	0.61
Other	1.349 (1.100–1.656)	0.004			1.240 (0.964–1.594)	0.09
BC stage						
I	1		1			
II	1.043 (0.818–1.330)	0.73	1.887 (1.039–3.425)	0.04		
III	1.837 (1.068–3.158)	0.03	5.377 (2.489–11.619)	<0.001		
IV	2.373 (1.383–4.073)	0.002	14.558 (6.025–35.173)	<0.001		

Table 4 (*continued*)

Table 4 (*continued*)

Variables	OS		BCSS		OCSS	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
OC stage						
I						
II						
III						
IV						
T stage of BC						
T0						
T1						
T2						
T3						
T4						
TX						
T stage of OC						
T0	1		1		1	
T1	0.134 (0.044–0.410)	<0.001	0.206 (0.023–1.845)	0.16	0.086 (0.020–0.378)	0.001
T2	0.277 (0.091–0.844)	0.02	0.209 (0.023–1.934)	0.17	0.262 (0.060–1.138)	0.07
T3	0.606 (0.206–1.784)	0.36	0.320(0.038–2.676)	0.29	0.737 (0.177–3.070)	0.68
TX	0.448 (0.152–1.327)	0.15	0.358 (0.042–3.083)	0.35	0.574 (0.133–2.486)	0.46
N stage of BC						
N0	1					
N1mi	0.641 (0.378–1.087)	0.10				
N1	0.972 (0.730–1.294)	0.85				
N2	0.727 (0.358–1.475)	0.38				
N3	1.211 (0.582–2.522)	0.61				
NX	4.665 (1.974–11.023)	<0.001				
N stage of OC						
N0	1		1		1	
N1	1.079 (0.857–1.359)	0.52	1.083 (0.522–2.248)	0.83	1.000 (0.764–1.309)	>0.99
NX	1.490 (1.138–1.952)	0.004	2.635 (1.280–5.425)	0.009	1.030 (0.721–1.470)	0.87
M stage of BC						
M0						
M1						
M stage of OC						
M0	1		1		1	
M1	1.808 (1.450–2.254)	<0.001	1.753 (0.901–3.410)	0.10	1.652 (1.274–2.142)	<0.001

BC, breast cancer; BCSS, breast cancer-specific survival; CI, confidence interval; HR, hazard ratio; OC, ovarian cancer; OS, overall survival; OCSS, ovarian cancer-specific survival.

P=0.002). For BCSS, the death risk of stage II, stage III and stage IV in BC was higher than stage I (HR =1.887, 95% CI: 1.039–3.425, P=0.04; HR =5.377, 95% CI: 2.489–11.619, P<0.001; HR =14.558, 95% CI: 6.025–35.173, P<0.001).

For OS and OCSS, the death risk of clear cell carcinoma in OC was higher than that of serous carcinoma (HR =1.556, 95% CI: 1.028–2.356, P=0.04; HR =2.052, 95% CI: 1.238–3.400, P=0.005). For OS and OCSS, the death risk of T1 in OC was lower than that of T0 (OS: HR =0.134, 95% CI: 0.044–0.410, P<0.001; OCSS: HR =0.086, 95% CI: 0.020–0.378, P=0.001), while the death risk of T2 in OC was significantly lower than that of T0 for OS (HR =0.277, 95% CI: 0.091–0.844, P=0.02). For OS and OCSS, the death risk of M1 in OC was higher than M0 (HR =1.808, 95% CI: 1.450–2.254, P<0.001; HR =1.652, 95% CI: 1.274–2.142, P<0.001).

Discussion

There were 3,095 cases of DPBOC in SEER databases of 17 registries. After excluding 1,668 patients with missing information, the BC molecular types of the rest of the patients were Luminal-type (1,270, 89%), HER2-positive (24, 1.7%), and TNBC (137, 9.6%). It can be seen that Luminal-type BC accounted for a high proportion in DPBOC, while the occurrence of OC in patients with HER2-positive BC and TNBC may be an incidental event. Therefore, HER2-positive and TNBC were ruled out in subsequent studies. Many previous studies have confirmed that most OC are ER-positive (18), and luminal-type BC is ER-positive. This may explain why patients with luminal-type BC are more likely to develop OC than HER2-positive BC and TNBC. However, regarding the correlation between BC, OC and *BRCA*, studies by Kataoka *et al.* and Krammer *et al.* both found that Luminal-type BC is more common in *BRCA2* mutation carriers (19,20). A study carried out by Resch *et al.* found that *BRCA1* mutation carriers are more likely to have OC than *BRCA2* mutation carriers (21), but the explanation for their correlation seems to differ from the previous one. *BRCA* is not involved in this study, therefore, more studies should focus on the correlation between ER, *BRCA* and BC, OC.

The current diagnostic criteria that are widely accepted for MPMNs come from the report published by Warren in 1932 (22). In the report, it is required: (I) each tumor should be confirmed to be malignant by histological examination; (II) each tumor should have an independent pathological morphology; (III) each tumor occurs in a different and independent site; (IV) the possibility of metastasis should be ruled out. According to Moertel's study, MPMNs include synchronous tumors (time interval ≤6 months) and metachronous tumors (time interval >6 months) (23). The grouping standard of this study is the occurrence order of tumor, we retrospectively analyzed the clinical characteristics, survival outcomes and prognostic factors of DPBOC, but whether the tumor is synchronous or metachronous is not discussed here.

The proportion of white people in this study (897, 83.5%) is higher than that of black people (70, 6.5%), but the mortality rate of white people is lower (50.9% *vs.* 57.1%). This indicates that through white women have higher BC and OC occurrence, black women have higher death rate, such is consistent with previous findings (24). Many studies have shown that black women have a higher *BRCA* mutation rate than white women (25,26), which seems to suggest that *BRCA* test is necessary for black women. However, Armstrong *et al.* found that after the *BRCA1/2* mutation probability, socioeconomic characteristics and other factors are adjusted, the possibility of black women with BC and OC family history to receive *BRCA1/2* assessment is lower than white women other same condition (27), suggesting that the poor prognosis of the disease may be due to the fact that some black women cannot receive timely *BRCA* test and effective clinical prevention and treatment.

A previous study showed that around 52% of BC patients developed SPC within 5 years of BC diagnosis (28), which is similar to the results we found in this study (median time interval: 48 months). Additionally, our study found that about 64% of DPBOC patients developed SPC within the first 60 months after being diagnosed FPC, and 90% occurred within the first 120 months. This proportion is higher than that reported in a study by Song *et al.*, indicating that the time interval between the two cancers in our study is shorter. However, it is important to note that the study by Song *et al.* focused on metachronous double primary cancers, which may have influenced the observed differences (29). Notably, 40% of patients developed SPC within 24 months, highlighting this period as a critical window of high SPC incidence. Furthermore, consistent with previous findings, our results suggest that the probability of developing SPC decreases as the time interval from FPC diagnosis lengthens. Importantly, table 4 shows that the time interval was an independent influencing factor of OS, BCSS, and OCSS (P<0.001; P=0.02; P=0.004). Using

the median interval of 48 months as the cutoff, patients with intervals ≥48 months exhibited significantly lower risks of adverse outcomes, with HRs of 0.323 (95% CI: 0.264–0.395) for OS, 0.527 (95% CI: 0.305–0.908) for BCSS, and 0.707 (95% CI: 0.559–0.894) for OCSS. These results suggest that longer time intervals between FPC and SPC diagnosis are associated with improved survival outcomes. Clinically, these findings underscore the importance of intensive follow-up during the early years after FPC diagnosis, particularly within the first two years when the risk of SPC is highest. Currently, BC patients in mainland China are generally reexamined every 3 months within the first 2 years post-surgery, focusing primarily on breast ultrasound, abdominal ultrasound, and chest CT. However, ovarian examinations are often overlooked. Given the significant impact of OC on the prognosis of BC patients, it is strongly recommended that routine gynecological evaluations, particularly ovarian assessments, be incorporated into follow-up protocols. Early and comprehensive surveillance for SPC could potentially enhance patient outcomes by enabling timely intervention.

Table 1 shows that the OC-related differences between the two groups of patients are statistically significant (P<0.05), while the BC-related differences are not statistically significant (P>0.05), which suggests that the difference in survival between the two groups may be more affected by OC. Furthermore, *Table 2* shows that 33.1% of patients succumbed to OC, with a significantly higher proportion of OC-related deaths in the BO group compared to the OB group (42.9% *vs.* 17.1%, P<0.001). This indicates that the survival outcome of DPBOC is primarily determined by OC, which aligns with the findings of a study by Tasca *et al.* (30). It has been found that OC in the context of HBOC is characterized by a high proportion of serous carcinoma and advanced tumors (31), which is likely related to *BRCA1* (32). *Table 4* shows that the pathological type and stage of OC are independent influencing factors of OS. The proportion of serous carcinoma and stage III and IV OC in the BO group were higher than those in the OB group, which may explain its lower survival rate. However, a study by Zaaijer *et al.* found that *BRCA*-related EOC patients with a history of BC had a worse prognosis than those without a history of BC, and this difference was not related to the grade, stage, or histological type of the tumor (33). Such point of view differs from the conclusion of this study. Moreover, the *BRCA* is not included in our study, so it is not sufficient enough to attribute the higher proportion of serous carcinoma and stage III and IV OC in the BO group to gene mutations. Therefore, more researches are needed to confirm it. Additionally, *Table 4* shows that the death risk of T0 in OC is higher than that of T2, T3, and T4. After analyzing the data, we found that the 4 T0 stage OC patients were all M1 stage, and 2 of them died of OC, which led to multivariate Cox regression showing that T0 was a high risk. These findings underscore the critical importance of considering distant metastasis (M stage) when evaluating early-stage tumors, as it can significantly influence survival outcomes. From a clinical perspective, when determining treatment strategies for DPBOC and assessing patient survival, careful consideration should be given to the pathological type and TNM stage of OC. Prioritizing the monitoring of OC and developing personalized management plans based on the presence of metastasis could help optimize disease control and improve patient outcomes.

Generally speaking, serous ovarian cancer (SOC), especially high-grade serous ovarian cancer (HGSOC), has a worse prognosis than other histological types (34). The death rate of SOC in this study (40.1%) is indeed higher than other types, but *Table 4* shows that patients with clear cell type OC had an even higher risk of death than SOC (OS: HR =1.556, 95% CI: 1.028–2.356, P=0.04; OCSS: HR =2.052, 95% CI: 1.238–3.400, P=0.005). Regarding this point, we have observed from clinical work that clear cell OC patients have a lower 5-year survival rate and are more likely to suffer from reoccurrence and drug resistance. While SOC patients will have a better prognosis if they have *BRCA* mutations or homologous recombination deficiency. A study by Kim *et al.* also showed that patients with advanced HGSOC with *BRCA1/2* mutations have better prognosis and longer progression-free survival than those without BRCA mutations (35). However, as this study did not collect data on BRCA mutations or treatment-related factors, we were unable to fully analyze the impact of these variables on patient survival. Future studies should incorporate genetic profiles and treatment data to further investigate the complex effects of different OC pathological types on survival outcomes. From a clinical perspective, our findings highlight the importance of personalized monitoring and treatment strategies for clear cell OC patients. Given their elevated risk of recurrence and drug resistance, more proactive interventions and follow-up strategies are essential to improving survival outcomes.

Figure 2 shows the survival curves of the two groups of patients, and the survival of the BO group was significantly worse than that of the OB group. According to the previous analysis, several factors may lead to the poor prognosis of

BO group: older age at diagnosis, shorter time interval, higher proportion of blacks, and higher proportion of serous and advanced OC. Besides, compared with the breast, the ovaries are located deep in the pelvic cavity, thus lesions are not easy to be found by patients. So it is comparatively easier for OC patients to find breast lesions, but BC patients often neglect ovarian monitoring. All these suggest that patients should pay attention to ovarian health and increase the frequency of screening.

There are certain limitations in this study. Firstly, this is a retrospective study so there may be selection bias. Secondly, the collinearity problem mentioned here means that there is a correlation between various independent variables, which makes the model estimation distorted. To address this problem, this study used collinearity diagnosis to eliminate independent variables with high VIF values, while larger data volume and better independent variable selection may better solve this problem. Additionally, the T and N stages of BC were excluded from the Cox regression analysis for BCSS due to the absence of BC-related deaths in certain subgroups, which could lead to biased or unstable estimates. Although this exclusion may limit the generalizability of conclusions related to tumor size and lymph node involvement, key prognostic factors were retained to ensure the robustness of the analysis. Alternative methods, such as penalized Cox regression, could be explored in future studies with larger sample sizes to address this limitation. Furthermore, though the treatment of FPC may have influence on SPC, it is not taken into consideration in this study. Finally, the SEER database does not include gene information, so the relationship between *BCRA1/2* and the above findings cannot to assessed. These shortcomings point to the direction for further researches.

Conclusions

This study analyzed the clinical characteristics, survival outcomes, and prognostic factors of DPBOC patients. These patients are mostly Luminal-type BC. Time interval is an independent influence factor of DPBOC. The longer the time after being diagnosed FPC, the lower the risk for patients to develop SPC and with better prognosis. The survival outcome of DPBOC is mainly determined by OC, and the prognosis of patients with BC as FPC is worse than that of patients with OC as FPC. To improve the prognosis for these patients, the other organ should be monitored as soon as possible after being diagnosed BC or OC. BC patients should especially pay more attention to ovarian lesions screening as well as the monitoring and treatment of OC.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-24-480/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The SEER database employed in this research is publicly accessible. Patient information within the SEER database is both publicly available and anonymized, thus obviating the need for informed consent in our study.

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