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Brain Metastases in Primary Ovarian Cancer: Real-world Data

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BACKGROUND

- Brain metastases are infrequently reported in patients with ovarian cancer (OC). The incidence of brain metastases in OC ranges from 0.3% to 11.5% with an average incidence of 2.6%.[1]
  - However, the incidence has been increasing over time, which may be the result of advances in imaging techniques and increased survival from treatment.[2,3]
- One-fifth (20%) of high-grade serous OCs have *BRCA*1/2 gene mutations (germline and somatic).[4]
- Previous data suggest a possible association between *BRCA* mutations (*BRCA*mut) and brain metastases in OC.[5-7]

OBJECTIVES

- To estimate the real-world incidence of brain metastases in OC.
- To assess whether *BRCA*mut increases the risk of brain metastases in patients with OC.

METHODS

- This retrospective study included 4515 OC patients diagnosed between January 1, 2011 and January 31, 2018 from the Flatiron Health database. Flatiron is a longitudinal, demographically and geographically diverse database derived from electronic health record data from over 265 cancer clinics and over 2 million active US cancer patients.
- The outcome of this study was the development of brain metastases after the OC diagnosis.
- A time-to-event analysis was conducted to assess whether patients with a known *BRCA*mut were more likely to develop brain metastases compared with patients with *BRCA* wild type (*BRCA*wt).

RESULTS

- Of 4515 OC patients, 2206 (49%) had *BRCA* testing and 2309 (51%) had *BRCA* status unknown or not tested (**Table 1**).
- Of the 2206 patients who underwent *BRCA* testing, 473 (21%) were *BRCA*mut, 1679 (76%) were *BRCA*wt, and 54 (2%) had unknown *BRCA* status.
- Overall, in this population, 46 (1%) patients developed brain metastases.
- *BRCA*mut rate was significantly higher in OC patients with brain metastasis (58%) as compared to those without (21%).
- Patients who developed brain metastases were younger than patients without metastases at the initial OC diagnosis (60 vs 63.5 years).

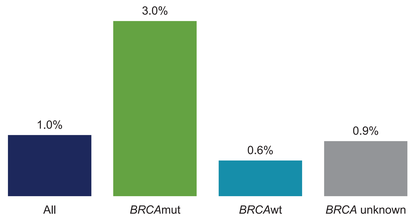
Table 1. Demographics and Disease Characteristics of OC Patients by Presence/Absence of Brain Metastases

Variable	Category	Total (N=4515)	OC with MBC (N=46)	OC without MBC (N=4469)	*P* value
Age at initial OC diagnosis, mean ± SD		63.5±12.36	60.0±10.63	63.5±12.37	0.05
BRCA tested, n (%)	Yes	2206 (49)	24 (52)	2182 (49)	0.65
	No/unknown	2309 (51)	22 (48)	2287 (51)	
BRCA mutation status*, n (%)	*BRCA*mut	473 (21)	14 (58)	459 (21)	<0.0001
	*BRCA*wt	1679 (76)	10 (42)	1669 (76)	
	Unknown	54 (2)	0 (0)	54 (2)	
Stage at OC diagnosis, n (%)	I	787 (17)	2 (4)	785 (18)	0.01
	II	349 (8)	1 (2)	348 (8)	
	III	1843 (41)	25 (54)	1818 (41)	
	IV	876 (19)	15 (33)	861(19)	
	Unknown	660 (15)	3 (7)	657 (15)	
Surgery, n (%)	Yes	3779 (84)	44 (96)	3735 (84)	0.03
	No/unknown	736 (16)	2 (4)	734 (16)	
Practice type, n (%)	Academic	596 (13)	13 (28)	583 (13)	0.002
	Community	3919 (87)	33 (72)	3886 (87)	

*BRCA*mut=*BRCA* mutation; *BRCA*wt=*BRCA* wildtype; MBC=metastatic brain cancer; OC=ovarian cancer; SD, standard deviation
BRCA mutation status among patients who had been tested.

- Brain metastases were observed in 3% (14/473) of *BRCA*mut patients compared with 0.6% (10/1679) of *BRCA*wt patients (**Figure 1**).

Figure 1. Brain Metastases Incidence by *BRCA* Status

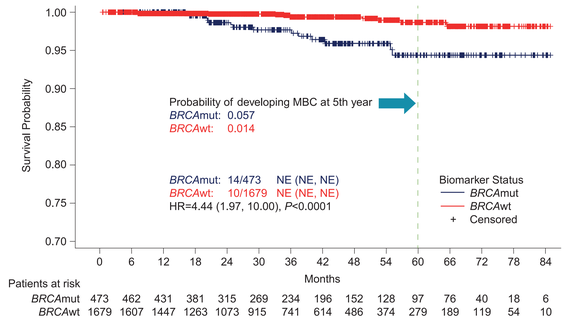


N	Regardless of *BRCA*	*BRCA*mut	*BRCA*wt	*BRCA* unknown
OC patients with CNS metastasis	46	14	10	22
OC patients	4515	473	1679	2363

*BRCA*mut=*BRCA* mutation; *BRCA*wt=*BRCA* wildtype; CNS=central nervous system; OC=ovarian cancer.

- The risk of developing brain metastases was significantly higher in the *BRCA*mut population compared with the *BRCA*wt population (hazard ratio [HR] 4.44; 95% confidence interval [CI] 1.97, 10.00; *P*<0.0001) (**Figure 2**).
  - The Kaplan-Meier estimate for the probability of patients developing brain metastases within 5 years of primary diagnosis was 5.7% in the *BRCA*mut population compared with 1.4% in the *BRCA*wt population.

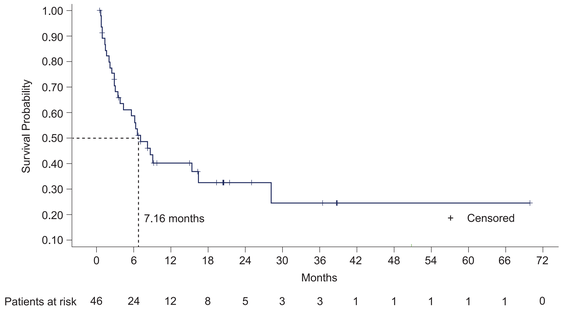
Figure 2. Time from OC Diagnosis to Diagnosis of Brain Metastases by *BRCA* Mutation Status



*BRCA*mut=*BRCA* mutation; *BRCA*wt=*BRCA* wildtype; HR=hazard ratio; MBC=metastatic brain cancer; NE=not evaluated; OC=ovarian cancer.

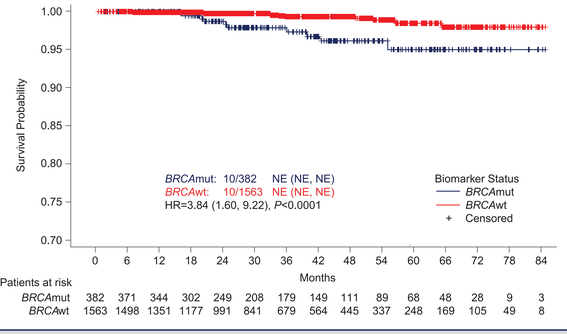
- The median overall survival after diagnosis of brain metastases was 7.16 months (95% CI 3.48, 16.49) (**Figure 3**). Survival after brain metastases diagnosis did not differ significantly by *BRCA* status (data not shown).

Figure 3. Overall Survival of Patients After the Diagnosis of Brain Metastases (Regardless of *BRCA* Mutation Status)



- In the sensitivity analysis, we excluded patients who were diagnosed with breast cancer (BC) before or after the OC diagnosis.
  - The risk of developing brain metastases was significantly higher in the *BRCA*mut population compared with the *BRCA*wt population when patients with BC (n=282) were excluded from the analysis (HR, 3.84; 95% CI 1.60, 9.22; *P*=0.001, **Figure 4**).

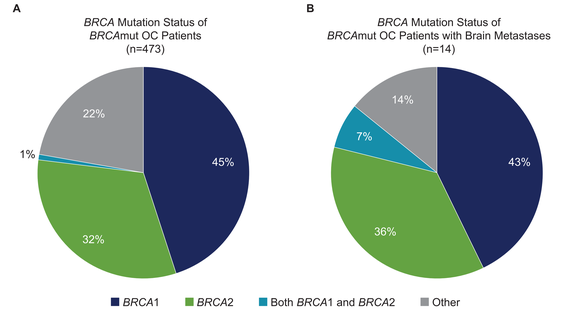
Figure 4. Time from OC Diagnosis to Diagnosis of Brain Metastases by *BRCA* Mutation Status, Excluding Patients Who Also Had a Diagnosis of BC



BC=breast cancer; *BRCA*mut=*BRCA* mutation; *BRCA*wt=*BRCA* wildtype; HR=hazard ratio; MBC=metastatic brain cancer; NE=not evaluated.

- Of the 473 *BRCA*mut patients, 211 (45%) had a *BRCA*1 mutation, 151 (32%) had a *BRCA*2 mutation, and 7 (1%) had both mutated *BRCA*1 and *BRCA*2 (**Figure 5A**).
- Of the 14 *BRCA*mut patients who developed brain metastases in the analysis, 6 (43%) had *BRCA*1 mutation, 5 (36%) had *BRCA*2 mutation, 1 (7%) had *BRCA*1 and *BRCA*2 mutations (included in the 2 prior cohorts as well), and 2 (14%) had a genetic variant that favors a polymorphism/*BRCA* not otherwise specified (**Figure 5B**).

Figure 5. *BRCA*1 and *BRCA*2 Mutations in OC Patients (A) and in OC Patients with Brain Metastases (B)



*BRCA*mut=*BRCA* mutation; OC=ovarian cancer.

CONCLUSIONS

- OC patients with a *BRCA* mutation displayed a 4-fold increased risk of developing brain metastases than patients without a *BRCA* mutation.
- Despite being a rare complication of OC, the possibility of developing brain metastases should be considered in these patients, especially those with *BRCA* mutation.
- The availability of new therapeutic options that may prolong overall survival could also lead to an increase of brain metastases in OC.

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