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Increased risk of brain metastases in ovarian cancer patients with *BRCA* mutations☆

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HIGHLIGHTS

- *BRCA* mutations may be associated with brain metastases in ovarian cancer.
- Real-world data were used to estimate ovarian cancer brain metastases risk.
- We assessed if *BRCA* mutation increases brain metastases risk in ovarian cancer.
- *BRCA* mutation increased the risk of brain metastases by 4-fold versus *BRCA* wildtype.
- Diagnosis of brain metastases was 8 months earlier with *BRCA* mutation.

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ABSTRACT

Purpose. To estimate the risk for brain metastases in patients with ovarian cancer using real-world data, and assess whether *BRCA* mutations increase that risk.

Methods. This retrospective study included 4515 patients diagnosed with ovarian cancer between January 1, 2011, and January 31, 2018, from the Flatiron Health database, a longitudinal, demographically, and geographically diverse database derived from electronic health records in the United States.

Results. Forty-six (1%) patients were diagnosed with brain metastases after being diagnosed with ovarian cancer. Of 4515 patients with ovarian cancer, 10% had a known *BRCA* mutation, 37% had *BRCA* wildtype (*BRCA*wt), and the *BRCA* status of the remaining 51% was unknown/untested. Brain metastases were observed in 3% of patients with *BRCA* mutations compared with 0.6% of those with *BRCA*wt. The Kaplan-Meier estimate for the proportion of patients with brain metastases within 5 years of diagnosis was 5.7% in the population with *BRCA* mutations compared with 1.4% in those with *BRCA*wt (hazard ratio 4.44; 95% confidence interval, 1.97, 10.00; $P < 0.0001$). These data demonstrate that patients with a *BRCA* mutation had a significantly higher risk for brain metastases than those without.

Conclusion. Despite being a rare manifestation of ovarian cancer, the possibility of developing brain metastases should be considered in these patients, especially in patients with a *BRCA* mutation. The availability of new therapeutic options that may prolong overall survival and may not cross the blood–brain barrier could also lead to an increase in brain metastases in patients with ovarian cancer.

1. Introduction

Ovarian cancer, defined as ovarian, fallopian tube, or primary peritoneal tumors, is the fifth leading cause of cancer death among women, with 7.2 deaths per 100,000 women per year in the United States [1]. A number of genes, including *BRCA1* and *BRCA2*, can be mutated in ovarian cancer, especially in high-grade serous ovarian cancer [2,3]. Twenty percent of patients with high-grade serous ovarian cancer carry *BRCA1/2* mutations (germline and somatic) [2]. The lifetime risk for ovarian cancer with mutations in either *BRCA1* or *BRCA2* ranges from 15% to 40% [4]. Both BRCA proteins play an important role in DNA damage repair. Mutations in *BRCA1/2* genes inactivate the BRCA proteins, leading to defective DNA repair machinery [5], increasing the chance of malignant transformation. *BRCA1* and *BRCA2* gene mutations are among the strongest

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known genetic risk factors for ovarian cancer. Patients with ovarian cancer and mutated *BRCA1/2* have different clinical characteristics from patients with *BRCA1/2* wildtype, including a family history of breast and/or ovarian cancer and aggressive high-grade ovarian cancer with serous pathology [6].

Brain metastases have been reported infrequently in patients with ovarian cancer. The incidence of brain metastases resulting from ovarian cancer ranges from 0.3% to 11.5% [7–10] with an average incidence of 2.6% [7]. However, the incidence has been increasing over time [10,11]; this may be the result of improved detection with advances in imaging techniques and increased survival from ovarian cancer treatment.

Previous data suggest a possible association between *BRCA* mutations and brain metastases in patients with ovarian cancer [12]. While the mechanistic relationship between BRCA proteins and brain metastasis is unclear, it has been suggested that impairment in BRCA and DNA repair may have some underlying role in ovarian cancer metastasis to the brain [13].

Clinical data taken from electronic health records (EHR) provide valuable real-world information to augment clinical trials. In this study, we used a large real-world dataset to estimate the risk for developing brain metastases in patients with ovarian cancer and examine the relationship between *BRCA* mutations and risk for brain metastases.

2. Methods

2.1. Data source

The Flatiron Health database is a longitudinal, demographically, and geographically diverse database derived from EHR data in the United States. It contains health information data from over 265 cancer clinics across approximately 800 sites of care, representing >2 million active US patients with cancer. Patient-level data include structured and unstructured data, processed via technology-enabled abstraction.

2.2. Study design and cohort definition

We conducted a retrospective observational study to examine the risk for brain metastases among patients with ovarian cancer with a known *BRCA* mutation, compared with patients with ovarian cancer and *BRCA* wildtype (*BRCA*wt). Patients were defined as having a *BRCA* mutation if they carried either a *BRCA1/2* mutation, genetic variant favor polymorphism, genetic variant of unknown significance, or *BRCA* mutation not otherwise specified. We identified all women with a diagnosis of ovarian cancer (i.e., ovarian, fallopian tube, and/or primary peritoneal cancer defined by *International Classification of Diseases*, *Ninth Revision* [ICD-9]: 183x, 158x; ICD 10: C56x, C57.0x, C48x) and at least 2 documented clinical visits for ovarian, fallopian tube, and/or peritoneal cancer between January 1, 2011, and January 31, 2018, from the Flatiron database. The index date was defined as the date of the first ovarian cancer diagnosis. Secondary brain metastases were identified using ICD codes (ICD-9: 198.3 for secondary malignant neoplasm of brain and spinal cord, and ICD-10: C79.31 for secondary malignant neoplasm of brain) after the initial ovarian cancer diagnosis.

2.3. Analysis

The primary outcome of interest was the development of brain metastases after an ovarian cancer diagnosis. The following covariates were included in the analysis to assess the potential impact on the risk for brain metastasis: age, year of initial diagnosis, stage of ovarian cancer at initial diagnosis, surgery status, practice type, and *BRCA* mutation status (i.e., somatic or germline mutation). We also assessed the impact of *BRCA1* versus *BRCA2* mutation on the risk for brain metastases. A descriptive analysis was conducted to compare baseline characteristics of patients who developed brain metastases versus those who did not.

A time-to-event analysis was performed to determine whether patient demographics and disease characteristics, including known *BRCA* mutation, were associated with an increased risk for brain metastases. Duration of follow-up for each patient was computed as the amount of time from the index date to the first of the following events: diagnosis of brain metastases, death, or study end. We plotted Kaplan-Meier curves stratified by *BRCA* mutation status. Next, we used a Cox proportional hazard model to examine the relationship between *BRCA* mutation status and brain metastases, adjusting for age, year of initial diagnosis, stage of ovarian cancer at initial diagnosis, surgery status, and practice type. Finally, we evaluated overall survival after the diagnosis of brain metastases stratified by *BRCA* status. To assess the robustness of the primary analysis findings, we conducted a sensitivity analysis excluding patients who were diagnosed with breast cancer before or after the ovarian cancer diagnosis.

Finally, to assess the *BRCA1*/*BRCA2*-specific association with brain metastases, we compared the hazard ratio (HR) for patients with *BRCA1* or *BRCA2* mutation relative to patients without *BRCA* mutations. In addition, we performed a time-to-event analysis to compare the probability of patients with both *BRCA1* and *BRCA2* mutations compared with the probability of patients with only *BRCA1* or *BRCA2* mutation.

3. Results

We retrospectively identified 4515 patients diagnosed with ovarian cancer between January 1, 2011 and January 31, 2018. Among 4515 patients, 2206 (49%) underwent *BRCA* testing and 2309 (51%) had *BRCA* status unknown or untested (Table 1). Of the 2206 patients who underwent *BRCA* testing, 473 (21%) had *BRCA* mutations, 1679 (76%) had *BRCA*wt, and 54 (2%) had *BRCA* status unknown. A total of 46 (1%) patients were diagnosed with brain metastases after receiving an ovarian cancer diagnosis. Of 2152 patients with a confirmed *BRCA* status, those with a *BRCA* mutation were more likely to have brain metastases (14 of 473 [3%]) than those without a *BRCA* mutation (10 of 1679 [0.6%]). Of the patients with *BRCA* status unknown or untested, 22 of 2309 (1%) patients developed brain metastases, consistent with the rate of brain metastases in the *BRCA* mutation known population (24 of 2206 [1%]; Table 1). Patients who developed brain metastases were younger than patients without metastases at initial ovarian cancer diagnosis (60 vs 63.5 years, respectively).

The Kaplan-Meier estimate for the proportion of patients developing brain metastases within 5 years of primary diagnosis was 5.7% in the population with *BRCA* mutations compared with 1.4% in those who had *BRCA*wt; this difference was statistically significant (HR 4.44; 95% confidence interval [CI] 1.97, 10.00; $P < 0.0001$) (Fig. 1). Multivariate models adjusting for other patient characteristics yielded similar HRs. Among patients who developed brain metastases, the median time from primary diagnosis to metastasis diagnosis was 27 months in patients with a *BRCA* mutation and 35 months in those without. The median survival after diagnosis of brain metastases was 7.16 months (95% CI 3.48, 16.49) (Fig. 2). Survival after brain metastasis diagnosis did not differ significantly by *BRCA* status (data not shown).

There were 282 patients with ovarian cancer in the database who were also diagnosed with breast cancer: 186 developed breast cancer prior to being diagnosed with ovarian cancer, 95 developed breast cancer after being diagnosed with ovarian cancer, and 1 patient developed breast cancer but the date of the diagnosis could not be identified. When these patients were excluded from the population analyzed ($n = 4233$), the HR for developing brain metastases over time among patients with *BRCA* mutations versus *BRCA*wt was 3.84 (95% CI 1.60, 9.22; $P = 0.001$) (Fig. 3).

Of the 473 patients with ovarian cancer and *BRCA* mutations, 211 (45%) had a *BRCA1* mutation, 151 (32%) had a *BRCA2* mutation, and 7 (1%) had mutated *BRCA1* and *BRCA2* (Fig. 4). Among 14 patients with *BRCA* mutations who developed brain metastases, 6 (43%) had *BRCA1* mutations, 5 (36%) had *BRCA2* mutations, 1 (7%) had *BRCA1* and

Table 1
Demographics and disease characteristics of the total sample of patients with ovarian cancer 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 diagnosis	Mean ± SD	63.5 ± 12.4	60.0 ± 10.6	63.5 ± 12.4	0.05
BRCA tested, n (%)	Yes	2206 (49)	24 (52)	2182 (49)	0.65
	No	2309 (51)	22 (48)	2287 (51)	
BRCA mutation status, n (%)[a]	*BRCA*mut	473[b] (21)	14 (58)	459 (21)	<0.0001
	*BRCA*wt	1679 (76)	10 (42)	1669 (76)	
	BRCA unknown	54 (2)	0 (0)	54 (2)	
Stage at 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	Yes	3779 (84)	44 (96)	3735 (84)	0.03
	No/unknown	736 (16)	2 (4)	734 (16)	
Practice type	Academic	596 (13)	13 (28)	583 (13)	0.002
	Community	3919 (87)	33 (72)	3886 (87)	

BRCA, *BRCA* human gene; *BRCA*mut, *BRCA* mutated; *BRCA*wt, *BRCA* wildtype; MBC, metastatic brain cancer; OC, ovarian cancer; SD, standard deviation.
[a] *BRCA* mutation status among patients who had been tested.
[b] 79 patients were identified from Variant of Unknown Significance (VUS).

BRCA2 mutations, and 2 (14%) had a genetic variant that favored a polymorphism/*BRCA* not otherwise specified.

Compared with *BRCA*wt, *BRCA1* mutation was associated with brain metastases with an HR of 4.4 (95% CI 1.67, 11.56; $P = 0.0011$), and *BRCA2* mutation was associated with an HR of 5.4 (95% CI 1.96, 14.87; $P = 0.0003$) (Supplemental Fig. 1A and B).

4. Discussion

In this study, we retrospectively identified 4515 patients with ovarian cancer from the large Flatiron EHR-derived database. Among these patients, approximately 1% developed brain metastases after an ovarian cancer diagnosis. This number is consistent with other reports and within the range (0.3% to 11.5%) of previously published literature [7–10]. Among patients with ovarian cancer and known *BRCA* status, patients with a mutated *BRCA* gene had a 4-fold higher risk for brain metastases than those who had *BRCA*wt. It is unlikely that this elevated risk is due to the longer overall survival or better management of these patients. Our data indicate that patients with ovarian cancer and *BRCA* mutations develop brain metastases 8 months earlier than those who had *BRCA*wt: 27 months versus 35 months median time from ovarian cancer diagnosis to brain metastases diagnosis, respectively. Furthermore, patients with ovarian cancer and brain metastases were younger than patients without metastases (60 vs 63.5 years, respectively). This is linked to the fact that patients with *BRCA*-mutated ovarian cancer are younger than those with *BRCA*wt. In addition, we found more *BRCA* mutations among patients with ovarian cancer and brain metastases (30% vs 10%, respectively).

Limited published data exist regarding *BRCA* status and brain metastases in women with ovarian cancer. Sekine et al. [12] conducted a retrospective analysis of 340 ovarian cancer cases from a single institution in Japan (Niigata University Hospital) from 1983 to 2007 to estimate the incidence of brain metastases. Among 7 (2%) cases of brain metastases that they identified, 4 were associated with *BRCA1*: 2 cases had loss of heterozygosity (LOH) at the *BRCA1* locus (LOH-positive), and 2 cases were LOH-positive and had *BRCA1* germline mutations. All 4 LOH-

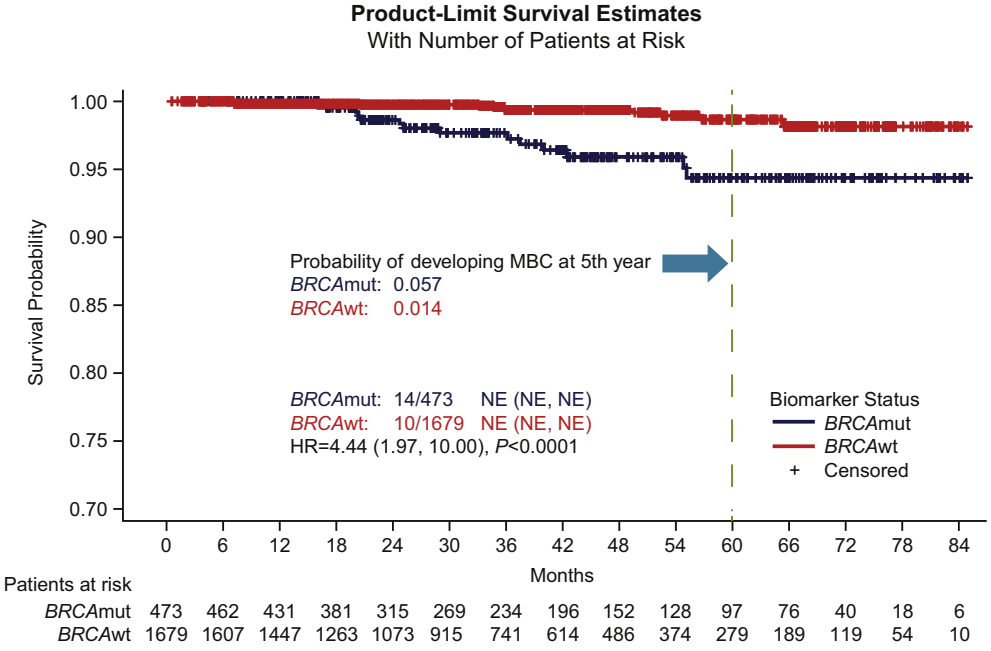

Fig. 1. Time from ovarian cancer diagnosis to brain metastases diagnosis by *BRCA* mutation status. *BRCA*, *BRCA* human gene; *BRCA*mut, *BRCA* mutated; *BRCA*wt, *BRCA* wildtype; HR, hazard ratio; MBC, metastatic brain cancer; NE, not evaluated.

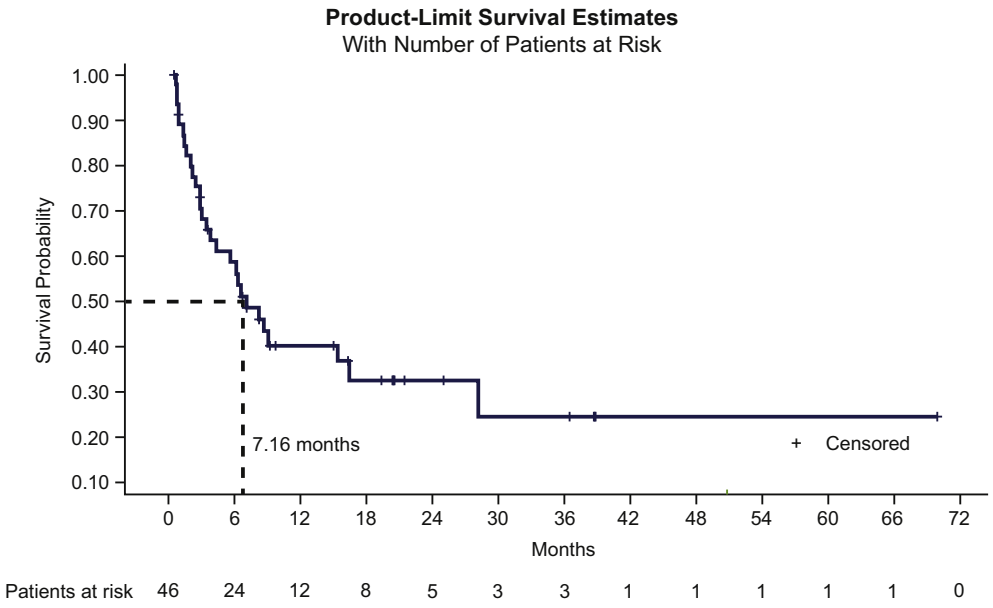

Fig. 2. Overall survival from time of brain metastases diagnosis.

positive patients had no BRCA protein expression. The remaining 3 of 7 cases did not have these genetic features and displayed BRCA nuclear staining. Thus, Sekine et al. hypothesized that *BRCA1* loss of function may be a contributing factor to ovarian cancer brain metastases. Root and Armaghany [14] presented a case report of a solitary brain metastasis secondary to ovarian cancer in a patient with a *BRCA2* mutation. A sequencing-based genomic profiling study by Balendran and colleagues [13] found that 7 of 8 brain metastasis samples of primary ovarian cancer had either a somatic *BRCA1* or a *BRCA2* pathogenic mutation.

Brain metastases from breast cancer have been detected in 13–30% of patients [15]. Among women with breast cancer, 5–10% may have a germline mutation in the *BRCA* genes [16]. An association between *BRCA* mutations and brain metastases has also been reported [17–19]. A retrospective, clinical database analysis of women with stage I–III triple-negative breast cancer comparing patients carrying *BRCA1* mutations versus noncarriers found that the overall incidence of brain metastases was 58% in *BRCA* mutation carriers versus 24% in noncarriers ($P = 0.06$) [18]. A more recent retrospective study of patients with breast cancer indicated that 15% of patients with *BRCA1/2* mutations developed brain metastases compared with 2.5% for matched controls [17]. Beyond gynecological cancers, studies have found putative associations between *BRCA1* and *BRCA2* alterations and brain metastases in patients with pancreatic ductal adenocarcinoma [20] and non–small cell lung carcinoma [21].

Currently, any mechanistic explanation for the involvement of BRCA proteins in brain metastasis remains speculative. Balendran and colleagues [13] found that *BRCA1/2* were among the most commonly altered genes, along with *TP53*, *ATM*, and *CHEK2*, in brain metastatic

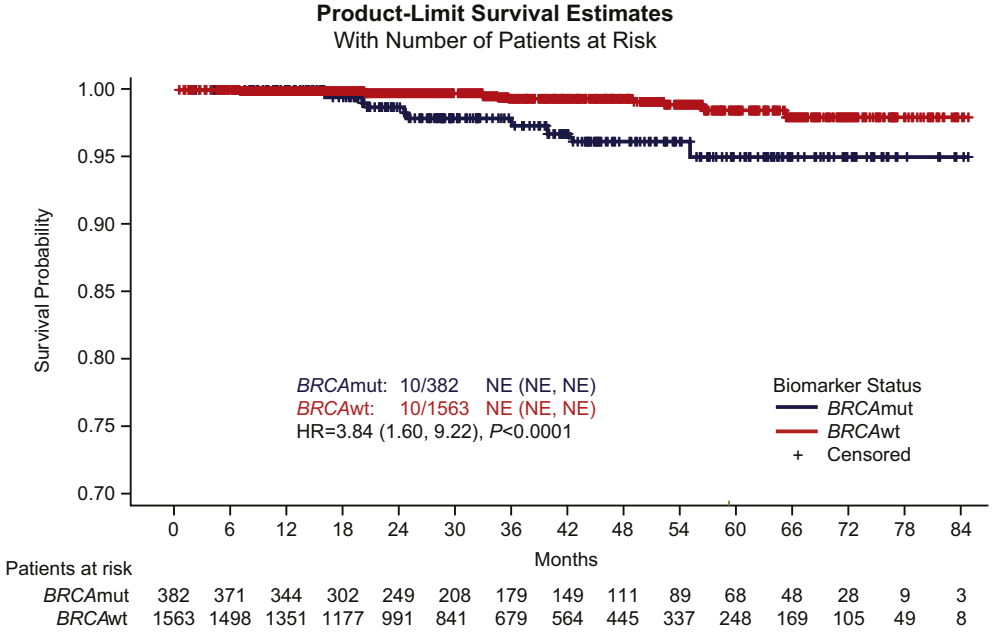

Fig. 3. Time from ovarian cancer diagnosis to brain metastases diagnosis by *BRCA* mutation status, excluding patients who were also diagnosed with breast cancer. *BRCA*, *BRCA* human gene; *BRCA*mut, *BRCA* mutated; *BRCA*wt, *BRCA* wildtype; HR, hazard ratio; MBC, metastatic brain cancer; NE, not evaluated.

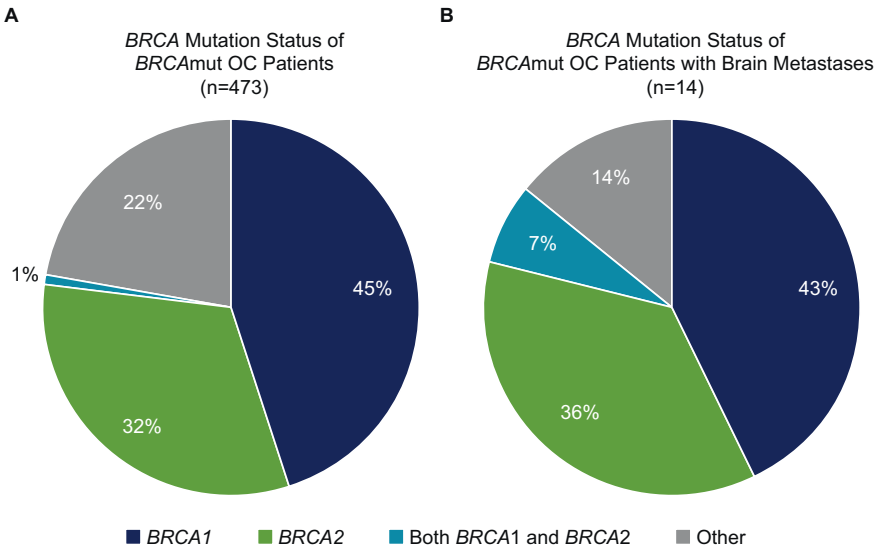

Fig. 4. *BRCA1* and *BRCA2* mutations in patients with ovarian cancer (A) and patients with ovarian cancer and brain metastases (B). *BRCA*, *BRCA* human gene; *BRCA1*, *BRCA1* human gene; *BRCA2*, *BRCA2* human gene; *BRCA*mut, *BRCA* mutated; OC, ovarian cancer.

tissue samples from women with ovarian cancer. Both BRCA proteins play a role in DNA repair [5]; whether this is functionally linked to ovarian cancer metastasizing to the brain remains unknown.

Balendran and colleagues [13] also found no significant differences in the risk for brain metastasis based on *BRCA1* versus *BRCA2* mutation status. However, their analysis was limited by a small sample size (n = 6, *BRCA1* mutations; n = 5, *BRCA2* mutations; n = 1, *BRCA1* and *BRCA2* mutations). The risk for *BRCA1*-linked ovarian cancers is higher (39% to 44%) than that of *BRCA2* (11% to 17%) [2,22]. However, further research is needed to determine whether this also translates into differences in risk for developing brain metastases.

We acknowledge that this study has several limitations. Our findings that patients with ovarian cancer and *BRCA* mutations develop brain metastases earlier than patients with *BRCA*wt could be the result of scanning bias, as physician-directed assessments may be more frequent in these patients than in patients with *BRCA*wt. The high number of patients with *BRCA* status unknown or untested may be an additional limiting factor in accurately estimating the risk for brain metastasis in patients with ovarian cancer. Furthermore, the prevalence of brain metastases in patients with ovarian cancer may be underrepresented because cranial MRI is not a part of screening after ovarian cancer diagnosis and therefore brain metastasis may remain undetected at the time of initial diagnosis.

In conclusion, this study demonstrated that patients with ovarian cancer and mutated *BRCA* had a 4-fold increased risk for brain metastases than patients with *BRCA*wt. Furthermore, we found that patients with ovarian cancer and a *BRCA* mutation were diagnosed with brain metastases approximately 8 months earlier than patients who had *BRCA*wt. We were unable to conclude whether one *BRCA* gene has a greater impact on brain metastases risk than the other. The relative infrequency of ovarian cancer brain metastases has impeded the establishment of a consensus protocol for the screening and treatment of affected patients. Our findings suggest that in the absence of central nervous system disease symptoms, *BRCA* mutations could be an important consideration to promote screening for brain metastasis in women with ovarian cancer.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.03.004.

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Author contributions

ER, MB, SH, and PKB designed, directed, and coordinated the study. MLG and EA performed data mining and statistical analysis. All authors edited the manuscript.

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