

BRCA1 or BRCA2 mutation variants in early breast cancer confer added prognostic information

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Abstract

Metastatic breast cancer to brain carries poor prognostic features with increased risks of occurrence in Triple-negative and HER-positive breast tumors. In addition, tumors with mutated BRCA tumors, carry as well increased metastatic incidence. However, new clinical evidence suggest distinct clinical features between BRCA1 or BRCA2 mutated breast cancer and brain metastasis. Review of literature may help characterize the distinctive differences between BRCA1 or BRCA2 breast tumors and subsequent metastasis to brain.

Keywords: Breast cancer, Brain metastasis, BRCA1, BRCA2, Mutation, Triple-negative, Hormone-receptor positive, Pathogenic variant, Prognosis, Early breast cancer

Introduction

The main function of BRCA1 and BRCA2 in the repair of double-strand DNA breaks is through homologous recombination. Thus, they are considered tumor suppressor genes and are associated with an increased risk of cancer including breast and ovarian cancers [1,2]. The pathogenic variants are generally heterozygous, resulting in its loss of function [3]. Phenotypes of breast cancer that are associated with germline BRCA mutations may also be further classified into germline BRCA1 (gBRCA1) and gBRCA2 pathologic variants, suggesting different mechanisms of homologous recombination [4]. Therefore, we find it useful to further clinically characterize patients with gBRCA1- or gBRCA2-mutated breast cancer with metastasis to the brain as it is a poor prognostic feature that is associated with significant morbidity and shortened survival.

Different BRCA Mutations Imply Different Clinical Outcomes and Management Strategies

Based on BRCA mutation status, patients with breast cancer may be subdivided into 3 groups: BRCA1 mutation carriers, BRCA2 mutation carriers, and non-BRCA mutation carriers. BRCA1 mutation carriers may, in addition, be further divided into triple-negative (TN), defined as estrogen- and progesterone- negative as well HER-2 negative (IHC <3+ or FISH non-amplified), or non-TN [4]. Additionally, BRCA1- and BRCA2-mutated breast cancers have different clinical differences. First, about 20% of patients with breast cancer carry BRCA1 mutations but only 8% carry BRCA2 mutations, and the majority (72%) do not have BRCA mutations [5]. Compared to patients with BRCA1 mutations, those with BRCA2 mutations tend to be older and have higher incidences of hormone receptor- or human epidermal growth factor receptor-positivity [4,6]. Another clinical distinction is the greater prevalence of visceral metastasis in BRCA1 carriers compared to BRCA2 and non-BRCA carriers (70% vs. 9% vs. 37%, respectively). Moreover, Patients with BRCA1-mutated breast tumors have statistically shorter 5-year survival rates compared to those with BRCA2-mutated or with non-BRCA-mutated tumors (73% vs. 96% vs. 92%, respectively with $p < 0.001$) [5]. The use of alkylating agents did not seem to affect the survival of patients with TN breast cancer (TNBC), whether they were gBRCA1 carriers or not [7]. Patients of Ashkenazi descent with BRCA1 mutations had poorer survival outcomes compared to BRCA2-mutated breast cancer patients; however, such

differences were abolished with the use of adjuvant chemotherapy [8]. Finally, patients with BRCA1 mutations and metastatic breast cancer have worse outcomes in terms of time to progression and overall survival, compared to other breast cancer clinical entities [6,8,9].

Genetic testing for gBRCA is recommended for patients with metastatic breast cancer, TNBC, and high-risk ER-positive breast cancer in whom the testing could help guide systemic therapy, and for patients with any stage breast cancer who are at a substantial risk for hereditary breast cancer based on family cancer history [10]. Genetic testing results support breast cancer screening, risk reduction strategies, and family counseling, and they are now integral to the treatment of breast cancer, including in the adjuvant and metastatic settings. Testing for BRCA in patients with early breast cancer (eBC) serves to optimize locoregional management and to select patients who may benefit from poly (ADP-ribose) polymerase (PARP) inhibitors in the adjuvant setting. However, the predictive value of BRCA1 vs. BRCA2 regarding patterns of recurrence, particularly that of brain metastasis, is not well understood.

Implications of BRCA Status for Use of PARP Inhibitors to Control Brain Metastasis

Tumor cells with mutated variants of BRCA1/2 are deficient in DNA double stranded breaks, whose repair is regulated by PARP enzyme. PARP inhibitors cause accumulation of unrepaired DNA damage resulting in cell death. The PARP inhibitors olaparib and talazoparib are shown to improve progression-free survival [11,12] and are United States Federal Drug Association (FDA)-approved options for the treatment of gBRCA-mutated, HER2-negative metastatic breast cancer. In addition, patients with a history of central nervous system (CNS) metastasis (N=63, 14%) benefited more from talazoparib compared to patients with no history of CNS metastasis (n=368, 86%) (hazards ratios of 0.32 and 0.58, respectively), suggesting that talazoparib may have helped control CNS disease, thus reflecting favorably on progression-free survival [11]. In another study of patients with gBRCA-mutated and HER2-negative metastatic breast cancer [13], the combination of chemotherapy with a PARP inhibitor showed improved progression-free survival compared to a placebo; however only 5% of the patients had CNS metastasis and were not analyzed separately for clinical outcomes.

Because of the introduction of various systemic treatment options and improved systemic disease control, we questioned whether we might see more frequent CNS metastases among patients with gBRCA, particularly if this subgroup has a predilection for brain metastasis [14-17], as was observed with HER2-positive breast cancer patients who showed high rates of CNS metastasis. A tucatinib-based therapy has demonstrated clear CNS activity in patients with HER2-positive tumors [18-20], and it may be likely, as well, that other drugs, such as PARP inhibitors, have similar impacts on brain metastasis in patients with gBRCA mutations [21-23].

Therefore, there is a need to figure out the association of brain metastasis and gBRCA in patients with eBC and to explore its potential impact on the survival and, be compared to that of non-gBRCA carriers, as well. In addition, there is a need to explore the potential to reduce the risk of developing brain metastasis in patients at high-risk for this metastasis. Therefore, the relatively high incidence of brain metastasis among patients with gBRCA-mutated tumors intensifies the need for clinical trials that use agents with CNS

activity and the inclusion of brain MRIs as part of the evaluation for distant recurrence and aim to prevent brain metastasis in high-risk breast cancer patients with BRCA mutations.

What has been Discovered about BRCA1 vs. BRCA2 in eBC

In a recent single-institution study [24], gBRCA1 or gBRCA2 patients with stage I-III breast cancer were evaluated. In this study, several characteristics were identified and differentiated aspects of natural history and clinical outcomes between the 2 groups: Both groups had similar distant recurrence rate (9 years) and 3-year distant metastasis-free survival rate; however, compared to the predominant HR-positive gBRCA2 tumors, gBRCA1 tumors have been shown to be more of the TN phenotypes, shorter lead time (2.4 vs 5 years), and a higher predilection to brain metastasis. Furthermore, patients with gBRCA1 tumors tend to spread to the brain at a younger age compared to patients with gBRCA2 tumors. Finally, patients with gBRCA2 tumors tend to have a higher incidence of multiple brain lesions (compared to that of solitary lesions) yet a longer overall survival than those with gBRCA1 patients.

Furthermore, distinctions between patients with gBRCA1 mutation carriers and non-gBRCA1 mutation carriers have been documented [7,16]; there is a higher tendency for brain metastasis in gBRCA1 patients compared to non-carriers [16]. However, when patients with BRCA2 mutations were included in a comparative analyses with patients with BRCA1 mutations or non-carrier [15], BRCA2 were predominantly HR – positive compared to the predominantly TN phenotypes associated with BRCA1 mutated patients, as well as with higher predilection to bone metastasis compared with higher predilection to lung or lymph node recurrences with BRCA1 mutated tumors. In one study, BRCA1 patients with metastatic breast cancer had worse outcomes compared with gBRCA2 patients or gBRCA non-carrier patients; however, brain metastasis was included among the visceral metastasis category and not accounted for separately [6].

In another study, patients with progressive TN metastatic breast cancer had worse outcomes if they had brain metastasis; however, the relevance of gBRCA was not accounted for as a prognostic feature [26]. Although it is abundantly documented that TN and HER2-positive tumors have a high predilection to brain metastasis [26], but attempts at sub-classifying non-HER-positive cases into BRCA1, BRCA2, and non-BRCA carrier tumors are not clearly characterized. BRCA1-associated tumors carry poorer prognostic features, added to tumor size and nodal status [27,28]. Furthermore, BRCA1 tumors were characterized to demonstrate high-grade, basal-like phenotypes, HR and HER2-negative, and to express CD5, CD6, and CD14 [27,29-31]. However, timing to brain metastasis is affected by several factors, such as being TN or HER2-positive, being younger than 35 years old, and having luminal A tumors in patients who are older than 60 years [32]. Yet, to our knowledge, BRCA1 or BRCA2 were not separately addressed in the literature until it was first reported that there was no apparent differences in rates of brain metastasis, including CNS parenchymal and leptomeningeal metastasis, in patients with gBRCA1- or gBRCA2-mutated breast tumors [16/30 (53%) vs. 16/32 (50%)], however, with only 67/270 (25%) of the gBRCA non-carriers developed brain metastasis, $p < .001$ and, with the gBRCA2 seems to be more associated with CNS metastasis when controlling for tumor subtypes, in a multivariate analysis ($p = .006$)

[15]. In contrast, another study [24] reported the frequency of CNS metastasis in the *gBRCA1* cohort was higher than that of the *gBRCA2* cohort (34/76 [45%] vs. 7/42 [16.7%]) and that of the non-BRCA-carrier patients with TNBC (65/182 [36%]).

Such reported differences may be explained by potential differences in timing to and/or referral biases to different tertiary institutions, for management of diagnosed or suspected brain metastasis. Furthermore, inclusion of leptomeningeal carcinomatosis in the parenchymal brain metastasis group may have, in part, increased the rate of CNS metastasis in the *gBRCA2* group. This finding raises an additional question whether *gBRCA2* patients have a predilection to leptomeningeal carcinomatosis, which is an issue that has not yet been addressed. It is probably safe to say that there is a higher rate of brain metastasis among *gBRCA1* patients and *gBRCA* non-carrier TNBC patients than in patients with *gBRCA2*. However, there is no clear clinical signal yet to say that *gBRCA* breast cancers, particularly *gBRCA1* breast cancers, have a unique predilection for CNS metastasis, particularly in the context of patients with TNBC. Small studies of brain metastasis in other BRCA-associated malignancies suggest that *gBRCA* ovarian cancer patients may have a high risk for brain metastasis, albeit a much lower risk than that of breast cancer patients. An alternative explanation would be the longer overall survival in *gBRCA* ovarian cancer patients is due to the enhanced chemosensitivity or the effectiveness of the PARP inhibitor maintenance therapy commonly employed with these patients [29,33-37].

Breast cancer brain metastasis shows increased homologous recombination deficiency in relation to the corresponding primary tumor [38,39]. *BARD1* and *RAD51* are overexpressed as well in metastatic brain lesions, but not necessarily so in the paired primary tumor [40]. More studies are needed to focus on the molecular features of *gBRCA* brain metastatic lesions, including but not limited to *gBRCA1* or *gBRCA2* mutations. In addition, TNBC tumors may also benefit from treatment with PARP inhibitors, as such tumors tend to become more BRCA-like upon seeding the brain. In early 2022, the FDA approved olaparib for the adjuvant treatment of patients with deleterious or suspected deleterious germline BRCA mutated high-risk breast cancer. This was based on the adjuvant OlympiA trial that randomized 1,836 HER2-negative high-risk eBC patients who completed definitive local treatment and neoadjuvant or adjuvant chemotherapy to treatment with a placebo or olaparib for 1 year. A statistically significant improvement in invasive disease-free survival and overall survival was seen in patients in the olaparib arm compared to those in the placebo arm. Therefore, it will be important to assess whether olaparib, as evaluated in the phase III OlympiA trial, was effective at preventing both systemic and CNS recurrences [25,39]. Retrospective analysis of the data may help in hypothesis generation that may pave the way for prospective brain metastasis prevention clinical trials in BRCA-mutated eBC.

In conclusion, *gBRCA1* patients and *gBRCA* non-carriers with recurrent TNBC have similar rates of brain metastasis. Breast cancer cells capable of CNS penetration and progression have increased homologous recombination deficiency, a characteristic intrinsic to BRCA1- and BRCA2-deficient tumors. The efficacy of PARP inhibitors for the treatment and therefore, potential prevention, of CNS recurrence in BRCA-mutated (germline or somatic) breast cancer is largely unknown. The prevalence of current published data, therefore, highlights the urgent need for clinical trials with PARP

inhibitors or other effective anti-breast cancer drugs with potential therapeutic CNS penetration in the *gBRCA*-mutated breast cancer brain metastases, particularly in patients with recurrent TNBC, both in *gBRCA1* carriers and noncarriers. Such strategy may eventually lead to the use of such proven effective drugs to be implemented in brain metastasis prevention trials.

Summary

1. BRCA1 vs. BRCA2 mutation status confers different clinical characteristics in patients with eBC. In addition to the well-documented, differential increased risks of developing bilateral breast or ovarian cancers, other distinguishing clinical characteristics can be listed when comparing eBC and later development of brain metastasis: Age at the time of diagnosis of eBC was younger in BRCA1 carriers compared to BRCA2 carriers.
2. Most BRCA1 carriers with brain metastasis were more likely to be TN, in contrast to BRCA2 carriers, who mostly had HR-positive/HER-negative tumors.
3. The incidence of brain metastasis is higher for BRCA1 carrier patients compared to that for BRCA2 carriers.
4. The incidence of brain metastasis was not different between BRCA1-carrier tumors and TN non-carrier tumors.
5. Patients with BRCA1 mutations displayed a higher incidence rate of brain metastasis at first metastasis, even compared to patients with TNBC.
6. Survival following brain metastasis was significantly shorter for BRCA1 carriers and non-BRCA carrier patients with TNBC compared to that of the BRCA2 carriers.

However, there was a paucity of data to address brain metastasis clinical outcomes among BRCA2 carriers. Although there were “visual” differences compared to BRCA1 carriers and non-BRCA1 carriers, such differences are not necessarily statistically different due to the small number of patients [24].

Despite the small numbers, given the relatively infrequent observations of patients with BRCA1 vs. BRCA2 mutations, published data to date, may be used to distinguish the different predilections to brain metastasis. Therefore, testing for BRCA status as a routine evaluation may help educate patients and clinicians about the likelihood of developing brain metastasis.

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Conflicts of interest

The author declares no competing financial or non-financial Interests.

References

1. Mavaddat N, Peock S, Frost D, Ellis S, Platte R, Fineberg E, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. *JNCI: Journal of the National Cancer Institute.* 2013 Apr 29;105(11):812-22.
2. Cobain EF, Milliron KJ, Merajver SD. Updates on breast cancer genetics: Clinical implications of detecting syndromes of inherited increased susceptibility to breast cancer. *Seminars in Oncology.* 2016 Oct 1;43(5):528-535.
3. Lord CJ, Ashworth A. BRCAness revisited. *Nature Reviews Cancer.* 2016 Feb;16(2):110-20.
4. Atchley DP, Albarracin CT, Lopez A, Valero V, Amos CI, Gonzalez-Angulo AM, et al. Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. *Journal of Clinical Oncology.* 2008 Sep 9;26(26):4282-8.
5. Moller P, Evans DG, Reis MM, Gregory H, Anderson E, Maehle L, et al. Surveillance for familial breast cancer: Differences in outcome according to BRCA mutation status. *International Journal of Cancer.* 2007 Sep 1;121(5):1017-20.
6. Bayraktar S, Gutierrez-Barrera AM, Lin H, Elsayegh N, Tasbas T, Litton JK, et al. Outcome of metastatic breast cancer in selected women with or without deleterious BRCA mutations. *Clinical & Experimental Metastasis.* 2013 Jun;30(5):631-42.
7. Lee LJ, Alexander B, Schnitt SJ, Comander A, Gallagher B, Garber JE, et al. Clinical outcome of triple negative breast cancer in BRCA1 mutation carriers and noncarriers. *Cancer.* 2011 Jul 15;117(14):3093-100.
8. Robson ME, Chappuis PO, Satagopan J, Wong N, Boyd J, Goffin JR, et al. A combined analysis of outcome following breast cancer: differences in survival based on BRCA1/BRCA2 mutation status and administration of adjuvant treatment. *Breast Cancer Research.* 2003 Feb;6(1): R8-R17.
9. Stoppa-Lyonnet D, Ansquer Y, Dreyfus H, Gautier C, Gauthier-Villars M, Bournstyn E, et al. Familial invasive breast cancers: worse outcome related to BRCA1 mutations. *Journal of Clinical Oncology.* 2000 Dec 15;18(24):4053-9.
10. Theriault RL, Carlson RW, Allred C, Anderson BO, Burstein HJ, Edge SB, et al. National comprehensive cancer network. Breast cancer, version 3.2013: Featured updates to the NCCN guidelines. *Journal of the National Comprehensive Cancer Network.* 2013;11(7):753-60.
11. Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee KH, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *New England Journal of Medicine.* 2018 Aug 23;379(8):753-63.
12. Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *New England Journal of Medicine.* 2017 Aug 10;377(6):523-33.
13. Diéras V, Han HS, Kaufman B, Wildiers H, Friedlander M, Ayoub JP, et al. Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology.* 2020 Oct 1;21(10):1269-82.
14. Albiges L, Andre F, Balleyguier C, Gomez-Abuin G, Chompret A, Delaloge S. Spectrum of breast cancer metastasis in BRCA1 mutation carriers: highly increased incidence of brain metastases. *Annals of Oncology.* 2005 Nov 1;16(11):1846-7.
15. Song Y, Barry WT, Seah DS, Tung NM, Garber JE, Lin NU. Patterns of recurrence and metastasis in BRCA1/BRCA2-associated breast cancers. *Cancer.* 2020 Jan 15;126(2):271-80.
16. Tung N, Gaughan E, Hacker MR, Lee LJ, Alexander B, Poles E, et al. Outcome of triple negative breast cancer: comparison of sporadic and BRCA1-associated cancers. *Breast Cancer Research and Treatment.* 2014 Jul;146(1):175-82.
17. Zavitsanos PJ, Wazer DE, Hepel JT, Wang Y, Singh K, Leonard KL. BRCA1 mutations associated with increased risk of brain metastases in breast cancer. *American Journal of Clinical Oncology.* 2018 Dec 1;41(12):1252-6.
18. Musolino A, Ciccolallo L, Panebianco M, Fontana E, Zanoni D, Bozzetti C, et al. Multifactorial central nervous system recurrence susceptibility in patients with HER2-positive breast cancer: Epidemiological and clinical data from a population-based cancer registry study. *Cancer.* 2011 May 1;117(9):1837-46.
19. Mounsey LA, Deal AM, Keith KC, Benbow JM, Shachar SS, Zagar T, et al. Changing natural history of HER2-Positive breast cancer metastatic to the brain in the era of new targeted therapies. *Clinical Breast Cancer.* 2018 Feb 1;18(1):29-37.
20. Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *New England Journal of Medicine.* 2020 Feb 13;382(7):597-609.
21. Exman P, Mallery RM, Lin NU, Parsons HA. Response to olaparib in a patient with germline BRCA2 mutation and breast cancer leptomeningeal carcinomatosis. *NPJ Breast Cancer.* 2019 Nov 29;5(1):46.
22. Kizilbash SH, Gupta SK, Chang K, Kawashima R, Parrish KE, Carlson BL, et al. Restricted Delivery of Talazoparib Across the Blood-Brain Barrier Limits the Sensitizing Effects of PARP Inhibition on Temozolomide Therapy in Glioblastoma Effect of Talazoparib on TMZ Efficacy in GBM. *Molecular Cancer Therapeutics.* 2017 Dec 1;16(12):2735-46.
23. Karginova O, Siegel MB, Van Swearingen AE, Deal AM, Adamo B, Sambade MJ, et al. Efficacy of Carboplatin Alone and in Combination with ABT888 in Intracranial Murine Models of BRCA-Mutated and BRCA-Wild-Type Triple-Negative Breast Cancer Carboplatin±ABT888 in BRCA and Non-BRCA Intracranial TNBC. *Molecular Cancer Therapeutics.* 2015 Apr 1;14(4):920-30.
24. Garber HR, Raghavendra AS, Lehner M, Qiao W, Gutierrez-Barrera AM, Tripathy D, et al. Incidence and impact of brain metastasis in patients with hereditary BRCA1 or BRCA2 mutated invasive breast cancer. *NPJ Breast Cancer.* 2022 Apr 7;8(1):1-8.
25. Tutt AN, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant olaparib for patients with BRCA1-or BRCA2-mutated breast cancer. *New England Journal of Medicine.* 2021 Jun 24;384(25):2394-405.
26. Lin NU, Claus E, Sohl J, Razzak AR, Arnaout A, Winer EP. Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: high incidence of central nervous system metastases. *Cancer.* 2008 Nov 15;113(10):2638-45.
27. Brekelmans CT, Seynaeve C, Menke-Pluymers M, Brüggewirth HT, Tilanus-Linthorst MM, Bartels CC, et al. Survival and prognostic factors in BRCA1-associated breast cancer. *Annals of Oncology.* 2006 Mar 1;17(3):391-400.
28. El-Tamer M, Russo D, Troxel A, Bernardino LP, Mazziotta R, Estabrook A, et al. Survival and recurrence after breast cancer in BRCA1/2 mutation carriers. *Annals of Surgical Oncology.* 2004 Feb;11(2):157-64.

29. Balendran S, Liebmann-Reindl S, Berghoff AS, Reischer T, Popitsch N, Geier CB, et al. Next-generation sequencing-based genomic profiling of brain metastases of primary ovarian cancer identifies high number of BRCA-mutations. *Journal of Neuro-Oncology.* 2017 Jul;133(3):469-76.
30. Lakhani SR, Jacquemier J, Sloane JP, Gusterson BA, Anderson TJ, van de Vijver MJ, et al. Multifactorial analysis of differences between sporadic breast cancers and cancers involving BRCA1 and BRCA2 mutations. *Journal of the National Cancer Institute.* 1998 Aug 5;90(15):1138-45.
31. Narod SA, Foulkes WD. BRCA1 and BRCA2: 1994 and beyond. *Nature Reviews Cancer.* 2004 Sep;4(9):665-76.
32. Hung MH, Liu CY, Shiau CY, Hsu CY, Tsai YF, Wang YL, et al. Effect of age and biological subtype on the risk and timing of brain metastasis in breast cancer patients. *PLoS One.* 2014 Feb 24;9(2):e89389.
33. Borella F, Bertero L, Morrone A, Gambella A, Bovetti M, Cosma S, et al. Brain metastases from ovarian cancer: current evidence in diagnosis, treatment, and prognosis. *Cancers.* 2020 Aug 4;12(8):2156.
34. Gourley C, Michie CO, Roxburgh P, Yap TA, Harden S, Paul J, et al. Increased incidence of visceral metastases in Scottish patients with BRCA1/2-defective ovarian cancer: an extension of the ovarian BRCAness phenotype. *Journal of Clinical Oncology.* 2010 May 20;28(15):2505-11.
35. Sekine M, Yoshihara K, Komata D, Haino K, Nishino K, Tanaka K. Increased incidence of brain metastases in BRCA1-related ovarian cancers. *Journal of Obstetrics and Gynaecology Research.* 2013 Jan;39(1):292-6.
36. Stasencko M, Cybulska P, Feit N, Makker V, Konner J, O'Cearbhaill RE, et al. Brain metastasis in epithelial ovarian cancer by BRCA1/2 mutation status. *Gynecologic Oncology.* 2019 Jul 1;154(1):144-9.
37. Ratner E, Bala M, Louie-Gao M, Aydin E, Hazard S, Brastianos PK. Increased risk of brain metastases in ovarian cancer patients with BRCA mutations. *Gynecologic Oncology.* 2019 Jun 1;153(3):568-73.
38. Diossy M, Reiniger L, Sztupinszki Z, Krzystanek M, Timms KM, Neff C, et al. Breast cancer brain metastases show increased levels of genomic aberration-based homologous recombination deficiency scores relative to their corresponding primary tumors. *Annals of Oncology.* 2018 Sep 1;29(9):1948-54.
39. Tyrán M, Carbuccia N, Garnier S, Guille A, Adelaïde J, Finetti P, et al. A comparison of DNA mutation and copy number profiles of primary breast cancers and paired brain metastases for identifying clinically relevant genetic alterations in brain metastases. *Cancers.* 2019 May 13;11(5):665.
40. Woditschka S, Evans L, Duchnowska R, Reed LT, Palmieri D, Qian Y, et al. DNA double-strand break repair genes and oxidative damage in brain metastasis of breast cancer. *JNCI: Journal of the National Cancer Institute.* 2014 Jul 1;106(7).