Breast cancer brain metastases show increased levels of genomic aberration based homologous recombination deficiency scores relative to their corresponding primary tumors

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**Background:** Based on its mechanism of action, PARP inhibitor therapy is expected to benefit mainly tumor cases with homologous recombination deficiency (HRD). Therefore, identification of tumor types with increased HRD is important for the optimal use of this class of therapeutic agents. HRD levels can be estimated using various mutational signatures from next generation sequencing data and we used this approach to determine whether breast cancer brain metastases show altered levels of HRD scores relative to their corresponding primary tumor. Patients and methods: We used a previously published next generation sequencing dataset of twenty-one matched primary breast cancer/brain metastasis pairs to derive the various mutational signatures/HRD scores strongly associated with HRD. We also performed the myChoice HRD analysis on an independent cohort of seventeen breast cancer patients with matched primary/brain metastasis pairs. Results: All of the mutational signatures indicative of HRD showed a significant increase in the brain metastases relative to their matched primary tumor in the previously published whole exome sequencing dataset. In the independent validation cohort the myChoice HRD assay showed an increased level in 87.5% of the brain metastases relative to the primary tumor, with 56% of brain metastases being HRD positive according to the myChoice criteria. Conclusions: The consistent observation that brain metastases of breast cancer tend to have higher HRD measures may raise the possibility that brain metastases may be more sensitive to PARP inhibitor treatment. This observation warrants further investigation to assess whether this increase is common to other metastatic sites as well, and whether clinical trials should adjust their strategy in the application of HRD measures for the prioritization of patients for PARP inhibitor therapy.

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