Tumor Mutation Burden Forecasts Outcome in Ovarian Cancer with BRCA1 or BRCA2 Mutations

**Background:** Increased number of single nucleotide substitutions is seen in breast and ovarian cancer genomes carrying disease-associated mutations in BRCA1 or BRCA2. The significance of these genome-wide mutations is unknown. We hypothesize genome-wide mutation burden mirrors deficiencies in DNA repair and is associated with treatment outcome in ovarian cancer. Methods and Results: The total number of synonymous and non-synonymous exome mutations (Nmut), and the presence of germline or somatic mutation in BRCA1 or BRCA2 (mBRCA) were extracted from whole-exome sequences of high-grade serous ovarian cancers from The Cancer Genome Atlas (TCGA). Cox regression and Kaplan-Meier methods were used to correlate Nmut with chemotherapy response and outcome. Higher Nmut correlated with a better response to chemotherapy after surgery. In patients with mBRCA-associated cancer, low Nmut was associated with shorter progression-free survival (PFS) and overall survival (OS), independent of other prognostic factors in multivariate analysis. Patients with mBRCA-associated cancers and a high Nmut had remarkably favorable PFS and OS. The association with survival was similar in cancers with either BRCA1 or BRCA2 mutations. In cancers with wild-type BRCA, tumor Nmut was associated with treatment response in patients with no residual disease after surgery.

Conclusions: Tumor Nmut was associated with treatment response and with both PFS and OS in patients with high-grade serous ovarian cancer carrying BRCA1 or BRCA2 mutations. In the TCGA cohort, low Nmut predicted resistance to chemotherapy, and for shorter PFS and OS, while high Nmut forecasts a remarkably favorable outcome in mBRCA-associated ovarian cancer. Our observations suggest that the total mutation burden coupled with BRCA1 or BRCA2 mutations in ovarian cancer is a genomic marker of prognosis and predictor of treatment response. This marker may reflect the degree of deficiency in BRCA-mediated pathways, or the extent of compensation for the deficiency by alternative echanisms.

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