Exome mutation burden predicts clinical outcome in ovarian cancer carrying mutated BRCA1 and BRCA2 genes

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Reliable biomarkers predicting resistance or sensitivity to anti-cancer therapy are critical for oncologists to select proper therapeutic drugs in individual cancer patients. Ovarian and breast cancer patients carrying germ line mutations in BRCA1 or BRCA2 genes are often sensitive to DNA damaging drugs and relative to non-mutation carriers present a favorable clinical outcome following therapy. Genome sequencing studies have shown a high number of mutations in the tumor genome in patients carrying BRCA1 or BRCA2 mutations (mBRCA). The present study used exome-sequencing and SNP 6 array data of The Cancer Genome Atlas (TCGA) to correlate the total exome mutation number (Nmut) to progression-free survival (PFS) and overall survival (OS) in the patients (n = 316) with high grade serous ovarian cancer (HGSOC) after debulking surgery and platinum-based chemotherapy. HGSOC in 70 patients of this cohort had either germline or somatic mutations of BRCA1 or BRCA2 genes. The results revealed that the Nmut was significantly lower in the chemotherapy-resistant mBRCA HGSOC defined by progression within 6 months after completion of first line platinum-based chemotherapy. We found a significant association between low Nmut and shorter PFS and OS in mBRCA HGSOC by Cox regression and Kaplan-Meier analyses. The association was also significant when the analysis was limited to germline BRCA1 or BRCA2 mutated patients with SNP array-determined loss of heterozygosity of the BRCA1 or BRCA2 locus in the tumors. In the mBRCA HGSOC tumors, Nmut was correlated with the genome fraction with loss of heterozygosity and with number of telomeric allelic imbalance, genomic measures evaluating chromosomal instability. However, no significant association between Nmut and PFS or OS was found in HGSOC carrying wild-type BRCA1 and BRCA2 genes. These results suggest that in cancers with DNA repair deficiency caused by functional BRCA loss, higher versus lower Nmut may reflect the status of deficiency or rescue by alternative mechanism(s) for DNA repair, with lower Nmut predicting for resistance to DNA-damaging drugs in mBRCA HGSOC. Our observations are consistent with the new concept that BRCA1/2 critically regulate error-free repair of nucleotide damage to suppress mutation formation, and may imply an activation of alternative repair mechanism(s) capable of bypassing the BRCA defect and restoring error-free DNA repair.

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