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19q12 amplified and non-amplified subsets of high grade serous ovarian cancer with overexpression of cyclin E1 differ in their molecular drivers and clinical outcomes

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Objectives: Readily apparent cyclin E1 expression occurs in 50% of HGSOC, but only half are linked to 19q12 locus amplification. The amplified/cyclin E1hi subset has intact BRCA1/2, unfavourable outcome and is potentially therapeutically targetable. We studied whether non-amplified/cyclin E1hi HGSOC has similar characteristics. We also assessed the expression of cyclin E1 degradation-associated proteins, FBXW7and USP28, as potential drivers of high cyclin E1 expression in both subsets.

Methods: 262 HGSOC cases were analysed by in situ hybridization for 19q12 locus amplification and immunohistochemistry for cyclin E1, URI1 (another protein encoded by the 19q12 locus), FBXW7 and USP28 expression. Tumours were classified by 19q12 amplification status and correlated to cyclin E1 and URI1 expression, (CHECK FOR SPACING), BRCA1/2 germline mutation, FBXW7 and USP28 expression, and clinical outcomes. Additionally, we assessed the relative genomic instability of amplified/cyclin E1hi and non-amplified/cyclin E1hi groups of HGSOC datasets from The Cancer Genome Atlas.

Results: Of the 82 cyclin E1hi cases, 43 (52%) were amplified and 39 (48%) were non-amplified. Unlike amplified tumours, non-amplified/cyclin E1hi tumour status was not mutually exclusive with gBRCA1/2 mutation. The non-amplified/cyclin E1hi group had significantly increased USP28, while the amplified/cyclin E1hi cancers had significantly lower FBXW7 expression consistent with a role for both in stabilizing cyclin E1. Notably, only the amplified/cyclin E1hi subset was associated with genomic instability and had a worse outcome than nonamplified/cyclin E1hi group.

Conclusions: Amplified/cyclin E1hi and non-amplified/cyclin E1hi tumours have different pathological and biological characteristics and clinical outcomes indicating that they are separate subsets of cyclin E1hi HGSOC.

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