

# Characterization of genetic alterations in ovarian cancer associated with chemotherapy response

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av

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Avdelningen för onkologi, Lunds universitet

Avhandlingen baseras på följande arbeten:

- I **Osterberg L**, Levan K, Partheen K, Helou K, Horvath G  
Cytogenetic analysis of carboplatin resistance in early-stage epithelial ovarian carcinoma.  
*Cancer Genetics and Cytogenetics* **163**(2): 144-50. (2005)
- II **Osterberg L**, Levan K, Partheen K, Staaf J, Sundfeldt K, Horvath G  
High-resolution genomic profiling of carboplatin resistance in early-stage epithelial ovarian carcinoma.  
*Cytogenetic and Genome Research* (2009)
- III **Osterberg L**, Levan K, Partheen K, Delle U, Olsson B, Sundfeldt K, Horvath G  
Potential predictive markers of chemotherapy resistance in stage III serous ovarian adenocarcinomas.  
*Manuscript, submitted*
- IV **Osterberg L**, Levan K, Partheen K, Delle U, Olsson B, Sundfeldt K, Horvath G  
High-resolution array CGH reveals specific copy number alterations associated with docetaxel/carboplatin response in ovarian carcinomas.  
*Manuscript*

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# Characterization of genetic alterations in ovarian cancer associated with chemotherapy response

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## ABSTRACT

Ovarian cancer is the most lethal of all gynecological malignancies, and exhibit an overall five-year survival rate of only 48% in Sweden. The high mortality in ovarian cancer is largely due to late diagnosis and chemotherapy resistance. Finding predictive markers of chemotherapy response and elucidating the resistance mechanisms would help to individualize and improve treatment of ovarian cancer patients.

With the aim to explore genetic alterations and to search for potential predictive biomarkers of chemotherapy response in ovarian cancer patients, a total of 133 epithelial ovarian carcinomas were investigated genetically. Initially, early-stage tumors of mixed histology from patients treated with carboplatin were analyzed with both metaphase comparative genomic hybridization (CGH) and array CGH. The main finding was that gain in chromosome arm 1q, and more specifically 1q25.1-41, was significantly associated with carboplatin resistance. Additionally, differences in the genetic alteration patterns were detected between the three histologic subtypes serous, mucinous and clear cell. Subsequently, stage III serous ovarian tumors from patients treated with combination therapy paclitaxel/carboplatin were analyzed with array CGH and quantitative real-time polymerase chain reaction (QPCR). Gain in 3q26.2 and losses in the regions 6q11.2-12, 9p22.3-21.3 and Xp22.2-11.1 were found significantly more frequent in the resistant cases than in the sensitive cases. When examining the gene expression of four genes located in these genomic regions, the *EVII* gene expression differed between samples with gain versus without gain, and exhibited higher expression in the gain group. Furthermore, based on the significant genomic regions, a decision tree was generated and loss in regions 6q11.2-12, Xp11.3 and Xp22.13 was the best combination to classify the tumor material according to chemotherapy response. Next, a patient material treated with combination therapy docetaxel/carboplatin and consisting of advanced stage serous ovarian tumors was analyzed with array CGH. Losses in 8p23.3-23.1 and 8p22 were significantly associated with sensitivity, and gains in six regions in chromosome 9 (9p13.2-13.1, 9q21.2-21.32, 9q21.33, 9q22.2-22.31, 9q22.32-22.33 and 9q33.1-34.11) were significantly associated with resistance. Interestingly, this was a different set of genetic alterations than the paclitaxel/carboplatin material generated, although the two materials exhibit similar clinical features and are given similar therapies. Altogether, specific genetic alterations associated with differential chemotherapy response and patient outcome were identified in these studies. The different chemotherapies were associated with different genetic alterations, which might lead to the establishment of separate predictive biomarkers.

Key words: Ovarian cancer, chemotherapy resistance, predictive markers

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