NOTCH SIGNALING PATHWAY COMPONENTS AS POTENTIAL BIOMARKERS FOR THE DIAGNOSIS OF OVARIAN CANCER

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Ovarian cancer is one of the most common gynecologic cancers, exhibiting the highest mortality rate. In 2020, over 313,000 women worldwide were diagnosed with ovarian cancer, leading to more than 207,000 confirmed [1]. Typically, ovarian cancer is diagnosed at an advanced stage, known as high-grade serous ovarian cancer (HGSOC). The elevated mortality is linked to the absence of specific symptoms for ovarian cancer and the absence of well-established biomarkers. Currently utilized biomarkers in the clinic, CA-125 and HE4, have limitations. For instance, CA-125 is elevated in only 50% of early-stage tumors, and HE4 testing is not recommended in routine practice due to contradictory studies [2,3]. Addressing the critical need for improved diagnostic tools, the NOTCH signaling pathway emerges as a promising biomarker, showcasing a crucial oncogenic role in HGSOC and contributing to the development of ovarian cancer [4].

The aim of this research was to investigate gene expression changes of the NOTCH signaling pathway ligands *JAG2*, *DLL1*, and signaling pathway target *HES1*, to evaluate these genes as promising genetic biomarkers for the diagnosis of ovarian cancer.

During the study, mRNA expression changes were analyzed in 66 patients' tissues, suspected of ovarian cancer (including 42 HGSOC, 15 other gynecological cancers, and 9 benign gynecologic tumors). Genes expression was examined using reverse transcription quantitative PCR. Results were normalized to the reference gene *GAPHD*, and the $\log_2(2^{-\Delta CT})$ method was used to calculate genes relative expression.

The results showed that all studied genes were downregulated in HGSOC when compared to benign gynecologic tumors tissues, with significant downregulation of *DLL1* and *HES1* genes. The combined ROC curve panel of all three genes for distinguishing the class with HGSOC risk from benign cases showed an AUC of 0.99, $p < 0.0001$, sensitivity of 92.86%, and specificity of 100%. Furthermore, significant differences in relative expression of *DLL1* and *HES1* genes were found between HGSOC and other gynecological cancers groups. Finally, before treatment, patients with higher CA-125 value showed statistically significant differences ($p = 0.02$) in *HES1* gene relative expression compared to the norm of this biomarker.

In conclusion, our pilot study suggests that components of the NOTCH signaling pathway show promise as potential biomarkers for future ovarian cancer diagnostics. However, further comprehensive studies, including non-invasive samples, are essential to validate these genes as suitable biomarkers for the development of new cancer tests.

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