

ASSOCIATION OF THE *FGFR4* P.GLY388ARG POLYMORPHISM WITH INCREASED OVERALL SURVIVAL IN HIGH GRADE SEROUS OVARIAN CARCINOMA

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INTRODUCTION

Ovarian cancer (OC) is the most lethal gynecological malignancy (Figure 1), mainly due to late diagnosis and the absence of effective early detection tools¹. Although most patients initially respond to surgery and platinum-based chemotherapy, about 70% relapse and up to 80% of these cases develop platinum resistance². Despite advances with PARP inhibitors, anti-angiogenic agents, and immunotherapy, survival gains remain modest in recurrent disease¹. Thus, identifying reliable prognostic and predictive biomarkers is essential to improve patient stratification and guide personalized therapies³.

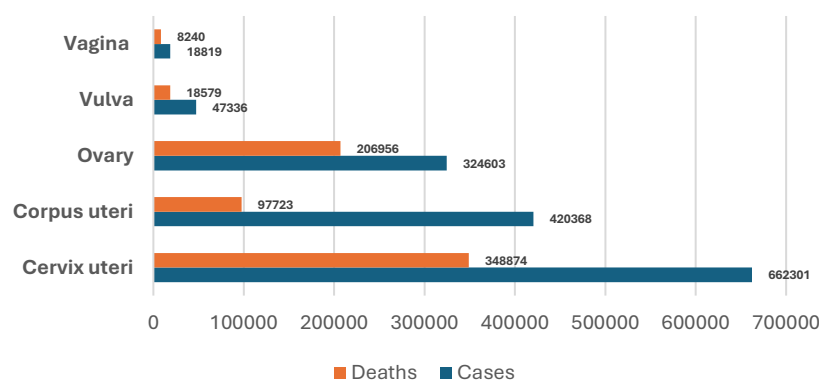


Figure 1. Incidence and mortality of gynecological cancers in 2022, showing their relative proportions. Although ovarian cancer ranks as the third most common type, it accounts for the highest mortality rate⁴.

OBJECTIVE

This study aims to identify and evaluate somatic variants with the potential to become prognostic markers in high-grade serous subtype OC (HGSOC) patients.

METHODS

DNA from 23 HGSOC patients was extracted from FFPE tumor samples, amplified using the Qiaseq Pan-cancer Multimodal Panel, and sequenced on the Illumina NextSeq 550. Read processing and variant calling were performed with the QIAGEN CLC Genomics Server. Survival curves were compared using the Gehan-Breslow-Wilcoxon test in GraphPad Prism, with $p < 0.05$ considered significant.

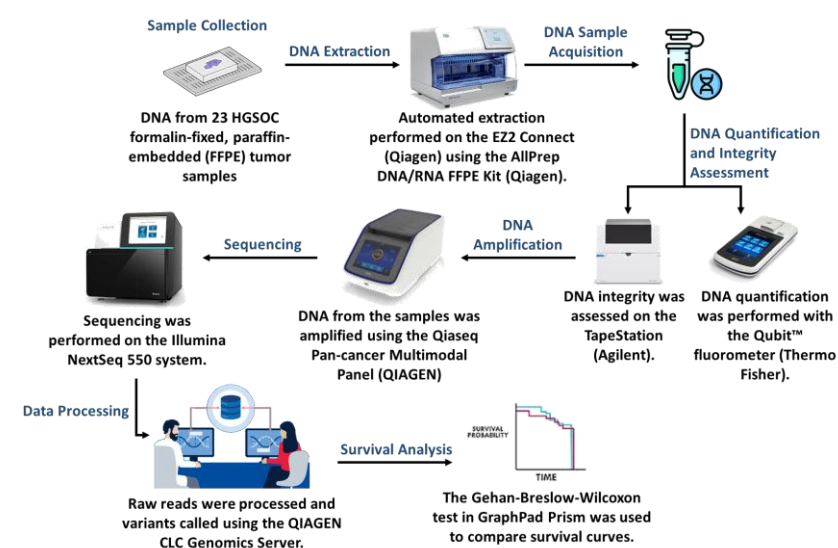


Figure 2. Methodological workflow of the steps performed to identify and evaluate somatic variants with potential as prognostic markers in HGSOC patients.

RESULTS AND DISCUSSION

Among the 23 patients, five were resistant to platinum. A total of 1186 somatic variants were identified across 523 genes, with 26% being synonymous. The *FGFR4* p.Gly388Arg (rs351855) SNP was present in 48% of patients (11/23) and was significantly associated with improved overall survival at 36 months after diagnosis ($p = 0.048$), regardless of platinum resistance (Figure 3).

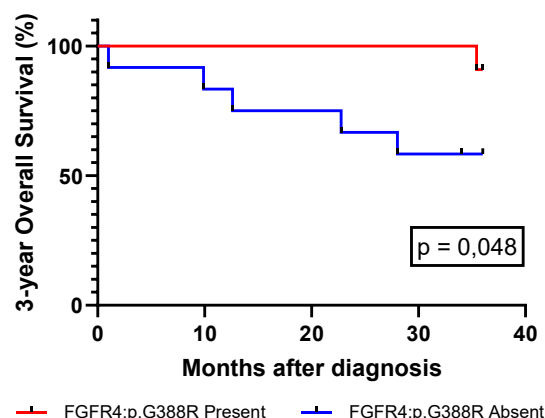


Figure 3. Kaplan-Meier curves showing overall survival according to *FGFR4* p.Gly388Arg polymorphism: present (red) vs. absent (blue). Presence of the SNP was associated with improved survival at 36 months ($p = 0.048$).

FGFR4 is a receptor tyrosine kinase involved in cell proliferation, migration, AKT/ERK signaling, and tumor progression⁵.

When amplified, *FGFR4* promotes proliferation, survival, metastasis, and chemotherapy resistance, primarily through FGF19-*FGFR4* signaling and activation of the PI3K-AKT, MEK-ERK, and GSK3 β - β -catenin pathways (Figure 4) ⁵.

In HGSOC, a study with 236 patients showed a significant association with prolonged progression-free survival (PFS) and overall survival (OS), corroborating the current results⁶.

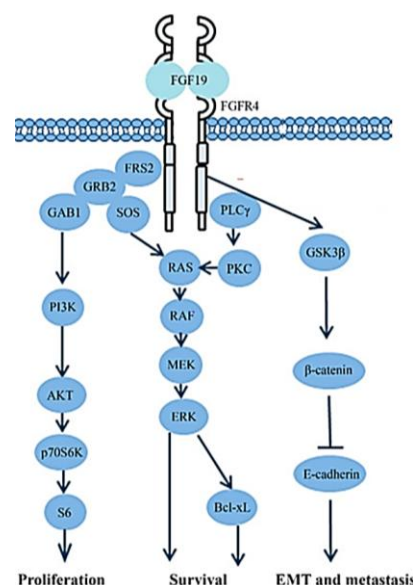


Figure 4. FGF19/*FGFR4* signaling cascades in cancer cells. Upon FGF19 binding, *FGFR4* activates multiple downstream pathways⁵.

CONCLUSION

This study reports an association between the *FGFR4* p.Gly388Arg polymorphism and improved overall survival in HGSOC patients. Although previous findings on its prognostic value are contradictory and its effect appears cancer dependent, our results, despite the small sample size, suggest its potential as a prognostic marker requiring further investigation.

REFERÊNCIAS

