ABSTRACT

OC is a significant global health concern, with Pakistan ranking 5th worldwide for incidence and 3rd for mortality related to this disease. Given the poor prognosis, early identification of individuals at risk is crucial. Genetic factors, particularly single nucleotide polymorphisms (SNPs) in metabolic genes, may play a role in OC susceptibility. This study investigated the association between SNPs of *CYP1A1*, *COX2*, *SOD2,* and *HIF1a* genes and OC risk in the Pakistani population. This prospective identification study was conducted between October 2019 and March 2022 at Shaukat Khanum Memorial Cancer Hospital and Research Centre and Mayo Hospital in Lahore. A sample size of 688 participants for empidemiological study (277 patients of oral cancer and 411 healthy individuals) and 625 participants (215 patients of oral cancer and 410 healthy individuals), for genetic variations analysis using High-Resolution Melting (HRM) and Sanger sequencing, and evaluating protein expression via ELISA.
Results indicated no significant associations between rs4646903, rs1048943, rs20417, rs11549467 SNPs and OC risk. However non-statisticant significant trend for the *SOD2* variant (rs4880) with three genotypes (AA, AG, GG) was observed. A was a major allele whereas; AG genotype frequency was greater (0.019) in patients than control (0.005). Within its allelic model the odd ratio [95% CI] 0.98[0.73~1.29] showed that G allele was associated with higher risk of OC than the A allele. Nevertheless, as the p-value (*p*=0.24) is greater than 0.005, this connection is not statistically significant. The protein expression levels of CYP1A1, COX2, HIF1α, and SOD2 were compared between OC cases and healthy controls. For CYP1A1, the average concentration in OC cases was 0.197ng/ml, compared to 0.191ng/ml in controls with non-statistical significant difference. The concentration of COX2 was higher in cases (2.801ng/ml) than in controls (2.746 ng/ml), with a statistically significant difference (*p*=0.014). A significant difference was also observed for HIF1α, where OC cases showed significantly higher concentration (3.620 ng/ml) than healthy controls (3.488 ng/ml; p <0.001). Conversely, SOD2 protein concentrations were significantly lower in OC cases (2.823ng/ml) than in healthy controls (4.206 ng/ml; p <0.0001). From this study we concluded that although single nucleotide polymorphisms in the *CYP1A1, COX2, SOD2,* and *HIF1α* gene did not reveal a significant connection with OC in our population, but we found that cases had higher
expression levels of COX2, HIF1α and reduced levels of SOD2 than controls. This disparity implies that these genes may contribute to OC pathogenesis via post-transcriptional regulation or other non-genetic pathways, necessitating additional research into the functional significance of these proteins and OC.