
## Association between Genetically Determined Blood Metabolites and the Risk of Oropharyngeal Cancer: A Mendelian Randomization Study

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**Objectives:** Blood metabolites play an important role in predicting or influencing the occurrence and development of cancers. There is limit evidence on the association between metabolites and oropharyngeal cancer (OPC) risk. Therefore, we aimed to assess the role of blood metabolites on the risk of OPC.

**Methods:** We used Mendelian randomization (MR) approach to assess metabolites for their role in OPC predisposition using genome-wide association studies of blood metabolite levels (n = 7824) and OPC (Discovery cohort: n = 1090 cases/2928 controls, Replication cohort: n = 494 cases/372016 controls). Functional annotation by online tools was further performed to explore potential biological background and screen the risk loci for OPC.

**Results:** We identified butyrylcarnitine as potential causal mediators for OPC among the 258 known blood metabolites, after accounting for Bonferroni correction (inverse-variance-weighted MR method: $\beta = 0.904$, $P < 0.001$). We observed per one unit increase in log-transformed genetically predicted butyrylcarnitine levels causally increased the risks of OPC (OR: 2.470, 95% CI: 1.530-3.987). Results were stable across sensitivity analyses, and had no presence of directional pleiotropy. Additionally, we found OASL/rs16950755 and POP5/rs7304812 may be a potential causal gene for OPC by further functional annotation and bioinformatics analysis.

**Conclusion(s):** Through the application of a genetic epidemiological framework, our research systematically assessed the impact of blood metabolites on OPC susceptibility, thus furnishing valuable insights into potential therapeutic targets. A more comprehensive exploration is necessitated to elucidate the precise underlying biological mechanism.