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Association of Genetically Proxied Cholesterol-Lowering Drug Targets and Head and Neck Cancer Survival: A Mendelian Randomization Analysis

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Abstract : Background: Preclinical and epidemiological studies have reported potential protective effects of low-density lipoprotein cholesterol (LDL-C) lowering drugs on head and neck squamous cell cancer (HNSCC) survival, but the causality was not consistent. Genetic variants associated with LDL-C lowering drug targets can predict the effects of their therapeutic inhibition on disease outcomes. Objective: We aimed to evaluate the causal association of genetically proxied cholesterol-lowering drug targets and circulating lipid traits with cancer survival in HNSCC patients stratified by human papillomavirus (HPV) status using two-sample Mendelian randomization (MR) analyses. Method: Single-nucleotide polymorphisms (SNPs) in gene region of LDL-C lowering drug targets (HMGCR, NPC1L1, CETP, PCSK9, and LDLR) associated with LDL-C levels in genome-wide association study (GWAS) from the Global Lipids Genetics Consortium (GLGC) were used to proxy LDL-C lowering drug action. SNPs proxy circulating lipids (LDL-C, HDL-C, total cholesterol, triglycerides, apoprotein A and apoprotein B) were also derived from the GLGC data. Genetic associations of these SNPs and cancer survivals were derived from 1,120 HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) and 2,570 non-HPV-driven HNSCC patients in VOYAGER program. We estimated the causal associations of LDL-C lowering drugs and circulating lipids with HNSCC survival using the inverse-variance weighted method. Results: Genetically proxied HMGCR inhibition was significantly associated with worse overall survival (OS) in non-HPV-drive HNSCC patients (inverse variance-weighted hazard ratio (HR IVW), 2.64[95%CI,1.28-5.43]; P = 0.01) but better OS in HPV-positive OPSCC patients (HR IVW,0.11[95%CI,0.02-0.56]; P = 0.01). Estimates for NPC1L1 were strongly associated with worse OS in both total HNSCC (HR IVW,4.17[95%CI,1.06-16.36]; P = 0.04) and non-HPV-driven HNSCC patients (HR IVW,7.33[95%CI,1.63-32.97]; P = 0.01). A similar result was found that genetically proxied PSCK9 inhibitors were significantly associated with poor OS in non-HPV-driven HNSCC (HR IVW,1.56[95%CI,1.02 to 2.39]). Conclusion: Genetically proxied long-term HMGCR inhibition was significantly associated with decreased OS in non-HPV-driven HNSCC and increased OS in HPV-positive OPSCC. While genetically proxied NPC1L1 and PCSK9 had associations with worse OS in total and non-HPV-driven HNSCC patients. Further research is needed to understand whether these drugs have consistent associations with head and neck tumor outcomes.

Keywords : Mendelian randomization analysis, head and neck cancer, cancer survival, cholesterol, statin
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