Metabolic disorders, metabolites, and risk of lung cancer: Evidence from population-based prospective cohort studies

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ABSTRACT

Introduction: We aimed to investigate the associations of metabolic syndrome (MetS) and circulating metabolic biomarkers with the risk of lung cancer and the potential underlying pathways. **Materials and Methods:** Multivariable Cox regression models were used to estimate the hazard ratio (HR) of MetS-related variables on lung cancer risk, both overall and by histologic subtype, in the UK Biobank. Stratified analyses were conducted by sex and tobacco use status. Nuclear magnetic resonance metabolomic profiling was conducted on baseline plasma samples. HRs were estimated for 164 metabolic biomarkers. Pathway analysis was conducted to investigate the potential metabolic pathways. **Results:** The HRs of MetS were 1.21 (95%CI: 1.09-1.33), 1.28 (95%CI: 1.10-1.50), and 1.16 (95%CI: 0.94-1.44) for the overall risk of lung cancer, adenocarcinoma, and squamous cell carcinoma, respectively. The relationship between MetS and lung cancer was modified by sex, with a stronger effect in women (P=0.031). The risk of lung cancer resulting from MetS was elevated mainly among tobacco users, although the modification effect of tobacco use was not statistically significant. A total of 109 metabolic biomarkers (30 metabolites and 79 lipoprotein subfractions) were associated with the risk of lung cancer. Glycoprotein acetyls demonstrated a positive association with lung cancer risk [HR = 1.13 (95%CI: 1.04, 1.22)]. Negative associations with lung cancer were found for albumin, acetate, valine, alanine, glucose, citrate, omega-3 fatty acids, linoleic acid, etc. The pathway analysis showed that the "linoleic acid metabolism" was statistically significant after the FDR adjustment (P=0.0496). **Conclusion:** The increased risk of lung cancer associated with MetS and multiple metabolites suggests the importance of taking metabolic status and markers into consideration for the primary prevention of lung cancer and the selection of high-risk populations for lung cancer screening.

Keywords: Metabolic disorders, lung cancer, population-based, cancer prevalence, cancer prevention