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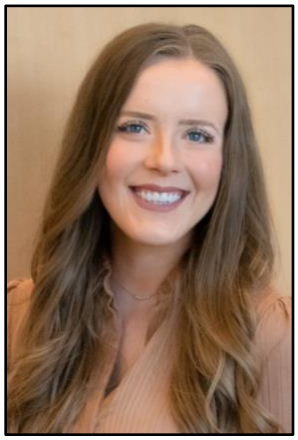

Associations between pre-diagnostic plasma metabolites and biliary tract cancer risk in the prospective UK Biobank cohort

Introduction: Annually, approximately 200,000 people are diagnosed with biliary tract cancer (BTC). Most present with metastatic disease which encompasses a 5-year survival rate of <5%. Etiology is poorly understood though some studies suggest metabolic dysregulation may contribute to development. Previous evaluations of metabolites and BTC risk have primarily been limited to case-control studies, few metabolites, or post-diagnostic blood samples.

Methods: We evaluated 248,285 UK Biobank participants with metabolite data. Metabolites were trimmed to two standard deviations, log-transformed, z-scored, and evenly divided into tertiles. Cox proportional hazards models (adjusted for age, sex, education, income, fasting time, and statins) evaluated associations of BTC risk per 1-standard deviation (SD) and across tertiles with hazard ratios (HR) and 95% confidence intervals (95% CI). A p-value of 0.001 (0.05 divided by 50, the number of independent tests) was considered statistically significant.

Results: After exclusions, the analyzed cohort included 232,781 UKB participants with a median follow-up time of 11.8 years and 268 first primary incident BTC cases. Multiple metabolites were significantly associated with BTC risk using continuous variables (per 1-SD increment). High triglyceride to total lipid ratios were associated with higher BTC risk, and the strongest association was for intermediate-density lipoproteins (the HR (95% CI) was 1.33 (1.15-1.54), p=0.0001). On the other hand, high cholesterol to total lipid ratios were associated with lower BTC risk, and the strongest association was for the free cholesterol to total lipids in small very-low-density lipoproteins (0.76 (0.66-0.88), p =0.0002). Analysis by tertile identified additional significant associations, including a higher polyunsaturated fatty acid to total fatty acid ratio being associated with lower BTC risk (the HR (95% CI) comparing the highest to lowest tertile was 0.50 (0.35-0.71), p-trend=0.0001).

Conclusions: Our findings indicate circulating metabolites may be biomarkers for BTC and suggest that triglycerides, cholesterols, fatty acids, phospholipids, and glutamine may be involved in BTC etiology.