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Variants of Inflammation-related Genes and the Risk of Gallstones and Biliary Tract Cancer: A population-based Study in China

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There is compelling evidence that chronic inflammation predisposes to biliary tract cancer. Previously we found that aspirin use and variants in the PTGS2 gene, both of which are closely linked to inflammation, were associated with biliary tract cancer risk in a population-based study in China. To test the inflammation hypothesis further, we examined the associations of variants in 20 genes involved in the inflammation pathway with risk of biliary tract cancer and stones in a large population-based case-control study in Shanghai, China. We genotyped 56 single nucleotide polymorphisms (SNPs) from 20 inflammation genes in 411 biliary tract cancer cases (237 gallbladder cancers, 127 extrahepatic bile duct cancers, and 47 ampullary cancers), 895 subjects with biliary stones, and 786 population controls. Unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association of individual SNPs and haplotypes with biliary stones and biliary tract cancer risk. Of the 56 SNPs examined, 20 showed some associations with biliary cancer and stones. Specifically, variants of the IL8, IL8RB, RNASEL, TGF-beta, and TNF-alpha genes were associated with gallstone risk, while variants in the IL1A, IL10, VEGF, and RNASEL genes were associated with gallbladder cancer risk. Adjustment for multiple comparisons did not materially change these results. Of the 10 genes with multiple SNPs, we

inferred halotypes; only one haplotype in the IL8RBgene was associated with gallstones. The haplotype frequency was significantly different between bile duct cancer cases and controls (p=0.007). A haplotype comprising 3 SNPs in the IL8RB gene (rs2230054, rs1126579, rs1126580) was associated with a 54% increased risk of bile duct stones (95% CI 1.14-2.07, p=0.02), relative to the most frequent haplotype. In summary, common variants in immune-related genes influencing inflammatory responses were associated with gallstones and biliary tract cancer, lending further support to the role of inflammation in the pathogenesis of biliary stones and biliary tract cancer. Future larger studies with more complete gene coverage are needed to confirm these results.