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Variants in motilin, somatostatin and their receptor genes and risk of biliary tract cancers and stones in Shanghai, China

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ABSTRACT

Altered motility of the gallbladder can result in gallstone and cholecystitis, which are important risk factors for biliary tract cancer. Motilin (MLN) and somatostatin (SST) are known important modulators of gallbladder motility. To determine whether genetic variants in motilin, somatostatin, and their receptor genes are associated with the risk of biliary tract cancers and stones, nine tag-SNPs were determined in 439 biliary tract cancer cases (253 gallbladder, 133 extrahepatic bile duct and 53 ampulla of Vater cancer cases), 429 biliary stone cases, and 447 population controls in a population-based case–control study in Shanghai, China. We found that subjects with the *MLNR* rs9568169 AA genotype and *SSTR5* rs169068 CC genotype were significantly associated with risk of extrahepatic bile duct cancer (OR = 0.49, 95% CI: 0.27–0.89; OR = 2.40, 95% CI: 1.13–5.13) compared to the major genotypes. *MLN* rs2281820 CT and rs3793079 AT genotypes had significantly increased risks of gallstones (OR = 1.52, 95% CI: 1.06–2.18; OR = 1.64, 95% CI: 1.20–2.25) compared to TT genotypes. Besides, haplotype analysis showed that *MLN* T-T-T haplotype (rs2281820–rs3793079–rs2281819) had a non-significantly elevated risk of gallstone (OR = 1.30, 95% CI: 0.91–1.86) compared with C-A-A haplotype. To the best of our knowledge, this is the first study to report an

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association between genetic polymorphisms in *MLN*, *MLNR* and their receptor genes and risk of biliary tract cancers and stones.

Introduction

Biliary tract cancers, which include cancers of the gallbladder, extrahepatic bile duct, and ampulla of Vater, are relatively rare but highly fatal malignancies, with age-adjusted incidence and mortality rates of 1.6 and 1.2 (per 100,000), respectively, for gallbladder cancer in China in 2008 (Ferlay et al., 2010). We previously showed that in urban Shanghai, the age-adjusted incidence rates of biliary tract cancers were 1.7 and 1.2 for females and males, respectively, during the period 1972 to 1974, and increased to 4.6 and 3.1 between 1996 and 1999 (Liu et al., 2004). These rates were much higher than the average incidence rate for biliary tract cancer in China. Reasons for this regional difference, as well as the rapid rise in incidence in urban Shanghai, are unclear.

Gallstones are one of the most important risk factors for biliary tract cancers. The prevalence rate of gallstone in Shanghai was increasing during the past decades in Shanghai, which was 4.4% in 1987, but rose to 10.7 during 2002 to 2003 in adults (Zhang et al., 2011; Zhu et al., 2010). In Shanghai, ever having gallstones was associated with significantly increased risks of gallbladder cancer (23.8-fold), extrahepatic bile duct cancer (8.0-fold) and ampulla of Vater cancer (4.2-fold) (Hsing et al., 2007a). Lipid metabolism is an important risk factor for the formation of gallstones, and variants in the lipid metabolism pathway genes have been identified in association with biliary tract cancer and stone risk in the Shanghai population (Andreotti et al., 2008; Xu et al., 2011). Another important risk factor for gallstone formation is impaired gallbladder motility since hypomotility of the gallbladder leads to stagnant bile, which creates an environment for cholesterol supersaturation and subsequently gallstone formation (O'Donnell and Fairclough, 1993). On the other hand, impaired gallbladder contractile also has relation with other diseases, such as chronic acalculous cholecystitis which is also important in carcinogenesis of biliary tract cancers (Merg et al., 2002). Gallbladder motility is mainly regulated by many neural and hormonal factors and their interactions (Montet et al., 2005). We previously showed that a mutation in the *CCKAR* (rs1800855) gene, which codes for the receptor for cholecystokinin, a gastrointestinal peptide that mediates gallbladder emptying, was associated with gallbladder cancer risk in females (Xu et al., 2013).

To further clarify whether other gallbladder motility-related genes are related to biliary tract cancer risk, we examined the associations of nine SNPs in gallbladder motility-related genes (MLN, MLNR, SSTR2, and SSTR5) with the risk of biliary tract cancers in a population-based case–control study conducted in Shanghai, China.

Materials and methods

Study subjects

The details of the study design and methods have been described in detail elsewhere (Hsing et al., 2007a, 2007b, 2008). Briefly, incident cancer cases were identified by a rapid reporting system established by the Shanghai Cancer Institute and 42 collaborating hospitals in Shanghai. Through this system, we identified more than 95% of all incident biliary tract cancer cases (International Classification of Diseases, Ninth Edition code 156) diagnosed among urban Shanghai residents between June 1997 and May 2001. A total of 627 incident biliary tract cancer cases were identified. For this study, we included 439 (70.0%) incident biliary tract cancer cases (253 gallbladder, 133 extrahepatic bile duct and 53 ampulla of Vater cancer cases) who were between 35 and 74 years old, completed the in-person interview and provided a blood sample. Population controls without a history of cancer were randomly selected from the Shanghai Resident Registry, which includes the records for approximately 6 million Shanghai urban residents. The controls were frequency matched to the cancer cases by age (by 5 year age groups) and gender. Patients with biliary stones without a history of cancer and undergoing cholecystectomy were also included and were frequency matched to the cancer cases by age (5 year age groups), gender and hospital of diagnosis.