Association of metabolic syndromes and risk factors with ampullary tumors development: A case-control study in China

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AIM: To evaluate the risk factors for ampullary adenoma and ampullary cancer.

METHODS: This case-control study included ampullary tumor patients referred to Peking Union Medical College Hospital. Controls were randomly selected from an existing database of healthy individuals at the Health Screening Center of the same hospital. Data on metabolic syndromes, medical conditions, and family history were collected by retrospective review of the patients' records and health examination reports, or by interview.

RESULTS: A total of 181 patients and 905 age- and sex-matched controls were enrolled. We found that a history of diabetes, cholecystolithiasis, low-density lipoprotein, and apolipoprotein A were significantly related to ampullary adenomas. Diabetes, cholecystolithiasis, chronic pancreatitis, total cholesterol, high-density lipoprotein, and apolipoprotein A were also significantly related to ampullary cancer.

CONCLUSION: Some metabolic syndrome components and medical conditions are potential risk factors for the development of ampullary tumors. Cholelithiasis, diabetes, and apolipoprotein A may contribute to the malignant transformation of benign ampullary adenomas into ampullary cancer.

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Key words: Metabolic syndromes; Ampullary adenoma; Ampullary cancer; Risk factors

Core tip: Although ampullary tumors are relatively rare, the rapid development of, and advances in, endoscopy and imaging techniques have profoundly increased their discovery rate. Despite the increasing numbers of published studies, the etiology for ampullary tumors is incompletely defined. This is the first study to evaluate the impact of metabolic syndromes on ampullary tumors patients.

He XD, Wu Q, Liu W, Hong T, Li JJ, Miao RY, Zhao HT. Association of metabolic syndromes and risk factors with ampullary tumors development: A case-control study in China. World J Gastroenterol 2014; 20(28): 9541-9548 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i28/9541.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i28.9541
INTRODUCTION

Although tumors of the ampulla can be benign or malignant, most are malignant[1-3]. Ampullary cancer is less aggressive and has a better prognosis after curative resection than cancer of the distal bile duct or the pancreas[4-6]. The favorable prognosis is thought to be due to its early clinical presentation with obstructive jaundice[6] and its high resectability rate[7]. Despite a relatively favorable outcome following resection, 32%-44% of patients have a relapse, either locally or distantly.

Ampullary adenoma may occur sporadically or in the setting of familial adenomatous polyposis[6]. It is considered a premalignant lesion leading to ampullary cancer because of its capacity for malignant transformation via the adenoma-carcinoma sequence[8-10], which is generally accepted as valid for colorectal tumors[10].

Numerous published studies investigated the clinicopathological aspects of ampullary tumors, most of which focused on the prognosis associated with this disease. Studies investigating risk factors associated with the proposed adenoma-carcinoma sequence are scarce, especially regarding metabolic syndrome components and ampullary tumors. The aim of this study was to evaluate, in detail, the relations between metabolic syndromes and other risk factors with ampullary cancer and the precursor lesions.

MATERIALS AND METHODS

Study population and design

We conducted a hospital-based case-controlled study that included 1086 subjects (181 patients with a histologically-confirmed ampullary tumor, 905 healthy controls) from Peking Union Medical College Hospital (PUMCH) in Beijing, China. This hospital is a major diagnostic and treatment center for peripapillary adenocarcinoma in China.

Using the PUMCH Patient Information Database, we compiled a list of all patients who had been diagnosed with ampullary adenoma or ampullary cancer between 2006 and 2010. Peripapillary adenocarcinomas, such as those of the pancreatic head, distal bile duct, and duodenum, as well as neuroendocrine tumors, were excluded. Patients who had undergone a primary attempt at curative resection and whose diagnoses were confirmed by pathology examination were included in this study. We performed a manual retrospective review of the patients’ records to collect demographic, clinical, and risk factor information. This included a detailed assessment of the family history of cancer, personal medical history, hormone and medication intake, and occupational exposure to chemicals. Data collection, including age, sex, demographic data, history of systemic diseases and gastrointestinal surgery, and a complete physical examination were conducted by the doctors before operating. Other related information was collected by interviewing patients or their family members, and was recorded by a physician in a structured data collection sheet. Such recording is routinely performed in our gastrointestinal oncology clinic, and the forms are kept as part of the patients’ medical records. Age, sex, history of hypertension or diabetes mellitus, hepatitis B virus (HBV) infection, metabolic syndromes, and previous cholecystectomy data were abstracted.

Using the Statistical Package for Social Science Program (version 13; SPSS, Chicago, II., United States), controls were randomly selected from an existing database of healthy individuals at the PUMCH Health Screening Center. They were frequency matched to cases by sex and exact age at a ratio of 5:1. The database consists of healthy individuals who are genetically unrelated family members, spouses, and friends of patients who had cancer other than gastrointestinal cancer. The PUMCH Health Screening Center is one of the major centers providing routine physical examinations in Beijing. Most of those who come for examinations are native residents.

We performed a manual retrospective review of the health examination reports to collect demographic, clinical, and risk factor information for the controls. Doctors at the physical examination center collected the data-including age, sex, demographic data, and history of systemic diseases and gastrointestinal surgery; and then performed a complete physical examination. Measurements of height without shoes and weight while clothed were recorded. The body mass index was used as a measurement of obesity. Other related information was collected and recorded in a structured data collection sheet. This information was recorded by examining physicians using the same procedure as was used for the current patients. Controls were interviewed between 2006 and 2010. Two participants were excluded from the study because of incomplete health examination records.

Ampullary tumors were diagnosed by endoscopy. All specimens were classified following an examination at the Department of Pathology, Peking Union Medical College Hospital. Cholelithiasis (including cholecystolithiasis, choledocholithiasis, and hepatolithiasis) and chronic pancreatitis were diagnosed using data from clinical imaging studies - abdominal ultrasonography (US), computed tomography (CT), endoscopic retrograde cholangiopancreatography, and magnetic resonance imaging - and by reviewing medical records. All patients underwent at least one of the aforementioned imaging studies. For control subjects, possible risk factors were determined based on abdominal US data and by reviewing health examination reports. All of the controls had previously undergone US screening for detection of stones.

Laboratory tests

Clinical nurses obtained blood samples via venipuncture from all study participants, who had fasted overnight. The blood was then sent for laboratory examination. Serum lipids, including triglyceride (Tri), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), apolipoprotein A (ApoA), and apolipoprotein B (ApoB), were measured using the Hitachi modular analytics system (Roche Modular DPP; Hitachi, Tokyo, Japan).
Hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) assays were performed using a second-generation, enzyme-linked immunosorbent assay (Abbott Laboratories, North Chicago, IL, United States). Chronic hepatitis B infection was diagnosed if both HBsAg and anti-HBc assays were positive.

Statistical analysis
Analyses of variables were carried out using SPSS software. Univariate analyses were performed using Fisher’s exact test for categorical variables. Variables with a P value of < 0.05 in the univariate analyses were further adjusted for age and sex in a multiple logistic regression analysis. The model was built using a forward selection process. Variables with a likelihood ratio test P value of < 0.05 were kept in the model and considered statistically significant.

RESULTS
We included 181 patients and 905 controls in the analysis. In the patient group, 57 had ampullary adenomas, and 124 had ampullary cancers. The ampullary tumor patients and the control group had the same mean age (61.8 ± 11.2 years, 61.7 ± 11.2 years, P = 0.934) and there were no differences between the two groups in sex (P = 1.000).

Ampullary adenoma
Ampullary adenoma patients had a significantly higher prevalence of hypertension (38.6% vs 23.2%), diabetes (19.3% vs 8.1%), cholecystitis (28.1% vs 4.2%), cholecystectomy (19.3% vs 2.5%), and chronic pancreatitis (7.0% vs 0.7%). They also had higher levels of TC (31.6% vs 15.5%), LDL (38.6% vs 16.8%), and ApoB (43.9% vs 27.1%). Their HDL (64.9% vs 89.8%) and ApoA (64.9% vs 99.3%) rates were lower than in the controls. During the multivariate logistic regression analysis, hypertension, cholecystectomy, chronic pancreatitis, TC, HDL, and ApoB failed to relate to the development of ampullary adenoma, but the other factors remained significant after adjustment for covariates (Table 1).

Ampullary cancer
In the univariate analyses for ampullary cancer, a history of diabetes (20.2% vs 11.3%), chronic pancreatitis (5.6% vs 0.3%), incidence of cholecystitis (23.8% vs 4.5%) and cholecystectomy (8.9% vs 3.7%), serum fasting blood glucose (FBG) level (33.9% vs 17.4%), TC (41.1% vs 13.5%), Tri (49.2% vs 30.1%), LDL (39.5% vs 16.1%), and ApoB (46.8% vs 25.3%) were significantly higher in ampullary cancer patients than in controls. The prevalence of HBsAg/anti-HBc+ (30.6% vs 50.0%) and the levels of HDL (41.9% vs 84.2%) and ApoA (47.6% vs 98.7%) were lower in the cancer patients than in the controls. In the multivariate logistic regression analysis, the incidence of cholecystectomy and HBV infection and the high levels of Tri, LDL, FBG, and ApoB failed to show a relation to the development of ampullary cancer, but the other factors remained significant after adjustment for covariates (Table 2).

DISCUSSION
The relation between risk factors and ampullary tumors has been rarely investigated. We believe this to be the first and the largest hospital-based case-control study to evaluate metabolic syndromes for ampullary tumors. Our results provide evidence that some metabolic syndromes (diabetes, ApoA-related) and cholecystolithiasis are associated with an increased risk of ampullary cancer. There is also evidence that their premalignant lesion, ampullary adenoma, may be involved in an adenoma-carcinoma transformation.

Diabetes is one of the major public health challenges in both industrialized and developing countries. Increasing epidemiological evidence supports the idea that longstanding diabetes is one of the most important risk factors for overall cancer incidence[11-13]. A recent case-control study reported a 4.7-fold increased risk of cancer in persons with diabetes[14]. However, few studies have addressed the association of diabetes with ampullary tumor risk. In this study, not only did we find a positive link between diabetes and ampullary cancer (odds ratio: 4.75), we also found that diabetes increases the risk of ampullary adenoma by 2.59 times. It is the first time that diabetes and the development of ampullary tumors have been linked by published evidence. However, unlike pancreatic adenocarcinoma, as reported by Gapstur et al[14] and Butler et al[15] and in our previous study, we did not find a positive relation between plasma glucose concentration and ampullary tumor development.

The exact role of diabetes in ampullary tumor development is still unknown, but some biological mechanisms have been used to explain this relationship between cancer and diabetes. People with diabetes have been known to generate more reactive oxygen species than healthy controls. Normal cell DNA may be damaged by direct oxidation or by interference with cell DNA repair[16], thus potentially leading to tumor development. Another mechanism may be hyperinsulinemia; in diabetic patients, insulin resistance and hyperinsulinemia is a common phenomenon[17]. Insulin is a growth promoter, it can upregulate the production of insulin-like growth factor-1, which can promote tumor development by inhibiting apoptosis, stimulating cell proliferation, and enhancing angiogenesis[18-20]. It has also been reported that insulin may promote the growth of most human pancreatic cancers[21,22] and increase the replication markers of pancreatic ductal carcinoma.

Hyperlipidemia has been recently reported to be associated with cancer development, which is generally characterized by high levels of TC, Tri, and LDL, and a low level of HDL in serum[23-26]. Some experts suggest that dyslipidemia are risk factors for prostate, colon, and breast cancers. However, to our knowledge, no previous studies have investigated the association between lipid metabolism and risk of ampullary tumor development. We found that dyslipidemia is indeed a risk factor for the development of ampullary tumors. Patients with a high level of LDL and a low level of ApoA were at high risk.
of developing ampullary adenoma. A high level of TC and low levels of ApoA and HDL were also contributing risk factors for ampullary cancer development.

While the exact molecular mechanism by which hyperlipidemia is involved is unclear, inflammation is a potential risk factor for cancer. Increased levels of triglycerides, LDL, and total cholesterol, and decreased levels of ApoA and HDL in serum have been reported to have a relationship with increased proinflammatory cytokines, such as interleukin-6, tumor necrosis factor-α, and

### Table 1  Risk factors for ampullary adenoma: univariate and multivariate logistic regression analyses using Fisher’s exact test

| Risk factor          | Controls | Cases | Univariate analysis | Multivariate analysis |
|----------------------|----------|-------|---------------------|-----------------------|
|                      | n (%)    |       |                      |                       |
|                      |          |       | P value | OR (95%CI) | P value | OR (95%CI) |
| Age                  |          |       |                      |                       |
| < 50 yr              | 45 (15.7)| 8 (14.0)| 1 (reference) |                       |
| ≥ 50 yr              | 240 (84.3)| 49 (86.0)| 0.843 | 1.148 (0.510-2.588) |                       |
| Sex                  |          |       |                      |                       |
| Female               | 145 (50.9)| 29 (50.9)| 1 (reference) |                       |
| Male                 | 140 (49.1)| 28 (49.1)| 1.000 | 1.000 (0.566-1.766) |                       |
| Smoking              |          |       |                      |                       |
| No                   | 225 (78.9)| 44 (77.2)| 1 (reference) |                       |
| Yes                  | 60 (21.1)| 13 (22.8)| 0.727 | 1.108 (0.561-2.189) |                       |
| Alcohol abuse        |          |       |                      |                       |
| No                   | 209 (73.3)| 48 (84.2)| 1 (reference) |                       |
| Yes                  | 76 (26.7)| 9 (15.8)| 0.094 | 0.516 (0.241-1.101) |                       |
| HBV                  |          |       |                      |                       |
| HBsAg-/anti-HBc-     | 147 (51.6)| 32 (56.1)| 1 (reference) |                       |
| HBsAg+/anti-HBc+     | 7 (2.5)  | _     | _                   |                       |
| Diabetes mellitus    |          |       |                      |                       |
| No                   | 262 (91.9)| 46 (80.7)| 1 (reference) |                       |
| Yes                  | 23 (8.1) | 11 (19.3)| 0.015 | 2.274 (1.244-5.965) |                       |
| Hypertension         |          |       |                      |                       |
| No                   | 219 (76.8)| 35 (61.4)| 1 (reference) |                       |
| Yes                  | 66 (23.2)| 22 (38.6)| 0.020 | 2.086 (1.145-3.801) |                       |
| Cholecystolithiasis  |          |       |                      |                       |
| No                   | 273 (95.8)| 41 (71.9)| 1 (reference) |                       |
| Yes                  | 12 (4.2) | 16 (28.1)| 0.000 | 8.878 (3.921-20.103) |                       |
| Cholecystectomy      |          |       |                      |                       |
| No                   | 278 (97.5)| 46 (80.7)| 1 (reference) |                       |
| Yes                  | 7 (2.5)  | 11 (19.3)| 0.000 | 9.497 (3.502-25.755) |                       |
| Chronic pancreatitis |          |       |                      |                       |
| No                   | 283 (99.3)| 53 (93.0)| 1 (reference) |                       |
| Yes                  | 2 (0.7)  | 4 (7.0)| 0.008 | 10.679 (1.907-59.79) |                       |
| TC (mmol/L) < 5.70   | 240 (84.2)| 39 (68.4)| 1 (reference) |                       |
| ≥ 5.70               | 45 (15.8)| 18 (31.6)| 0.008 | 2.462 (1.294-4.682) |                       |
| Tri (mmol/L) < 1.7   | 200 (70.2)| 40 (70.2)| 1 (reference) |                       |
| ≥ 1.7                | 85 (29.8)| 17 (29.8)| 1.000 | 1.000 (0.557-1.862) |                       |
| HDL (mmol/L) < 0.93  | 29 (10.2)| 20 (35.1)| 1 (reference) |                       |
| ≥ 0.93               | 256 (89.8)| 37 (64.9)| 0.000 | 0.210 (0.108-0.408) |                       |
| LDL (mmol/L) < 3.63  | 237 (83.2)| 35 (61.4)| 1 (reference) |                       |
| ≥ 3.63               | 48 (16.8)| 22 (38.6)| 0.001 | 3.104 (1.675-5.752) |                       |
| FBG (mmol/L) < 6.1   | 242 (84.9)| 42 (73.7)| 1 (reference) |                       |
| ≥ 6.1                | 43 (15.1)| 15 (26.3)| 0.052 | 2.010 (1.026-3.939) |                       |
| ApoA (g/L) < 1       | 2 (0.7)  | 20 (35.1)| 1 (reference) |                       |
| ≥ 1                  | 283 (99.3)| 37 (64.9)| 0.000 | 0.013 (0.003-0.058) | 0.000 | 105.282 (22.229-498.635) |
| ApoB (g/L) < 1       | 208 (72.9)| 32 (56.1)| 1 (reference) |                       |
| ≥ 1                  | 77 (27.1)| 25 (43.9)| 0.017 | 2.110 (1.176-3.788) |                       |
| BMI (kg/m²) < 25.0   | 164 (57.5)| 40 (70.2)| 1 (reference) |                       |
| ≥ 25.0               | 124 (42.5)| 17 (29.8)| 0.078 | 0.576 (0.312-1.065) |                       |

BMI: Body mass index; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TC: Total cholesterol; FBG: Fasting blood glucose; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen.
interleukin-1\(^{29,30}\). Additionally, increased levels of LDL are associated with oxidized LDL, which is linked with an increase in reactive oxygen species\(^{31,32}\). It is well known that reactive oxygen species can cause DNA damage by activating oncogenes and inactivating tumor suppressor genes\(^{33}\), all of which have been found to play a role in carcinogenesis. Together, these data suggest that dyslipidemias may play a role in ampulla tumor development.

Our retrospective cohort study did not confirm the exact roles of the various lipids in ampullary adenoma and
ampullary cancer. Although further studies are needed to clarify the potential roles, we believe that dyslipidemia plays a key role in the development of ampullary tumors.

Observational studies in humans have shown relations between several medical conditions and an increased risk of pancreaticobiliary adenocarcinoma, including cholecystitis[34,35], cholecystectomy[36], chronic pancreatitis[12,37-39], obesity[40], and HBV infection[41,42]. However, findings to support these associations have been somewhat contradictory. In the present study, cholecystolithiasis was an independent factor for an increased risk of developing ampulla adenoma (odds ratio: 11.068) and ampulla cancer (odds ratio: 14.06). It may even be involved in the transformation from adenoma to carcinoma. It is reported that there might be some relationship between diabetes and cholelithiasis[43,44]. Given the possibility that the relationship between ampullary tumors and cholelithiasis might be confounded by diabetes, we excluded the diabetes patients and found that the results did not change the association (data not shown).

We believe we are the first to observe a significant positive linear trend that chronic pancreatitis might be a risk factor for ampullary tumors, which is also a strong risk factor for both pancreatic and ampullary cancers (OR = 8.863). The χ² test indicated that chronic pancreatitis is associated with the risk of developing ampullary adenoma, but a multivariate logistic regression test indicated that chronic pancreatitis is not correlated with ampullary adenoma formation.

Hepatitis B virus infection is a major public health burden in China[45-47]. The association between HBV and pancreatobiliary adenocarcinoma has been proven, however, our results do not show a relationship between HBV infection and ampullary tumors development, whereas cigarette smoking, alcohol abuse, cholecystectomy, and obesity are risk factors.

This study revealed that some metabolic syndromes and medical conditions independently increased the risk of ampullary tumor development. Among them, a history of diabetes, cholelithiasis, and a high ApoA level were associated with progression to malignancy and may be involved in the adenoma-carcinoma transformation (Figure 1). Our study is the first one to evaluate risk factors involved in the adenoma-carcinoma sequence, so our results should be of value to the surgical and oncological communities.

**COMMENTS**

**Background**

Tumors of the ampulla can be benign or malignant, although in most series the majority of ampullary neoplasms are malignant. Although ampullary tumors are relatively rare, the rapid development of, and advances in, endoscopy and imaging techniques have profoundly increased their discovery rate. Despite the increasing numbers of published studies, the etiology for ampullary tumors is incompletely defined. This is the first study to evaluate the impact of metabolic syndromes on ampullary tumor patients.

**Research frontiers**

Numerous published studies investigated the clinicopathological aspects of ampullary tumors, most of which focused on the prognosis associated with the disease. Studies investigating risk factors associated with the proposed adenoma-carcinoma sequence are scarce, especially regarding metabolic syndrome components and ampullary tumors.

**Innovations and breakthroughs**

In recent years, numerous published studies investigated the clinicopathological aspects of ampullary tumors, most of which focused on the prognosis associ-
ated with this disease. This study found that some metabolic syndrome components and medical conditions are potential risk factors for the development of ampullary tumors. Cholelithiasis, diabetes, and apolipoprotein A may contribute to the malignant transformation of benign ampullary adenomas into ampullary cancer.

Applications
This study revealed that some metabolic syndromes and medical conditions independently increased the risk of ampullary tumor development. Better understanding of the underlying pathophysiology of the association between the risk factors and ampullary tumors may provide new insights into the potential additive or synergistic effects of the components of the metabolic syndromes and the development of ampullary tumor treatment modalities. This will strengthen the clinical relevance of treating patients who meet the criteria for this syndrome.

Terminology
Metabolic syndrome, also known as insulin resistance syndrome, has become a major public health problem worldwide. It consists of obesity, hyperglycemia, hyperinsulinemia, dyslipidemia, and hypertension.

Peer review
This paper is a well-written, original, and the first study to evaluate the impact of metabolic syndromes on ampullary tumors patients. The findings in this study will strengthen the clinical relevance of treating patients who meet the criteria for this insulin syndrome.

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