




Risk factors for the occurrence of ampullary tumors: A case-control study

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Abstract

Background: The incidence of ampullary tumors is increasing but data on association with an increased exposure to certain risk factors are scanty.

Objective: To investigate risk and protective factors associated with the occurrence of ampullary tumors and whether these factors differ between ampullary tumors of the intestinal and pancreatobiliary subtypes or between adenomas and carcinomas.

Methods: The association between a large set of exposome features and ampullary tumors occurrence was investigated in a bi-centric case-control study after ethic committee approval and power calculation.

Results: In 223 histologically confirmed patients and 446 controls, previous cholecystectomy (odd ratio [OR] = 2.07; 95% confidence interval [CI] = 1.34–3.20) and proton pump inhibitors use (OR = 1.66; 95% CI = 1.16–2.37) were associated with increased risk of ampullary tumors, aspirin use (OR = 0.57; 95% CI = 0.36–0.90) and light alcohol intake (OR = 0.54; 95% CI = 0.38–0.76) with reduced risk. A previous cholecystectomy was also associated with tumors of intestinal subtype and with both adenomas and carcinomas, and proton pump inhibitors use with adenomas only. Smoking, body mass index, family history of cancers, previous ulcer, diabetes and use of statins, insulin and metformin were not significant factors.

Conclusion: This is the first case-control study specifically highlighting factors associated with the occurrence of ampullary tumors. We report factors that are novel and plausible, in keeping with mechanisms described for other gastrointestinal tumors and with potential clinical relevance.

KEYWORDS

alcohol, ampullary tumors, aspirin, cholecystectomy, proton pump inhibitors, risk

Gabriele Capurso and Paolo Giorgio Arcidiacono share the last authorship.

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INTRODUCTION

Ampullary tumors (AT) are relatively rare neoplasms with an incidence of less than 1 per 100,000 per year and, although representing only 0.6%–0.8% of all digestive cancers are the most common neoplasm type in the small bowel.¹ Despite being often grouped with other periampullary neoplasms such as extrahepatic cholangiocarcinoma (CCA) and pancreatic adenocarcinoma (PDAC), ATs account for less than 10% of tumors at this site and represent a distinct clinicopathologic entity with a generally better outcome.² Their favorable prognosis is partially explained by an early clinical presentation, often with obstructive jaundice, and consequent high resectability rates compared to PDAC and CCA.³

The term AT encompasses malignant ampullary cancers (AC) and ampullary adenomas (AA) in an adenoma-carcinoma sequence, which in intestinal subtype cases resembles the one described in the colon.^{1,2}

The incidence of ATs has increased during the last 20 years, especially in younger adults.^{2,4,5} While a quote of ATs occurs in the setting of familial polyposis syndromes such as familial adenomatous polyposis (FAP),⁶ the majority are sporadic and risk factors associated with their occurrence have been poorly investigated.

As a quote of ATs are asymptomatic, whether their increased reported incidence is due to wider availability of endoscopy and imaging and occasional diagnoses, or to changed exposure to risk factors is, therefore, uncertain. Also, risk factors may differ between ATs of the intestinal and pancreatobiliary subtypes that likely derive from distinct precursors and have distinct prognosis.^{2,7} However, there are few studies specifically investigating the epidemiology of ATs, with data being often extrapolated from those associated with non-ampullary duodenal tumors.^{8,9}

The primary aim of this study was, therefore, to investigate risk and protective factors associated with the occurrence of ATs. The secondary aim was to investigate whether these factors differ between ATs of the intestinal and pancreatobiliary subtypes or between AAs and ACs.

PATIENTS AND METHODS

Study design and setting

This is a bi-center case-control study, conducted at San Raffaele Research Hospital, Milan, and Gemelli Research Hospital, Rome, Italy (January 2015–July 2021) upon ethic committee approval (AMP-RISK159/INT/2021). A retrospective analyzes of prospectively maintained databases containing information of patients with sporadic AT (AA or AC) was performed. Inclusion criteria for cases were having a histologically proven diagnosis of AT (AA or AC) with available recorded variables. Patients with other ampullary neoplasms (neuroendocrine neoplasms, paragangliomas, GIST and others were not included). Controls were hospital non-patient visitors and patients matched for sex and age (± 2 years) with benign digestive

Key summary

Established knowledge on this subject

- The incidence of ampullary tumors is on the rise. They encompass lesions with a distinct histological, intestinal or pancreatobiliary subtype, and both adenomas and carcinomas.
- Risk factors associated with the occurrence of ampullary tumors are poorly investigated and whether their increased incidence is due to exposition to certain factors that has become more frequent is unexplored.
- It has not been investigated whether different subtypes or stages of ampullary tumors are associated with specific risk factors.

New findings of this study

- A previous cholecystectomy and the use of proton pump inhibitors are associated with increased risk of ampullary tumors, aspirin and light alcohol intake with reduced risk.
- A previous cholecystectomy is associated with tumors of intestinal subtype and with both adenomas and carcinomas, and proton pump inhibitors use with adenomas only.

disorders seen at the two same Centers, as previously described.^{10,11}

As for controls, to avoid possible bias, subjects specifically referred for a screening examination for ascertained or suspected cancer familiar syndromes were excluded, as well as subjects with an active cancer (diagnosed within the past 5 years) or those diagnosed with an active/recent (within 4 weeks) peptic ulcer bleeding. Data are reported in keeping with the Strengthening the reporting of observational studies in epidemiology (STROBE) guidelines for case-control studies.¹²

Data collection and exposure definition

The following clinical, epidemiological, therapeutic and morphological parameters were available: sex, age, tobacco and alcohol intake, body mass index (BMI), first and second degree family history (FH) of cancers, in particular, PDAC, colorectal (CRC) and gastric cancer (GC), history of diabetes mellitus (DM), peptic ulcer disease (PUD) and previous cholecystectomy, chronic use of drugs, such as, insulin, metformin, aspirin, statins and proton pump inhibitors (PPI). The data included in the databases were recorded on a standardized form by a trained physician through direct patient interview.

For ever-smokers, a consumption of at least 100 cigarettes or more than 6 months of smoking were needed to be considered a smoker. The total amount of smoking was evaluated as pack-years, defined as the product of packs smoked per day and the total years of smoking. A cut-off of 20 pack-years was set to define heavy smokers.

For ever-drinkers, a consumption of at least 12.5 g (1 unit) of alcohol/week was needed to be considered a drinker. One glass of wine, one pint or can of beer, one shot of hard liquor was each considered approximately equal to 12.5 g of alcohol. A cut-off of 21 units/week (262.5 g of alcohol) was set to define heavy drinkers, as previously described.^{10,11} BMI was reported as the usual adult weight/height² (kg/m²) with obesity considered as BMI ≥ 30 kg/m². Diabetes mellitus was recorded as a potential risk factor when diagnosed >1 year before the diagnosis of AT or at any time before the interview for controls. Aspirin, statin, insulin, metformin, or PPI use was defined as the ever use of the medication for at least three consecutive months. Subjects were asked about these factors as present 12 months before diagnosis or at presentation to avoid bias. These potential risk and protective factors were investigated because they have been previously associated with other tumors of the periampullary region (PDAC, CCA). Both cases and controls demonstrated the will and ability to participate providing these personal data.

Statistical analyzes

An a priori power calculation was performed. We estimated sample size based on frequencies of exposures in PDAC and controls in previous studies,¹⁰ with a 1:2 ratio and statistical power of 80% and an alpha error = 0.05. We hypothesized that factors associated with increased PDAC risk may similarly affect AT risk. In previous studies¹⁰ the reported prevalence of ever smoking in controls was $\approx 45\%$, with OR = 1.8 and that of first or second degree PDAC FH $\approx 3.5\%$ in controls, with OR ≈ 3 . Sample size's estimate of cases and controls, to show true differences whether existing, were, respectively, 184 cases and 368 controls for smoking and 214 cases and 428 controls for PDAC FH. Characteristics of cases and controls were compared by chi-square test for categorical or Student's *t*-test for continuous variables. Significant variables were analyzed by multivariable logistic regression analyzes. All statistical analyzes were performed using MedCalc.13 (MedCalc Software).

RESULTS

Study cohort

Two-hundred-twenty-three AT patients and 446 matched controls were enrolled, 52% males with median age 70 years in both groups. The demographics and clinical features of cases and controls are detailed in Table 1. One hundred and forty five cases had AC and 78 AA, either with low ($n = 52$) or high-grade dysplasia ($n = 26$) (LGD or HGD, respectively). Histological intestinal and pancreatobiliary subtypes, were reported in 134 (60%) and 50 (40%) of cases, respectively, while the subtype was not defined in the pathology report in the remaining 39 cases. Of the 223 AT patients, 148 (66.3%) were treated by surgical and 60 (26.9%) by endoscopic ampullectomy, seven had advanced disease and were treated with chemotherapy

while eight only received palliative care (stenting) due to age and/or comorbidities. In those last 15 cases bioptic samples but not the full lesion were available for histological examination.

Risk factors for ampullary tumors

There were no significant differences between cases and controls in terms of BMI, smoking, cancer FH, previous diabetes or peptic ulcer and statin use. Data on body weight, hence BMI, 12 months before diagnosis were missing for three cases and two controls who did not recall this information. Compared to controls, AT cases were less frequently light alcohol drinkers and on chronic aspirin treatment, meanwhile, they had more frequently a previous history of cholecystectomy and chronic PPI use. These four factors were associated with AT risk at multivariable analyzes (Table 1).

Risk factors for subtypes of ampullary tumors

Subgroup analyzes were done to test our hypotheses that risk factors may differ between histological subtypes, or between AA and AC. In the 134 intestinal ATs and the 268 matched controls, light alcohol intake and aspirin use remained associated with reduced AT risk and previous cholecystectomy with increased risk (Table 2). There were, instead, no significant factors associated with the risk of ATs of the pancreatobiliary subtype.

Previous cholecystectomy and PPI exposure were associated with increased AA risk; meanwhile, light alcohol intake was associated with decreased and previous cholecystectomy with increased AC risk (Table 2).

DISCUSSION

AT are rare neoplasms that have shown a trend toward increased incidence, especially in younger subjects. As risk factors for this disorder have not been specifically investigated before, we designed the first case-control study specifically aimed to explore them after power calculation. We also hypothesized that risk factors may differ between ATs of the intestinal subtype, that likely follow an adenoma-carcinoma sequence, and pancreatobiliary ones. A history of cholecystectomy, and to lesser extent aspirin, and PPIs use, and light alcohol intake emerged as factors associated with the risk of ATs. This holds true particularly for the intestinal subtype, while we could not identify factors associated specifically with the risk of pancreatobiliary ATs, possibly due to their low number. Notably, a recent paper provided evidence that pancreatobiliary ATs resemble pancreatic cancer in several aspects.¹³ One may therefore hypothesize that risk factors for pancreatobiliary ATs are distinct from those of the intestinal ATs.

In keeping with findings of the present study, gallbladder surgery has been previously associated with risk of periampullary cancers,

TABLE 1 Characteristics of ampullary tumor cases and controls by selected variables of family history, chronic conditions, and lifestyle

	Cases N = 223 (%)	Controls N = 446 (%)	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
Male sex	118 (51.9)	236 (51.9)	1 (0.72–1.38)	1		
Age, median (range)	70 (63–78)	70 (63–78)	1 (0.98–1.01)	0.97		
BMI, median (range)	25.3 (22.9–28.1)	25.6 (23.4–28)	0.99 (0.96–1.04)	0.96		
BMI ≥ 30	37 (16.6)	56 (12.5)	1.42 (0.91–2.23)	0.12		
Ever smoking	107 (47.9)	207 (46.4)	1.06 (0.77–1.47)	0.70		
Heavy smoking (PY ≥ 20)	59 (26.5)	131 (29.4)	0.86 (0.60–1.24)	0.43		
Light alcohol intake (>1 unit/month <21 units/week)	69 (30.9)	206 (46.2)	0.52 (0.37–0.73)	0.002	0.54 (0.38–0.76)	0.0005
Heavy alcohol intake (≥ 21 units/week)	9 (4.03)	30 (6.7)	0.58 (0.27–1.25)	0.16		
1 st degree FH of multiple cancers	32 (14.3)	60 (13.4)	1.08 (0.68–1.71)	0.75		
1 st degree FH of PDAC	9 (4.03)	13 (2.9)	1.41 (0.59–3.33)	0.44		
2 nd degree FH of PDAC	6 (2.7)	4 (0.9)	3 (0.85–10.94)	0.08		
1 st or 2 nd degree FH of PDAC	15 (6.7)	17 (3.8)	1.82 (0.89–3.71)	0.10		
1 st degree FH of CRC	26 (11.6)	49 (10.9)	1.07 (0.64–1.77)	0.79		
2 nd degree FH of CRC	7 (3.1)	9 (2.01)	1.57 (0.58–4.28)	0.37		
1 st or 2 nd degree FH of CRC	33 (14.7)	58 (13)	1.14 (0.74–1.78)	0.54		
1 st degree FH of gastric cancer	12 (5.4)	26 (5.8)	0.92 (0.45–1.86)	0.81		
Diabetes mellitus	25 (11.2)	42 (9.4)	1.21 (0.72–2.05)	0.47		
Metformin use	18 (8.07)	25 (5.6)	1.48 (0.79–2.77)	0.22		
Insulin use	8 (3.6)	10 (2.2)	1.62 (0.63–4.17)	0.31		
History of PUD	16 (7.2)	31 (6.9)	1.03 (0.55–1.93)	0.91		
Previous cholecystectomy	53 (23.8)	52 (11.6)	2.36 (1.55–3.60)	0.0001	2.07 (1.34–3.20)	0.0009
Aspirin use	34 (15.2)	97 (21.7)	0.64 (0.42–0.99)	0.04	0.57 (0.36–0.90)	0.017
Statin use	38 (17.04)	93 (20.8)	0.78 (0.51–1.18)	0.24		
PPI use	88 (39.5)	135 (30.3)	1.5 (1.07–2.1)	0.01	1.66 (1.16–2.37)	0.006

Note: Bold values are statistically significant.

Abbreviations: BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; FH, familial history; OR, odd ratio; PDAC, pancreatic adenocarcinoma; PPI, proton pump inhibitor; PUD, peptic ulcer disease; PY, pack year.

but data were limited, heterogeneous, and focused on PDAC and CCA.^{8,9} As for ATs, in a recent meta-analyses, gallstones were associated with a three-fold increased risk of ATs,¹⁴ but the role of gallbladder removal was not investigated. The increased and continuous flow of bile acids in the duodenum following cholecystectomy may cause DNA damage through oxidative stress and production of reactive oxygen species.¹⁵ In addition, cholecystectomy alters the gut microbiota that in turn may affect AT risk.¹⁶ Given the retrospective study design, we wondered whether a reverse-causation bias was possible, as cholecystectomy could also result to be secondary to a chronic modification of the biliary flow following a damage on the sphincter of Oddi caused by AT leading to vesicular tension, associated symptoms and a consequent surgery. However, we believe that this is unlikely, as the recorded cholecystectomies took place >12 months before diagnosis with a mean time to AT diagnosis of 169 months.

We also report for the first time an association between PPI use and increased AT risk. A previous case-control study reported an association between PPI use and increased periampullary cancers risk, albeit without a specific analyzes for ATs.¹⁷ Possible plausible mechanisms include hypergastrinemia, with a well described trophic effect on the gastrointestinal mucosa, and dysbiosis, favoring overgrowth of potentially harmful bacteria.¹⁸ Notably, others have reported an association between non-ampullary duodenal tumors and the presence of Barrett's esophagus and of fundic glands polyps,¹⁹ conditions that are in turn associated with long-term PPI use. However, this association should be considered with caution, as unfortunately no data on dose and duration of PPI use were available, reinforcing a plausible biological effect.

Furthermore, we observed that light-moderate alcohol consumption is associated with decreased AT risk. Whether this finding is due to recall bias inherent to the study design that may lead to AT

TABLE 2 Subgroup analyses of factors significantly associated with ampullary tumors of the intestinal subtype and with either ampullary cancers or adenomas

	Cases	Controls	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
Intestinal subtype	134	268				
Light alcohol intake	38 (28.3%)	125 (46.6%)	0.45 (0.29–0.71)	0.0005	0.47 (0.30–0.74)	0.001
Previous cholecystectomy	30 (22.4%)	31 (11.6%)	2.21 (1.27–3.83)	0.005	2.03 (1.16–3.57)	0.01
Aspirin use	18 (13.4%)	59 (22%)	0.55 (0.31–0.98)	0.04	0.54 (0.30–0.97)	0.04
Ampullary cancer	145	290				
Light alcohol intake	48 (33.1%)	142 (48.9%)	0.51 (0.34–0.78)	0.002	0.56 (0.37–0.86)	0.008
Previous cholecystectomy	34 (23.4%)	32 (11%)	2.47 (1.45–4.2)	0.001	2.2 (1.28–3.78)	0.004
Ampullary adenoma	78	156				
Previous cholecystectomy	19 (24.3%)	17 (10.9%)	2.63 (1.28–5.42)	0.009	2.41 (1.15–5.05)	0.02
PPI use	31 (39.7%)	41 (26.3%)	1.85 (1.04–3.29)	0.03	1.79 (0.99–3.22)	0.05

Notes: There were no significant factors associated with the risk of pancreato-biliary ampullary tumors. Bold values are statistically significant. Abbreviations: OR, odd ratio; PPI, proton pump inhibitors.

patients minimizing their exposure to alcohol, or to a genuine protective effect is uncertain²⁰. Heavy alcohol consumption has been linked to increased risk of several digestive cancers, including cancer of the colorectum, liver, pancreas, and gallbladder,²¹ but not with ATs. Also, the effect of light to moderate drinking on cancer risk and mortality remains debated. A recent meta-analyses of 87 studies showed a J-shaped relationship between alcohol consumption and all-cause mortality, finding a protective effect of low-volume drinking.²² Alcohol stimulates gastric acid output and modulates the GI microbiome,²¹ thus there may be explanations that deserve further investigation.

This is the largest study investigating the potential chemo-preventive effect of aspirin use on AT occurrence, demonstrating for the first time its association with a decreased AT risk, in keeping with its chemo-preventive effect along the GI tract.²³ A previous population-based study found a non-significant reduction in risk of CCA and AC with aspirin, but in that study the number of ACs was limited to 68 cases.²⁴ As the risk of ATs recurrence after endoscopic recurrence is relatively high, the present findings may pave the way to further investigation on the use of aspirin as a potential chemo-preventive agent in this setting.

The secondary aim of the present study was to explore whether risk factors for intestinal and pancreatobiliary ATs or for the initial and final stage of AA and AC differ. Interestingly, previous cholecystectomy remained a significant risk factor for intestinal ATs and both for AA and AC, while the use of PPI was a significant factor for AA but not for AC possibly suggesting a role in initiation of the process. However, these analyzes may well be underpowered, especially the one on the small subgroup of pancreatobiliary ATs and no firm conclusions can be drawn.

The present study displays some strengths, including the relatively large sample size for a rare tumor type, histological confirmation, the preliminary power calculation, and the comprehensive set of investigated variables. Also, the study hypotheses and findings are novel. However, there are limitations besides those intrinsic to the retrospective case-control design of the study, such as possible bias

due to enrollment in two tertiary referral Centers and limited power to account for multiple comparisons. Another potential matter of concern, as for any case-control study, regards the selection of the control population. We opted for a mixed control group that we believed to represent the same population as the case group, as living in the same catchment area of the corresponding cases, to limit possible bias that could have been specific of either hospital controls or visitors. Also, potentially, some of the controls might have harbored ampullary lesions, as these can only be ruled out by specific endoscopic investigations. However, as the incidence of ampullary tumors is extremely low and a part of the controls received some sort of work-out that may have included blood tests, ultrasound and gastroscopy for gastrointestinal complaints, we think that this is extremely unlikely.

At any rate, additional studies might be important to confirm the present findings including the lack of significant association with variables such as smoking.

In conclusion, the present study reports factors associated with AT occurrence, especially of the intestinal subtype, with novel and plausible findings and mechanisms reported for other gastrointestinal tumors. Our findings support a role of cholecystectomy and to lesser extent of PPI use in increasing the risk of ATs. As both these factors have become more frequent over the past decades, one may speculate that they may partially account for the reported increased incidence of ATs in this period.

AUTHOR CONTRIBUTIONS

Gabriele Capurso, Piera Zaccari, Livia Archibugi, Stefano Crippa, Massimo Falconi, Alberto Larghi, Antonio Gasbarrini, Paolo Giorgio Arcidiacono: planning and conducting the study; Enrico Nista, Giuseppe dell'Anna, Guido Costamagna, Tommaso Schepis, Matteo Tacelli, Giulio Belfiori, Francesca Aleotti, Maria Chiara Petrone, Alberto Mariani: collecting and interpreting data; Gabriele Capurso and Piera Zaccari: drafting the manuscript. All authors critically revised the manuscript and approved its final form.

ACKNOWLEDGMENTS

None to report.

CONFLICTS OF INTEREST

None to report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Zaccari P, Archibugi L, Belfiori G, Nista E, dell'Anna G, Crippa S, et al. Risk factors for the occurrence of ampullary tumors: a case-control study. *United European Gastroenterol J*. 2022;10(7):732–7. <https://doi.org/10.1002/ueg2.12281>