

Epidemiological aspects of biliary tree tumors in a region of northern Italy: emerging trends and sex-based differences

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Background Cholangiocarcinoma (CCA) and gallbladder cancer are the second cause of liver malignancy after hepatocellular carcinoma. Epidemiological data point to an increase in the incidence of CCA in both western and eastern countries; however, data on more recent years are lacking.

Aims The aim of this study was to elucidate the more recent epidemiology of CCA and gallbladder carcinoma in north-east Italy using automatically collected regional data on hospital admissions over a 10-year period.

Materials and methods We performed a retrospective analysis of the Veneto region (north-east Italy) database of patients' hospital discharge records, identifying cases with the following codes: intrahepatic cholangiocarcinoma (155.1), primary gallbladder cancer (156.0), and primary extrahepatic biliary tract cancer (156.1). Hospitalizations were recorded according to the surgical or medical procedures involved (based on International Classification of Diseases-9 procedure codes), and only the first hospitalization was considered for the 2005–2009 period.

Results The number of hospitalizations for biliary tumors as a whole has remained stable over the past 10 years. The hospitalization rate of intrahepatic CCA is increasing; this

cancer is more frequent in males than in females. The hospitalization rate for gallbladder cancer is increasing with age. However, the figures for extrahepatic CCA have remained stable over the past 10 years. The duration of survival was significantly longer for patients who underwent radical surgery than for those who did not.

Conclusion Efforts are needed to prevent CCA, bearing in mind the emerging conditions associated with its onset. Secondary prevention of these tumors will substantially improve the duration of survival. *Eur J Gastroenterol Hepatol* 00:000–000 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Cholangiocarcinoma (CCA) is a malignant neoplasm of the biliary duct system, accounting for 10–25% of primary hepatic malignancies worldwide [1–3]. Anatomically, CCA can be classified as intrahepatic or extrahepatic; the extrahepatic site most frequently involved is the hilum (Klatskin tumor). The increasing interest in CCA in recent years is because of a number of reasons, including the identification of several different risk factors associated with the intrahepatic variant [i.e. primary sclerosing cholangitis (PSC), flukes, hepatitis B and C, etc.], together with a trend toward an increase in its incidence [1].

Intrahepatic CCA is prevalent in individuals in their 50s and 60s, with no difference between men and women; the survival duration is up to 6 months without surgery, and 20–40% of patients are alive at 5 years after resection [4]. Extrahepatic CCA is prevalent among individuals in their 60s and 70s and mainly affects men; the duration of survival is very short (up to 3–4 months without surgery), and up to 50% of patients are alive at 5 years after surgery [5]. Data obtained from the Italian Association of Tumor Registries (accounting for incidence) and from the Italian National Institute of Statistics (accounting from mortality) indicate that the incidence of intrahepatic CCA and related

mortality has gradually increased in the past two decades [3], whereas extrahepatic CCA appears to have remained stable over time [3]. This trend has been observed in various European and American studies [6]. According to the report on the population-based data from the National Cancer Institute's Surveillance, Epidemiology, and End Results cancer registry program, the incidence of intrahepatic CCA remained constant between 1992 and 2000 [7]. In Denmark, a decrease in the incidence rates for both intrahepatic and extrahepatic CCA from 1978 through 2002 was reported [8]. Recent epidemiological data on the incidence and mortality of CCA in Italy are lacking [9].

The aim of our study was to elucidate the more recent epidemiology of CCA and gallbladder carcinoma in north-east Italy using automatically collected regional data on hospital admissions over a 10-year period.

Materials and methods

We performed a 10-year (2000–2009) retrospective analysis of Veneto region's database of patients' hospital discharge records (HDRs), which records all hospitalizations in the region's hospitals, providing a complete coverage of all major surgical procedures performed in the regional population.

As of 1 January 2010, the total population of Veneto region was 4 773 554 inhabitants (2 338 057 male and 2 435 497 female) (ISTAT – National Institute for Statistics). There were ~900 000 discharges from regional hospitals each year. Diagnoses and treatment procedures were recorded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (2002 and 2007 versions). One primary and up to five secondary diagnoses and one primary and up to five secondary procedures were recorded in patients' HDR.

Patients with biliary tract cancer were identified by selecting all HDRs containing one of the following codes in the ICD-9-CM: intrahepatic cholangiocarcinoma (155.1), primary gallbladder cancer (156.0), primary extrahepatic biliary tract cancer (156.1), malignant neoplasm of other specified sites of the gallbladder and extrahepatic bile ducts (156.8), and malignant neoplasm of the biliary tract, part unspecified site (156.9). Hospitalizations were recorded according to surgical or medical procedures (based on ICD-9 procedure codes).

Incident cases were analyzed to calculate the radical treatment rate focusing on three tumors with a specified location, namely intrahepatic CCA, extrahepatic CCA, and primary gallbladder cancer; thus, tumors of unspecified sites (156.8 and 156.9) were excluded from the analysis. Incident cases between 2005 and 2009 were selected. If a patient was repeatedly admitted for biliary tract cancer during the study period, only the first admission was considered. Finally, the cohort was linked to the regional mortality registry for the years 2005–2009, enabling an estimation of the overall survival by the type of cancer. All hospitalization and mortality data were routinely collected by the regional health service and linkage was performed on previously anonymized records to make identification of individuals impossible (all record linkages relied on the patients' tax codes).

Statistical analysis

The rates are standardized to Veneto region's population in 2010. Bivariate analyses were performed using the χ^2 -test. Thereafter, Kaplan–Meier survival curves were plotted and log-rank statistics were calculated to identify the variables that influenced survival duration. All analyses were performed using the SAS 9.1 statistical package (SAS Institute Inc., Cary, North Carolina, USA).

The study was approved and patient privacy assured by the Veneto Regional Authority in accordance with legal requirements. The study protocol complied with the ethical requirements of the 1975 Helsinki Declaration.

Results

Table 1 shows the distribution by tumor site of origin in cases of biliary tree cancer identified in the HDRs from 2000 to 2009. The majority of the patients involved received medical care, whereas less than one in three underwent surgery during their hospital stay. The absolute number of HDRs relating to intrahepatic CCA progressively increased during the 10-year period. The absolute number of HDRs with respect to cases of extrahepatic CCA remained stable during the period considered. The absolute number of HDRs with respect to gallbladder cancer dropped slightly over the same period (Fig. 1).

Table 2 shows the total number of incident cases of specified location of the biliary tree and gallbladder cancers recorded between 2005 and 2009; of the 2035 cases observed, in all, 599 (29.4%) were of intrahepatic CCA, 791 (38.8%) were of extrahepatic CCA, and 645 (31.7%) were of gallbladder cancers. Radical treatments were administered to 426 patients (20.9%), whereas the others received only palliative therapies.

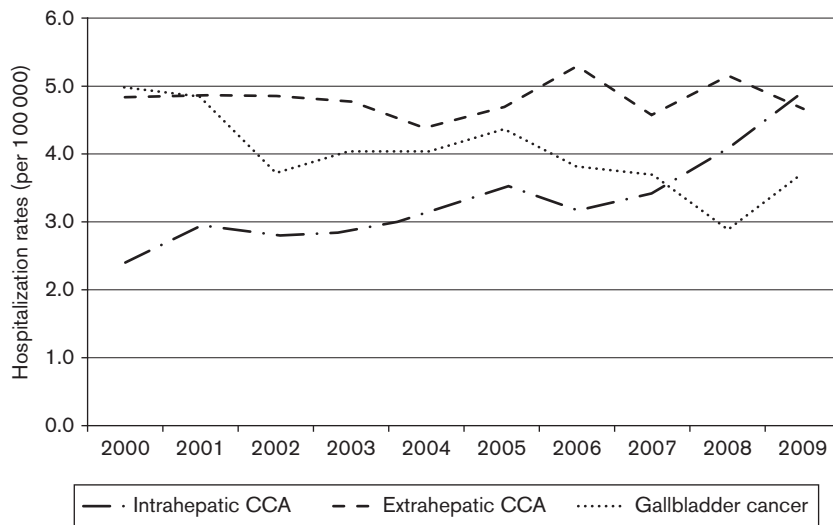
The age-adjusted and sex-adjusted rates of hospitalization for biliary tree cancers are shown in Fig. 2. The highest rates of intrahepatic CCA occurred in 65–74-year-old individuals, with men involved more often than women. Male and female patients were equally represented among the 55–64-year-olds and in patients over the age of 75 years. As for the cases of extrahepatic CCA, there was a trend toward higher hospitalization rates with increasing age, and more men compared with women were involved in all groups. The hospitalization rates for gallbladder cancer increased with age, and there was a female predominance in all age groups (Fig. 2).

There were 1792 deaths in the cohort considered, ~50% of which occurred within 6 months after the first discharge from hospital. Patient survival rates were similar for the three types of biliary tree cancers (Fig. 3). Men survived for a significantly longer duration compared with women (40 vs. 30% at 18-month follow-up; $P < 0.001$), and younger patients (between 44 and 65 years old) survived for longer durations compared with older patients (50 vs. 22% at the same 18-month follow-up;

Table 1 Distribution by subsite of origin of the total number of 5799 hospital discharges from 2000 to 2009

Diagnostic codes	Year									
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Intrahepatic cholangiocarcinoma (155.1)	115	140	133	136	149	168	151	163	197	234
Primary gallbladder cancer (156.0)	238	232	176	192	192	209	182	176	137	176
Primary extrahepatic cholangiocarcinoma (156.1)	232	241	231	228	209	223	252	219	246	222
Total	585	613	540	556	550	600	585	558	580	632

Fig. 1

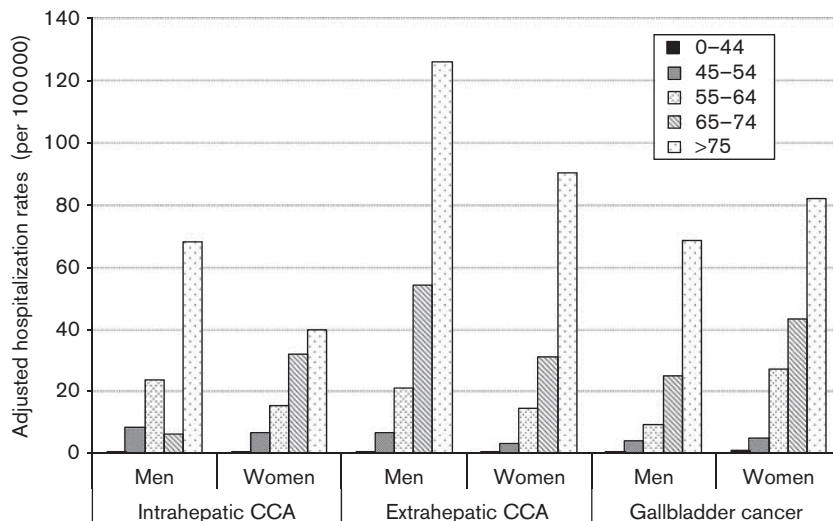


Hospitalized rates (per 100 000 inhabitants) according to biliary tree tumors in the Veneto region (2000–2009). Dashed and dotted line, intrahepatic cholangiocarcinoma (CCA); dotted line, gallbladder cancer; dashed line, extrahepatic CCA.

Table 2 Incident cases for cholangiocarcinoma and gallbladder cancer observed between 2005 and 2009 treated with surgical intervention and palliation

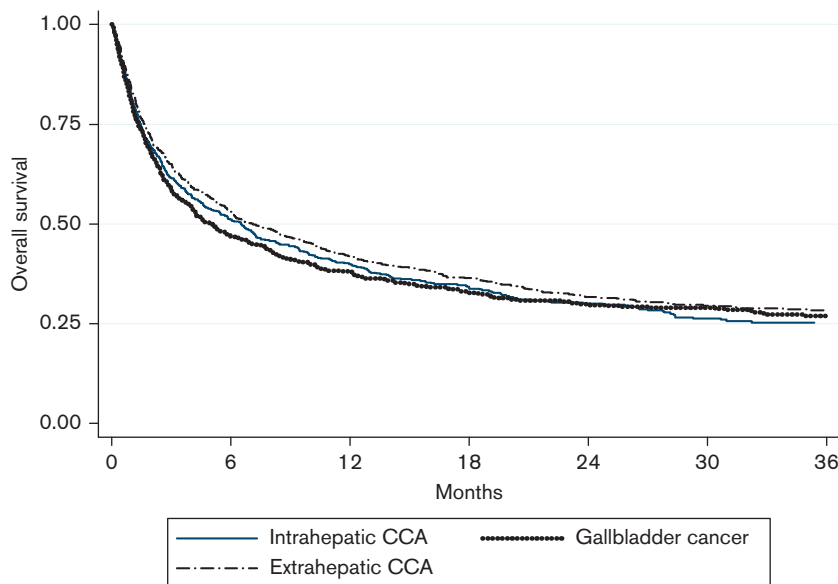
	Incident cases	Intrahepatic cholangiocarcinoma (155.1)	Primary gallbladder cancer (156.0)	Primary extrahepatic cholangiocarcinoma (156.1)
Radical intervention	426	80 (18.8%)	206 (48.4%)	140 (32.8%)
Palliation	1609	519 (32.2%)	439 (27.3%)	651 (40.5%)
Total number	2035	599 (29.4%)	645 (31.7%)	791 (38.9%)

Fig. 2



Age-adjusted and sex-adjusted hospitalized rates (per 100 000 inhabitants) according to biliary tree tumors in the Veneto region (2000–2009).

Fig. 3



Survival over time for patients in the three groups of biliary tree neoplasms.

$P < 0.001$). Patients who underwent radical biliary tree surgery survived for longer durations than those who did not ($P < 0.001$).

Discussion

The results of our study indicate the following: (a) the total number of hospitalizations for biliary tumors has remained stable over the past 10 years; (b) the frequency of intrahepatic CCA is increasing, and this cancer is more common in men than in women; (c) the hospitalization rates for gallbladder cancer increase with age; (d) the incidence of extrahepatic CCA has remained stable over the past decade; and (e) patients undergoing radical surgery survive for significantly longer durations compared with patients given medical treatment.

The trend toward an increasing incidence of intrahepatic CCA confirms the findings reported by Alvaro *et al.* [3] on the basis of epidemiological data collected from the Italian Association of Tumour Registries and the Italian National Institute of Statistics. In particular, our data show that the trend continued over the past 5 years. This behavior is particularly evident considering the annual increase rate from 2000 to 2009, which shows a doubling absolute number over 10 years.

Intrahepatic CCA has a peak incidence among 65–74-year-old individuals, an age at which it is more common in men than in women (however, this sex-related difference is not apparent in younger or older age groups). This could probably be explained by the several risk factors that have recently been found to have a significant role in this type of

cancer. PSC is one of the main risk factors for intrahepatic CCA. A Mayo Clinic Study [10] found that most CCA cases were diagnosed during the first 2.5 years after a patient had been initially diagnosed with PSC. In PSC patients diagnosed at an older age, a history of colorectal dysplasia or CCA, smoking, and present or former alcohol use (> 80 g/day) have all been suggested as additional risk factors for CCA. Liver fluke infestations represent a negligible factor for the development of CCA in Italy, but the possibility of an association between flukes and CCA should be borne in mind for cases among immigrants from China and eastern Asian countries [11,12].

A higher risk of CCA has recently been reported in patients with chronic hepatitis C virus (HCV) or hepatitis B virus infection. A prospective study of 600 HCV-infected individuals in Japan found a 2.3% incidence of CCA, which is higher than the rate in the general population [13]. In a hospital-based case-control study, liver cirrhosis and chronic HCV infection were identified as possible risk factors for intrahepatic CCA, whereas heavy alcohol consumption was a risk factor for both intrahepatic and extrahepatic CCA [14]. Similarly, an increased incidence of CCA has been reported in patients with a chronic hepatitis B infection [15]. Results from a recent meta-analysis also indicate an association between diabetes and a higher risk of CCA (be it intrahepatic or extrahepatic) [16]. Finally, intrahepatic stones, bile duct adenoma or papilloma, choledocal cysts, and even a history of cholecystectomy have been identified as conditions predisposing to CCA [1]. Indeed, a large, population-based cohort study with a complete follow-up

lasting up to 43 years showed that gallstones raise the risk of both intrahepatic and extrahepatic CCA, whereas the risk of developing these cancers gradually drops back to a level same as that in the general population with time elapsing after cholecystectomy [17]. In our study population, 6.5% of intrahepatic CCA patients and 5.8% of extrahepatic CCA patients had a history of cholecystectomy: the difference between them is not statistically significant, and the figures coincide with the present rate of cholecystectomies in the general population [18]. As expected, male sex was predominant among the cases of extrahepatic CCA, whereas more women compared with men had gallbladder cancer. However, there were no sex-related differences among patients over the age of 75 years.

A limitation of our study is that our mortality records were not compared with the Veneto Cancer Registry data. This is because the latter data were only available for the years 1998–2002, which is a 5-year period before the one considered in our study. In addition, the Veneto Region Cancer Registry did not distinguish between intrahepatic and extrahepatic forms of CCA. Over the earlier 5-year period, the Cancer Registry recorded 275 cases of extrahepatic CCA and 214 cases of gallbladder cancer/year (<http://www.registrotumoriveneto.it>). These figures are consistent with the epidemiological findings of our study.

Finally, mortality data indicate that survival curves were significantly better in patients with any form of biliary tree tumor who underwent radical surgery than in those who received palliation alone. Efforts should therefore be made to ensure an early diagnosis of these cancers. At present, there are no useful biochemical markers for selecting patients at risk of biliary tree tumors. Special attention should be paid to patients with chronic diseases of the biliary tree, including von Meyenburg hamartomas [19], Caroli's disease [1], and intrahepatic stones [20]. A preventative use of ursodeoxycholic acid is not recommended in such patients, nor is long-term treatment with ursodeoxycholic acid indicated in patients who undergo cholecystectomy. Further prospective studies are warranted, including patients with biliary tree abnormalities, to shed more light on the potential risk factors and early diagnosis of biliary tree tumors.

Conclusion

Our study confirmed a rise in incidence of CCA in recent years. There are clear sex-related differences in various forms of biliary tree tumors. Efforts should be made to prevent CCA, bearing in mind the emerging conditions associated with its onset. Secondary prevention of these tumors will substantially improve the duration of survival.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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