

# Prevalence and risk factors associate with cholangiocarcinoma: A clinical study in tertiary care teaching hospital

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## Abstract

**Background:** Cholangiocarcinoma, including intra-and extrahepatic cholangiocarcinoma, is a rare but highly lethal cancer. Despite effort in finding the risk factors of cholangiocarcinoma, the causes of most cholangiocarcinoma remain unknown. There are considerable geographic and demographic variations in the incidence of cholangiocarcinoma. Although it comprises only 10-15% of hepatobiliary neoplasms, its incidence is increasing. There are several established risk factors for CC and few are modifiable which will help in reducing the incidence.

**Aims and Objectives:** To study the Prevalence and risk factors of cholangiocarcinoma at GMC Budaun.

**Material and Methods:** All types of cholangiocarcinoma cases above age of 40 years admitted to Department of Surgery, GMC Budaun U.P., were studied for risk factors over a period of two years.

**Results:** An incidence of cholangiocarcinoma was 0.032% in present study. Peak incidence of cholangiocarcinoma was 4th to 6th decade of life with mean age of 61.92 years. out of 26 patients 13 patients (50%) were smoker and in those 13 patients 12 (92%) were smoking for more than 10 years and 13 patients (100%) were smoking more than 10 cigarettes or bidi per day. 18 patients were using chulha (69%) for cooking meals with coal as a primary fuel.

**Conclusion:** In conclusion, we found associations with PSC, smoking and alcohol consumption; however, further studies are needed to establish the risk factors in our country Long term exposure to pesticides in patients, who are chronic smoker and exposed to smoke from chulha are at higher risk of developing CCA than others in this socio-economic scenario.

**Keyword:** Hepatic cancer, prevalence, cholangiocarcinoma, incidence, pesticides, smoking, chulla, risk factors

## Introduction

Cholangiocarcinoma, including intra-and extrahepatic cholangiocarcinoma (ICC and ECC), is rare but highly lethal. The established risk factors for cholangiocarcinoma are primary sclerosing cholangitis, liver flukes (*Opisthorchis viverrini* and *Clonorchis sinensis*) in endemic regions, cholelithiasis or hepatolithiasis and congenital biliary tract abnormalities

associated with Caroli's syndrome such as choledochal cysts <sup>[1]</sup>. Cholangiocarcinoma (CCA)

is a fatal cancer of the biliary epithelium, arising either within the liver (intrahepatic) or in the extrahepatic bile ducts (extrahepatic). There are considerable geographic and demographic variations in the incidence of cholangiocarcinoma. Although it comprises only 10-15% of hepatobiliary neoplasms, its incidence is increasing <sup>[2]</sup>. However, cholangiocarcinoma remains a relatively rare disease accounting for <2% of all human malignancies <sup>[3]</sup>. Its prevalence also varies considerably from one region to another. According to recent literature, the prevalence of intrahepatic cholangiocarcinoma is increasing while that of extrahepatic cholangiocarcinoma remains constant or decreasing <sup>[3]</sup>. It is more common in men than in women, occurring most frequently between the 6th and 7th decades. Asians are affected almost 2 times more than whites and blacks. There are several established risk factors for CC including parasitic infections, primary sclerosing cholangitis, biliary-duct cysts, hepatolithiasis, and toxins. Other less-established, potential risk factors include inflammatory bowel disease, hepatitis C virus, hepatitis B virus, cirrhosis, diabetes, obesity, alcohol drinking, tobacco smoking, and host genetic polymorphisms <sup>[4]</sup>.

## Materials and Methods

This observational study was carried out in the Department of Surgery of GMC Budaun, a period of 2 years. The patients were taken up for the study from the indoor basis. Detailed history of the patient was taken. The patients were evaluated thorough Lyon the basis of exposure to risk factors, Hepato-Pancreato-Biliary pathologies and infections to HBV, parasites (liver fluke).

### Inclusion criteria

1. All types of Cholangiocarcinoma.
2. Age group above 40 year.
3. Patients admitted in Surgery department of GMC Budaun.
4. Newly diagnosed as well as old diagnosed cases.

### Exclusion criteria

1. Age below 40 years.
2. Outpatients who have diagnosed multiple surgery procedures or recently done another surgery.

### Statistical analysis

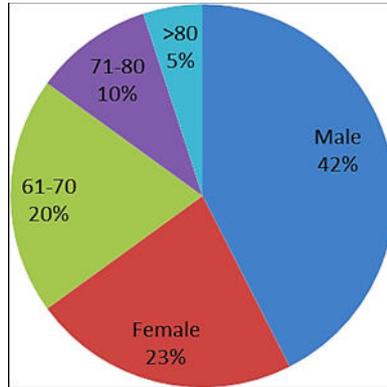
Collected data was compiled in MS excel sheet 2007 for analysis. SPSS version 20 software was applied. Qualitative data was represented in form of frequency and percentile.

### Results

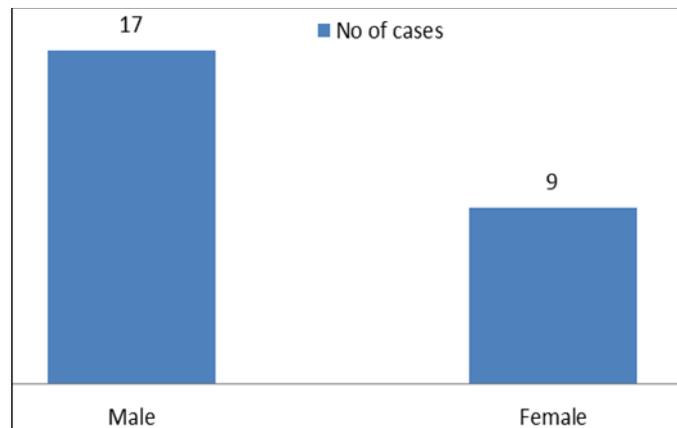
In present study out of the 80,028 patients studied, 26 patients were positive for cholangiocarcinoma with incidence of 0.032% in GMC Budaun. Cholangiocarcinoma is more common after 4th decade of life, in present study of 26 cases, peak incidence of Cholangiocarcinoma was found to be 4<sup>th</sup> to 6<sup>th</sup> decade of the life. The youngest patient was of 42years old and the oldest was of 85years with mean age of 61.92±11.61 years. Incidence in male was 65% and female is 35%, which suggest disease was more common in male patients with male to female ratio 1.9:1.

**Table 1:** Demography of the Subjects involved in the study

Age group (Years)	No of cases	Percentage %
40-50	8	31%
51-60	4	15%
61-70	8	31%
71-80	4	15%
>80	2	8%

**Fig 1:** Showing the demography of cases**Table 2:** Sex Distribution

Sex	No of cases	Percentage %
Male	17	65%
Female	9	35%

**Fig 2:** Sex Distribution**Table 3:** Socio-economic Class Distribution

Class	No of cases	Percentage %
Lower	0	0%
Upper Lower	7	27%
Lower Middle	14	54%
Upper Middle	3	12%
Upper	2	8%

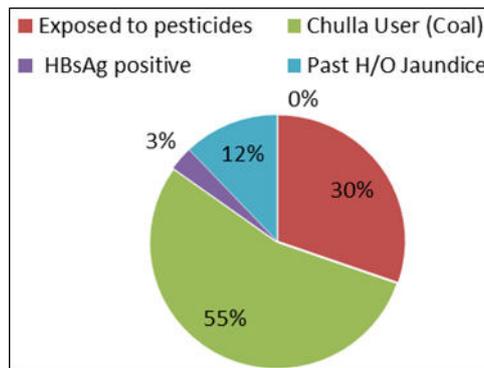


Fig 3: Class Distribution

Table 4: Occupation Distribution

Class	No of cases	Percentage %
Farmer	10	38%
Factory workers	3	12%
Labourer	3	12%
House wife	4	15%
Others	6	23%

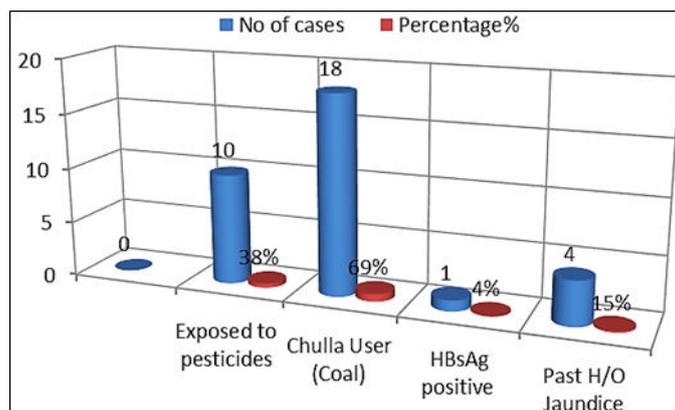


Fig 4: Occupation Distribution

In this study, Kuppuswami classification of socioeconomic status was used to stratify patients according to socioeconomic status. Patients were classified as per their education, occupation and income. As per this study most of the patients (54%) were from lower middle socioeconomic class with average education upto middle school. The present study shows that out of 26 patients of cholangiocarcinoma, majority patients were farmer 10 (38%) by occupation and 6 were having different occupations (23%). Thus farmers have high chances (38%) of cholangiocarcinoma as compare to others due to related risk factors Table 1, 2, 3, 4 and Fig-1, 2, 3, 4.

Table 5: Distribution according to the Co-Morbidities

Co-Morbidities	No of cases	Percentage %
COPD	4	15%
Diabetes mellitus	3	12%
Hypertension	3	12%
Bronchial Asthma(BA)	3	12%

Out of the 26 patients with cholangiocarcinoma, 13 patients had co-morbidities. Four (15%) had COPD and three (12%) had Diabetes Mellitus and Hypertension and Bronchial Asthma

(BA) as co-morbidities, as in Table-5.

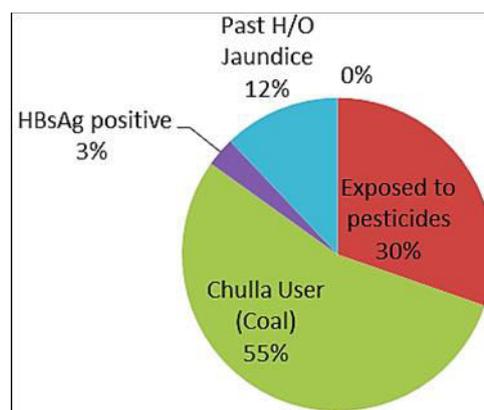
**Table 6:** Distribution of Cases according to Addictions and Frequency

Addictions	No of cases	Percentage %
Smoking	13	50%
Alcohol	3	12%
More than 10 years	12	92.3%
Smoking [n=13]	1	7.7%
No of Bidi and cigarettes smoking/day.	13	100%
More than 10 years		
Less than 10 years	0	0
Alcohols intake more than > 80 ml/day for 10years	3	100%
	0	0

Chances of cholangiocarcinoma is high in smokers (50%) as compare to non-smokers (42%) and in smokers, incidence of cholangiocarcinoma was more, with history of smoking more than 10 years (92%) as compare to smokers with history of smoking less than 10 years (7.7%). In present study, out of 26 patients 13 patients (50%) were smokers, out of that 13 patients all were smoking cigarette or bidi per day since more than 10 years, so chances of cholangiocarcinoma is high in smokers who smokes more than 10 cigarette or bidi per day (100%) as compare to smokers who smokes less than 10 cigarette or bidi per day. Three patients (12%) out of 26 patients were consuming alcohol more than 80 ml per day for more than 10 years.

**Table 7:** Distribution of patients according to Risk Factor associated with occupation.

Risk Factors associated with occupation	No of cases (N=26)	Percentage %
Exposed to pesticides	10	38%
Chulha User (Coal)	18	69%
HBsAg positive	1	4%
Past H/O Jaundice	4	15%
Cholelithiasis	8	31%



**Fig 5:** Distribution of cases according to risk associated with occupation

In our study, patients were studied for risk factors associated with their occupation for developing cholangiocarcinoma. Out of 26 patients, 10 were farmers and all of them were exposed to pesticides used in farm. All 10 patients were exposed to pesticides for more than 5 years. Thus, there are higher chances of cholangiocarcinoma in patients who are exposed to pesticides in farm. 18 patients were using chulha (69%) for cooking meals with coal as a primary fuel. Thus, all were exposed to fumes of coal which contains various chemicals which are risk factor for development of cholangiocarcinoma. Only 1 out of 26 patients was HBs Ag positive. Eight patients (31%) were having cholelithiasis which may be a possible

risk factor for cholangiocarcinoma. Four (15%) out of 26 patients having history of jaundice in past as in Table-7 and Fig-5.

## Discussion

We found an overall prevalence of intrahepatic cholangiocarcinoma of 7.7%; unfortunately, these patients were diagnosed at advanced stages. Smoking and primary sclerosing cholangitis were the positive risk factors for its development in this population. Cholangiocarcinoma is the second most common primary hepatic malignancy. Its outcome is poor and diagnosed in late stage of disease. CCA are rare tumors accounting 3% of all gastrointestinal tumors. Incidence of cholangiocarcinoma in worldwide was ranges between 0.01-0.2%<sup>[6]</sup>. In present study an incidence of cholangiocarcinoma was 0.032%, which is less than previous data. Considerable geographic and demographic variations in the incidence of cholangiocarcinoma were observed in the literatures. Male to female ratio of cholangiocarcinoma in previous study Parkin DM *et al.*<sup>[7]</sup> shows 2.2:1, whereas in present study the ratio of male to female was 1.9:1 which correlates with findings of previous study. Cholangiocarcinoma mainly occur after the 4th decade of life. In present study peak incidence of cholangiocarcinoma was 4th to 6th decade of life with youngest patient of 42 years and oldest being 85 years and mean age to be 61.92 years. In previous study by Tyson GL *et al.* cholangiocarcinoma is more common between 6th and 7th decade of life. Thus age incidence which is around 6th decade of life correlates with previous study. In present study, patients were stratified socioeconomically according to Kuppuswami classification of socioeconomic status and found that majority of the patients belong to lower middle socioeconomic class. In present study only possible risk factors were discussed. Out of 26 cases, 10 patients (38%) were farmer who were exposed to pesticides more than 5 years. Abhilash PC studied that more pesticides exposure causes more chances of immune suppression, hormone disruption, diminished intelligence, reproductive abnormality abdominal cancer. A vast majority of population in India is engaged in agriculture so more chances of exposure<sup>[8]</sup>. Study in Thailand for association between exposure of pesticides and cholangiocarcinoma was not statistically significant. Thus, present study has significant number of patients 40% exposed to pesticides may be a factor of developing CCA in this geographical area. In present study, out of 26 patients 13 patients (50%) were smoker and in those 13 patients 12 (92%) were smoking for more than 10 years and 13 patients (100%) were smoking more than 10 cigarettes or bidi per day. Xiao-Hua Ye *et al.* did meta-analysis and they assessed the association between smoking and the risk of CCA. Smokers had a 23% increased risk of CCA as compared with non-smokers<sup>[9]</sup>. Direct carcinogenic properties of smoking might be mediated by various metabolites generated in cigarettes including formaldehyde, benzene, and chromium. As early as the 1970s, it was suggested that tobacco compounds exert carcinogenic effects on the epithelial cells of the bile ducts as a result of exposure via blood flow<sup>[10]</sup> and this may underlie the relation between smoking and CCA specially ECC. Thus, smoking may be a one of the factor which is present in 50% of present study subject. In present study, 3 patients (12%) were alcoholic who has habit of taking more than 80ml of alcohol per day since more than 10 years. A study in China shows the association between alcohol consumption and the risk of developing CCA was positive but not significant. Alcohol enhances the activation of different pre carcinogenic elements. Therefore, alcohol may be associated with CCA mainly ECC via co-effects of different mechanisms<sup>[11]</sup>. Shaib YH *et al.* studied a dose-response relationship between alcohol consumption and CCA specially ECC was observed in one study, in which the risk of ECC development was higher in heavy drinkers who consumed at least 80g of ethanol per day<sup>[12]</sup>. Thus, heavy alcohol drinking may be one of the factor which is present in 12% of present study subjects. In present study, 8 out of 26 patients had cholelithiasis accounting for 31% study group signifying cholelithiasis as a possible risk factor which correlates with study of

Sheen Chen SM *et al.* reported 10-14% patients of cholangiocarcinoma having cholelithiasis which might be due to bile stasis. In present study, 26 cholangiocarcinoma patients were studied and their occupation related risk factor found and their association with CCA seen. Three patients out of 26 were suffering from diabetes mellitus accounting for 12% of total cases. Huxley R *et al.* study states significant association between DM and cholangiocarcinoma found in non-Asian region and Asian region<sup>[13]</sup>. Epidemiological studies have provided strong evidence that diabetes can increase the incidence of many types of cancer (including cancers of the breast, endometrium, non-Hodgkin's lymphoma, pancreas, and the liver). The results from Junshan Li *et al.* study suggests that diabetes may be a pathogenic factor for the development of cancer<sup>[13]</sup>. Studies have confirmed that insulin can stimulate growth of many malignant tumour cell lines, and thus up-regulate the level of IGFs<sup>[14]</sup>. Some studies have suggested that diabetes increases the incidence of CCA and level of IGF-1 associated with the development and progression of CCA<sup>[11, 15, 16]</sup>. Thus, DM may be a pathologic factor for the development of cholangiocarcinoma which is present in 12% of present study subjects. In present study of 26 cases, 2 patients (12%) were factory workers in different field like rubber factory and sugar factory and were exposed to asbestos. Giovanni Brandi *et al.* studied that asbestos fibers in the liver can give rise to a chronic inflammatory status with production of oxygen radicals, cytokines and growth factor leading to impaired cell proliferation and apoptosis. Thus, asbestos exposure may be one of the factor in present study subject. In present study, 18 patients (72%) were chulha user and all were exposed to fumes of burning coal which contains various chemicals which is dangerous to health. As Indian population use coal as their day to day activity, exposure to fumes of burning coal is increased. Fumes of coal contain various chemicals which is carcinogenic and increase chances of cancer development. As fumes of coal is similar to cigarette smoke may cause high chances of CCA. Thus, in particular geographical area there may be more chance 72% of development of CCA with exposure to fumes of burning coal.

### Conclusion

In conclusion, CCA was the second most prevalent primary malignant liver tumor in this our population. It is typically diagnosed at advanced stages, which reduces the patient's chances of survival. We found associations with PSC, smoking and alcohol consumption; however, further studies are needed to establish the risk factors in our country.

This study concludes that long term exposure to pesticides in patients, who are chronic smoker and exposed to smoke from chulha are at higher risk of developing CCA than others in this socio-economic scenario.

**Conflicts of interests:** None.

**Source of supports:** None.

### References

1. Khan SA, Thomas HC, Davidson BR, Taylor-Robinson SD. Cholangiocarcinoma. *Lancet* 2005;366:1303-1314.
2. Chung YE, Kim MJ, Park YN, Choi JY, Pyo JY, Kim YC *et al.* Varying appearances of cholangiocarcinoma: Radiologic-pathologic correlation. *Radiographics* 2009;29:683-700.
3. Tyson GL, El-Serag HB. Risk factors for cholangiocarcinoma. *Hepatology* 2011;54:173-184.
4. Carriage MT, Henson DE. Liver, gall bladder, extrahepatic bile duct and pancreas. *Cancer* 1995;75:171-190.
5. Parkin DM, Srivatanakul P, Khlat M *et al.* Liver cancer in Thailand. A case control study of cholangiocarcinoma. *Int J Cancer* 1991;48:328-8.
6. Abhilash PC, Singh N. Pesticide use and application: An Indian scenario. *J Hazardous*

- Materials 2009;165(1-3):1-12.
7. Xiao-Hua Ye, Jia-Ping Huai, Jin Ding, Yan-Ping Chen, Xue-Cheng Sun. Smoking, alcohol consumption and the risk of extrahepatic cholangiocarcinoma: A meta-analysis. *World J Gastroenterol* 2013;19(46):8780-88.
  8. Malik, R., Nandal, Naveen and Gupta, Prakhar. (2021), The Impact of online shoppers to price and quality: a survey study in Delhi-NCR, *Efflatounia*, 5 (2), pp. 376 – 389.
  9. Wynder EL, Mabuchi K, Maruchi N, Fortner JG. Epidemiology of cancer of the pancreas. *J Natl Cancer Inst* 1973;50:645-667.
  10. Moerman CJ, Bueno de Mesquita HB, Runia S. Smoking, alcohol consumption and the risk of cancer of the biliary tract; a population-based case-control study in The Netherlands. *Eur J Cancer Prev* 1994;3:427-436.
  11. Shaib YH, El-Serag HB, Davila JA, Morgan R, McGlynn KA. Risk factors of intrahepatic cholangiocarcinoma in the United States: a case-control study. *Gastroenterology* 2005;128:620-626.
  12. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A *et al.* Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer* 2005;92:2076-83.
  13. Junshan Li, Tianjie Han, Linlin Xu, Xiaotian Luan. Diabetes mellitus and the risk of cholangiocarcinoma: an updated meta-analysis. *Prz Gastroenterol* 2015;10(2):108-117.
  14. Lee J, Park SH, Chang HM *et al.* Gemcitabine and oxaliplatin with or without erlotinib in advanced biliary-tract cancer: a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol.* 2012;13:181-188.
  15. Welzel TM, Graubard BI, El-Serag HB *et al.* Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population- based case-control study. *Clin Gastroenterol Hepatol* 2007;5:1221-8.
  16. Grainge MJ, West J, Solaymani-Dodaran M *et al.* The antecedents of biliary cancer: a primary care case-control study in the United Kingdom. *Br J Cancer* 2009;100:178-80.
  17. Malker HS, McLaughlin JK, Stone BJ, Weiner JA, Ericsson JL, Blot WJ. Biliary tract cancer and occupation in Sweden. *Br J Ind Med* 1986;43:257-262.