

# Lifestyle, reproductive factors and risk of gallbladder cancer

Shukla V K, Chauhan V S, Mishra R N, Basu S

## ABSTRACT

**Introduction:** Lifestyle and dietary habits play an important role in carcinogenesis. Carcinoma of the gallbladder is no different. The present study was carried out to evaluate the roles of lifestyle, menstrual and reproductive factors in gallbladder cancer.

**Methods:** A prospective case-control study involving 78 newly-diagnosed cases of carcinoma of the gallbladder and 78 age- and gender-matched controls with cholelithiasis were investigated for their lifestyle history, with an emphasis on habits with chewing betel nut and tobacco, alcohol consumption and smoking. Besides this, female patients were investigated for their menstrual and reproductive factors. Odds-ratio and significance were calculated.

**Results:** A Hindu preponderance was seen. About half of the patients with carcinoma of the gallbladder and gallstone were either illiterate or had a very low level of education (primary or below). Religion, education, family income, chewing of tobacco as well as smoking were comparable. But numbers of chewing tobacco and smoking per day differed significantly. Alcohol was consumed by 11.6 percent of carcinoma and 4.1 percent of gallstone patients. Lower age of menarche, higher number of pregnancies and higher age at menopause had a significantly increased risk of gallbladder carcinogenesis. A significant difference in carcinogenesis was seen in the postmenopausal women compared with the menopausal group.

**Conclusion:** Carcinoma of the gallbladder was common in tobacco chewers. Females with lower age at menarche, higher number of pregnancies and childbirths and higher age at last childbirth had an increased risk of gallbladder cancer.

**Keywords:** biliary tract cancer, carcinogenesis, gallbladder carcinoma, lifestyle, reproductive factors

## INTRODUCTION

Carcinoma of the gallbladder is highly malignant with a poor survival rate.<sup>(1)</sup> There is a striking difference in incidence with regard to age, gender, race, genetic influence and geographical distribution.<sup>(2,3)</sup> Cholelithiasis is associated in 68%–98% of patients with carcinoma of the gallbladder,<sup>(4,5)</sup> and a high incidence among females suggest a role of female hormones in the aetiology of the disease.<sup>(6)</sup> Younger age at menarche, early age at first pregnancy, multiple pregnancies and prolonged fertility may increase the risk of biliary tract cancer because of elevated levels of oestrogen and progesterone.<sup>(7)</sup> Positive association between the number of live-births and carcinoma of the gallbladder has been found.<sup>(8)</sup> A significant association of early menarche and prolonged reproductive period has also been reported.<sup>(9)</sup> Chao and Greager demonstrated the postmenopausal state as a risk factor was associated with development of carcinoma of the gallbladder.<sup>(10)</sup> LaVecchia et al reported a higher risk of carcinoma of the gallbladder in pregnant women.<sup>(11)</sup>

Oral contraceptive use is however not associated with a higher incidence.<sup>(12,13)</sup> A chronic typhoid carrier state may be a predisposing factor for carcinoma of the gallbladder.<sup>(14)</sup> Higher incidence of this carcinoma is reported in relation to lifestyle factors like smoking, tobacco chewing and alcohol consumption.<sup>(15-17)</sup> A few studies have also emphasised the role of dietary factors in the aetiology of carcinoma of the gallbladder and biliary tract.<sup>(18)</sup> The present study was carried out with an aim to evaluate the roles of lifestyle, menstrual and reproductive factors in carcinoma of the gallbladder in the northern part of India.

## METHODS

A prospective case-control study was carried out at University Hospital, Banaras Hindu University, India, over a period of five years (1999–2003). 78 patients with gallbladder cancer (proven either on preoperative/peroperative biopsy or computed tomography [CT]- or ultrasound-guided fine needle aspiration cytology), were compared with 78 age- and gender-matched cholelithiasis cases without cancer which served as controls. The study was approved by the hospital ethics committee. Informed consent was obtained from the patients before inclusion in the study. Cases and controls were taken up consecutively and worked-up as per a predefined proforma designed to

Department of  
General Surgery,  
Institute of Medical  
Sciences,  
Banaras Hindu  
University,  
Varanasi 221005,  
India

Shukla VK, MS,  
MCh, FAMS  
Professor

Chauhan VS, MS  
Junior Resident

Basu S, MS  
Lecturer

Department of  
Community Medicine

Mishra RN, PhD  
Professor of  
Biostatistics

Correspondence to:  
Prof Vijay K Shukla,  
Tel: (91) 542 230 9512  
Fax: (91) 542 236 7568  
Email: vkshuklabhu@  
satyam.net.in

**Table I. Comparison of the demographics of patients with carcinoma of the gallbladder and those with gallstones.**

Demographic parameters	No (%) of cancer cases (n = 78)	No (%) of gallstone cases (n = 78)	Statistics		
			$\chi^2$	df	p
Religion			0.144	1	> 0.70
Hindu	61 (78.2)	59 (75.6)			
Muslim	17 (21.8)	19 (24.4)			
Education			0.744	1	> 0.30
Primary & below	56 (71.8)	51 (65.4)			
Middle & above	22 (28.2)	27 (34.6)			
Education of spouse			0.108	1	> 0.70
Primary & below	29 (37.2)	31 (39.7)			
Middle & above	49 (62.8)	47 (60.3)			
Monthly family income (Indian rupees)			0.964	1	> 0.30
≤ 3000	44 (56.4)	50 (64.1)			
> 3000	34 (45.6)	28 (35.9)			

**Table II. Dose-duration profile of tobacco chewers and smokers in gallbladder cancer and gallstone cases.**

Variable	Cancer (n = 78)	Gallstone (n = 78)	t-value	p-value
Tobacco chewing				
Age started (years)	26.2 ± 7.7	27.6 ± 9.3	1.024	> 0.30
Age stopped (years)	46.1 ± 6.6	43.7 ± 13.2	1.436	> 0.10
Number per day	8.9 ± 4.5	5.1 ± 3.2	6.078	< 0.001
Smoking				
Age started (years)	28.3 ± 11.5	25.7 ± 4.6	1.864	> 0.05
Age stopped (years)	43.2 ± 8.7	42.5 ± 9.7	0.474	> 0.70
Number per day	2.6 ± 1.5	1.8 ± 1.2	3.678	< 0.001

Data is expressed as mean ± SD

include various personal habits like tobacco chewing, smoking and alcohol consumption. Female patients were assessed for menstrual and reproductive factors, and details of parity. Minor details about the types of smoking and chewing were collected. Odds-ratio (OR) and 95% confidence interval (CI) were calculated, and tests of significance applied.

## RESULTS

The mean age of the patients with carcinoma of the gallbladder was 50 ± 1.39 years, and that for cholelithiasis without malignancy was 42.6 ± 1.03 years. Female patients comprised 68% of both the cancer group and gallstone group. A preponderance of the Hindu religion was found in both groups. Over half of the patients belonged to the low income bracket (below Rs 3,000 per month; USD 65), and about two-thirds had an education below or up to the primary school level (Table I). A statistical difference was observed for the average number of tobacco chewing and number of cigarettes per day (Table II). The habit of chewing tobacco in any form was present in 41.03% of patients with carcinoma of the gallbladder and in 21.79% of gallstone patients. The increase in risk was statistically significant in cancer patients who chewed tobacco (OR 2.50; 95%CI 1.24–5.05). An increased OR was seen with chewing tobacco (OR 2.71; 95%CI 1.22–6.02).

Statistically, there was an increased risk of carcinoma in patients who were smokers (Table III). The history of alcohol consumption was seen in 11 (11.6%) and 5 (4.7%) of cancer and gallstone patients, respectively. Four patients consumed country-made liquor. The cancer patients had started consuming alcohol at an early age and had consumed for a longer duration than the gallstone patients. Lower age at menarche (< 13 years), higher number of childbirths (> 4), higher number of pregnancies (> 4) and higher age at last childbirth (> 25 years) were factors responsible for a relatively increased risk of carcinoma of the gallbladder (Table IV). A higher risk was also observed in the postmenopausal women, and this was statistically significant.

## DISCUSSION

Since the original description of carcinoma of the gallbladder by Maxmillan de Stol in 1777, studies have established a characteristic pattern of late diagnosis and ineffective treatment of this disease. Its hallmark lies in the tenacity with which it keeps the initiation and progression a secret for quite some time. When detected, in most cases the disease has progressed beyond cure. This, coupled with its aggressiveness, makes it a potential killer. Carcinoma of the gallbladder ranks fifth in the incidence of gastrointestinal malignancy and represents three-quarters

**Table III. Chewing, smoking habits and risk of gallbladder cancer.**

Variable	No. (%) cancer cases (n = 78)	No. (%) gallstone cases (n = 78)	OR	95% CI
<b>Chewing</b>				
Betel leaf	18 (23.08)	15 (19.23)	1.26	0.58–2.72
Adding areca nut in chew	19 (24.36)	13 (16.67)	1.61	0.73–3.54
Tobacco	24 (30.77)	11 (14.10)	2.71	1.22–6.02
Adding lime in chew	22 (28.21)	15 (19.23)	1.65	0.78–3.49
Other condiments	7 (8.97)	5 (6.41)	1.44	0.44–4.75
Paan masala	6 (7.69)	5 (6.41)	1.22	0.36–4.17
Any form of chewing tobacco	32 (41.03)	17 (21.79)	2.50	1.24–5.04
<b>Smoking</b>				
Cigarette	6 (7.69)	3 (3.85)	2.08	0.50–8.65
Bidi	10 (12.82)	3 (3.85)	3.68	0.97–13.92
Cigar/churrute	4 (5.13)	3 (3.85)	1.35	0.29–6.25
Any form of smoking	17 (21.79)	8 (10.26)	2.44	0.98–6.05

**Table IV. Reproductive and menstrual factors in female patients with gallbladder cancer and gallstones.**

Factor	Cancer (n = 53)	Gallstones (n = 53)	OR	95% CI
<b>Age at menarche (years)</b>				
Mean ± SD	12.4 ± 1.3	14.2 ± 1.2	2.63 (age >13)	1.45–6.03*
Median	12	14		
<b>Age at marriage (years)</b>				
Mean ± SD	17.1 ± 2.9	18.1 ± 3.2	1.32 (age >18)	0.52–2.93
Median	17	18		
<b>Number of childbirths</b>				
Mean ± SD	6.1 ± 2.3	4.3 ± 2.4	3.69 (> 4)	1.6–9.6*
Median	6	4		
<b>Mean ± SD no. of abortions</b>				
	0.4 ± 1.1 (21 abortions in 11 women)	0.5 ± 1.1 (48 abortions in 27 women)	1.51 (>1)	0.461–3.92
<b>Number of times pregnant</b>				
Mean ± SD	7.1 ± 2.4	4.8 ± 3.3	6.15 (> 4)	1.7–21.3*
Median	6			
<b>Mean ± SD age (years)</b>				
At first childbirth	21.2 ± 2.9	22.3 ± 3.6	0.69 (age > 20)	0.39–1.9
At last childbirth	33.5 ± 6.9	28.4 ± 6.8	2.89 (age > 25)	1.21–7.69*
<b>Menstrual status</b>				
Premenstrual	20 (31.25)	70 (59.8)	0.30	0.13–0.66*
Postmenstrual	54 (84.3)	52 (44.44)	6.75	3.1–14.52*

\* statistically significant

of extrahepatic biliary tract carcinoma.<sup>(19)</sup> Although its exact aetiology is unknown, several risk factors have been proposed. Variant analysis has shown that gallstones form an important independent risk factor.<sup>(20)</sup> Gallstones were detected in 75% of surgical cases and 90% of autopsy cases with carcinoma of the gallbladder. Maran et al observed a 2–3 times higher frequency of gallbladder and biliary tract cancer in patients with cholelithiasis.<sup>(21)</sup> About 40%–100% cases of carcinoma of the gallbladder have been found to be associated with gallstones.<sup>(14,22)</sup> Metaplastic change of the gallbladder epithelium is present in chronic cholecystitis, as was found by Sheth et al, and was proposed to be a precursor of carcinoma.<sup>(1)</sup>

Previously-published data on the relationship of alcohol consumption and chewing tobacco with

gallbladder carcinoma is inconclusive. Some studies suggested an increased risk, while others suggested that long-term alcohol use may actually play a protective role, perhaps by reducing the cholesterol saturation of bile.<sup>(23,24)</sup> The risk of carcinoma of the gallbladder was increased in patients having a history of smoking in the present study, and it was particularly more in the patients who started smoking lately. Statistical analysis for patients with a history of alcohol consumption was not carried out due to their small numbers. This was because the majority of the carcinoma patients were females belonging to the lower/middle income class which in the Indian social setting rarely consume alcohol. Most of the rural women consume bidis (tobacco wrapped in tendu leaves). The smoking-related risk of gallbladder disease is highest soon

after the first exposure in women.<sup>(25)</sup> The risk of cancer was more than twice in patients who used to chew tobacco. An increased risk was however present in any kind of tobacco chewing, whether it is pan (lime, areca nut, catechu, betel leaf with tobacco), *khaini* (raw tobacco with lime) or *paan masala* (processed tobacco, catechu, areca nut and lime).

An increased risk of carcinoma of the gallbladder was seen in patients with lower age at menarche (OR 2.63), higher number of pregnancy (OR 6.15) and higher age at last childbirth (OR 2.89). All the results were statistically significant. Similar results have been reported earlier. Postmenopausal status was an increased risk of developing cancer (OR 6.75). Contrary to earlier results, premenopausal status probably had a protective role in the development of gallbladder cancer (OR 0.30). It is proposed that the lithogenicity of bile increases in pregnancy due to the effect of oestrogen and progesterone hormones, predisposing to gallstone formation and probably carcinoma of the gallbladder.<sup>(26)</sup> Human gallbladder contains both oestrogen and progesterone receptors, and this may explain the sensitivity of gallbladder tissue to these hormones.<sup>(27)</sup> Mean age at menarche was lower in carcinoma patients, as compared to the controls. Higher and prolonged exposure to female sex hormones (oestrogen and progesterone) may be a predisposing factor. Similarly, higher number of childbirths and higher age at menopause may predispose the gallbladder epithelium to prolonged effects of the female sex hormones and to carcinoma formation.

Lifestyle factors have been consistently found to be associated with most of the systemic malignant diseases. Carcinoma of the gallbladder is no different. Lifestyle modification, particularly abstaining from smoking and tobacco chewing, may go a long way to prevent carcinogenesis in the gallbladder. Studies have established the role of female sex hormones and menstrual status in benign gallbladder diseases. It may also have a similar predisposing role in carcinogenesis. In conclusion, results of this study indicate a probable role of tobacco chewing, smoking and other lifestyle factors in the causation of carcinoma of the gallbladder in the North Indian population. The menstrual and reproductive factors may also play an important role as aetiological factors of this deadly disease in the same ethnic group.

## REFERENCES

- Sheth S, Bedford A, Chopra S. Primary gallbladder cancer: Recognition of risk factors and the role of prophylactic cholecystectomy. *Am J Gastroenterol* 2000; 95:1402-10.
- Diehl AK. Epidemiology of gallbladder cancer. A synthesis of recent data. *J Natl Cancer Inst* 1980; 65:1209-14.
- Khan ZR, Neugut AI, Ahsan H, et al. Risk factors for biliary tract cancers. *Am J Gastroenterol* 1999; 94:149-52.
- Perpetuo MD, Valdivieso M, Heibrun LK, et al. Natural history study of gallbladder cancer: Review of 36 years experience at MD Anderson Hospital and Tumor Institute. *Cancer* 1978; 42:330-5.
- Siik YN, Douglass HO Jr, Nava HR, et al. Carcinoma of the gallbladder: The Roswell Park experience. *Ann Surg* 1989; 210:751-7.
- Sheih CJ, Dunn E, Standard JE. Primary carcinoma of the gallbladder: a review of the 16 year experience at the Waterbury Hospital Health Center. *Cancer* 1981; 47:996-1004.
- Moerman CJ, Berns MP, Beuno de Mesquita HB, et al. Reproductive history and cancer of the biliary tract in women. *Int J Cancer* 1994; 57:146-53.
- Lambe I, Trichopoulous D, Hsieh CC, Ekblom A, Adami HO, Pavia M. Parity and cancers of the gallbladder and the extra hepatic bile ducts. *Int J Cancer* 1993; 54:941-4.
- Singh S, Sharma LB, Ayub M, Gautam A, Shankarnarayan R, Singh TB, Shukla VK. Epidemiological study in gallbladder with gall stones. *Indian J Gastroenterol* 1997; 16 (Suppl 2) 118:A75.
- Chao TC, Greager JA. Primary carcinoma of the gallbladder. *Taiwan J Surg Oncol* 1996; 61:49-55.
- LaVecchia C, Negri E, D'Avanzo B, Franceschi S, Boyle P. Risk factors for gallstones disease requiring surgery. *Int J Epidemiol* 1991; 20:209-15.
- Yen S, Hsieh CC, MacMohan B. Extrahepatic bile duct cancer and smoking, beverage consumption, past medical history and oral contraceptive use. *Cancer* 1987; 59:2112-6.
- Zatonsky WA, Lowenfels AB, Boyle P, et al. Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH program of the International Agency for Research on Cancer. *J Natl Cancer Inst* 1997; 89:1132-8.
- Shukla VK, Khandelwal C, Roy SK, Vaidya MP. Primary carcinoma of the gallbladder. A review of 16-year period at University Hospital. *J Surg Oncol* 1985; 28:32-5.
- Dutta U, Garg PK, Kumar R, Tandon RK. Typhoid carriers among patients with gallstones are increased for carcinoma of the gallbladder. *Am J Gastroenterol* 2000; 95:784-7.
- Tseng M, Everhart JE, Sandler RS. Dietary intake and gallbladder disease: a review. *Pub Health Nutr* 1999; 2:161-72.
- Moerman CJ, Bueno de Mesquita HB, Smeets FWM, Runia S. Life style factors including diet and cancer of the gallbladder and bile duct: a population based case-control study in the Netherlands. *Eur J Cancer Prev* 1997; 6:139-42.
- Zatonski WA, LaVecchia C, Przewozniak K, et al. Risk factors for gallbladder cancer: a Polish case-control study. *Int J Cancer* 1992; 51:707-11.
- Vaittinen E. Carcinoma of the gallbladder: A study of 390 cases diagnosed in Finland 1953-1967. *Ann Chir Gynaecol (Suppl)* 1970; 168:71-8.
- Hart J, Madan B. Factors affecting survival of patients with gallbladder neoplasm. *Arch Intern Med* 1975; 129:931-4.
- Maran ES, Ludwig J, Kurland LT, Brian DD. Carcinoma of the gallbladder and extrahepatic biliary ducts in Rochester, Minnesota 1935-71. *Am J Epidemiol* 1979; 109:152-7.
- Piehler JM, Crichlow RW. Primary carcinoma of the gallbladder. *Surg Gynaecol Obstet* 1978; 147:929-42.
- Kato I, Nomura AM, Stemmerman GN, et al. Prospective study of the association of alcohol with cancer of the upper aerodigestive tract and other sites. *Cancer Causes Control* 1992; 3:145-51.
- Chow WH, Johnson C, Gridley G, et al. Gallstones, cholecystectomy and risk of cancer of the liver, biliary tract and pancreas. *Br J Cancer* 1999; 79:640-4.
- McMichael AJ, Baghurst PA, Scragg RK. A case control study of smoking and gallbladder disease: importance of examining time relations. *Epidemiology* 1992; 3:519-22.
- Nakagaki M, Nakayama F. Effect of female sex hormones on lithogenicity of bile. *Jpn J Surg* 1982; 12:13-8.
- Singletary BK, Van-Thiel DH, Eagon PK. Estrogen and progesterone receptors in human gallbladder. *Hepatology* 1986; 6:574-8.