

A study of demographic profile of carcinoma gall bladder in a Teaching Hospital, Varanasi

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Abstract

Introduction: Carcinoma of gall bladder is fifth most common malignancy of gastrointestinal tract. It accounts for 0.76% to 1.2% of all carcinomas and 5% of all carcinomas discovered at autopsy¹. It is more commonly seen in seventh decade of life and 90% cases occur above the age of 50. Females are at 4-5 times higher risk than males to develop this malignancy. In view of the high occurrence of carcinoma gall bladder in Varanasi and its adjoining areas to the tune of 0.76% to 1.2%,⁽²⁾ the investigators decided to carry out "A Clinico-epidemiological Study of Gall Bladder Carcinoma in SS Hospital, Varanasi."

Materials and Methods: A case-control Design was undertaken for the study, Seventy nine cases of gall bladder carcinoma matched in age and sex, preferably of the same family as control, were selected from one of the surgical unit of SS Hospital on the basis of snow ball sampling technique. It was decided to observe the personal and family profile of gall bladder carcinoma cases attending SS Hospital, Banaras Hindu University, Varanasi. It was objectified, to record the clinical features and presenting pattern of gall bladder carcinoma in SS Hospital, Banaras Hindu University, Varanasi and to compare the characteristics of gall bladder carcinoma to their matched control in the study area. The questionnaire cum interview technique was administered to collect the required information. The 24 hours food intake was recorded on the basis of recall method using Standardized Utensil Technique. Laboratory and histo-pathological investigations were carried out with the help of standard techniques employed for the same purpose. Statistical analysis was done as required using SPSS 16 version.

Observations: The Mean age \pm SD of the cases was observed as 50.19 \pm 09.45 as compared to the control as 50.44 \pm 08.89 (t = 0.171; DF = 15.6; P > 0.05, NS). The sex ratio of cases was observed as Male: Female Ratio was almost 1:5. Education wise there was no difference between cases and controls. Cases to the tune of 69.62 % were domestic workers and illiterate. Hindus accounted for 88.61% with a higher group from the General caste (57.53 %) category in both cases and controls. In the cases 62.03% were rural dwellers, 74.68 % had a monthly income between 500 to 1500 only, 54.43% were treated by modern medicine followed by quacks (43.04%), 45.57 % did not have any food fads or choice of taste, while age at menarche, age at first birth or age at first pregnancy, no of child birth or any Pregnancy related factors, did not show any significant difference in women patients.

Introduction

Carcinoma of gall bladder is a common malignancy of hepatobiliary tract and is fifth most common malignancy of gastrointestinal tract. In Varanasi it is third most common malignancy of gastro-intestinal tract, constituting 4.4% of all malignancies.⁽¹⁾ It accounts for 0.76% to 1.2% of all carcinomas and 5% of all carcinomas discovered at autopsy. It is more commonly seen in seventh decade of life and 90% cases occur above the age of 50. Females are at 4-5 times higher risk than males to develop this malignancy.⁽²⁾ Incidence of carcinoma of gall bladder varies greatly in different parts of the world.

High incidence is reported from Israelis, American Indians of Mexican origin and Japanese immigrants to USA. This geographical difference suggests the role of environmental, ethnic and genetic factors in the aetiopathogenesis of this dreaded disease². Parity, younger age at menarche and early age at first pregnancy have all been shown to increase the risk of gall bladder cancer in females.⁽³⁾

Among the predisposing factors for gall bladder carcinoma the presence of gall stones (70%) has been claimed as the major risk factor, which show a high

female to male ratio, an increasing incidence with age & identical variation among ethnic groups. Ulcerative colitis has a well-known association with biliary tract malignancy. Increased incidence is also reported in rubber industry & automobile workers⁽⁴⁾ Occupational exposure & experimental studies suggests the role of chemical carcinogens in its causation. Notable among them is 4-hydroxynoneal (HNE) which is produced by oxidative peroxidation of polyunsaturated fatty acids. Bile acids are tumor promoters and comutagens. Increased degradation of primary bile acids to secondary bile acids in gall bladder bile has been observed in patients with gall bladder cancer. Combination of bile stasis and bacterial infection of biliary system producing altered bile salts were thought to be related to carcinogenesis (Lowerfeh et al, 1970). An association of typhoid infection, carrier state & hepatobiliary cancer has also been noted (Axelrod et al, 1971). Risk of gall bladder cancer in typhoid carriers is six times higher than the risk of general population (Welton et al, 1979).

The clinical presentation of carcinoma gall bladder varies widely. It depends upon the stage of disease with which patient comes. Presentation also depends upon

pre-existing biliary symptoms. A noticeable change in the pre-existing biliary symptoms offers a valuable clue to the malignant transformation of a benign disease. Early carcinoma of gall bladder is usually asymptomatic. Vague symptomatology of carcinoma gall bladder makes early diagnosis of the disease a challenge to the physician (Chao and Greager, 1991). Usually symptoms arising from invasion of surrounding structures offers a clue to diagnosis (Shukla et al; 1985). It has been recorded that there may be history suggestive of cholecystitis 45% patients, palpable mass with jaundice in 60%, pain in 85%, weight loss in 15%, anorexia in 40% and nausea & vomiting in 24.7% of cases.

With the advent of newer facilities like histopathological study by FNAC, dynamic ultra-scanning, the accuracy rate of diagnosing gall bladder malignancy has gone up to 90%. Older diagnostic facilities like oral cholecystography and various cholangiographies are of little help in accurately diagnosing the lesions in early stages. Gross appearance of cancer gall bladder is of locally invasive lesion; frequently entire organ may be involved. It may appear thickened, lobulated, contracted or plastered into the liver. It may be filled up with pus, mucus or stones. Early carcinoma is usually found in fundus of gall bladder appearing as mucus irregularity, polypoid or discrete thickening of the wall. It is reviewed that there had been adenocarcinoma in 82.3% cases, undifferentiated carcinoma in 6.9%, squamous cell carcinoma in 3.3%, carcinoma in situ in 7% and mixed malignant lesion of epithelial origin in 1%. It is reported that there had been well differentiated adenocarcinoma in 57.3%, moderately differentiated in 19.1% and poorly differentiated in 13.1% cases (Ogura et al, 1991).

Keeping in view the high incidence of carcinoma gall bladder in Varanasi and its adjoining areas to the tune of 0.76% to 1.2% of all carcinoma (Shula et al, 1985), the investigators decided to carry out "A clinico-epidemiological study of gall bladder carcinoma in SS Hospital, Varanasi."

Institutional Objectives

- (1) To observe the personal and family profile of gall bladder carcinoma cases attending Sir Sunderlal Hospital, Banaras Hindu University, Varanasi.
- (2) To record the clinical features and presenting pattern of gall bladder carcinoma in the present study population
- (3) To compare the characteristics of gall bladder carcinoma to their matched control and find out the probable risk-factors for this disease in the study area.

Departmental Objectives

- (1) To study personal, familial and bi-social profile of gall bladder carcinoma patients and of controls matched by age and sex, attending Sir Sunderlal Hospital, Varanasi.

- (2) To record presenting physical complaints and history of any kind of associated complaints with present illness and account the nutrient intake of the cases and controls under study.
- (3) To know the type of treatment taken and investigations performed before coming to the apex hospital and thereafter.
- (4) To account the cost incurred on the treatment of the disease since beginning.

Selection of Area

The patients suffering from gall bladder carcinoma and attending one of surgical units of SS Hospital were considered for present study. The SS Hospital, of BHU is an apex hospital where the cases from the various medical institutions are referred for proper treatment of the illnesses and disabilities. The catchment area of this hospital are Uttar Pradesh, Bihar, northeast part of Madhya Pradesh of this country and southern part of neighbouring country Nepal.

Materials & Methods

The cases and controls were selected from one surgical unit of the above mentioned apex hospital for one year. Consisting of case-control nature of the "Experimental Design", seventy nine cases of gall bladder carcinoma matched by age and sex preferably of the same family as control, were selected, on the basis of hospital snow ball sampling technique.

The questionnaire cum interview technique was administered to collect the required information. In this context a fully structured and pretested questionnaire having all the relevant information was employed for this purpose. The 24 hours food intake was recorded on the basis of recall method. The utensils used by investigators were well compared with standardized measures. Laboratory and histo-pathological investigations were carried out with the help of standard techniques employed for the same purpose. Data was subjected to suitable statistical tools and information was concluded accordingly

Inclusion Criteria:

- (1) All the patients suffering from carcinoma gall bladder attending study desired surgical unit were included for present study.
- (2) The attendants or any family member accompanying the specific patients matched in age and sexes were considered as control cases.
- (3) In the absence of required attendants, the attendants of other diseases were also considered as control cases.

Exclusion criteria:

- (1) The patients, who were not co-operating to our study or did not sign the Helsinki declaration form of agreeing for study, were excluded from our study.

- (2) The patients, whose questionnaires were incomplete due to their death, lost to follow up or some other reasons were also excluded from the study.

Results and Discussion

The risk of gall bladder carcinoma is significantly more in females than male counter parts because of the pregnancy or associated cause and the major risk factors of gall bladder carcinoma are presence of gall stone, different gallbladder pathologies, dietary and hormonal factors including the Genetic reason. The present study is a part of a large study covering details of different aspects of study. The detail history of each patient regarding their age, sex, place of residence, socio-economic status was noted as mentioned in Performa. Main complaints of the patients were recorded in chronological order such as pain, jaundice, fever, weight loss, nausea and vomiting. Patients' dietary history was recorded by 24 hours recall method using standardized utensil technique. Personal history, obstetrical history in case of female patients, and all other history having association with gall bladder carcinoma were also recorded. Physical Examination was done in detail. The patient's general condition, degree of jaundice, mass per abdomen, ascitis and lymphadenopathy were documented All body systems like CNS, GIT, CVS were properly examined. The Investigations such as blood for Haemoglobin, Total & differential Leukocyte Count, Blood urea, Serum Cretanine, Serum K⁺ level, Serum Na⁺ level, Blood Sugar, Liver Function Tests, Serum Bilirubin, Total Protein ,Albumin, Globulin, A;G ratio, Serum Alkaline Phosphatase, SGOT, SGPT. All patients were subjected to Ultrasonography examination. Those accidentally diagnosed on operation or histology had their ultrasound. Findings were noted with regard to site of growth, presence of stones, lymph nodes at portahepatis and secondary's in liver and other sites. Some patients were examined by X-ray, CT scan or ERCP as per requirement. Cyto-histopathological examination of gall bladder mass.

Fine needle aspiration of gall bladder mass performed with 10ml disposable syringes and 22 G needle. Smears prepared were fixed in alcohol and stained with Papanicolaou or Haemtoxylin and eosin (H & E).

Following gross examination of cholecystectomy specimens or gall bladder biopsy, representative tissue pieces were taken and fixed in 10% formalin. After processing of tissues, blocking and preparation of H & E stained Paraffin section were prepared by Standard routine laboratory methods for histopathological evaluation of the gall bladder tissue. Grading of the gall bladder carcinoma was performed as follows:

Histologically carcinoma of the gall bladder was categorized as well differentiated (Grade-I), moderately differentiated (Grade-II) and poorly differentiated

(grade-III) adenocarcinoma depending upon the degree of glandular differentiation and nuclear anaplasia.

Details of treatment of each case were noted. Different mode of therapy-surgery, radiotherapy and chemotherapy were re-observed and recorded minutely. Responsiveness and unresponsiveness of different modes of treatment, dose of treatment, duration of treatment, and duration of recurrence were also recorded.

Table 1: Age wise distribution of the gall bladder carcinoma cases and controls

Age group (yrs)	Types of subjects			
	Gall Bladder Carcinoma		Control	
	No.	%	No.	%
<40	9	11.39	7	8.84
40-50	33	41.77	34	43.04
50-60	27	34.18	28	35.44
60-70	7	8.86	8	10.13
>70	3	3.80	2	2.53
Total	79	100.0	79	100.0
Mean±SD	50.19±09.45		50.44± 08.89	
Statistical Significance t = 0.171; DF = 15.6; P >0.05, NS				

The **Table 1** More than two fifth cases and controls belonged to age group 40-50 years, followed by 50-60 years. The mean ± SD ages of the cases and controls were ascertained 50.19±9.45 and 50.44± 8.89 years respectively. There was no significant difference between mean ages of the cases and controls (t=0.171; P.0.05; NS). Hence the cases of Gall Bladder Carcinoma (Ca GB) are more seen at the 4th through 6th decade of life and with higher predilection for females (**Table 2**).

Table 2: Sex wise distribution of the gall bladder carcinoma cases and controls

Sex	Matched Patients/Controls		Remarks
	No.	%	
Male	13	16.46	Male: Female Ratio 1: 5.08
Female	66	83.45	
Total	79	100.00	

Majority of the cases and controls (83.54%) belonged to female sex, while male subjects contributed 16.46% only. The occurrence or case reporting of gall bladder carcinoma was found five times higher in females than their male counter-parts (M : F=1:5). Majority of the subjects (68.35%) belonged to illiterate group (**Table 3**). The history of educational status of the patients and controls was found statistically similar ($\chi^2 = 0.116$; DF=1; P>0.05; NS). Most of them were either agricultural workers or business people.

Table 3: Educational status of the gall bladder carcinoma cases and controls

Education al status	Type of subjects				Total	
	Patient		Control			
	No	%	No	%	No	%
Illiterate	55	69.62	53	67.08	108	68.35
Educated	24	30.38	26	32.01	50	31.62
Total	79	100.00	79	100.00	158	100.00

Statistical Significance $\chi^2 = 0.116$; DF = 1; P>0.05; NS

These people eat packed food from home after a time lag. This might be exposing to some fermentation or infection which might be leading to Ca GB (**Table 4**). However it cannot be too emphatically predicted from the present study and separate food study need to be undertaken. However, majority of the cases and controls belonged to domestic occupation (69.62%), followed by business (16.46%). Male patients were mainly from agriculture (46.15%) while females were busy in their traditional domestic work (**Table 4**).

Table 4: Sex and occupation wise distribution of gall bladder carcinoma cases

Type of Occupation	Sex of the cases				Total	
	Male		Female			
	No.	%	No.	%	No.	%
Service	3	23.08	02	3.03	05	06.33
Agriculture	6	46.15	-	-	06	07.59
Business	4	30.77	09	13.64	13	16.46
Domestic Work	-	-	55	83.33	55	69.62
Total	13	100.0	66	100.0	79	100.0

Hindus showed a higher reporting of Ca GB than Muslims, may be due to their higher health seeking behavior. Never the less this observation was not statistically significant. (**Table 5**)

Table 5: Details of religion of the gall bladder carcinoma cases and controls

Religion	Type of subjects				Total	
	Patients		Controls			
	No.	%	No.	%	No.	%
Hindu	70	88.61	73	92.41	143	90.51
Muslim	09	11.39	06	07.59	15	09.49
Total	79	100.0	79	100.0	158	100.0

Statistical Significance $\chi^2 = 0.663$; DF = 1; P>0.05; NS

More than half of the patients and controls (59.44%) belonged to general group of upper castes, followed by other backward caste (37.06%). The caste structure of Hindu cases and controls was statistically similar ($\chi^2 = 0.319$; DF=2; P>0.05; NS.) The significant difference again points out for high health conscious behavior of the general caste people (**Table 6**).

Table 6: Caste structure of Hindu subjects of gall bladder carcinoma cases and controls

Caste Structure	Type of subjects				Total	
	Patient		Control			
	No.	%	No.	%	No.	%
SC/ST	02	02.86	03	04.11	5	03.50
OBC	25	35.71	28	38.36	53	37.06
Others	43	61.43	42	57.53	85	59.44
Total	70	100.0	73	100.0	143	100.0

Statistical Significance $\chi^2 = 0.319$; DF = 2; P>0.05; NS

More than three fifth subjects (63.92%) were residents of rural areas, followed by semi-urban (25.95%). The places of residence of patients (**Table 7**) and controls were found statistically similar ($\chi^2 = 0.363$; DF = 2; P>0.05; NS).

Table 7: Residential status of the gall bladder carcinoma cases and controls

Place of Residence	Type of Subjects				Total	
	Patient		Control			
	No.	%	No.	%	No.	%
Urban	09	11.39	07	08.86	16	10.13
Semi-Urban	21	26.58	20	25.32	41	25.95
Rural	49	62.03	52	65.82	101	63.92
Total	79	100.0	79	100.0	158	100.0

Statistical Significance $\chi^2=0.363$; DF =2; P>0.05: NS

The mean per capita monthly income of the study subjects was ascertained to be Rs. 1129.75±554.17. There was no significance difference in mean of per capita monthly incomes (Table 8) of the patients and controls (t = 0.286; DF = 156; P> 0.05; NS).

Table 8: Details of per-capita monthly income of gall bladder carcinoma cases and controls

Income Group (Rs.)	Type of Subjects				Total	
	Patient		Control			
	No.	%	No.	%	No.	%
< 500	06	07.59	05	06.33	11	06.96
500-1000	31	39.24	29	36.71	60	37.98
1000-1500	28	35.44	30	37.98	58	36.71
1500-2000	08	10.13	09	11.39	17	10.76
2000-2500	03	03.80	04	05.06	07	04.43
> 2500	03	03.80	02	02.53	05	03.16
Total	79	100.0	79	100.0	158	100.0
Mean± SD	1123.42± 557.40		1148.73± 554.41		1129.75± 554.17	

Statistical Significance t = 0.286; DF =156; P> 0.05; NS

As per Table 9, more than half (54.43%) of the patients availed treatment from modern medicine practitioners, still the input of quacks was to the tune of 43.04%. In this regard multiple responses were obtained.

Table 9: Types of treatment availed by the patients before admission to SS Hospital (N=79)

Types of Treatment®	No. (n=79)	%
Quacks	34	43.04
Homeopathy	08	10.13
Ayurvedic	07	08.86
Modern	43	54.43

Table 10: Duration of treatment availed by the patients before admission to SS Hospital

Duration of treatment (months)	Patients		Remarks
	No.	%	
<3	31	39.24	Mean ± SD duration 5.49±4.10 months.
3-6	17	21.52	
6-9	12	15.19	
9-12	12	15.19	
>12	07	08.86	
Total	79	100.0	

More than one third (39.24%) patient took treatment for less than 3 months, followed by 3-6 mths (21.52%). The mean duration of treatment was ascertained to be 5.49±4.10 months. In other words, majority of the patients did lost a long duration in trying to get treated at other sources and there by lingering the disease period and exposing the condition to be more sever (Table-10).

Table 11: Amount of money spent on treatment before admission to SS Hospital

Amount of money spent	Patients		Remarks
	No.	%	
<500	38	48.10	Mean± SD amount of money spent = Rs.7680.99± 6900.80.
5000-10000	22	27.85	
10000-15000	07	08.86	
15000-20000	05	06.33	
20000-25000	04	05.06	
25000-30000	03	03.80	
Total	79	100.0	

The cost of expenditure also increased by the delay in treatment. Nearly half of the patients (48.10%) spent less than Rs. 500/- on the treatment. The mean amount of money spent on the treatment was accounted Rs. 768.99 ± 690.80 (Table 11). The higher standard division shows that there is hardly any difference

between the ranges, in other words the expenditure is approximately around Rs 8000/in most cases.

More than half of the patients (54.43%) used to like tasty, spicy, fatty or salty food items, while 67.09% of the controls used to like normal ordinary diet. The diet,

as per table 12, of the patients was found significantly different ($\chi^2=9.480$; DF=1; $P<0.01$) (Table 12).

Table 12: Details of food liking of the gall bladder carcinoma cases and controls

Types of foods liked	Type of Subjects				Total	
	Patient		Control		No.	%
	No.	%	No.	%		
Salty	03	03.80	01	01.27	04	02.53
Tasty	21	26.58	08	10.13	29	18.35
Spicy	10	12.66	07	08.86	17	10.76
Fatty	09	11.39	10	12.66	19	12.03
Normal	36	45.57	53	67.09	89	56.33
Total	79	100.0	79	100.0	158	100.0

Statistical Significance $\chi^2=9.480$; DF = 1; $P<0.01$ ®

The patients of gall bladder carcinoma were habituated with smoking (35.44%), tobacco chewing (22.78%), alcohol (21.52%), chewing of betel quid (16.46%) and pan masala (10.13%). Various habits of addiction were found statistically similar in patients and controls. ≠Multiple responses were obtained (Table 13).

Table 13: Habit of addiction of the subjects

Number of Addiction	Type of Subjects						
	Patients (n=79)		Controls (n=79)		Total (n=158)		
	No.	%	No.	%	No.	%	
Chewing Betel Quid	13	16.46	11	13.92	24	15.19	Z= 0.45,P>0.05, NS
Use of Pan Masala	08	10.13	04	5.06	12	07.59	Z=1.28,P>0.05, NS
Tobacco chewing	18	22.78	14	17.72	32	20.25	Z=0.79,P>0.05, NS
Smoking	28	35.44	29	36.71	57	36.08	Z=1.67,P>0.05, NS
Alcohol	17	21.52	03	03.80	20	25.32	Z= 0.81,P>0.05, NS

Table 14: Positive family history in study subjects

Family History	Type of Subjects				Total	
	Patient		Control		No.	%
	No.	%	No.	%		
Positive	21	26.58	05	06.33	26	16.46
Negative	58	73.42	74	93.67	132	83.54
Total	79	100.0	79	100.0	158	100.0
Statistical Significance	$\chi^2= 11.786$; DF = 1; $P<0.001$. Highly significant					

The details of risk and additional risk factors have been shown in Tables 15 & 16. Nearly one fourth patients (26.58%) gave the history that some member of their families suffered with gall bladder carcinoma, on the other hand only 6.33% controls had positive family history of the disease. There was significant association between family history and type of subjects ($\chi^2= 11.786$; DF = 1; $P<0.001$).

Table 15: Details of risk factors and Odd's ratios

Description		No. of Cases	No. of Controls	Crude Odd's Ratio	95% CI
Sex	Male	13	13	1.00 (Matched controls were taken)	
	Female	66	66		
Occupation	Agriculture	06	06	1.00 (Matched controls were taken)	
	Non-Agriculture	03	03		
Educational Status	Illiterate	55	53	1.124	0.16-2.20
	Literate	24	26		
Religion	Other than Hindu	09	06	1.564	0.144-4.62
	Hindu	70	73		
Family History	Present	21	05	5.359	1905-15.07
	Absent	58	74		
Type of Food	T Normal	45	63	2.975	1.467-6.03
	Salty/Spicy/Tasty	34	16		
Chewing betel Quid	Yes	13	11	1.218	0.385-2.91
	No	66	68		

It was observed that the risk occurrence of gall bladder carcinoma increases five times with positive family history (COR= 5.359; 95% CI= 1.905 to 15.073).⁽²⁾ The factors like educational status, religion and chewing of betel quid had no role for the occurrence of the disease. The early age of menarche, marriage, pregnancy and first birth by the woman subjects increased the risk of gall bladder carcinoma twice to 13 times in comparison to their counterparts. In addition number of births and abortion were also found responsible to enhance the risk of the disease many folds. Almost similar observations were also made by Shkula et al⁽¹⁾ and Tiwari et al⁽³⁾ may be due to that fact both those studies were also conducted in the same hospital chattering the same population. This signifies that the demographic pattern of Ca GB has not changed in hospitals since 1994. It is high time serious Cancer Counseling Centers are opened in these apex hospitals to spread the message how cancer can be prevented.

Table 16: Additional risk factors in female subjects and Odd's ratio

Description		No. of Cases	No. of Controls	Crude Odd's Ratio	95% CI
Age at Menarche	≤13 yrs	29	22	1.568	0.210-3.18
	≥14 yrs	37	44		
Age at Marriage	≤17 yrs	45	24	3.750	1.117-4.57
	≥18 yrs	21	42		
No. of pregnancy	≥4	59	21	18.061	2.597-46.26
	≤3	07	45		
Age at first Birth	≤18 yrs	44	31	2.258	1.117-4.57
	≥19yrs	22	35		
No. of Births	≥4	53	15	13.862	6.006-31.99
	≤3	13	51		
No. of abortions	Aborted	57	15	21.533	8.679-53.43
	Nil	09	51		

Reference

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