Original Article-II

Risk Factors for Gallbladder Cancer : A Population Based Case-Control Study in Delhi

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ABSTRACT

Background: **Gallbladder (GB) cancer ranks among the first five common cancers in females in Delhi, India. The incidence rate of GB carcinoma is higher in North India compared to South India.**

Methods: **A population based case-control study on 333 GB incident cases was carried out in Delhi to identify the risk factors. Cases were matched with two controls based on age (± 5 years), sex and marital status (in case of females)**

Results: **Smoking and alcohol consumption increase the risk of GB cancer. The risk among those who smoke cigarette (OR=3.05, CI=1.33-6.98) was higher than that seen among bidi smokers (OR=2.25, CI=1.38-3.69). History of typhoid in the past and cholelithiasis increased the risk of GB cancer. Post menopausal women had a significant risk of GB cancer than the menstruating women. Consumption of urad dhal, moong dhal, milk, cottage cheese and butter also increased the risk of GB cancer.**

Conclusion: **Smoking, alcohol consumption, typhoid in the past, cholelithiasis and certain dietary items are the some of the most important risk factors for gallbladder cancer.**

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INTRODUCTION

Cancer of Gallbladder (GB) is a rare neoplasm with varying demographic distribution in different parts of the world. Though this type of cancer is uncommon in US and and Europe, it is more common in Chile, Peru, Japan and Korea.[1] In India, cancer of GB shows varying geographic distribution, as the incidence is much higher in Delhi population as compared to South India.[2] Detailed analysis shows an increasing trend in the incidence rate of this cancer in the urban population of Delhi. The age adjusted incidence rate which was 1/100,000 in males and 3.3/100,000 in females in the year 1987 gradually increased to 3.9/100,000 in males and 9.0/100,000 in females in 1996. Comparison of the data from the various population based cancer registries in India indicates that it is common in Northern India. Epidemology studies demonstrate a close association between GB cancer and gall stone.[3-9] The incidence of GB cancer parallels the prevalence of gallstone disease; large and longstanding gallstones being associated with a higher risk of GB carcinoma.[10] The risk of GB carcinoma in patients with gallstones has been reported to have increased four to seven times.[11,12] The strength of this relationship varies considerable between various ethics groups. Even though ethnic and geographic variation in the incidence of gallstone is well known, the cause of gallstone formation is obscure. Now progress has been made in understanding the process of gallstone formation. Researchers believe that gallstones may be caused by a combination of factors, including inherited body chemistry, body weight, GB motility (movement), and perhaps

diet. Cholesterol gallstones develop when bile contains too much cholesterol and not enough bile salts. Besides gallstone, the other only strong risk factor observed for GB cancer was obesity[10,13,14]. Hereditary, diet and environmental factor are other risk factors, which need to be studied to elucidate the underlying chances of developing the disease. To provide further information in this issue a case-control study on GB carcinoma was conducted in Delhi.

METHODS

This study was conducted between 1st April 1997 and 31st July 2001. Cancer cases were defined as the newly diagnosed and resident cases of Delhi for more than 1 year identified through the Delhi Population Based Cancer Registry. The diagnosis was confirmed through histological or cytological examination. For each case two controls were taken. One control was a healthy neighborhood whereas the second was the healthy relative of the patients. If the healthy relative was not available then another healthy neighborhood control was taken. Controls were matched to cases by ± 5 years of age, sex and marital status (in case of females only).

The cases and control were interviewed in Hindi by trained social investigator using standard questionnaire. The interviewers were intensively trained by the senior staff of the registry for one month in abstracting information, medical terminology etc. The training level was compared using Kappa Statistic and it was 0.8.

A pilot study was conducted and anomalies found in the questionnaire were removed and the questionnaire was revised.

The variables included in the questionnaire were demographic characteristics, medical history, marital history, history of past/present illness, family history of cancer, life style factors, reproductive history and diet presumed to be risk factor for gall bladder cancer. Numerous food and beverage items that were commonly consumed among Delhi population (either daily or weekly or monthly or rarely) were included in the questionnaire and were evaluated using dietary recall method. The food items that were evaluated as potential risk factors for gall bladder cancer are beef, meat, chicken, green vegetables, bread, rice, wheat, milk, coffee, tea, bear, others liquors, carrot, citric fruit, other fruits and other types of food items like dhal, sweets various types of oil etc.

All the cases were interviewed as soon as they were diagnosed, either in the hospital itself or in their home. The same interviewer interviewed both the cases and controls.

Standard measurements were used to elicit information about the quantity of dietary items consumed. The measurements used were Katori/bowl (contains 200 gm of food items) teaspoon, tablespoon, cup and glass.

Frequencies were obtained for all variables, and cross tabulations for each potential risk factor versus case control status were made. The unadjusted conditional odds ratio (OR) was used as the measure of association between variables of interest and GB cancer.[15] Multivariate logistic regression analysis was also performed.[16] Statistical significance was assessed using 95% confidence intervals (CI) along with p-values. The data were analyzed using SPSS software.

RESULTS

This study population consisted a total of 999 persons with 333 GB cancer cases and 666 controls. Their distribution by matching and other variables that were included in the study are shown in table 1. As expected the majority of case patients were women and most were middle aged or older.[17-20] Majority of cases and controls were Hindus, illiterate and the total monthly family income was more than five thousand rupees.

HISTORY OF PAST/PRESENT ILLNESS

To examine history of past/present illness the following variables were evaluated: typhoid, hepatitis, amoebiasis, other liver diseases, TB, peptic ulcer, diabetes, GB diseases, Pancreatic

Table-1: Distribution of Cases and Controls by Age, Sex, Education, Religion and Income

	Cases		Controls		P - value
	No.	%	No.	%	
Age					
< 40					
40 – 45	26	7.8	60	9.0	
45 – 49	35	10.5	73	11.0	
50 – 55	42	12.6	73	11.0	
55 – 59	47	14.1	117	17.5	
60 – 64	52	15.6	113	17.0	
65 – 69	46	13.8	94	14.1	
70 & above	47	14.1	52	7.8	0.10
Sex					
Male	91	27.3	182	27	
Female	242	72.7	484	73	1.00
Religion					
Hindu	287	86.2	604	91.0	
Muslim	28	8.4	37	5.6	
Christian	1	0.3	3	0.5	
Sikh	16	4.8	2	0.3	
Others	1	0.3	0	0	0.00
Education					
IIIiterate	120	36.0	204	30.6	
Literate	49	14.7	129	19.4	
Primary	54	16.2	132	19.8	
Middle	39	11.7	73	11.0	
High School	34	10.2	84	12.6	
Technical & Above	37	11.1	44	6.6	0.02
Monthly income (in rupees)	88	26.0	202	30.3	
<3000	93	28.0	153	23.7	
3000-5000	152	46.0	311	47.0	0.33
5001+					

diseases, Heart diseases, hypertension and family history of other diseases. The odds ratio of history of typhoid in the past (Table 2) was predictive of GB cancer (OR = 8.92, CI=5.0-15.9) p<.001. Though there was an increased risk of GB cancer in persons with family history of GB cancer, it was not significant p<.06. There was an elevated risk for GB cancer for the patients with cholithaiasis (OR =446.56, CI =107.88-2629.15) , p<.001.

Lifestyle Habits (chewing, smoking, drinking)

The data in table 3 indicate the risk associated with the life style factors like smoking, drinking and chewing.

Table 2 History of past or present illness and risk of Gallbladder cancer

Variable	Cases	Controls	OR (95% C.I)	p-value
History of typhoid				
No	226	645	1	
Yes	67	21	8.92 (5.0 - 15.9)	<0. 001
Family history of Gall bladder cancer				
No	325	660	1	
Yes	8	6	2.94 (0.95 - 9.10)	0.061
Cholelithiasis				
No	142	664	1	
Yes	191	2	446.56 (107- 2629)	<0.001

Smoking

For smoking odds ratio were calculated using non smokers as reference group. The ever smokers had increased risk of GB cancer (OR=2.38, CI=1.54-3.66) p<.001. The OR of past smokers was higher than the current smokers. Among the type of smoking-both cigarette (OR=3.05, CI=1.33-6.98) and bidi smokers had (OR=2.25, CI=1.38-3.69) significantly increased risk of GB cancer. Also an increased risk of GB cancer was observed among the current cigarette and bidi smokers than the past smokers.

Drinking Alcohol

Alcohol consumption habit was significantly associated with the risk of GB cancer (OR =2.40, CI =1.32 - 4.36). Past drinker had higher risk of GB cancer (OR= 31.32, CI= 4.03-4.36), p<.001. No consistent pattern was evident which type of alcohol increased the risk. All types had elevated odds ratio except beer, with wine showing the highest odds ratio (4.25).

Chewing

The OR was calculated using non-chewers as reference category. Non significant elevated risk was seen for the habit of chewing (OR = 1.51, CI =0.85 - 2.67), p=.164.

Reproductive history

There was an increase in risk of GB cancer as there was an increase in the age at menarche but the association was not statistically significant (Table 4). Also the menopausal women had a significant risk of GB cancer than the menstruating women (OR = 3.17, CI =1.56-6.47), p<.001.

As the numbers of abortions increased, there was an increased risk of GB cancer but the relationship was not statistically significant. Similarly there was an increased risk of GB cancers with higher no of pregnancies.

Dietary habits

Various dietary items that were commonly consumed were evaluated. A significant reduction in odds ratio was seen with the consumption of channa (OR=0.5, CI=0.33 – 0.75), brinjal (OR=0.49, CI=0,30 - 0.80) and bhindi (OR=0.52, CI=0.33 – 0.82). On the other hand a statistically significant increase in odds ratio was observed with consumption of urad dhal (OR=2.07, CI=1.52 – 2.82), moong dhal (OR=1.54, CI=1.12-2.11), milk (OR=1.45, CI=1.06-1.99), cottage cheese (OR=1.85 CI=1.09-3.13), butter (OR=4.06, CI=1.98-8.32), curd (OR=1.53, CI=1.05-2.24), mustard leaves (OR=3.92, CI=1.72-8.93), tamarind (OR=1.82, CI=1.07,3.08), papaya (OR=1.43, CI=1.01-2.03), pineapple (OR=1.70, CI=1.00-2.90) and pomegranate (OR=2.72, CI=1.35-5.46). Table-5 presents the list of

Table 3 Life style factors and risk of Gallbladder cancer

Variable	Cases	Controls	OR 95%	p-value
Smoking				
No	252	580	1	
Yes	81	106	2.38 (1.54 - 3.66)	<.001
Current Smoking				
No habit	252	560	1	
Yes	63	99	1.94 (1.23 - 3.06)	<.001
No	18	7	7.48 (2.88-19.41)	<.001
Type of smoking				
No	252	580	1	
Cigarette	14	17	3.05 (1.33 - 6.98)	0.008
Bidi	49	70	2.25 (1.38 - 3.69)	0.001
Pipe	4	3	2.86 (0.64 -12.87)	0.17
B+C	11	9	4.51 (1.68 -12.06)	0.003
Others	3	7	1.09 (0.27 - 4.29)	0.907
Cigarette				
No	252	580	1	
Current	25	26	3.46 (1.72 - 6.98)	<0.001
Past	56	80	2.15 (1.37 - 3.39)	<0.001
Bidi				
No	252	560	1	
Current	60	79	2.39 (1.50 - 3.83)	<0.001
Past	21	27	2.33 (1.23 - 4.40)	0.009
Age started smoking				
No	252	580	1	
<20	13	22	1.76 (0.77 - 4.02)	0.178
20-24	28	41	2.13 (1.13 - 4.01)	0.019
25+	40	43	2.8 (1.62 - 4.80)	<0.001
Alcohol				
No	294	618	1	
Yes	39	48	2.4 (1.32 - 4.36)	0.004
Alcohol drinking				
No	294	618	1	
Current	25	45	1.58 (0.82 – 3.05)	0.175
Past	14	2	31.32 (4.03 – 243.0)	<0.001
Chewing				
No	306	626	1	
Yes	27	40	1.51 (0.85 - 2.67)	0.164

dietary items that showed significant increase in odds ratio on consumption. Though rice, wheat, masoor dhal, beans, capsicum, green peas, mushroom, sulgum, red chilly, sweets, orange, fish, beef, mutton, chicken, groundnut oil, mustard oil, palm oil, sunflower oil and coffee increase the risk of GB cancer the difference was not statistically significant.

Table 4 Reproductive history and risk of Gallbladder cancer

Variable	Cases	Controls	OR	95% Cl	p-value
Age at menarche (in years)					
<13	5	12	1		
13	120	243	1.22	(0.28 - 5.42)	0.792
14	91	205	1.10	(0.24 - 4.97)	0.901
>14	6	11	1.40	(0.23 - 8.39)	0.715
Unknown	20	13	5.41	(1.01-29.01)	0.049
Whether still menstruating					
Yes	58	147	1		
No	184	337	3.17	(1.56 - 6.47)	0.001
Number of abortions					
0	195	411	1		
1	31	59	1.31	(0.81 - 2.12)	0.272
2	10	19	1.14	(0.50 - 2.58)	0.755
3+	6	4	3.11	(0.87-11.04)	0.080
Number of pregnancies					
1	4	9	1		
2	11	56	0.39	(0.09 - 1.67)	0.204
3	31	101	0.66	(0.17 – 2.53)	0.544
4	56	115	1.13	(0.31 – 4.13)	0.859
5	54	83	1.55	(0.41 - 5.84)	0.515
6	29	44	1.74	(0.45 - 6.75)	0.421
7	21	32	1.80	(0.45 - 7.12)	0.403
8	16	18	2.26	(0.53 - 9.68)	0.272
9	6	12	1.66	(0.34 - 8.19)	0.534
10+	14	14	3.11	(0.69 - 4.01)	0.140

Weight

There was an inverse relationship between the weight of person in kilograms and risk of GB cancer (table 6). As the weight increase (>60 kgs), the risk of GB cancer decreases and it was statistically significant. There was no relationship between the Quit let's index and GB cancer.

Multivariate Analysis

Regression analysis (Table 7) showed typhoid in the past topped the list of risk factors for development of GB cancer followed by butter and mustard leaves. Patients who had typhoid in the past had 9 times increased risk of GB cancer (OR=9.12, CI=4.6-18.08). Smoking, alcohol, consumption of pomegranate, urad dhal and radish were other risk factors for development of GB cancer. Channa and bhindi have protective factor.

DISCUSSION

Typhoid in the past was found to be one of the important risk factors for the development of GB cancer in the current study. Some other studies also confirmed the relationship between physician diagnosed typhoid and GB carcinoma[17,21] Chronic *S. typhi* infection can be

Table 5 Dietary variables as risk of Gallbladder cancer

Variable	Cases	Controls	OR 95% C.I	p-value
Urad dhal				
No	112	319	1	
Yes	221	347	2.07 (1.52 - 2.82)	<0.001
Moong dhal				
No	95	242	1	
Yes	238	424	1.54 (1.12 - 2.11)	0.007
Channa				
No	80	109	1	
Yes	253	557	0.5 (0.33 - 0.75)	<0.001
Milk				
No	200	444	1	
Yes	133	222	1.45 (1.06 - 1.99)	0.020
Cottage cheese				
No	252	530	1	
Yes	81	136	1.85 (1.09 - 3.13)	0.023
Curd				
No	197	428	1	
Yes	136	238	1.53 (1.05 - 2.24)	0.028
Butter				
No	307	649	1	
Yes	26	17	4.06 (1.98 - 8.32)	<0.001
Mustard leaves				
No	7	48	1	
Yes	326	618	3.92 (1.72 - 8.93)	0.001
Brinjal				
No	37	40	1	
Yes	296	626	0.49 (0.30 - 0.80)	0.004
Tamarind				
No	284	593	1	
Yes	49	73	1.82 (1.07 – 3.08)	0.026
Bhindi				
No	54	71	1	
Yes	279	595	0.52 (0.33 - 0.82)	0.005
Radish				
No	44	116	1	
Yes	289	550	0.52 (0.33 - 0.82)	0.038
Pomegranate				
No	306	637	1	
Yes	27	29	2.72 (1.35 - 5.46)	0.005
Papaya				
No	121	277	1	
Yes	212	389	1.43 (1.01 - 2.03)	0.043
Pineapple				
No	302	625	1	
Yes	31	41	1.70 (1.00 - 2.90)	0.051

Table 6 Weight and Qetelet's index and risk of Gallbladder cancer

Variable	Cases	Controls	OR	95% Cl	p-value
Weight (in kilograms)					
<55	119	135	1		
55-59	89	152	0.60	(0.41 - 0.86)	0.006
60-64	54	166	0.29	(0.19 - 0.45)	<0.001
65-69	28	99	0.24	(0.14 - 0.41)	<.0.001
70+	26	78	0.24	(0.13 - 0.45)	<.0.001
Unknown	17	36	0.48	(0.22 - 1.02)	0.057
Quetelet's index					
1	44	73	1		
2	55	127	0.56	(0.29 - 1.08)	0.084
3	13	24	0.87	(0.35 - 2.16)	0.761
Unknown	221	442	0.56	(0.21 -1.53)	0.057

Table 7 Odds ratio and 95% confidence interval of regression analysis.

Variable	OR	95% CI	p-value
Typhoid in the past	9.12	(4.6 - 18.08)	<0.001
Butter	7.54	(3.02 - 8.84)	<0.001
Urad dhal	2.09	(1.45 - 3.00)	<0.001
Smoking	2.27	(1.33 - 3.66)	0.003
Mustard leaves	4.05	(1.51-10.89)	0.006
Bhindi	0.52	(0.30 - 0.88)	0.016
Alcohol	2.32	(1.09 - 4.90)	0.028
Radish	2.05	(1.16 - 3.63)	0.014
Chana	0.61	(0.38 - 0.97)	0.037
Pomegranate	2.24	(1.01 - 4.98)	0.048

carried in the GB. Chile has an extremely high incidence of typhoid and a high prevalent of typhoid carriage and is known to have a very high risk of GB cancer.[17] Several other studies also suggested an association between GB cancer and typhoid carrier state [21-26]. However, the association found in the current study can be only suggestive and was not confirmed by the serological examination. So this hypothesis must be reevaluated in subsequent studies.

The other medical variable that have been postulated to be associated with GB cancer was history of cholelithiasis [8,17,27] which was also confirmed in the current study and a high proportion of patients had long-term symptoms of cholelithiasis before discovery of tumour.[4,5] However, it is worth mentioning that two cohort studies did not find any association between GB and gallstones.[28,29]

As carcinoma of GB, gallstone and typhoid carrier state are all more common in women, it was not surprising to find female preponderance among the cases and controls.[30] Women with higher parity were at an increased risk for developing GB cancer. This finding is consistent with some previous studies on the association of parity and GB cancer.[8,9,31,32] A combination of factors such as malnutrition, decreased antioxidants in the diet may be operating on them.

The present study also has shown a relationship between the smoking habit and GB cancer. It is consistent with several other studies.[25,26,27] Several dietary items such as green chili, bhindi, onion, brinjal etc. and fruits like mango, banana etc. have shown a protective effect, which was consistent with other studies.[35] But some other dietary items have been shown to increase the risk. In our study tea was found to be a protective factor. This observation was consistent with some other studies. Researchers have proposed that tea might protect against cancer because of its antioxidant content.[36] A study contacted on Poland reported an inverse association with the amount of tea drunk throughout life.[9] In our study coffee was found to be a risk factor for GB cancer. Coffee has been suggested to be carcinogenic due to presence of mutagens. A study reported that regular coffee was consumed by 74.5% of the subjects and trend was seen towards slightly higher prevalence of GB stones in coffee drinkers [37]. But a study in Japan, reported a low risk of GB cancer with frequent intake of coffee.[8] A statistically non significant increased odds was observed for sweet consumption in our study. Sugar has been stated to be one of the risk factors for biliary tract cancer. In a study it was found that for GB cancer the association with the intake of sugar was significant and there was a two-fold increase in risk in the upper tertile of intake [38]. However another case-control study found a positive association between low intake of sugar as soft drinks with GB cancer.[39]

The Indian diet is a complex one and is subject to various biases. So it is better to examine the ingredients in these factors in depth before drawing any conclusion.

Obesity is known to be very strong risk factor for cholelithiasis.[40] Our study shows an inverse relationship between the weight and GB cancer even though a statistically significant association was found between cholilithiasis and GB cancer. So, this study shows that there is no relationship between cholilithiasis and weight, which is consistent with a study reported by Khuroo et al.[41] Another reason for inverse relation may be due to cachexia in GB cancer cases. Under such circumstances the weight may be an effect rather than the cause of GB cancer.

In this study there was an inverse relationship between Quitlet's index and GB cancer. This is consistent with Framingham Study,[42] which showed a consistent and strong association with total calorie intake, but not with Quitlet's index.

The main limitation of this study is the recall bias. There are problems of reliability of information concerning the distant past which the subject may forget to recall.

In conclusion, this study reconfirms the association between typhoid in the past, cholelithiasis and gallbladder cancer. The data are also suggestive of an association with smoking and certain dietary patterns.

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