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Statistical Analysis of Gall Bladder Cancer Patients with Application to Logistic Regression Model

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KEYWORDS

Cholelithiasis, Female, Food adulteration, Gallbladder carcinoma

ABSTRACT:

Gallbladder carcinoma is a biliary tract tumor with a high mortality rate. The objectives of this study were to explore the risk factors of Gallbladder carcinoma in patients with gallstones and to establish effective screening indicators. The study suggest that the gallbladder cancer is constantly evolving, with much of this change caused by lifestyle, cultural and dietary factors. Balanced diet, prevention of malnutrition/adulteration, tobacco prevention and early intervention for cholelithiasis may help in decreasing the incidence of this dreaded disease. More structured studies need to be carried out to ascertain risk factors for GBC in our population subgroup such the religion, native language and education.

Introduction: Carcinoma of the Gall Bladder is one of the few non sex related neoplasms more frequent among females. In India, Cancer of gall bladder shows a geographic distribution as the incidence is much higher in Delhi population based cancer registry as compared to registries in South India. 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 of 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 clearly indicates that it is common in Northern states of India. Epidemiologic studies demonstrate a close association between gall bladder carcinoma and presence of gall stone. The strength of the relationship varies considerably between various ethnic groups. Even though ethnic and geographic variation in the incidence of gall stone is well known, the cause of gall stone formation is obscure. Besides gall stone, which have consistently emerged as a risk factor in several studies, the only strong risk factor observed was obesity. Heredity, diet and environmental factors are other risk factors which need to be studied to elucidate the underlying chances of developing the disease. To provide further information on this issue a Case Control Study on Gall bladder carcinoma was conducted in Delhi.

The aim of the study was:-

1.To identify the risk factors for gall bladder carcinoma.

2 To estimate the fraction of gall bladder cancers attributable to Cholelithiasis; and

3.To investigate the interaction between diet, reproductive history, oral contraceptives usage, past gastrointestinal disease and other risk factors in gall bladder carcinoma.

Material and Methods: The study design was a prospective population-based case control one. Cases were patients newly diagnosed as gall bladder cancer during 1st April 1997 to 31st July 2001. Patients of both sexes and Delhi residents were included. The diagnosis

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was confirmed histologically or cytological. For each case, two controls were taken. One control was a healthy neighborhood control whereas the second was the healthy relative of the patient. If the healthy relatives are not available then another healthy neighborhood control was taken. Controls were matched to cases by age 15 years, sex and marital status (in the case of females). Data was collected by using a standardized questionnaire by interview method. Variables included in the questionnaire were Demographic details, marital history, history of past/present illness, family history of cancer, life style factors, reproductive history and dietetic history. Standard measurements were used to elicit information about the quantity of dietary items consumed. The measures used were bowl (contain 200 mg food items), teaspoon, tablespoon, cup and glass. All the cases and controls were interviewed by the trained medical social workers. Medical social workers were given an Intensive training for one month in administrating the questionnaire. Cases were identified from outpatient departments and pathology and medical records of various hospitals as soon as they were diagnosed or operated. They were interviewed either in the hospital itself or in their homes. Both the case and its controls were interviewed by the same medical social worker. Unadjusted unconditional odds ratio and unadjusted conditional odds ratio along with 95% confidence interval and p-values are calculated. A multivariate regression analysis was also done.

Statistical Analysis: In biomedical research one is often interested whether a certain health related event will occur or not i.e., the outcome variable is of binary nature and the other important factors that influence its occurrence may be of binary of continuous nature. Since the dependent variable is constrained to the limits of 0 and 1 the conventional multiple regression analysis as a modeling strategy to evaluate the role of independent risk factors in causation of disease cannot be employed. It is also of interest to know the probability of development of disease in the presence of certain variables known as risk variables or risk factors as compared to the situation when these variables are absent. Multiple logistic regression analysis is the most suited approach for the above situation.

Logistic Regression Analysis: Mantel-Hansel technique for stratified case control analysis had served the epidemiologist for a long time. Most of the calculations were simple enough to carry out using simple calculators. The situation is quite different when many potentially confounding factors need to be controlled: A stratified analysts-will-ultimately break when individual strata become large in number and small in size thus resulting in loss of data for analysis. The basic tool which allows controlling the above mentioned problem is linear logistic model. It is multivariate procedure specifically used in case control or cohort studies for estimating the effect of certain factors when others are controlled. It is a modification of conventional regression analysis where the dependent variable is of continuous nature. It derives its name (logistic) from the fact that 'logit' transformation of disease probability in each risk category is expressed-as-a-linear function of regression variables. Let P denote the disease risk the logit transformation Y (dependent variable taking value as 0 & 1) results in it taking limits from - infinity to + infinity, thus satisfying the condition of conventional regression analysis.

$Y = \log it\ P = \log(P/1-P)$; or P can be expressed as

$P = (e^{y}/1+e^{y})$; denote the disease odds.

This model also helps to provide the estimate of relative risk considering a single factor (X) with two risk categories, exposed and unexposed. The logistic regression can be represented as:

$$Y = \log it\ P = \alpha + \beta X$$

When X=0 (unexposed) and $\log it\ P_0 = \alpha$ when x=1, (exposed)

$$\log it\ P_1 = \log it\ P_0 + \beta$$

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$$\text{log it } P_1 = \text{log it } P_0 + \beta$$
$$\beta = \log\left(P_1(1-P_0)/P_0(1-P_1)\right)$$

or

$$e^{\beta} = [P_1(1-P_0)/P_0(1-P_1)]$$

= odds ratio (OR)

Hence the odds ratio can be estimated from the exponential of regression coefficients.

When there are K regression variables the generalized form of model is given by

$$\text{log it } P_i = \alpha + \sum_{j=1}^{k} \beta_i X_{ij}$$

$$P_i = \frac{e^{\alpha + \sum_{j=1}^{k} \beta_i X_{ij}}}{\left[1 + e^{\alpha + \sum_{j=1}^{k} \beta_i X_{ij}}\right]}$$

The above expression provides the probability of development of disease for a particular case with k set of explanatory variables. Maximum likelihood estimation procedure is employed for estimation of the parameters in logistic regression analysis by iterative procedure, whereas conventional linear regression analysis adopts method of least square.

The univariate and multivariate odds ratios shall also be worked out along with 95% confidence interval.

$$CI = OR \pm 1.96 se(\beta)$$

$$se(\log_e OR) = \left[\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}\right]^{\frac{1}{2}}$$

Then $100(1-\alpha)\%CI \text{ for } \log_e(OR)$ is given by $\log_e(OR) \pm Z_\alpha se(\log_e(OR))$, the confidence interval for OR is computed by taking antilog of confidence limits for $\log_e$. Considering the above theory various computations have been carried out based on unconditional logistic regression model.

Results: The study population consisted of 333 gall bladder cancer cases and 666 controls. Table 1 & 2 shows the Age & Sex distribution of controls & cases. Table 3 to 6 shows the Religion, Mother tongue, Education and monthly family income with unconditional or, 95%. CI and p-value. Among the cases 91 (27%) were males and 242 (73%) were females. Amongst controls there were 182 (27%) males and 484 (73%) females. The majority of cancer cases (86%) and controls (91%) were Hindus with a small proportion of Muslims. Sikhs and other religious Mother tongue for majority of the cases and controls was Hindi followed by Punjabi and Urdu. Thirty six percent of cases and 31% of controls in the study were illiterates. Majority of cases (46%) and controls (47%) monthly family income were more than rupees five thousand. There was no significant association between gall bladder cancer and the education levels of patients, but the odd ratio was 1.49 (with 95% CI=0.79-2.81) in the highest category of education.

Table 1: Distribution of controls & cases by Age

Age groups	Control	Percentage	Cases	Percentage
<40	60	9.01	26	7.81
40-44	73	10.96	35	10.51
45-49	73	10.96	42	12.61
50-54	117	15.57	47	14.11
55-59	113	16.97	52	15.62
60-64	94	14.11	46	13.81
65-69	84	12.61	38	11.41

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70+	52	7.81	47	14.11
Total	666	100.00	333	100

Table 2: Distribution of control & cases by Sex

Sex	Control	Percentage	Cases	Percentage
Male	182	27.33	91	27.33
Female	484	72.67	242	72367
Total	666	100.00	333	100.00

Table 3: Distribution of control & cases by Religion

Religion	Control	Cases	OR	95% CI	p-value
Hindu	604	287	1.00	No convergence	
Muslim	37	28	2.45		
Christian	3	1	0.71		
Sikh	22	16	1.66		
Others	0	1	Infinite		

Table 4: Distribution of control & cases by Mother Tongue

Mother Tongue	Control	Cases	OR	95% CI	p-value
Hindi	590	283	1.00		
Punjabi	38	23	1.38	0.74-2.55	0.307
Urdu	24	15	1.73	0.65-4.58	0.271
Others	14	12	2.15	0.87-5.29	0.097

Table 5: Distribution of control & cases by Education

Education	Control	Cases	OR	95% CI	p-value
Illiterate	204	120	1.00		
Literate	129	49	0.53	0.33-0.86	0.010
Primary	132	54	0.61	0.39-0.96	0.031
Middle	73	39	0.82	0.48-0.14	0.451
High School	84	34	0.66	0.38-1.15	0.140
Technical & above	44	37	1.49	0.79-2.81	0.215

Table 6: Distribution of control & cases by Monthly Family Income (in Rupees)

Rs.	Control	Cases	OR	95% CI	p-value
<5000	202	88	1.00		
5000-8000	153	93	1.51	1.00-2.27	0.049
8000+	311	152	1.21	0.77-1.88	0.408

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There was an increase in risk of gall bladder cancer as there was an increase in the age at menarche, but the association was not statistically significant (Table 7). Also, the menopausal women had a statistically significantly higher risk of gall bladder cancer than the menstruating women (OR=3.17, CI=1.56-6.47) (Table 8).

Table 7: Distribution of controls & caves by Age at menarche

Age at menarche	Control	Cases	OR	95% CI	p-value
<13	12	5	1.00		
13	243	120	1.22	0.28-5.42	0.792
14	205	91	1.10	0.24-4.97	0.901
>14	11	6	1.40	0.23-8.39	0.715
Unknown	13	20	5.41	1.01-29.01	0.049

Table 8: Distribution of control & cases by whether still menstruating.

Whether still menstruating	Control	Cases	OR	95% CI	p-value
Yes	147	58	1.00		
No	337	184	3.17	1.56-6.47	0.001

Table 9 & 10 shows the number of abortions & no. of pregnancies with unconditional OR, 95% CI & p-value. As the number of abortions increased, there was a increased risk of gall bladder cancer but the relationship was not statistically significant. Also, as the number of pregnancies is 4 or more, there was an increased risk of gall bladder cancer, and the association was not statistically significant.

Table 9: Distribution of controls & cases by Number of abortions

Number of abortions	Control	Cases	OR	95% CI	p-value
0	411	195	1.00		
1	50	31	1.31	0.81-2.12	0.272
2	19	10	1.14	0.50-2.58	0.755
3+	4	6	3.11	0.87-11.04	0.080

Table 10: Distribution of controls & cases by Number of Pregnancies

Number of Pregnancies	Control	Cases	OR	95% CI	p-value
1	9	4	1.00		
2	56	11	0.39	0.09-1.67	0.204
3	101	31	0.66	0.17-2.53	0.544
4	115	56	1.13	0.31-4.13	0.859
5	83	54	1.55	0.41-5.84	0.515
6	44	29	1.74	0.45-6.75	0.421
7	32	21	1.80	0.45-7.12	0.403
8	18	16	2.26	0.53-9.68	0.272
9	12	6	1.66	0.34-8.19	0.534

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10+	14	14	3.11	0.69-14.01	0.140

The unadjusted conditional odds ratio with 95% confidence interval is given for selected significant variables in table 11.

Table 11: Unadjusted conditional odds ratios with 95% Confidence intervals for selected risk factors.

Risk Factors	No. of Control	No. of Cases	OR	95% CI	p-value
Cholelitthisasis					
Yes	664	142	1		
No	2	191	446.56	107-2629	<0.001
History of typhoid					
Yes	645	226	1		
No	21	67	8.92	5.0-15.9	<0.001
Family History of Gallbladder					
Yes	660	325	1		
No	6	8	2.94	0.95-9.10	0.061

There was a relationship between cholelithiasis, and gall bladder cancer and it was highly significant (OR=446.56, CI-107 88-2629.15) History of typhoid in the past was significantly associated with gall bladder cancer with (OR=8.92, CI-5.00-15.91, p<0.001). Though there was an increased risk of gall bladder cancer in persons with family history of gall bladder cancer, the relation was not statistically significant.

The odd ratios for selected dietetic variables were shown in table 12. Consumption of Urad dal, Moong dal, milk, cottage cheese, butter, mustard leaves and pomegranate were associated with significantly higher risk of gall bladder cancer whereas consumption of Channa was associated with statistically significant lower risk of gall bladder cancer.

Table 12: Unadjusted conditional odds ratios with 95% confidence intervals for selected dietary variables

Risk Factors	No. of Control	No. of Cases	OR	95% CI	p-value
Urad Dal					
No	319	112	1		
Yes	347	221	2.07	1.52-2.82	<0.001
Moong Dal					
No	242	95	1		
Yes	424	238	1.54	1.12-2.11	0.007
Channa					
No	109	80	1		
Yes	557	253	0.5	0.33-0.75	<0.001
Milk					
No	444	200	1		
Yes	222	133	1.45	1.06-1.99	0.020
Cottage cheese					
No	530	252	1		

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Yes	136	81	1.85	1.09-3.13	0.023
Butter					
No	649	307	1		
Yes	17	26	4.06	1.98-8.32	<0.001
Mustard Leaves					
No	48	7	1		
Yes	618	326	3.92	1.72-8.93	0.001
Pomgrenate					
No	637	306	1		
Yes	29	27	2.72	1.35-5.46	0.005

Eating of masoor dal, coffee, epinard, beans, capsicum, green peas, mushroom, tamarind, radish, sweat potato, red chilli, apple, sweats, orange, papaya, pineapple, other fruits, fish, beef, mutton, chicken, groundnut oil, Mustard oil, palm oil and sunflower oil though increased the risk of gall bladder cancer, but the relationship was not statistically significant.

Table 13: Unadjusted conditional odds ratios with 95% CI for smoking, chewing and drinking habits.

Risk Factors	No. of Control	No. of Cases	OR	95% CI	p-value
Smoking habit					
No	560	252	1		
Yes	106	81	2.38	1.54-3.66	0.178
Age Started smoking					
No habit	560	252	1		
<20	22	13	1.76	0.77-4.02	<0.001
20-40	41	28	2.13	1.13-4.01	0.019
25+	43	40	2.8	1.62-4.80	<0.001
Type of smoking					
No habit	560	252	1		
Cigarette	17	14	3.05	1.33-6.98	0.008
Bidi	70	49	2.25	1.38-3.69	0.001
Pipe	3	4	2.86	0.64-12.87	0.170
B+C	9	11	4.51	1.68-12.06	0.003
Others	7	3	1.09	0.27-4.29	0.907
Cigarette					
No habit	560	252	1		
Current	26	25	3.46	1.72-6.98	<0.001
Past	80	56	2.15	1.37-3.39	<0.001
Bidi					
No habit	560	252	1		
Current	79	60	2.39	1.50-3.83	<0.001

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Past	27	21	2.33	1.23-4.40	0.009
Chewing habit					
No	626	306	1		
Yes	40	27	1.51	0.85-2.67	0.164
Alcohol					
No	618	294	1		
Yes	48	39	2.4	1.32-4.36	0.004

A higher risk of gall bladder cancer was seen in persons with tobacco chewing habits as compared to non-chewers. However, this relation was not statistically significant. Table13: shows the unadjusted conditional odds ratio for smoking chewing and alcohol habits. Smoking significantly increased the risk of gall bladder cancer as compared to non-smoker (OR =2.38, CI=1.54-3.66). Age of started smoking <20 years and 25+ years and higher risk of gall bladder cancer (OR=2.8, CI=1.62-4.80, p<0.001) and the association was statistically highly significant. Cigarette and Bidi smoking had at statistically significant high risk for gall bladder cancer (OR=3.05, CI=1.33-6.98) and (OR=2.25, CI=1.38-3.69) respectively. Current (OR=3.46, CI=1.72-6.98) and past (OR=2.15, CI=1.37-3.39) cigarette smoker had a higher risk of gall bladder cancer then the non-smokers.

Current bidi smoking (OR=2.39, CI=1.50-3.83) and past pipe smoking (OR=2.34, CI=1.50-3.65) and other type of smoking in past (OR=2.59. CI=1.65-4.07) had also increased the risk of gall bladder cancer and the relationship were highly statistically significant.

Alcohol habit (OR=2.40, CI=1.32-4.36) was significantly associated with the risk of gall bladder cancer. Past drinker had higher risk of gall bladder cancer (OR=31.32, CI=4.03-243.60) and the association was highly statistically significant.

No consistent pattern was evident showing which type of alcohol increased the risk. All types had elevated odds ratio except beer, with Wine showing the highest odds ratio (4.25). There was an inverse relationship between the weight of person in kilograms and risk of gall bladder cancer. As the weight increases (>60 kgs) the risk of gall bladder cancer decreases and it was statistically significant. Quetlet's index had no relationship with gall bladder cancer. Table 14 shows a regression analysis carried out using forward inclusion method. The odds ratio with 95% confidence intervals along with p-values was calculated for selected variables. Typhoid in the past, butter and urad dal has a highly statistically significantly associated with risk of gall bladder cancer (P<0.001). Smoking and mustard leaves also have a significant relationship with gall bladder cancer (P<0.01). The other variable Alcohol, Radish and Pomegranate are also significant (P<0.05). Channa and bhindi was statistically associated with the lower risk of gall bladder cancer (P<0.05).

Table 14: Odds ratio and 95% confidence interval of regression analysis Risk factor.

Risk Factor	OR	95% Confidence Interval	p-value
Typhoid in the past	9.12	4.60-18.08	<0.001
Butter	7.54	3.02-18.84	<0.001
Urad Dal	2.09	1.45-3.00	<0.001
Smoking	2.27	1.33-3.86	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

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Raddish	2.05	1.16-3.63	0.014
Channa	0.61	0.38-0.97	0.037
Pomgrenate	2.24	1.01-4.98	0.048

Typhoid in the past topped the list of risk for gall bladder cancer (OR=9.12, CI=4.6-18.08) followed by use of butter (OR=7.54, CI=3.02-18.84), mustard leaves (OR=4.05, CI=1.51-10.89), alchol (OR=2.32, CI= 1.09-4.9), Smoking (OR=2.27, CI=1.33-3.863), Pomegranate (OR= 2.24, CI=1.01-4.98), Urad dhal (OR=2.09, CI=1.45-3.0) and radish (OR=2.05, CI=1.16-3.63) be using backward Inclusion method. When adjusted for age and other variables (table 15) typhoid in the past, urad dal and batter are highly related to gall bladder cancer (P<0.001). Channa dal was inversely related to gall bladder cancer and it was statistically significant. (OR=0.55, 95% CI=0.34-0.91).

Table15: Odds ratio and 95% confidence interval when adjusted for age and other variables.

Risk Factor	OR	95% Confidence Interval	p-value
Typhoid in the past	10.89	5.23-22.65	<0.001
Smoking	1.99	1.13-3.49	0.017
Alcohol	2.71	1.23-5.97	0.014
Urad Dal	1.94	1.32-2.86	<0.001
Channa	0.55	0.34-0.91	0.021
Butter	6.3	2.40-16.53	<0.001
Mustard leaves	4.8	1.68-13.74	0.003
Bhindi	0.5	0.28-0.88	0.017
Raddish	2.15	1.18-3.91	0.012
Pomgrenate	2.01	0.88-4.62	0.099

Conclusion: The present study shows that history of typhoid in the past. Cholithiasis, consumption of alcohol, smoking, chewing and certain dietetic habits like consumption of urad dal, moong dhal, milk, cottage cheese, butter, mustard leaves and pomegranate increased the risk of gall bladder cancer. There is no much difference in the risk factors of gall bladder cancer between males and females. Whereas consumption of channa and bhindi was statistically associated with the lower risk of gall bladder. There was an inverse relationship between the weight of person in kilograms and risk of gall bladder cancer. As the weight Increases (>60 kgs) the risk of gall bladder cancer decreases, and I was statistically significant.

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