Field Study of Gallbladder Diseases in Rural Gangetic Basin of North India, Impact of Environmental and Life Style Risk Factors

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Paper presented at Annual Meeting of Population Association of America
15-17 April 2010
Dallas, Texas, USA

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INTRODUCTION

Gallbladder cancer (GBC) is relatively rare but with high incidence in certain world populations. The highest GBC incidence rates worldwide per 100,000 are for women in Delhi, India 21.5, South Karachi, Pakistan 13.8 and Quito, Ecuador 12.9. Female-to-male incidence ratios are around three. The role of genetic, lifestyle factors and infections in gallbladder carcinogenesis is poorly understood.[1] Gallstones are said to have major role in causation of GBC[2]. Chronic inflammation and dysplasia is proposed to explain the association of Gallstones and cancer. Other factors linked to gall bladder diseases (GBD) are obesity, multiparity and chronic infections like Salmonella typhi and S. paratyphi.[1]

In India, high risk for GBC is in a wide band of northern India.[3]. They are the states of Uttar Pradesh, Bihar, Orissa, West Bengal and Assam. GBC is twice more in women than men and is leading digestive cancer in women in the cities Delhi and Bhopal.[4] In Eastern India, GBC is 6.4% of 11,700 registered in Calcutta, more in women.[5] In cancer registries of Indian Council of Medical Research, GBC incidence per 100,000 is low 0.3 in the South India in Bangalore and Madras compared to North India, Delhi 1.1 and Bhopal 1.2. The age-adjusted rate for females was 1.4 in Madras (south India), but 9.4 in Delhi (North India) showing a nine-fold difference.[6]

These statistics from hospitals and cancer registries may not give a full picture of actual prevalence. A detailed geographic tracking of 773 GBC patients coming to Tata Memorial Hospital, Mumbai India, a tertiary referral centre, over six years (1990-1995) showed maximum were from Uttar Pradesh (41.9%), Bihar (35.8%), West Bengal (8.1%) and parts of Madhya Pradesh (7.3%) and Assam (7.0%). There appears to be a higher incidence of GBC in the Gangetic basin, Uttar Pradesh (65%) and Bihar 51%.[7,8] Though high prevalence of GBD is well documented, there are few community based studies from these areas. It is possible that prevalence is overestimated in the hospital based urban studies. Both Uttar Pradesh and Bihar have a predominantly rural population living in river belt of Ganga with few community based studies from these areas. A multi-institutional specialized field study was planned and executed by the GANGA (Gallbladder Abnormalities in Northern Gangetic area) study group to estimate

community based prevalence of GBD in these rural areas and to reflect on the possible risk factors responsible.

METHODOLOGY

Sample Design

Specific sampling design was adopted to estimate prevalence and also identify risk factors. The prevalence of gallstone disease in North India is reported at six percent [9]. Considering the low prevalence of gallstone disease at 6%, a sample of 7000 subjects provides the estimate between five to seven percent with 95 percent confidence. Sixty villages (20 in each district-: Varanasi, Patna and Vaishali were selected and subdivided based on size of population/household - high, medium and low. The villages were ranked on the level of literacy. From this list, 20 villages were selected with systematic sampling with a single random number. All households in these villages were enumerated and persons aged 30 years and above were interviewed in detail since prevalence of gallstones was quite low at younger ages.[10]

Information was obtained concerning socioeconomic and demographic status, educational level, marital status, reproductive factors, and occupation. Questions on lifestyle included tobacco use (smoke or non-smoking) and alcohol consumption by duration of use. Information on previous medical conditions with confirmed diagnosis, food habits and consumption of different food items by frequency were also collected.

Specific symptoms ascertained for GBD were: jaundice or pain in upper abdomen specifically pain after taking food or fatty food, acidity, gases, vomiting, loss of appetite and loss of weight with duration. Those with ever or current medical diagnosis of gallbladder disease/surgery, and jaundice were noted. In others with symptoms, only those suffering currently in last one year were considered ‘symptomatic’ persons. The surveyed population was categorized as groups ‘with symptoms’ or ‘asymptomatic’. They were further stratified based on a) sex, b) age (30-49 or 50 and above), and c) whether symptomatic (yes/ no). All persons with symptoms, irrespective of their age and sex, except pregnant women were directed to undergo ultrasonography test. Asymptomatic persons, matched for age, sex and environment in a 3:1 ratio, were also directed for ultrasound test. This selection was done not with equal probability but with those having symptoms given a higher chance of selection than those without symptoms. This helps select adequate number with GBD for risk factor analysis. Otherwise, the

disease not being common, a sample selected with equal probability might fail to provide enough cases with the disease and could bias the estimate of prevalence of the disease. To minimize the bias, appropriate weights have been used to obtain population based estimates.

Ultrasound test: The estimate of the prevalence is based not on self-reported symptoms but by exposing the subjects to ultrasonography provided at the site. Real time ultrasonography is a non-invasive technique shown to have high sensitivity and specificity for the detection of gallstones. [11, 12] Hence, we adopted ultrasonography for this community level study on GBD. The survey is on the prevalence of all GBD including gallstones, cholecystitis, gallbladder cancer and other abnormalities, which can be ascertained with ultrasonography. However since the literature in several surveys relates to gallstones which are said to have major role in causation of gallbladder cancer, their incidence is also shown separately.

Statistical Analysis

The data was entered in SPSS format [13]. Double data entry was carried out to check the consistencies. Standard of living index was calculated by weighted sum of consumer durables and household infrastructure as proxy of economic status.[14]

The diagnostic value of different symptoms was evaluated by calculating the sensitivity (proportion of subjects with GBD among those having symptoms) and specificity (proportion of subjects without GBD/gallstone among those without symptoms). Age sex adjusted prevalence was determined for GBD. The association between prevalence and age, socio-economic characteristics, consumption of food items, indicators of life style and other diseases was evaluated by chi-square test. Only medically confirmed diseases were included in the analysis. Multivariate analysis was performed by logistic regression and using all the variables which were significant at bi-variate analyses. Adjusted odds ratios (ORs), as estimate of relative risk, of GBD /gallstone, together with their 95% confidence intervals (CI) were obtained by unconditional multiple logistic regression analysis. Models were fitted separately for GBD by sex respectively. All models included specific variables for identifying risk factors for GBD: In logistic analysis, only those variables that are not highly correlated with other independent variables are considered taking into account the importance of variable. Further, only those variables that were significant in the bivariate analysis are considered.

Apart from logistic analysis, two-step cluster analysis is used as an exploratory tool designed to reveal natural groupings (or clusters) within a dataset that would otherwise not be apparent.

The algorithm employed by this procedure has several desirable features that differentiate it from traditional clustering techniques: It can handle categorical and continuous variables. By assuming variables independent, a joint multinomial-normal distribution can be placed on categorical and continuous variables. In the cluster analysis, GBD as categorical variable and soil and water testing result of presence of nickel, chromium, cadmium and DDT as continuous variables are used.

Assessment of water and soil

Testing of drinking water and soil could be carried out for all the selected villages only in Bihar. Samples of drinking water are taken from tap or tube wells or bore wells commonly used by most of the villagers. Soil was collected from three randomly selected fields. All water and soil samples were analyzed for presence of Nickel, Cadmium, Chromium, and DDT at the Industrial Toxicology Research Centre, Lucknow, Uttar Pradesh.

Data was analyzed separately for males and females, and for asymptomatic and symptomatic individuals. Prevalence was determined for GBD (i.e. any sonographic abnormality in gallbladder), which includes gallstones, cholecystitis, polyps and gallbladder cancer.

In this mass screening study, ultrasonography findings were treated as standard since histological confirmation is not possible.

RESULTS

Response rate

Of 8,421 identified ‘symptomatic’ directed for screening, only 5,100 reported for ultrasonography. In the asymptomatic group of 2971, only 1448 reported to be screened as control. The proforma for ultrasonography contained: height, weight, symptomatic /asymptomatic, diagnosis, and major findings of the ultrasonography test. Those found with a gallbladder abnormality were advised to get treated. Table 1 gives details of response rate by sex and district.

The response rate of males is lower than that of females a pattern observed in most Demographic and Health Surveys as men are often not available at home during the day. Only 5100 (2078 men and 3022 women) i.e. 60% of those directed have actually have undergone ultrasound. Among asymptomatic persons, 1,448 (547 Men and 901 women) have undergone sonography. The absence was partly reluctance to fast for ultrasound or loss of daily wages for the test, more so in persons without symptoms.

Table 1: Number of households, male and female interviewed and undergone ultrasonography in each of the three districts

Interviews	Patna	Varanasi	Vaishali	Total
Number of Households	3885	4851	4598	**13334**
Males interviewed	3355	3580	3417	10352
Females interviewed	3323	5411	3775	12509
Total interviewed	**6678**	**8991**	**7192**	**22,861**
Symptomatic Males identified	1454	1038	1329	3821
Symptomatic Females identified	1433	1845	1322	4600
Total symptomatic persons	**2887**	**2883**	**3973**	**8421**
Symptomatic Males who Underwent ultrasonography	840	427	811	2078 (54.4%)
Symptomatic Females who underwent ultrasonography	1013	1012	997	3022 (65.7%)
Total symptomatic persons who underwent ultrasonography	**1853**	**1439**	**1808**	**5100 (60.6%)**
Control Males who underwent Ultrasonography	246	110	191	547
Control Females who underwent Ultrasonography	296	333	272	901
Total control undergone ultrasonography	**542**	**443**	**463**	**1448**
Total number of ALL persons underwent sonography	**2395**	**1882**	**2271**	**6548**

Since the response rate for sonography of symptomatic persons was 60 per cent, and all asymptomatic persons were not called for test, the demographic characteristics age, education, occupation of those who underwent sonography and those who did not are compared. There were only minor demographic differences and almost the same socio-economic characteristics between respondent and non-respondents showing that our results are not biased. In addition, the characteristics of all respondents in both symptomatic and asymptomatic groups who underwent sonography are compared. This analysis showed that our matching criteria are not influenced by non-response and both symptomatic and asymptomatic persons have almost similar age and other characteristics. As the sample is not self-weighted and the response rate is not the same for symptomatic and asymptomatic persons, weights were used separately for symptomatic and asymptomatic males and females to estimate the prevalence rate. Prevalence is estimated using weights for each category separately as well as for the combined rate.

Characteristics of sample villages and respondents

Proximity of river

Villages in five-kilometer range from a river / tributary were identified. Households near river Ganga are 40 per cent in Varanasi; in Patna District 30 per cent are near river Ganga and 25 percent near river Punpun ; in Vaishali 66 percent are near river Gandak.

Background of Households

Among the households, 53 percent have a 'low standard of living'; 36 percent 'medium' and only 11 percent 'high standard'. Among males 68 percent and in females only 18 percent are literate. Majority of respondents belong to Hindu religion; Muslims, Sikhs and Christians constitute only small percentage (3 % males and 4 % females).

Prevalence of Gall Bladder Diseases

'Gallbladder diseases' surveyed include; cholecystitis (acute, chronic); gallstones (solitary, multiple); gallbladder polyp; gallbladder cancer. Of these majority relates to cholecystitis and gallstones. Gallbladder cancer incidence was only 51 per 100,000 population (Confidence interval 6-184).

Overall prevalence of GBD in the sample of population with age 30 and above is 6.22 percent, with female 7.35 percent and male 4.46 percent respectively (Table 2). Prevalence of gallstone is two percent lower than overall gall bladder disease prevalence. About two percent population in the study area is suffering from cholecystitis and.other gallbladder diseases. Prevalence of GBD and gallstone is higher among females than males in Patna and Vaishali districts. However, in Varanasi district, males have higher prevalence of total GBD than females. On the other hand, it may be noted in Varanasi that gallstone prevalence among females is higher (4.3%) than males (1.35%) with males 5.72 percent suffering from other diseases of gallbladder and females only 1.28 percent.

Since age structure of males and females is not the same, age adjusted prevalence rate was calculated. Age adjusted prevalence shows that percentage of females suffering from GBD is almost double that of males. Only in Varanasi, prevalence of GBD among males is found slightly higher (6.4) than in females (5.8).

Relevance of Symptoms

The prevalence of GBD is almost twice among symptomatic persons than asymptomatic persons. In males, symptomatic persons have almost four times higher chance of having GBD. This shows that symptoms have high sensitivity for males. In case of females prevalence among asymptomatic persons around four percent is half of the symptomatic persons. This needs to be investigated to ascertain whether females are more asymptomatic or they have different symptoms.

Table 2: Prevalence of Gallbladder Disease per 100 persons

		Total Gallbladder diseases (%)	Gallstones (%)	Other diseases of gallbladder %	Age adjusted GB diseases
Patna	Male	3.24	2.42	0.82	2.50
	Female	5.58	4.65	1.03	5.80
	Total	4.55	3.67	0.88	4.40
Varanasi	Male	7.07	1.35	5.72	6.40
	Female	5.58	4.30	1.28	5.80
	Total	6.19	3.47	2.72	6.00
Vaishali	Male	4.33	1.88	2.45	4.20
	Female	10.85	7.56	3.29	11.20
	Total	7.96	5.04	2.92	7.90
	Symptomatic male	5.31	2.44	2.87	4.70
	Asymptomatic male	1.37	0.34	1.03	1.00
	Symptomatic female	8.27	6.02	2.25	8.50
	Asymptomatic female	4.40	3.66	0.74	4.30
	Symptomatic persons(all)	7.08	4.58	2.50	6.90
	Asymptomatic persons	3.26	2.41	0.85	3.00
All Districts	Total	6.22	4.09	2.13	-
	Males	4.46	1.99	2.47	3.90
	Females	7.35	5.47	1.88	7.50

Variation in the Prevalence by Characteristics

The results of logistic analysis are shown in Table 3 for total (Model I), males (Model II) and females (Model III) separately along with odd ratio and its confidence interval. After controlling for all other variables, females have 1.8 times higher chance of having GBD than males. Person of age 50 and above have higher chance of having the disease in all three models, but in males it is not significant (5 % level of significance). Variable 'parity' considered only in the third model of females, shows prevalence significantly higher for women with more than three children.

Medical history and heredity of having gallbladder diseases are also incorporated in the models. Previous medical history of abdominal surgery, diabetes and arthritis are positively associated with GBD significant only for female model. Genetic history of any blood relative suffering from GBD also shows positive and significant association.

Table 3: Variation in Prevalence of Gallbladder Disease : Logistic Analysis

Demographic Characteristics		Total(Model I)		Male(Model II)		Female(Model III)	
		Number	EXP(B) and 95.0% C.I.	Number	EXP(B) and 95.0% C.I.	Number	EXP(B) and 95.0% C.I.
Sex	Male(ref.)	2526	1	-	-	-	-
	Female	3801	1.853*	-	-	-	-
			1.304 - 2.635	-	-	-	-
Age group	30-49(ref.)	4177	1	1457	1	2676	1
	50+	2150	1.626*	1069	1.403	1072	1.703*
			1.293 – 2.044		0.887 – 2.221		1.292 – 2.245
Children	0-3(ref.)	-	-	-	-	869	1
	4+	-	-	-	-	2879	1.862*
		-	-	-	-		1.306 – 2.655
Abd. Surgery	NO (ref.)	6096	1	2424	1	3622	1
	Yes	231	2.733*	102	1.957	126	3.335*
			1.822 – 4.099		0.971 – 3.944		1.949 – 5.705
Diabetes	NO (ref.)	6210	1	2454	1	3703	1
	Yes	117	3.285*	102	4.271*	45	1.724
			2.045 – 5.276		2.130 – 8.566		0.830 – 3.585
Blood relatives with GBD /Ca	NO (ref.)	5813	1	2299	1	3468	1
	Yes	514	1.795*	227	2.115*	280	1.564*
			1.310 – 2.458		1.213 – 3.688		1.049 – 2.334
Food Chick peas	NO (ref.)	5330	1	2119	1	3167	1
	Yes	997	1.636*	337	2.546*	581	1.354
			1.261 – 2.122		1.563 – 4.146		0.981– 1.860
Drinking water	Tap/Hand pump(ref.)	5407	1	2189	1	3173	1
	Well/River/ Pond	920	1.758*	337	3.835*	575	1.202
			1.338 – 2.310		2.368 – 6.209		0.814 – 1.431
Habits	NO	3719	1	705	1	2971	1
	Yes	2608	0.766*	1821	1.023	777	0.691*
			0.590 – 0.994		0.645 – 1.623		0.495 – 0.964
Education	Illiterate(ref)	3861	1	337	1	3016	1
	Literate	2466	1.676*	806	1.179	732	1.849*
			1.270 – 2.212		0.717 – 1.939		1.302 - 2.625
SLI	Low(ref.)	3357	1	1347	1	1996	1
	Medium	2266	1.217	893	1.427	1356	1.079
			0.962 – 1.540		0.897– 2.272		0.814 – 1,431
	High	704	0.873	286	0.516	406	1.098
			0.599 – 1.273		0.227 – 1.172		0.708 – 1.703
River proximity	NO (ref.)	3719		844		1119	
	Yes	2608	1.024	1682	0.608*	2629	1.204
			0.809 -1.296		0.393 – 0.938		0.902 – 1.606
District	Patna	2311	1	1026	1	1268	1
	Varanasi	1784	1.221	509	1.694	1255	0.979
			0.903 – 1.650		0.944 – 3.040		679 – 1.410
	Vaishali	2232	1.874*	991	1.222	1225	2.202*
			1.429 – 2.458		0.728 – 2.050		1.592 – 3.046

* Significant (< 5%) ; number of cases may not add to total cases. 'Ref': reference category 'Exp B' - Odds ratio of having the outcome in a specific category

Information on consumption of many food items was collected in the survey. There is not much variation in the pattern of food habits and its association with GBD. However, consumption of chickpeas has higher odd of having GBD. Source of drinking water is included in the model to examine its association with GBD. All those people who are drinking water from unsafe sources (well/river/pond) have higher odd of getting the GBD. Habits (chewing tobacco/ smoking/ alcohol consumption), standard of living and river proximity are not showing systematic relationship over three models. Among literate persons GBD prevalence is higher in comparison to illiterate person. In terms of district level odd ratios, Vaishali district persons show higher chance of having GBD.

Clustering analysis

To examine the clustering of cases, water and soil results along with result of ultrasound are used for analysis. Water and soil testing is carried out only in districts of Patna and Vaishali (table 4). It is found that 90 percent of those suffering from GBD in these two districts are clustered in Cluster I. From Vaishali district 73% of the cases and only 19% from Patna have fallen in cluster I. Mean value of all pollutants are higher in the Cluster I than Cluster II (except soil Nickel and Chromium which have almost same value in both the clusters). Cluster analysis points to a close correlation with pollutants in water and higher incidence of GBD in Vaishali district.

Table 4: Result of Cluster Analysis with number and mean of selected variables

Characteristics	Number and mean	
	Cluster I	Cluster II
Ultrasound cases*	1287	2646
	32.7%	67.3
Gallbladder disease cases	212	26
	89.1%	10.9%
Ultrasound cases from Patna	444	1890
	19.0%	81.0%
Ultrasound cases from Vaishali	1065	395
	72.9%	27.1%
Nickel in water	7.7764	5.8857
Cadmium in water	2.8727	1.9228
Chromium in water	2.9600	0.5400
DDT in water	0.0400	0.0000
Nickel in soil	10.1916	10.9132
Cadmium in soil	0.8830	0.3470
Chromium in soil	5.3570	5.6940
DDT in soil	12.2994	0.1789

Discussion

This is the largest field survey of rural population of north India in areas suspected to have high incidence of gall bladder diseases. Members of the research team consist of experts in the field survey specializing in population studies along with medical and surgical oncologists, radiologists from different institutions. The sample size was large enough to assess the prevalence of GBD. Ultrasonography a reasonably accurate procedure was adopted for screening GBD in view of sample size at community level (where histological diagnosis is not feasible). Real time ultrasonography is reported as a non-invasive technique with high sensitivity and specificity for the detection of gallstones. [11,12]

The selected villages are representative of the rural population of north India. The studied population belongs mostly to lower and middle income group with less than one-fifths enjoying a high standard of living. This could be one of the main reasons for low prevalence rates of gallstones in this group[15].

The prevalence of GBD in the present study is lower than a survey with ultrasonography in ethnic groups of United States (5.3 - 8. 6%) - age-adjusted (13.9 - 16.6%) [16]. The lower prevalence in our study contrasts from hospital based reports in north India may be due to referral bias or higher prevalence in urban communities with different life style (Varanasi- 13.44 % asymptomatic GBD and 11.14 % cholelithiasis[17]; Chandigarh- gallstone 3.3 % in the asymptomatic and 64.9 % in the symptomatic [18]; New Delhi- gallstones 29.8 % of 1,680 dyspeptic patients[19).]

In the present study the prevalence of GBD and gallstone is higher in those with symptoms now or before compared to those who never had symptoms. At the same time about a third detected with gallstones were asymptomatic. The prevalence rates for gallstones in this survey are similar to another smaller survey in Kashmir[9] reporting 6.12 percent (women 9.6% and men 3.07%). Prevalence of GBD and gallstone is higher in women than men in the districts of Patna and Vaishali. In Varanasi prevalence of GBD among females is marginally lower than that among males. We could not ascertain a cause for this anomalous distribution. Others reported female preponderance with GBC.[20, 21] In rural population (1,058) in Bangladesh prevalence of gallstones is 5.4 percent higher in women (7.7%) than men (3.3%). [10] The present study with 22,861 persons suggests similar prevalence of gallstones in India and Bangladesh, Indo-Gangetic areas.

The prevalence of GBD is more than 1.5 times in persons aged 50 and above compared to those aged 30-49 as also reported in previous studies[2].Past history of surgeries was linked with GBD.[22] In the survey, previous medical history of abdominal surgery and diabetes are positively associated with GBD. In case of male and female models, these variables have positive association but not all are significant. Genetic history of any blood relative suffering from GBD also shows positive association. Significant associations were reported between family history of GBC and GBC.[23]

Multiple pregnancies and use of oral contraceptive in females is one of the listed risk factors of GBD.[24] Our results show that women with multiple pregnancies have a higher chance of GBD. Relative risk is not calculated for oral contraceptives with only 17 of 3,022 females using them (sample less than 25 cases).

The factors specifically significant to this area surveyed appear to be items of food and water. The consumption of food item chickpeas and drinking unprotected water from well, pond and river are local factors. The influence of proximity of river appears significant in Vaishali District. This is further strengthened by the cluster analysis where mean value of all pollutants are higher in Vaishali District.

Prevalence of gall bladder cancer is high in our survey, though confidence interval is wide due to small absolute numbers of patients with GBC. We did not have a histological confirmation to verify. However, the ultrasonography was reviewed by two expert radiologists. This survey also leads us to observe that lower gallstone prevalence does not translate to low gall bladder cancer rates and factors other than gallstones need to be studied to understand the carcinogenic pathway. The use of ultrasonography at field level is a useful procedure for mass screening for gallbladder disease.

Acknowledgements: We thank International Institute for Population Sciences for funding this project. We gratefully acknowledge the partial financial assistance from Sir Ratan Tata Trust Mumbai towards procuring the mobile sonography units.

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Kumar, Raghubansh Mani Singh, Smita Dwivedi, Nazish Zafar, Sarita Pawar, Jeba Kumar, Pratima Zore

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