RISK FACTORS FOR GALL BLADDER CANCER IN KARACHI

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Background: Frequency of gallbladder cancer in Karachi has been reported to be 8% and that from other parts of Pakistan varies between 6-7%. This is very high as compared with the Western studies. With this in mind a case control study was designed to identity risk factors responsible for gallbladder cancer. **Methods:** This case control study included 107 histologically proven cases of gall bladder cancer from Jinnah Postgraduate Medical Centre, Civil Hospital and two private hospitals of Karachi. Age and sex matched controls were of two types. Those with and without cholelithiasis screened sonographically. Demographic, socio-economic factors, life-style, dietary habits and dietary intake were recorded on a proforma. The cases and controls were compared for various factors using odds Ratio. **Results:** Among 107 cancer cases 27 were males and 80 females (M:F=1:3). Mean age of males was 59 years (range 35-82 years) and females 53years (range 31-70 years). One hundred and five (98%) had associated choleliathiasis. Important risk factors appeared to be gallstones, high parity, young age at first delivery, low fiber and Vitamin A intake ($p<0.01$), high fat intake ($p<0.01$), prolonged fasting hours/habit of missing dinner(OR:6.8), using repeatedly boiled or improperly stored ghee or oil(OR:2.6). **Conclusions:** According to this case-control study major risk factors for gall bladder cancer were gallstones, dietary mal practices and poorly balanced diet. Poorly stored/ processed food acts as a promoter in the presence of gall stones and may favour cancer development.

Key words: Gallbladder carcinoma, choleliathiasis, diet, dietary habits.

INTRODUCTION

Gall bladder carcinoma carries a high mortality and a low five year survival rate (<2.1%).[1-3] Although uncommon in the West[4]a high frequency (6-8%) of this malignancy has been reported from Pakistan.[5-7] In its early curable stage this cancer is asymptomatic and symptoms when present mirror those of choleliathiasis.[1] Inspite of high frequency and grave mortality risk factors for this disease have not been clearly understood.[8]

Some risk factors identified by various researches are gallstones, duration of disease, dietary factors including vitamin intake and smoking. Many of those suggested in reality may be a consequence of the older age of the population.[9]

This study is one of the few to approach the question of identification of risk factors for gallbladder cancer using a case-control study, comparing gall bladder carcinoma patients with normal subjects and patients with choleliathiasis. Controls are age and sex matched to determine the age independent risk factors involved in the causation of gallbladder carcinoma.

MATERIAL AND METHODS

One hundred and seven (107) histologically proven cases of gall bladder cancer were taken from the surgical and radiotherapy departments of Jinnah Postgraduate Medical Centre (JPMC),Civil Hospital, and few private hospitals of Karachi. Two types of age and sex matched controls were used, those with and without gallstones (Controls with gallstones: 205 and controls without gallstones i.e normal controls: 203). Controls were screened for presence or absence of gallstones by ultrasongraphy. Both cases and controls were interviewed using a questionnaire which included demographic and socioeconomic factors, smoking, alcohol and tobacco use, betel chewing, life-style, dietary habits and past medical history. A validated diet history was used to estimate the daily intake of calories, fats, carbohydrates, proteins, cholesterol, fiber and vitamin A. Regarding dietary habits a detailed history was taken about the habit of missing meals especially dinner indicating prolonged fasting hours, which increase lithogenicity of bile and thereby precipitate stone formation. The practice of storage and processing of food was also recorded in detail.

Data was analyzed by using SPSS Version-10. Descriptive statistics like mean, standard deviation, percentage etc. was computed for data presentation. Association between gallbladder cancer and different risk factors was determined by Odds ratio (OR). Student's t-test for independent samples was used for comparison of age at first delivery and dietary intake. Significance of test was taken at $p<0.05$.

RESULTS

Among 107 cancer cases 27 were male and 80 female (M:F=1:3). Mean age of males was 59 years (range 35-82) and females 53 years (31-70 years)(Table-1). All except 2 patients (in whom only biopsy was taken during laparotomy with no mention of presence or absence of stones) had stones (98%). Prolonged history of gall stones (diagnosed on ultrasound) was present in 79(75%) cases. In 205 controls, with cholelithiasis, disease was of 1-3 years duration. High parity, young age at first delivery (Table-2) high fat and low fiber intake (Table-3) and habit of missing dinner (Table-4) were common in patients with cancer and controls with cholelithiasis. Factors specific to cancer group were, consumption of edibles stored at room temperature for 10 hours or more and/rewarming of repeatedly thawed food.

Table-1: Age (Mean ± SD) according to sex in cases and controls

Sex	Cases Gall bladder Ca (n=107)	Controls (Gall stones) (n=205)	Controls (Normal) (n=203)
Male	59±12(n=27)	58±13 (n=41)	57±12(n=54)
Female	53±8 (n=80)	52±10(n=164)	52±11(n=149)

Table-2: Women Age (Mean ± SD) of First delivery and Parity

Parameters	Cases Gall bladder Ca (n=80)	Controls Gall stones (n=164)	Controls Normal (n=149)
Age first delivery	18 ± 3	18 ± 4	20 * ± 3
Parity	8 ± 4	8 ± 4	6 * ± 3

*P<0.05 compared with Cases (Gall bladder Ca) and Controls

Table-3: Diet of Subjects

Subjects	Cases Gall bladder Ca (n=107)	Controls Gall stones (n=205)	Controls (Normal) (n=203)
Caloric intake	2434 ± 417	2648± 468	2576± 480
Total protein	67 ± 20	74 ± 21	85± 24
Fats	102 ± 35	111 ± 22	57 ± 18
Carbohydrates	314 ± 72	329 ± 82	410 ± 86
Fiber	24 ± 14	23 ± 7	27 ± 8
Vitamin "A"	302 ± 192	574 ± 304	650 ± 392
Iron	18 ± 5	18 ± 5	22 ± 5

Difference significant: P<0.01 as compared to Controls (Normal)

Table-4: Dietary Habits of Subjects

Dietary habits	Cases (Ca GB)	Controls (Normal)	Odd Ratio Cases (Ca GB vs Controls (Normal)
Missing dinner	51 (48%)	24 (12%)	6.8 (3.7-12.5)
Reuse of boil-ed Ghee / oil	74 (69%)	73 (36%)	4.0 (2.4-6.8)

Many female cancer cases of this study worked as maid to financially support their family. From there they received left over eatables of previous day which were already stored overnight these eatables were used by them not before eight to ten hours, as they worked in three to four houses and reached their home by evening. From these houses they also received ghee or oil which was left over from frying fish and others eatables. They stored this ghee or oil at room temperature and used it in making their bread and other dishes. At times they also fried eatables and stored the left over ghee or oil to be used later. Male cancer cases were mostly labourers coming to Karachi for jobs. They had no proper house in Karachi and took meals from small hotels or hawkers where preparation of meals was mostly done by using repeatedly boiled ghee or oil left over from frying eatable and stored for future use. Smoking and tobacco use were also more common in cancer cases (Table 5). Histologically 73 (68.2%) cases had adenocarcinoma, 25 (23.5%) squamous cell carcinoma, 7 (6.5%) undifferentiated and 2(1.7%) other types of tumors.

DISCUSSION

This study suggests that the major etiological factor for carcinoma gall bladder in study population were gall stones which were present in 105 (98%) cases. A significant association between chololiathiasis and biliary cancer (OR=19.5) has also been reported in a recent hospital based study from United States.[9]

Among Chile, Swedes and Czeckoslovak-ians the risk of gallbladders cancer was 7 times more among patients with stones than those without stone.[10-12] Duration of gall bladder disease was of 10 years or more in 75% of our cases, whereas in controls with stones the duration was only 1-3 years. This indicates that the length of time for which stones are harboured play an important role in the etiology of gall bladder carcinoma. As previously observed, both gall bladder cancer and choleliathiasis occurred at a relatively younger age in Pakistan.[5]

Mean age in the current study was 59 years for males, and 53 years for females with a peak frequency in the sixth decade of life and more than 86% of the patients were under 60 years of age. The age in other studies[11-12] varied from 60 to 80 years and no case of cancer was encountered below the age of 50 years.[13] This age difference may be more apparent than real as the life expectancy in Pakistan is low but even after the adjusting the present data according to age and sex distribution of Karachi 80% cancer occured below the age of 60 years while a study from Canada[14] showed that 84% of the cases were above the age of 60 years. Women were affected three times more often than men.

The relation of parity and age at first delivery showed positive correlation with gall bladder cancer. Parity increased the risk of gall bladder cancer, when the first birth occurred before the age of 25 years. The risk was reduced when first birth occurred after the age of 30 years.[13] All cases in the present study were below 30 years and 98% were under 24 years at the time of first delivery. Thus this study indicates significant inverse relationship of age at first delivery and risk of gall bladder cancer among parous women. High levels of estrogen during pregnancy may explain the observed pattern.[13]

Table-5: Addiction among Cases and Controls

Smoking	Cases (Ca GB)	Controls (Gall Stones)	Controls (Normal)	Odds Ratio	
				Cases(G.B.Cancer) vs ControlsGall stones	Cases(G.B.Cancer) vs Controls (Normal)
Smoking	20 (74%)	21(51%)	19(35%)	2.7 (0.8-9.0)	6.8(2.2-21.3)
Tobacco	2 (7%)	-	3(6%)	N.A	1.6(0.2-13.1)
Female	(n=80)	(n=164)	(n=149)		
Smoking	10 (12%)	13 (8%)	11(7%)	1.7 (0.6-4.3)	1.8 (0.7-4.8)
Tobacco	36 (45%)	49 (30%)	35 (24%)	1.9 (1.1-3.5)	2.7 (1.4-5.0)

Analysis of diet showed that cancer risk was positively associated with low total calorie, high fat and low fiber and vitamin A intake. These results further suggest total calorie intake and other dietary factors which are potentially linked with cholelithiasis, probably play an important role in causation of gall bladder cancer.

Detailed analysis of dietary habits of cases and controls indicated that prolonged fasting hours, storage of food at room temperature for long periods, improper processing of food and reuse of boiled ghee were more frequent. OR being 6.8, 11.2, 4.1 and 2.6 respectively (Table-4). When compared with both gallstone controls and healthy controls. Prolonged fasting affects the size of bile acid pool and promotes gall stone formation. Defective storage, especially in hot and humid climate promotes contamination with carcinogenic mycotoxin such as Aflatoxin B produ-ced by Aspergillus Flavus. Improper processing and repeated heating of food produce some type of carcinogens.[14,15] Carcinogens may also be ingested due to social habits, like betel chewing and tobacco use. Smoking, betel chewing and tobacco use was relatively more common in cases (Table-5) than in two types of controls. This is in accordance with reported association.[9] Most important risk factors postulated for gall bladder cancer were gall stones and defective diet and

dietary habits. Many recent investigations have speculated that diet may be causative in as much as 30-40% of cancers in men and 60% of cancers in women.

CONCLUSIONS

Change of cultural practices i.e. early marriage/ pregnancies improvement of dietary habits and early elective surgery for both asymptomatic and symptomatic patients with gallstones are likely to reduce the risk of gall bladder cancer.

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