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Gall Bladder Cancer and some epidemiological factors: A cross sectional study.

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Abstract

Gall bladder cancer is the most common malignancy of the gastrointestinal tract in women. Cholelithiasis is frequently associated with carcinoma gallbladder and is the most common associated factor independent of age or sex. Diet has been a suspected risk factor for gallstones since long time. We investigate the association of some clinical, non-clinical and dietary risk factors with gall bladder cancer in North Indian population. In this cross Sectional Study, total 82 patients aged 18-70 year with gallbladder cancer were enrolled. A detail questionnaire was filled through the counseling to take their dietary history and other information. Lipid profile was done by using the commercially available kit. Our result showed that most of the subjects were postmenopausal female belongs to age group of 51-60 years, high parity and upper lower socioeconomic status having gallstone, jaundice, high triglycerides, high cholesterol and low high density lipoprotein (HDL) level. The use of contraceptive pills was strikingly high in premenopausal female patients. In conclusion, our data of demographic, clinical, non clinical and dietary habit is positively associated with gall bladder carcinoma.

Keywords: Gall bladder cancer, Gallstone, epidemiological factors.

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Introduction

These days the world is heading towards various types of non-communicable diseases, which are also known as modern epidemics. Among these modern epidemics, cancer is the second most common cause of mortality in developed countries and tenth most common cause of mortality in the developing countries. Cancer, which is defined as abnormal growth of cell, can affect any tissue or organ of body. Gallbladder cancer was first described in 1777. More than 200 years later, late diagnosis and absence of effective treatment for many patients remain typical features of this disease [1, 2].

Gallbladder cancer (GBC) is the most common biliary tract malignancy worldwide and more common than cholangiocarcinoma, which somehow has received more attention than gallbladder cancer from surgeons. Incidence rates of gallbladder cancer are low (around 1 per 100 000 per year) in the west (United States, United Kingdom, Australia, and New Zealand). Areas of high incidence rates are in Central and South America, Central and Eastern Europe, and Japan. Recently, the Indian Council of Medical Research1 has reported that incidence rates for gallbladder cancer in women in Northern India- more than 9 per 100000 per year are one of the highest in the world. Gallbladder cancer is the most common malignancy of the gastrointestinal tract in women [3] and the most common cause of malignant surgical obstructive jaundice in northern India [4]. Several northern Indian centers had reported many experiences with gallbladder cancer in the 1970s and 1980s [5-8]. The All India Institute of Medical Sciences (AIIMS), New Delhi group has highlighted the dismal prognosis in patients with gallbladder cancer [9, 10]. The highest frequency of the disease is found among females over the age of 65[11].

Cholelithiasis is frequently associated with carcinoma gallbladder in up to 40%-100% patients and is the most common associated factor independent of age or sex [12]. The risk of carcinoma gall bladder in patients with gall stones may be increased 4 to 7 times [13] and patients with gallstones >3cm in diameter have a much higher risk [14]. Hypercholesterolemia is common finding in adults and pure cholesterol gallstones are more common as compared to other types of gallstones [15]. Cholesterol is water insoluble lipid, and it is digested in intestine after micelles formation. Micelles are aggregates of phospholipids, bile salts, and cholesterol, and vesicles are closed spherical bilayers of phospholipids with associated cho-

lesterol. There are three stages of gallstone formation, super saturation, nucleation and aggregation [16]. Cholesterol crystals form on the surfaces of these vesicles and grow within the mucin gel. Cholesterol crystals are glued together by bile proteins to make gallstones [17-20]. Although the mechanism underlying this association is unclear both gallstones and gallbladder cancer predominate in females and are associated with obesity and multiple pregnancies, conditions related to higher levels of estrogens, suggesting that endogenous estrogens are involved in the pathogenesis of these conditions by altering bile acid composition and gallbladder motility [21-23].

Female sex hormones are the obvious basis for this gender difference. It is therefore not surprising to find that parity is a risk factor [24]. During pregnancy, biliary sludge (consisting of cholesterol crystals, calcium bilirubinate and mucin) develops in up to 30%, [25] while gallstones form in 1-3% [26]. The link may be biliary sludge, a potential precursor to cholesterol gallstone formation. Following delivery, sludge disappears in over half, even as 30% of small stones (<10 mm diameter) vanish [25]. Such a return to normal, likely accounts for parity being only a modest risk factor. Estrogen is the culprit [27]. The current use of low-dose (compared to high dose >50 mg) oral contraceptives presents quite a modest risk that may even decrease with time [28]. In contrast, postmenopausal women on estrogen replacement therapy have a definitely increased risk [29]. Diet has long been a suspected risk factor for gallstones. One source of evidence for this is the presumed link between cholesterol and gallstones. In fact, cholesterol overfeeding is the primary means of inducing supersaturated bile and cholesterol gallstones in animal models [30]. Therefore, we conducted a cross-sectional study to assess the association of some demographic, clinical, non- clinical and dietary risk factor with gallbladder cancer in North Indian population.

Material and Methods

The present cross-sectional study was carried out in the department of Physiology with the collaboration of Department of General Surgery at King George's Medical University, Uttar Pradesh, Lucknow during 2011-2012. The demographic characteristics include age, sex and socioeconomic status. Non-clinical risk factor includes parity, menstrual status and use of contraceptive pills among premenopausal female. Diagnosis of gallstone, jaundice serum level of triglycerides, total cholesterol and high-density lipoprotein were taken as clinical risk factor. Use of vegetarian diet, non-vegetarian diet, mustard oil and refined oil were included in dietary habit.

Total 90 patients reported to the outdoor patients department (OPD) of General Surgery for the stomach pain or some gastric problem and with a provisional clinical diagnosis of gall bladder cancer were included in the study. However due to incomplete data, 8 subjects were excluded and 82 subjects were registered for the study. 3.0 ml blood sample was taken from each registered subjects for the estimation of lipid profile. The study was approved by institutional ethics committee and informed consent was obtained from all the subjects. Interview technique was used to collect the information about demographic characteristics, non-clinical characteristics and dietary habit. A questionnaire developed specially for the study was used for the interview. Socioeconomic status was determined as per the modified *Kuppuswamy's socio-economic scale* [50]. Gallbladder cancer and stone was confirmed by the ultrasound and C.T Scan report. The estimation of lipid profile was done by Merk KIT with the help of Merk Semi Auto Analyzer.

Result

The demographic characteristics of subjects are illustrated in Table 1. Majority of the subjects included in the study belong to 51-60 years age group and upper lower socioeconomic scale. During the random selection of subjects, only 6 male and 76 female subjects were found. As most of the subjects were female, we also focused on the menopausal status, parity, and use of contraceptive pills among premenopausal females as non-clinical risk factors (Table 2). Most of the females were with high parity and postmenopausal. 85.7% premenopausal females were contraceptive users. As clinical risk factor, most of the subjects had gallstone, Jaundice, high triglycerides, total cholesterol and low high-density lipoprotein (Table 3).

Table 1. *Distribution of Study Subjects According to Demographic Characteristics*

Characteristics	Number of subjects n=82 (%)
Age (in years)	
< 40	21 (25.6)
41-50	12 (14.6)
51-60	30 (36.5)
61-70	19 (23.1)
Sex	
Male	6 (7.3)
Female	76 (92.6)
Socio-economic status	
Upper	12 (14.6)
Upper middle	15 (18.2)
Lower middle	18 (21.9)
Upper lower	25 (30.4)
Lower	12 (14.6)

Table 2: *Distribution of female Subjects According to Non-clinical risk factors*

Characteristics	Number of subjects n=76 (%)
High Parity (>3child)	69 (90.7)
Menstrual status	
Premenopausal	21 (27.6)
Postmenopausal	55 (72.3)
Contraceptive Users (premenopausal females)	18 (85.7)

Table 3: *Distribution of Study Subjects According to Clinical risk factors*

Characteristics	Number of subjects n=82 (%)
Gallstones	79 (96.3)
Jaundice	62 (75.6)
High Triglyceride (>150 mg/dl)	70 (85.3)
High Cholesterol (>200 mg/dl)	59 (71.9)
Low HDL (in female<50 mg/dl & in male <40 mg/dl)	55 (67.0)

Table 4: *Distribution of Study Subjects According to their Dietary patterns*

Characteristics	Number of subjects n=82 (%)
Vegetarian `	12 (14.6)
Non-Vegetarian	50 (60.9)
Vegetarian and Non-Vegetarian both	20 (24.3)
Mustered Oil Users	75 (91.4)
Refined oil Users	4 (4.8)
Mustered oil and Refined oil users both	3 (3.6)

Table 4 includes the dietary pattern of all subjects in which most of the subjects were non-vegetarian and mustard oil user in comparison to the use of vegetarian diet and refined oil.

Discussion

In the present study, we have investigated the association of some demographic, clinical, non-clinical and dietary habit with the gallbladder cancer in North Indian population. There are several considerations why it seems reasonable to investigate these characteristics as risk factor in relation to the gall bladder cancer. First of all Gallbladder carcinoma is a relatively infrequent neoplasm but shows a marked geographic, ethnic and socioeconomic variation [31-33]. The main victims of the disease were elderly postmenopausal females as compared to the males with median age of 51 to 60 years. In some studies including our study most of the subjects belonged to upper lower socio-economic status [34, 35]. The reason behind it might be the lack of knowledge in person with upper lower socio-economic status, sedentary life style at higher age and hormonal imbalance due to high parity because it was already reported that metabolic and life style factors including obesity, dietary habits, infection and parity also contributes to the occurrence of gallbladder cancer [36-38]. Moreover, as our finding suggested that increased use of oral contraceptives among premenopausal female might be a serious risk factor for the disease. This observation was consistent with a previous report showing that current use of oral contraceptives presents quite a modest risk that may even decreases with the time[28] and meanwhile others reported inconsistent observations [35, 39].

The greater incidence of gallstones in older persons is frequently reported in the literature [40]. This tendency was also reported in the present study. Biochemical analysis has shown that cholesterol gallstones form an important independent risk factor [41]. The occurrence of obstructive jaundice was also found in majority of subjects and seems to play an important role in disease development. Although it's exact etiology is unknown and several risk factors have been proposed. Our findings suggest that the high serum level of triglyceride, total cholesterol and low level of high-density lipoprotein was strongly associated with gall bladder cancer. This finding was consistent with a previous report from different countries [42-45] while some could not find such relationship with gallbladder cancer [46, 47]. The exact reason for this controversy was still unknown.

The role of dietary factors in gallbladder carcinogenesis is now well defined. Our result showed that non-vegetarians were more prone to gallbladder cancer rather than vegetarians and the fact was supported by *Panday et. al. (2002)* who had shown the protective effect of vegetables on gallbladder carcinogenesis while consumption of red meat was associated with increased risk of gallbladder cancer [48]. The study of *Misra S, et al, (2003)* was consistent with our finding that the consumption of carcinogenic impurities in mustard oil may contribute to elevated incidence of gall bladder cancer in North India [49].

On the basis of findings of present study prognosis in our study group was very poor specially in advance stages. The information about other risk factors like family history of gallstone, life style information, and fertility were either insufficient or incomplete for statistical analysis. Thus, here we were only presenting the percentage value of our selected parameters, but the given data might be helpful to raise the new hypothesis and understanding of new parameters related with the development of gall bladder cancer.

Conclusion

Based on the findings of our study the postmenopausal females with age group of 51-60 years and upper lower socioeconomic status were more prone for the gall bladder cancer. The increased use of oral contraceptives among premenopausal female might be a serious risk factor for the disease. The consumption of non-vegetarian diet, mustard oil and lack of knowledge regarding the health may also be a risk factor in upper lower socioeconomic person. The limited number of studies and their contradictory results give rise to a need of more studies with large population in this direction.

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Competing interest:
All authors declare that they have no conflicts of interest.