Epidemiological Factors in Gall Bladder Cancer in Eastern India-A Single Centre Study

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Abstract India has high incidence of Gallbladder carcinoma with regional variation in incidence possibly due to environmental factors. Prospective study of all the gall bladder cancer in our hospital over 18 months analysing how the epidemiological factors are influencing the disease. Incidence-Four cases per 100,000 populations per year. The peak incidence was in 41 to 50 years group (49.20 %). Male to female ratio was 1:3.8. Majority (69.84 %) were in lower socio-economic group. 61 out of 63 patients (96.62 %) were non-vegetarians. 60.34 % and 19.04 % patients weighed between 50 and 55 kg and 55 and 60 kg respectively ($p=0.003$). Male smokers had significantly higher risk ($p=0.0001$). Gall stones were present in 45 out of 63 cases (71.42 %). 45 out of 63 patients were typhoid carriers ($p<0.05$). Pain abdomen was the commonest complaint (87.30 %), followed by pallor, lump in right upper quadrant, nausea & vomiting and jaundice in 71.42 %, 69.84 %, 66.66 %, 31.74 % patients respectively. This data highlights high prevalence of gall bladder carcinoma in Eastern India. Better hygiene and water supply to prevent

typhoid carriers, prevention of malnutrition, early intervention for cholelithiasis, importance of balanced diet, increase in awareness about risk of tobacco and alcohol consumption-all are highlighted as significant modifiable factors.

Keywords Gallbladder carcinoma · Epidemiology · Cholelithiasis

Introduction

Gallbladder cancer is a rare malignancy with a dismal outlook owing to its insidious onset, rapid local invasion and progression. It is more common in northern India while rarer in southern part of the country. Data on eastern part of the country is poor. Gall stones, choledochal cysts, chronic infections of the gallbladder and environmental exposure to specific chemicals such as Thorotrast are known predisposing factors.

There exists opportunity to identify prevalent factors in any specific geographic area. The use of focussed area specific primary prevention can reduce the incidence of this dreaded disease.

We took up a prospective study of all the gall bladder cancer presenting in our tertiary care hospital in eastern India over 18 months period. It is a mix of urban, semi urban and rural population with a catchment area of approximately 11 million populations. We assessed the incidence, presentation, and tried to identify any relevant risk factors Table 1.

Materials and Methods

All cases presented with gall bladder cancer over 18-months period were included in this prospective study. All

This study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study has been omitted.

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Table 1 A table comparing epidemiological factors with other studies that have highlighted them before

1.	Age Reference [6] and [25]	5th decade	Varies from 5th to 7th decade
2.	Sex (M:F) Reference [5]	1:3.5	1:3.4
3.	Low socioeconomic Background Reference [6, 26].	Significant ($p=0.001$)	Varies from significant ($p=0.03$) to non significant.
4.	Associated Gallstone Reference [14, 15, 27, 28]	Significant, (71.43 %)	Significant , varies from 69 to 90 %
5.	Diet (Non vegetarian) Reference [27, 29]	Significant $p<0.001$	Significant (especially for meat and egg, but varies with local composition) $p<0.05$
6.	Weight Reference [11]	Significant ($P=0.003$) (>55 kg)	Significant ($P=0.05$) (>60 kg)
7.	BMI Reference [22]	Less significant ($P=0.07$)	Significant ($P=0.02$)
8.	Smoking Reference [24]	Significant	Association less Significant
9.	Blood group (A+ and AB+) Reference [17]	Significant ($p=0.001$)	Less significant ($p>.05$)
10.	Typhoid carriers Reference [20]	Significant ($p<0.05$)	Significant ($p<0.05$)
11.	Reproductive factor [A] Parity Reference [22] [B] Menarche age Reference [24] [C] Higher age of last child birth Reference [24, 30–32] [D] Postmenstrual Reference [21, 30–32]	Significant ($P=0.001$) For four or more pregnancies. Significant ($p<0.05$) for <12 years Significant ($p<0.05$) (for >33 years) Significant	Significant ($P=0.02$) For three or more pregnancies. Significant ($P<0.05$) for <13 years Significant ($P<0.05$) (For 35 years compared to nullipara) [30–32] or (25 years) [24] Varies from inconsistent results [30–32] to significant [21]
12.	Clinical presentation Reference [4]		
	Pain abdomen (most common presentation overall)	87.30 %	85 %
	Pallor	71.42 %	Not specified
	Lump in right upper quadrant	69.84 %	40 %
	Nausea & vomiting	66.66 %	64 %
	Icterus	31.74 %	60 %

Cut off value for significance $P<0.05$

cases had histological proven diagnosis. Diagnostic modalities were clinical followed by imaging with Contrast Enhanced Computerised Tomography/Ultrasound/image guided biopsy and or laparotomy. Test of proportion/chi square test were used for statistical inferences.

Results

1. Total case 63 out of total hospital admission of 101 343 i.e. 0.062 % and total surgical unit admission of 9,893 patients i.e. 0.63 % (including all malignant cases for palliative or

therapeutic purpose) and out of 1,468 cases of patients with diseases of gall bladder i.e.4.29 percentage. Among 2,152 carcinoma patients admitted in the hospital during the same period, 63 cases (2.92 %) was gall bladder carcinoma. Out of 358 gastrointestinal tract carcinoma patients admitted in department of surgery during the same duration, 63 cases (17.59 %) had gall bladder carcinoma.

2. Age incidence: The peak incidence was in 41–50 years age group. Thirty-one patients (49.20 %) were in this age group. Gall bladder carcinoma is significantly higher for the patients older than 40 years both among males ($p=0.001$) and females ($p=0.000$ 1).

3. Male Female Ratio: Out of 63 gall bladder carcinoma cases, 50 were females. Male to female ratio in this study was 1:3.8, significantly higher for females ($p=0.001$)
4. Socio-economic: Out of 63 cases, 44 patients (69.84 %) were in class IV (Kuppuswamy's scale). Fourteen (22.22 %) and five (7.94 %) patients were in class III and II, respectively. Proportion of gall bladder carcinoma patients is significantly higher for socioeconomic class IV than class II ($p=0.0001$) and class III ($p=0.001$).
5. Occupational groups: Seven out of 13 male patients were manual labourers. Out of 50 females, 29 were housewives, six labourers and 11 maids. Only three and one patients were vendors and teacher respectively. Chi square test shows that there is significant association between occupation and occurrence of gall bladder cancer ($p=0.04$).
6. Dietary groups: 61 out of 63 patients (96.62 %) were non-vegetarians. Proportion of gall bladder cancer is significantly higher among non-vegetarians ($p=0.000001$).
7. Personal habits: Out of 13 male patients, 11 smoked "bidis" and cigarettes, 3 consumed alcohol and nine were betel nut chewers. Some of the male patients were both smokers and betel nut chewers/alcoholic. Out of 50 females, 23 chewed betel nut and 27 did not have any addiction. Chi-square test shows that incidence of gall bladder carcinoma is significantly higher among tobacco users in males ($p=0.0001$) and females ($p=0.04$).
8. Blood group: Out of 13 males' seven patients had A+ blood group, three patients had AB+, two had B+ and one had O+ blood group. Out of 50 females, 22 had AB+, 16 patients had A+ blood group, eight had B+, four had O+ blood group. Chi square test shows there is significant association between blood group and occurrence of gall bladder cancer ($p=0.001$). For males, proportion of patients having blood group A+ is significantly higher than B+ ($p=0.05$) and O+ ($p=0.04$). There is no significant difference between A+ and AB+. For females, proportion of patients having blood group AB+ is significantly higher than B+ ($p=0.02$) and O+ ($p=0.01$) there is no significant difference between A+ & AB+.
9. Body Weight: 60.34 % and 19.04 % patients were in the 45–55 kg and 55–65 kg body weight range respectively. Chi Square test shows that there is significant association between occurrence of gall bladder carcinoma and body weight ($p=0.003$).
10. Typhoid carrier state: Out of 13 male patients, 9 tested positive for carrier status (69.23 %) and out of 50 female patients, 36 tested positive (72.00 %). Chi square test shows that there is significant association between typhoid carrier status and occurrence of gall bladder carcinoma ($p<0.05$).
11. Reproductive factors: Out of 50 female patients
 - a. Mean age at menarche was 12.4 ± 1.3 Standard Deviation ($p=0.00001$)
 - b. Mean age at marriage (yrs) was 12.1 ± 2.9 Standard Deviation ($p=0.0001$)
 - c. Number of child births were 4.2 ± 2.1 ($p=0.001$)
 - d. Number of abortions were 0.4 ± 1.1 ($p=0.06$)
 - e. Number of times pregnant status was 4.3 ± 2.2 ($p=0.01$)
 - f. Mean age at first child birth was 19.2 ± 2.9 ($p=0.001$)
 - g. Mean age at last child birth was 33.5 ± 6.9 ($p=0.00001$)
 - h. Five patients (10 %) had pre-menstrual status.
 - i. Ninety percent had postmenopausal status (45 patients).
Chi square test shows that there is significant association between age of menarche, number of childbirths, and age of first and last childbirth, pre-menstrual and postmenstrual status and occurrence of gall bladder carcinoma.
12. Gallstones were present in 40 cases (88.88 %) as per ultrasonography and per operative findings.
13. Clinical features and Biochemical investigations:
 - a. Pain abdomen in 55 cases (87.30 %).
 - b. Jaundice in 20 cases (31.74 %).
 - c. Pallor in 45 cases (71.42 %).
 - d. Nausea and vomiting in 42 cases (66.66 %).
 - e. Fever was present in 11 cases (17.46 %).
 - f. Bowel obstruction present in 10 cases (15.87 %).
 - g. Weight loss was present in 40 cases (63.49 %).
 - h. Lump in right hypochondrium was present in 44 cases (69.84 %).
 - i. Clinically, ascites was present in 14 cases (22.22 %).
 - j. Leucocytosis was present in nine cases (14.28 %).
 - k. Bilirubin was raised in 20 cases (31.74 %).
 - l. SGOT and SGPT were raised in 49.20 % and 52.38 % respectively.
 - m. ALP was raised in 20 cases (31.74 %).

Discussion

The present study is an attempt to study the epidemiological parameters in a tertiary care teaching institution in a metropolitan city in Eastern India, with a drainage area and patient referral from both urban and rural areas of adjacent districts and states. After analysing our data, we compared the results with the data of other National and International Institutions.

Incidence

There are wide geographical variations. Some of the highest incidences are reported from countries of central and Eastern Europe (5–7.1/100 000 per year), Israel (especially in Jews of

European origin), Japan, and central and south America (4.2–14.6/100 000 per year) [1]. SEER estimates revealed an incidence of 1.1 cases per 100,000 populations per year in the United States [2]. In India, carcinoma of gall bladder is much more common in women in north and central part than in the west and south. In Kashmir, it is the third most common cancer in females after cancer cervix and breast cancer. In Delhi, gall bladder carcinoma is the fourth commonest malignancy, and most frequent gastrointestinal cancer in women [3]. It is the most common biliary-tract and third most common gastrointestinal-tract malignancy, constituting to about 0.3 % of total hospital admissions and 4.4 % of all malignancies in and around the Varanasi [4].

In our present study incidence of gall bladder carcinoma was found to be four cases per 100,000 population per year (calculating the drainage area population of 11 million population approximately and adjusting the data taken over 18 months) which appears similar to other parts of Gangetic belt in northern India. However, the percentage of this disease out of total hospital admission (0.062 %) and among all cancer patients (2.92 %) is actually lower than few other northern Indian parts, probably because the higher percentage of sick population attending in Hospital and higher incidence of other forms of malignancy.

Age

Worldwide, the incidence gall bladder carcinoma steadily increases with age, reaching its maximum in the seventh decade of life. In our study, the cases ranged from 28 to 72 years with peak incidence in 41 to 50 years age group (49.20 %).

Sex Ratio

Male: Female ratio is around 1:3.5 as per published literature [5]. In the study, 13 were male and 50 were female constituting a male to female ratio of 1:3.8 which is consistent with other studies.

Socioeconomic, Educational and Occupational Factors

Gallstones and lower socio economic status are independent determinants for early onset of gall bladder carcinoma [6]. Lower socio-economic status is indirectly a result of illiteracy and poor education standards. This leads to unemployment and decreased livelihood capacity influencing preventive aspects of Gall bladder cancer [7].

In our study (2009–2010), majority of the gall bladder, carcinoma patients (69.84 %) were in lower socio-economic group-IV as per the scale set by Kuppuswamy. One possible factor is neglect of health care in this strata specially delay in seeking treatment for gallstone disease.

Diet, Personal Habits and Body Weight

The regions of Eastern U.P. and Western Bihar where gall bladder carcinoma is highly prevalent, as is our catchment area, lie downstream of the river Ganges, which is the main source of water for drinking and irrigation. The river Ganges receives untreated domestic sewages and industrial effluents. It is quite likely that certain environmental pollutants are acting as carcinogens.

Red meat increases risk of gall bladder cancer while vegetables are protective [8]. There is also increased risk of gall bladder carcinoma in patients with taste for oily food and intake of animal proteins and fats such as fish, eggs, red meat etc. [9]. Ingestion of fruits and vegetables lowers the risk of gall bladder cancer. There is increased risk with increase in total calorie intake. A weaker association with carbohydrate, protein and cholesterol also exists. An inverse relationship for incidence of gall bladder carcinoma exists with fibre, vitamin C and E intake. Lowering of risk associated with vegetable consumption and increase in risk with added sugar in desserts and drinks is seen in gall bladder carcinoma [10].

In our study, 61 out of 63 patients (96.62 %) were non-vegetarians eating mainly fish, added on with chilli and spices. Majority of the gall bladder carcinoma patients reside along the Gangetic belt region. Combined effects of environmental pollutants and dietary factors could have a role in high incidence of gall bladder carcinoma in this region.

Weight of the person in kilograms and risk of gall bladder carcinoma are inversely related. As the weight increases (>60 kg), the risk of gall bladder carcinoma decreases significantly. Low BMI is a risk factor for gall bladder carcinoma [11].

In our study, 60.34 % and 19.04 % patients weighed between 50–55 kg and 55–60 kg respectively ($p=0.003$) before they started losing weight due to cancer cachexia. Majority of the patients in our set up are from low socio economic strata and not only the body habitus but overall malnutrition may be contributing to increased gall bladder cancer.

Personal Habits

Earlier published data on the relationship of alcohol consumption and chewing tobacco with gall bladder carcinoma remained inconclusive. Some studies suggested an increased risk, while others suggested that long-term alcohol use might play a role by reducing the cholesterol saturation of bile. Recent data however point more in favour of the conclusion that Alcohol intake, smoking (cigarettes per day) and number of tobacco chewing per day are all independent risk factors for gall bladder carcinoma [7, 12].

In the present study, the risk of gall bladder carcinoma was increased significantly in male patients having a history of smoking ($p=0.0001$). Statistical analysis for patients with a history of alcohol consumption was not carried out due to their small numbers. However, the risk is more in patients with habits of combination of smoking, alcohol consumption and tobacco chewing. In females, tobacco chewing is an important risk factor for the gall bladder carcinoma. Alcohol did not constitute a risk factor in females. May be the females patients, who were mostly from lower socioeconomic strata in our social setting, rarely consume alcohol.

Cholelithiasis

The association of cholelithiasis with gall bladder carcinoma is very strong. The gallstones are the commonest factor leading to gall bladder carcinogenesis. Chronic trauma and inflammation can induce epithelial dysplasia, carcinoma in situ and invasive cancer but a cause and effect relationship is not proven [13].

Gallstones are associated with gall bladder carcinoma in a range of 40–100 % cases, mostly 70 to 80 % cases [14, 15].

In our study, gallstones were found in 45 out of 63 gall bladder carcinoma patients (71.42 %). Consistent with other gall bladder carcinoma case series, our study also showed high incidence of cholelithiasis in gall bladder carcinoma patients.

Blood Group

Since the first report in 1953, which reported an association between blood group A and gastric cancer, numerous other reports have documented a high incidence of blood group A in various cancers including salivary gland, colon, uterus ovary and pancreas [16]. The increased risk of developing gastric and colonic cancer has been explained by expression of Forssman antigen in patients with these cancers. This antigen is similar to blood group A antigen. Due to this similarity, antibodies to blood group A also attack cancerous and pre-cancerous cells expressing Forssman antigen. Patients with blood group A and AB lack antibodies to antigen A. and hence, are more prone to development of cancer. Similar mechanism has also been implicated in gall bladder carcinogenesis with significant association of blood group A and AB and gall bladder carcinoma [17].

In our study, out of 13 male patients, seven had A+ blood group and three had AB+ blood group. Out of 50 female patients, 22 had AB+ and 16 had A+ blood group. Chi square test shows that there is significant association between blood group and occurrence of gall bladder carcinoma ($p=0.001$). Consistent with the study by Shukla, our study showed a significant association of AB+ and A+ blood groups and gall bladder carcinoma [17].

Typhoid Carrier Status

Among microbial agents, salmonella typhi has been implicated frequently with gall bladder carcinoma. Axelord first reported the association of typhoid carrier state and gall bladder carcinoma in 1978 [18]. Mellemgaard reported a six fold higher risk for hepatobiliary cancer among typhoid carriers but the exact mechanism of carcinogenesis is yet to be established [19]. Shukla found 8.5 times higher risk of carcinoma in culture positive carriers as compared to culture negative carriers [20]. Possible mechanism suggested is that Salmonella typhi, by degrading primary bile to secondary bile acids, promotes carcinogenesis.

In our study, 45 patients out of 63 gall bladder carcinoma patients were typhoid carriers ($p<0.05$). Majority of the patients came from lower socio-economic strata who consume unhygienic water. They were more prone to suffer from typhoid and become a risk category for gall bladder carcinoma [20].

Reproductive Factors

Increased frequency of gall bladder carcinoma in females suggested a possible role of hormonal factors. Human gall bladder contains both oestrogens and progesterone receptors, predisposing to gall stone formation and probably gall bladder carcinoma. Younger age at menarche, early age at first pregnancy, multiple pregnancies, number of live births and prolonged fertility may increase the risk of biliary tract cancer including gallbladder malignancy because of prolonged elevated levels of oestrogen and progesterone. Chao and Greager demonstrated the postmenopausal state as a risk factor associated with the development of gall bladder carcinoma [21]. La Vecchia reported a higher risk of gall bladder carcinoma in pregnant women [22]. Oral contraceptive use is however not associated with a higher incidence.

In our study, among the 50 female patients, mean age at menarche was 12.4 ± 1.3 . Number of childbirths was 4.2 ± 2.1 . Forty-five patients out of 50 patients were in postmenstrual group. Chi square test showed significant association between age of menarche, number of childbirths, postmenstrual status and occurrence of gall bladder carcinoma. Increased duration of exposure of estrogens and progesterone may play a role in gall bladder carcinogenesis.

Clinical Presentations

Gall bladder carcinoma has been quite difficult to diagnose preoperatively as the symptoms and signs are vague and non-specific. In most cases, it is discovered quite late, in a stage where cure is difficult, if not impossible. Pain is a presenting feature in nearly all the cases (97 %) followed by weight loss (77 %), hepatomegaly (65 %) and nausea and

vomiting (64 %) [23]. Shukla reviewed 315 patients and reported pain to be the commonest symptom (85 %) followed by icterus (60.3 %), lump and loss of appetite (40 % each) [4]. They noted hepatomegaly in 85.7 % and gall bladder was palpable in 47 %. Al-Hadeedi reported Pain abdomen, anorexia, jaundice, weight loss, right upper quadrant mass in 47.3 %, 39.4 %, 36.4 %, 39.4 % and 34.2 % respectively out of 38 patients of gall bladder carcinoma from Queen Mary Hospital, Hong Kong [24].

In our study, pain abdomen was the commonest complaint (87.30 %), followed by pallor, lump in right upper quadrant, nausea & vomiting and jaundice in 71.42 %, 69.84 %, 66.66 %, 31.74 % patients, respectively similar to previous results.

Conclusion

This sample data highlights high prevalence of gall bladder carcinoma in Eastern India. Factors like better hygiene and water supply to prevent typhoid carriers, prevention of malnutrition, and early intervention for cholelithiasis are important. Balanced diet, decreasing the red meat and increasing low fat, mineral and antioxidant rich diet, increase awareness about risk of tobacco and alcohol consumption-all are highlighted as significant factors which can prevent/decrease incidence of this otherwise dreaded disease. Overall socio economic improvement along with environmental pollution control and education to increase awareness can play important part for prevention.

Conflicts of Interest The authors declare that they have no conflict of interest.

References

- Diehl AK, Beral V (1980) Epidemiology of gall bladder cancer: synthesis of recent data. *J Natl Cancer Inst* 65(6):1209–1214
- <http://seer.cancer.gov/faststats/selections.php?#Output>
- Nandakumar A (ed) National Cancer Registry Programme. Consolidated Report of the Population Based Cancer Registries. Incidence and Distribution of Cancer:1990–96. Indian Council of Medical Research, New Delhi. pp 52–53. http://www.icmr.nic.in/ncrp/ncrp_p/cancer_reg.pdf
- Shukla VK, Khandelwal C, Roy SK, Vaidya MP (1985) Primary carcinoma of the gall bladder: a review of a 16 year period at the University hospital. *J Surg Oncol* 28:32–35
- Mallik IA (2003) Clinicopathological features and management of gall bladder cancer in Pakistan. A prospective study of 233 cases. *J Gastroenterol Hepatol* 18(8):950–953
- Dutta U, Nagi B, Garg PK, Sinha SK, Singh K, Tandon RK (2005) Patients with gallstones develop gall bladder cancer at an early age. *Eur J Cancer Prev* 14(4):381–385
- Tyagi BB, Manohar N, Raina V (2008) Risk factors for gall bladder cancer: a population based case control study in Delhi. *Indian J Med Paediatr Oncol* 29:16–26
- Pandey M, Shukla VK (2002) Diet and gallbladder cancer. A case control study. *Eur J Cancer Prev* 11:365–368
- Kato S, Nakagawa T, Kobayashi H, Arai E (1994) A report on gall bladder cancer. *Surg Today* 24:534–537
- Moerman CJ, Berns MP (1994) Reproductive history and cancer of the biliary tract in women. *Int J Cancer* 57:146–153
- Weiderpass E, Pukkala E (2006) Time trends in socioeconomic differences in incidence rates of cancers of gastrointestinal tract in Finland. *BMC Gastroenterol* 6:41
- Shukla VK, Chauhan VS, Misra RN, Basu S (2008) Lifestyle reproductive factors and risk of gall bladder cancer. *Singapore Med J* 49(11):912
- Dowling GP, Kelly JK (1986) The histogenesis of adenocarcinomas of the gall bladder. *Cancer* 58:1702–1708
- Chaudhary A, Dhar P, Sachdev A (1979) Primary carcinoma of the gall bladder. *Langenbecks Arch Chir* 350:33–42
- Mishra S, Chaturvedi A, Misra NC, Sharma ID (2003) Carcinoma of the gall bladder. *Lancet Oncol* 4(7):393–394
- Aird I, Bental HH, Fraser Roberts JA (1953) A relationship between carcinoma of stomach and ABO blood group. *Br Med J* 1:799–801
- Shukla VK, Pandey M, Gautam A (1995) ABO, Rh blood groups in cholelithiasis and carcinoma of the gall bladder. *Br Med J* 10:1693
- Axelord L, Munster AM, O'Brian TF (1978) Typhoid cholecystitis and gall bladder cancer after interval of 61 years. *JAMA* 217:83
- Mellemgard A, Gaarslev K (1988) Risk of hepatobiliary cancer in carriers of Salmonella typhi. *J Natl Cancer Inst* 80:288
- Shukla VK, Singh H, Pandey M, Upadhyay SK, Nath G (2000) Carcinoma of the gall bladder: is it a sequel of typhoid. *Dig Dis Sci* 45:900–903
- Chao TC, Greagar JA (1996) Primary carcinoma of the gall bladder in Taiwan. *J Surg Oncol* 61:49–55
- La Vecchia C, Negri E, D'Avanzo B, Franceschi S (1991) Risk factors for gall stone disease requiring surgery. *Int J Epidemiol* 20:209–215
- Perpetuo MCMO, Valdivieso M, Heliburn LK (1978) Natural history of gall bladder cancer. *Cancer* 42:330–335
- Al-Hadeedi SY, Moorehead RJ, Leaper DJ, Wong J (1991) Carcinoma of the gall bladder: a diagnostic challenge. *J R Coll Surg Edinb* 36:174–177
- American Cancer Society. Key Statistics for Gallbladder Cancer. Available at http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_are_the_key_statistics_for_gall_bladder_cancer_68.asp?sitearea=
- Weiderpass E, Pukkala E (2006) Time trends in socioeconomic differences in incidence rates of cancers of gastrointestinal tract in Finland. *BMC Gastroenterol* 6:41
- Pandey M, Shukla M, Shukla V (2008) Diet and gallbladder cancer. *Indian J Med Paediatr Oncol* 29:6–7
- Hsing AW, Gao Y-T, Han T-Q, Rashid A, Sakoda LC, Wang B-S et al (2007) Gallstones and the risk of biliary tract cancer: a population-based study in China. *Br J Cancer* 97(11):1577–1582, 3
- Rai A, Mohapatra SC, Shukla HS (2004) A review of association of dietary factors in gallbladder cancer. *Indian J Cancer* 41(4):148–151
- Randi G, Franceschi S, La Vecchia C (2006) Gallbladder cancer worldwide: Geographical distribution and risk factors. *Int J Cancer* 118:1591–1602
- Zatonski WA, Lowenfels AB, Boyle P, Maisonneuve P, Bueno de Mesquita HB, Ghadirian P et al (1997) Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH program of the international agency for research on cancer. *J Natl Cancer I* 89(15):1133–1138
- Pandey M, Shukla VK (2003) Lifestyle, parity, menstrual and reproductive factors and risk of gallbladder cancer. *Eur J Cancer Prev* 12(4):269–272