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Epidemiology of Gallbladder Cancer: An Update

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Abstract

Background: Carcinoma of the gallbladder is relatively rare tumor. It is characterized by selective geographical distribution and female preponderance. The disease is often detected late and has poor prognosis.

Methods: An extensive search of literature was carried out on Pubmed to identified epidemiological studies on gallbladder cancer. The studies were subdivided by various known factors or those who have been investigated.

Results: A total of 338 articles were reviewed. The proposed and investigated factors identified are chronic cholecystitis and cholelithiasis, racial ethical and genetic factors, dietary and life style factor, menstrual factor, carcinogens, occupational exposure, obesity, body mass index and many others.

Conclusion: The results of the present review show that there is no consensus on the cause of gallbladder cancer. Most of the studies lack sufficient power to decisively conclude any of the factors studied as the cause.

Key words: Gallbladder, cancer, carcinoma, neoplasm, epidemiology, gall stones, obesity, BMI, race, Diet

Introduction

cancer of the gallbladder continued to be a diagnostic and therapeutic challenge since the original description by M deStoll in 1777 [1]. In the United States population, the reported incidence of carcinoma of the gallbladder is 1-2.5 per 100,000 population [2-4]. The highest incidence is reported in females, from Poland 23.1/100,000 followed by Israel 13.8/100,000 and Japan [5]. It is commonest biliary tract and 3rd common gastrointestinal tract malignancy, constituting 4.4% of all malignancies and 0.3% of total hospital admission in Sir Sunderlal Hospital, Varanasi [6]. Gallbladder cancer is predominantly a disease of the elderly females with peak incidence in 5th to 7th decade. Reported age range at presentation in literature is 40-80 years [7-15]. The mean age at presentation reported from Varanasi was 50 years with a range of 40-60 years [6]. This suggests an early onset of disease in women of Indian subcontinent. Reported male female ratio ranges from 1:2-3.2 [6, 10-16]. The exact cause of carcinoma of the gallbladder is still unknown, many causative factors and hypothesis have been proposed. These are briefly reviewed in this section.

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Chronic Cholecystitis and Gallstones

The observation by Piehler and Crichlow that 40-50% of the patients with gallbladder carcinoma had a history of antecedent chronic cholecystitis led to the theory that chronic cholecystitis *per se* is a causative factor in pathogenesis [10]. However, frequent association of stones

precludes isolation of the effect of inflammation. Calcification of the wall of the gallbladder, the so-called porcelain gallbladder, is believed to be an end stage of chronic cholecystitis. The incidence of carcinoma in calcified gallbladder is 12.5-61% [17, 18], thus indicating it to be a high-risk group for developing carcinoma. In a recent population based study from Shanghai the risk of gallbladder cancer was found to be two fold in patients with gallstones again suggesting higher risk [19].

In the United States general population the frequency of gallstones reported in the Framingham study was 11% [20]. However, the incidence of association of gallstones in various series has varied from 40-100% [6, 9, 10, 16, 21-25]. Carcinoma of the gallbladder is extremely rare in Bantu population, which is also rarely affected by cholelithiasis [26], on the other hand there is a high incidence among South-western American Indians, where cholelithiasis too has been found to occur more frequently and at an early age than Caucasians [27] suggesting an association with gall stones. Approximately, Twenty-five percent of carcinoma, occurs without documented cholelithiasis [10]. Kijima *et al* [28] proposed that chronic trauma and inflammation of the gallbladder mucosa, caused by presence of gallstones induces epithelial dysplasia, which predispose to carcinoma, similar observations have also been made by Alonso deRuiz [29]. The size of calculi too correlate with probability of developing gallbladder carcinoma [30]. There are only a few epidemiological studies looking at malignant transformation in gall stones. Comfort *et al* [31] followed silent gallstones for 10-25 years and found that only fewer than 1% patients developed carcinoma. In another prospective randomized trial, 123 patients with gallstones were followed for more than 1000 person years, none of the patients developed carcinoma [32]. The clinical data does not establish a direct causative role for the gallstones, although the association is quite frequent to suggest a common antecedent or at least a facilitative role, how, is the question that still remains unanswered. Further, there is controversy over the cause or effect relationship with scientist suggesting that stone may develop later due to biliary bile acid condensation or gallbladder dysmotility that develop after carcinoma.

Racial and Ethnic Factors

There is a marked geographical difference in distribution of the carcinoma of the gallbladder. Observance of high prevalence of carcinoma of the gallbladder in certain population groups led to speculation about possible role of racial and ethnic factors in carcinogenesis. Sievers and Marquis [33] found carcinoma of the gallbladder to be the 2nd most common disease of gastrointestinal tract in American Indians. Richenbach [27] reported a six time higher incidence in Southwest American Indians compared to non-Indian population. Rudolph *et al* [34] found carcinoma in 4.5-6.0% of American Indians undergoing cholecystectomies. Krain [35] reported a high incidence of carcinoma of the gallbladder in Japanese, and Hart *et al* [36] found an incidence of 2.7/100,000 among Israeli population, incidence was also high in European born females who later migrated to Israel. Klein and Finck [37] found carcinoma of the gallbladder to be twice more frequent in Mexican population of Southwest America similar results are also reported by others [38]. Shukla *et al* [6] reported an incidence of 0.3% of total hospital admissions in Varanasi in India. In another study from Sweden looking at the gallbladder cancer incidence in migrant population it was found that this cancer was higher only in migrants from Indian subcontinent (3.84) and Chile [39].

Klein and Finck [37] reported abnormal hepatic bile with low ratio of bile acid and lecithin to cholesterol among southwest American Indians both with and without gallstones. Davion *et al* [40] reported racial difference in gallbladder motor functions among North American Indians and African blacks and suggested a possible role in cholelithiasis. Social and economical factors affecting dietary intake [41] and environmental factors may also be responsible for this wide geographical variation observed in various groups with carcinoma of the gallbladder [42].

Familial

The greater risk of developing same cancer in first degree relative of breast, stomach, colon and prostate cancer is well established [43]. Patients suffering from gallbladder carcinoma are known to develop second malignancy in 15% and family history of other organ cancer is present in 33% of the cases [44]. The first report of familial occurrence of carcinoma of the gallbladder was by Devor and Buechley [45] in 1979, from two families of Hispanic New Mexicans. The other report is by Trajber *et al* [46] from Brazil and by Garber and Shipley [47]. The nationwide Swedish Family-Cancer Database covering 10.2 million individuals for the years 1961-1998 from the Swedish Cancer Registry was studied and 1121 offspring with Liver and biliary tract cancers were identified [48].

A high risk for familial gall bladder cancer (SIR 5.21 (95% CI 2.07-10.80)) was identified and maternal transmission was suspected, this study provided the first evidence of familial occurrence of gallbladder cancer [48]. Fernandez *et al* from Spain to reported a relative risk to be 13 times for development of gallbladder cancer among family members [49]. Despite reports of cases and retrospective series, the exact role of genetic factors in causation of gallbladder carcinoma is still not clear however mechanisms like genetic predisposition [50], familial occurrence of anomalous pancreaticobiliary duct union [51], familial occurrence of gallstones [19], Association with other familial syndromes like Gardner's or familial adenomatous polyposis etc. [52, 53] and Methylenetetrahydrafolate Reductase Gene Polymorphism (MTHFR) have been reported [54].

Biliary Tract Anomalies

Anomalous Junction of pancreaticobiliary duct system is a congenital defect characterized by union of common bile duct outside the duodenal wall, because of the action of sphincter muscle this does not affect the union functionally but is associated with various complications such as cholangitis, gallstones, biliary tract cancers, pancreatitis and pancreaticolithiasis [55]. Attention has recently been focused on high incidence of cancer of the biliary tract in this anomaly [51, 56-61]. The incidence of malignant changes has been reported to be 15-40 percent [56, 58, 59]. There is an especially high incidence of cancer of the gallbladder in anomalous junction without bile duct dilatation [62]. The incidence of gallstones in patients with carcinoma of the gallbladder associated with anomalous junction is very low [59]. The reflux of pancreatic juice into the gallbladder with consequent chronic cholecystitis with intestinal metaplasia, a precancerous condition leading to differentiated carcinoma has been implicated [58], the concentration of bile within the gallbladder of these patients may also promote gallbladder carcinogenesis [58, 63].

Xanthogranulomatous Cholecystitis

Lipids accompanying with bile pigments enter into connective tissue of the gallbladder wall, resulting into inflammatory process. This lipid is sometimes oxidized to a colored chromolipid and the condition is called ceroid granuloma [64] or ceroid like histiocytic granuloma [65] or fibroxanthogranulomatous inflammation [66]. These terms now have been replaced by xanthogranulomatous cholecystitis [67], a descriptive term first used by McCoy *et al* in 1976.

Incidence of xanthogranulomatous cholecystitis ranges from 0.7% in Illinois [68] to 1.8% in Sheffield with Japan having an intermediate rate of 1.2% among routine cholecystectomy specimens [65]. Although recent studies from Japan claim an incidence of 9% [65, 69].

Xanthogranulomatous cholecystitis not only mimics carcinoma in various ways, but there appears to be a possible association between the two [70]. Gallbladder carcinoma was over represented in a series of patients from Sheffield, with xanthogranulomatous cholecystitis [71] and the condition was more frequent than expected in series from Manchester [72]. The reason for this association is not clear. However, it may simply be

that, xanthogranulomatous cholecystitis and adenocarcinoma are both complications of cholelithiasis and cholecystitis of particular duration or degree, or it could be due to the tissue disruption by carcinoma facilitating the entry of bile into stroma [72]. The association, nevertheless, is important as both lesions are represented in the same specimen, and there is always a possibility of overlooking the carcinoma altogether [73-81].

Bacterial Infections

The role of anaerobic and aerobic bacteria in biliary tract disease is well investigated [82, 83]. Among aerobes *E. Coli*, other coli form bacilli and enterococci are frequently encountered. *Clostridium perfringens* is the most common anaerobic organism [84, 85] along with anaerobic gram +ve cocci [86], *B. fragilis*, lactobacilli [87] and actinomycetes [88] in small number of cases.

Dawson [89] demonstrated the toxicity of unconjugated bile acids and reported that unconjugated deoxycholate in concentration of $5x10^{-3}$ Molar causes dissolution of mucous membranes with loss of villi. Anaerobic bacteria very effectively deconjugate bile acids whereas aerobic bacteria except *Streptococcus feacalis* and few other species are inactive [90], suggesting a possible role of bacterial deconjugation in tumorigenesis. Lowenfels [91] proposed that in patients with gallstones the secondary bacterial infection releases cancer initiator or promoters from bile.

Kinoshita *et al.,* [92] reported formation of highly reactive intermediates during glucronidase action of biliary glucronides, which binds to DNA and so is potentially carcinogenic. Shukla *et al*., [93] reported an increased bacterial degradation of primary to secondary bile acids, which are potent tumor initiator and promoter. They suggested this to be a possible mechanism of carcinogenesis in patients with gallstones [94].

Recently, lots of interest has generated in *Helicobacter species* in gallbladder carcinogenesis. Pandey *et al*., studied the *Helicobacter bilis* in 50 cases of gallbladder cancer and failed to demonstrate any association with gallbladder cancer [1.05 (95% CI 0.49 to 2.24)] [95]. However, in the meta analysis of the pooled data of 10 identified case control studies a higher risk was found in patients who had *H. bilis* infection 4.13 (95% CI 2.68-6.36) [95]. In another study they looked at all Helicobacters reviewing 15 studies hepatobiliary cancers identified on Pubmed, Scopus and Google scholar search. Of these, five were single group and 10 were case control. These 10 case control studies were included in the meta-analysis. The cumulative sample size of cases was 205, of which 115 were positive (56%) for *Helicobacter*, while among 263 controls 53 (20%) were positive for *Helicobacter* infection. The positivity rate in case control studies was higher than that in single group studies. The cumulative odds ratio for the study sample was 8.72 (95% CI 4.78e15.91) (Z 7.07; $p < 0.00001$) [96].

Typhoid Carriers

The production of tumor promoters and initiator by bacterial degradation of bile in gastrointestinal tract is well established [97]. Association of chronic typhoid carrier state and carcinoma of the gallbladder was first reported by Axelord. Welton *et al*., [98] observed an excess of cancer of hepatobiliary system in typhoid carriers; this has been later confirmed by other studies [99, 100].

Caygill *et al*., [101] studied the cancer mortality in cases of Aberdeen typhoid outbreak of 1964, who did not become carriers and the carriers registered with communicable disease (Scotland) unit and found increased mortality from cancers in chronic typhoid carriers concluding that a) progression to chronic carrier states and not typhoid infection per se carries the excess cancer risk, b) in hepatobiliary system the main risk appears to be in the gallbladder. Their results suggested the lifetime risk of developing gallbladder cancer in 6% of the typhoid carriers [101]. Higher association has also been reported from India [102].

Ulcerative Colitis

The association of ulcerative colitis and biliary tract diseases is known. A less frequent lesion is carcinoma of the extrahepatic biliary tract which is 5-10 times more frequent in patients with ulcerative colitis than in general population [103, 104]. Majority of these carcinomas are of the bile duct, eight patients which carcinoma of the gallbladder is reported [103-107]. The cause of this malignant transformation is not known. They frequently occur without pre-existing hepatobiliary disease, and have been known to occur up to 53 years after total colectomy. Carcinoma of the gallbladder in association with ulcerative colitis therefore seems to have a different pathogenesis. A causative role of altered bile metabolism is also speculative [10, 89].

Benign Neoplasms

Benign neoplasms of the gallbladder have been identified in 0.15-8.5% of the resected gallbladders [10]. With increased use of grey scale ultrasonography (USG), as the investigation of choice in the patients with biliary symptoms, has led to the increased detection of benign neoplasms, which until the last decade were considered to be of little significance and unlikely to undergo malignant change [108, 109]. Christensen and Ishak [110] reviewed and classified 180 gallbladder tumors and found three cases of carcinoma *in situ* associated with nonpapillary adenoma.

Evidence for adenoma-adenocarcinoma sequence comes from the study by Kozuka *et al* [111] who reviewed 1605 gallbladders and found seven adenoma with malignant changes besides 79 invasive carcinomas, all the benign adenomas were less than 12 mm in diameter. All adenoma showing malignant changes were over 12 mm and most invasive carcinomas were over 30 mm. There was a female preponderance in both adenoma and invasive carcinomas. The need to define the precise relationship between the benign gallbladder neoplasm and the carcinoma was emphasized by Aldrich and Bismuth in their review[112]. Only five cases of carcinoma gallbladder developing in adenomyomatosis have been reported in literature [113-115], despite the fact that adenomyomatosis constitute 40% of benign gallbladder neoplasms.

Carcinogens

The chemical similarity of carcinogen methyl cholanthrene to naturally occurring bile acids has led to speculation that carcinoma of the gallbladder could be caused by such chemical transformation, *in vivo*. Methyl cholanthrene has not been identified as such in bile of patents with carcinoma [12, 23, 29, 116]. Fortner and others [117-119] had been able to induce cancer by implanting pellets of chemicals into gallbladder of cats and dogs. Simmers and Podolak [120] failed to produce carcinoma by inserting methyl cholanthrene pellets in the gallbladder of guinea pig, establishing a significant species difference. Introduction of foreign body in gallbladder is also known to cause carcinogenesis. Petrov and Krotkina [121] induced carcinoma by inserting glass rods in guinea pig gallbladder.

Feeding numerous other chemicals including O-aminoazotoluene and various nitrosamines has induced carcinoma of the gallbladder [26, 116, 122-124]. Cryer and Krissanne linked biliary tract cancer to benzidine, 3, 3-dichloro benzidine and M-toluenediamine [116, 125]. Kowalewski and Todd reviewed the probable multifactorial etiology of this disease by inserting cholesterol pellets in the gallbladder of hamsters and later feeding them dimethyl nitrosamine, 67% developed cancer compare to 6% controls fed on carcinogen only [126].

Occupational Exposure

The California tumor registry review of 1,808 cases of gallbladder and bile duct cancer found a significant association between gallbladder cancer and workers of rubber [124], automobile, wood finishing and metal fabricating industries [10]. Kelly and Chamberlain found 27.6% of their patients employed in rubber industry, 23.4% in

non-rubber industries [26]. However, they concluded it to be only a coincidence.

Secondary Bile Acids

Interest in the hypothesis that bile acids are possible precursors of carcinogenic aromatic hydrocarbons has now faded. However, there is a large body of evidence that bile acids are tumor promoters and co-mutagens [127-129], can cause dysplastic changes in colonic mucosa [130-132], and are strongly implicated as tumor promoters in colon carcinogenesis [133, 134], and in gastric cancer [135]. Bile acids are also reported to influence the growth and morphology of cultured human fibroblasts [136] and promote hepatoma formation in rats. Shukla *et al*., [93] reported higher levels of secondary biliary bile acids in patients with carcinoma of the gallbladder, suggesting a possible role in gallbladder carcinogenesis. Similar results are also reported by Jain *et al*., who found the ratio of secondary to primary bile acids to be significantly higher in GBC cases than gallstone controls (20.8 vs. 0.44) [137].

Free Radical

Free radical mechanism is increasingly being implicated in almost all disease states [138-147]. Their relationship to neoplastic transformation in particular has, attracted much attention [148-152]. Biological oxidation involves generation of electrons from mitochondria and if improperly managed by cellular antioxidants, is liable to induce generation of reactive oxygen species (ROS). The ROS may cause oxidant damage to enzymes, nucleic acids, cytosolic and membrane proteins and the cellular lipids, largely present in cell membrane.

Carbon tetrachloride and halogenoalkanes are most common chemical pollutants produced by industries and automobiles. These can be absorbed from the skin or ingested through water and produces hepatotoxicity in virtually all species. The hepatotoxicity of halogenoalkanes involves reductive dehalogenation by cytochrome p450, of the hepatic microsomal mixed function oxygenase system to form trichloromethyl (CCl_3, and trichloromethylperoxy CCl_3O_2) radicals, [152-157]. Although a consensus on direct proof for generation of carbon tetrachloride free radicals has not yet been reached, indirect evidence of the microsomal formation of this is overwhelming [157]. Genetic variants of OGG1 and XRCC1, important enzymes that participate in base excision repair pathway, have been thought to confer interindividual variations in susceptibility to gallbladder cancer (GBC). Observed OGG1 Cys/Cys genotype frequency was significantly higher in GBC patients (OR = 2.93; 95% CI = 1.14-7.51). The increased risk was more prominently observed in female patients (OR = 5.92; 95%CI = 1.20-29.13), and those with gallstone (OR = 5.50; 95%CI = 1.99-15.16)[158]. The Gln/Gln and Arg/Gln genotypes conferred significantly low risk for GBC while XRCC1 Arg194Trp polymorphism showed no association. The carriers of Arg-Gln haplotype consisting of 194Arg and 399Gln alleles of XRCC1 were also found at significant low risk, interaction with tobacco was not found to modulate the risk [158].

Carcinogenesis is thought to occur in two stages, first the initiation stage during which a physical, chemical or biologic agent directly causes an irreversible alteration in molecular structure of DNA and second, the promotion stage during which the expression of genes that regulate the cell growth and differentiation is altered [159]. Recent experiments strongly suggest that free radicals are active in both the initiation and promotion stages of cancer, making it an

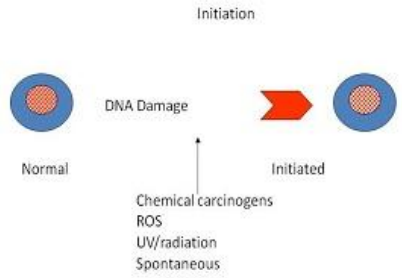

Figure 1: Showing the stage of initiation wherein a normal cell on exposure to reactive oxygen species acquire mutations and become initiated.

important etiological agent in carcinogenesis [160] [Figure 1,2].

Lipid Peroxidation Products

Polyunsaturated fatty acids (PUFA) are particularly vulnerable to free radical attack. The oxidative damage is termed as lipid peroxidation and causes a reduction in membrane fluidity and permeability besides producing highly genotoxic and tumorigenic aldehydic lipid peroxidation products [153, 157, 161-166]. Linolenic acid (C18:2) and arachidonic acid (C20:4) contain number of methylene interrupted double bonds, which are particularly prone to hydrogen abstraction. This process can be autocatalytic. However, it can be halted by the action of free radical scavenger molecules [156, 167-176]. The NADPH-cytochrome p450 electron transport chain present in liver microsome act as electron donor and promote generation of free radicals, thereby initiating lipid peroxidation [155, 156].

Of various lipid peroxidation products, 4-hydroxynonenal (HNE) has a high neoplastic potential [177-184]. Shukla *et al*, have shown an increase in concentration of HNE in gallbladder bile of patients with carcinoma of the gallbladder [164]. A further significant decrease in concentration of polyunsaturated fatty acids (linolenic and arachidonic acid) in patients with

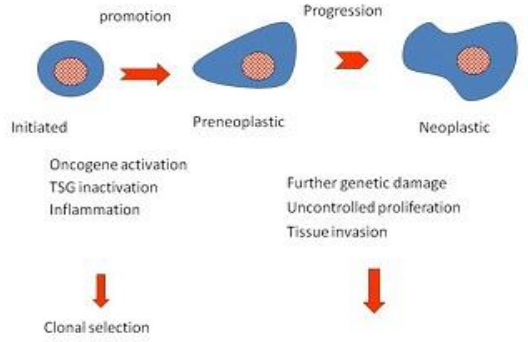

Figure 2: Showing the stages of Promotion and progression wherein an initiated cell continues to accumulate mutations and become preneoplastic and thereafter progress to neoplasia. Some of the reactive oxygen species and lipid peroxidation are thought to act in the stage of promotion as well.

gallstones has been demonstrated [165, 166, 185-187] leading to speculation that increase lipid peroxidation along with non-functioning of the gallbladder which causes HNE to be retained in gallbladder for long duration and in high quantity may be responsible for the malignant conversion [165, 188].

Heavy Metals and Metallothionein

A wide variety of trace metals including copper, lead, cadmium, iron, molybdenum, chromium, silicon, and silver are reported in increasingly high quantity in persons with cancer [189-194]. Inutsuka *et al.,* reported an elevated copper/zinc ratio in malignancy, including one case of carcinoma of the gallbladder, and further increase in advance disease especially with liver metastasis [195]. Morgan reported a high cadmium concentration in renal and hepatic tissues of patients with bronchogenic carcinoma. He attributed this cadmium toxicity to its role as antimetabolite of zinc [196]. It is reported that cadmium is a potent uncoupler of oxidative phosphorylation *in vitro* and defective respiration is characteristic of tumor cells [197]. The incidence of gallbladder cancer in the Gangetic plain rises from Varanasi to Patna in Bihar, a belt of 300Kms. These region lie downstream on Ganges which is the main source of drinking, irrigation and bathing water in these part and also receives untreated domestic sewage and industrial and agricultural waste. The main source of pollution is the tanneries upstream in Kanpur which uses heavy metal based compounds for leather tanning. High concentration of cadmium has been reported in sewage, irrigation water and vegetables grown in this area. The heavy metal concentrations recorded are much higher than WHO recommendations. Metals especially cadmium, are excreted by liver and concentrate in gallbladder, and are known carcinogens [95, 198, 199].

To investigate the association of toxic heavy metals with gallbladder cancer Shukla VK *et al* (1998) carried out a case-control study [200]. The results showed significantly higher biliary

concentrations of cadmium, chromium and lead among cancer patients when compared to biliary concentrations among patients with gallstones. However, no association was made with the drinking water and food heavy metal levels. High levels of heavy metals in the bile of patients with carcinoma of the gallbladder have been reported [200-202].

Metallothionein (MT) are a group of closely related low molecular weight proteins with high affinity for the metals of group I and IIB of the periodic table [203]. High levels of endogenous MT bound to copper are observed in mammalian liver during gestation, and early postnatal period [204, 205]. The exact role of metallothionein is not yet clear, however, it points to intercellular storage of essential metals [206]. MT synthesis can be induced by injection of certain metals [207-210]. Increase MT expression has been demonstrated in patients of carcinoma of the gallbladder compared to controls and patients with cholecystitis [211], suggesting a possible role of heavy metal toxicity in gallbladder carcinogenesis and as cadmium replaces copper from endogenous MT, increase concentration of cadmium may give rise to increase concentration of copper in hepatic tissue and hence an altered copper/zinc ratio as has been observed by various workers [195, 203, 210].

Altered gallbladder motility

Altered duodenal motility is less talked about as a probable cause of gallbladder cancer. However, it has been extensively studied in patients with cholelithiasis [212-215]. The cholesterol nucleation theory gives further strength to this observation. Altered gallbladder motility has been observed during pregnancy [216, 217] in patients administered female sex hormones [217, 218] and among patients on parental nutrition [219, 220] patients with gall stones too have been found to have altered gallbladder motility [221-226].

The contractile response of gallbladder smooth muscle cells to cholecystokinin is reduced in patients with gallstones, Chijiiwa *et al*., isolated smooth muscle cells from the gallbladders of patients either with or without gallstones and their direct contractile responses to cholecystokinin-octapeptide (CCK-8) were examined at physiological concentrations [227]. No difference in contractile response to CCK-8 was found between the patients with cholesterol gallstones and those with black pigment stones suggesting no difference in contractile response of normal or diseased gallbladder [227]. The development of gallstones is a well recognized complication of therapy with the long-acting somatostatin analogue, octreotide in patients with acromegaly [228]. Fasting cholecystokinin levels were examined and showed no significant change over 6 months, whereas the post-prandial levels demonstrated a significant decrease (p less than 0.01) during therapy, yet remained significantly higher than fasting levels [228]. Three of these four patients with persistently impaired gall bladder motor function were subsequently shown to have developed either gallstones or biliary sludge during the course of therapy suggesting that only those who have persistent gallbladder dysfunction only develop gallstone [228]. Bile acids have been found to be negative regulator of cholecystokinin [229]. Everson *et al*., reported in an autopsy study that the incidence of gall stone was not high in patients receiving oestrogen treatment, but the cholecystectomy rate was higher, suggesting impaired emptying [230]. Another study concluded that in some individuals with continuing symptoms suggesting gallbladder disease but normal oral cholecystograms, cholecystokinin cholecystography may be helpful in identifying physiologic dysfunction of the gallbladder [231]. Cholecystokinin (CCK) is an important modulator of gallbladder motility through CCK type-A receptor (CCKAR).

CCKAR rs1800855 AA genotype is found to be associated with increased risk of gallbladder cancer (odds ratio = 2.37, 95% confidence interval (CI): 1.36-4.14) compared with subjects with the TT genotype [232]. Also female carriers of the CCKAR haplotype C-T-C-T (rs2071011-rs915889-rs3822222-rs1800855) had a reduced risk of

gallbladder cancer (odds ratio = 0.61, 95% confidence interval: 0.43-0.86) compared with those with the G-C-C-A haplotype [232]. Estradiol dipropionate treatment and castration in experimental studies have been found to induce gallbladder cancer in male hamsters [233]. One of the mechanism through which the diet and other carcinogens are thought to work is reduced motility of the gallbladder and effect of various enzymes on the gallbladder and sphincter of Oddi function. Zhang *et al.,* evaluated the effect of vasointestinal peptide (VIP) and cholecystokinin (CCK) on Sphincter of Oddi function in Guinea pigs [234]. They noted the inhibitory effect of VIP and stimulatory effect of CCK on the function. Xu *et al*., done extensive work on gallbladder dysmotility and the gallstones and found that beside CCK, Cavolin 3 is also associated with decreased motility, they further observed improvement in motility with use of prokinetic agents [235-239]. An study evaluated different pharmacological diets failed to elicit any relationship with gallbladder emptying [240, 241] even though its generally understood that diet rich in fiber and fat elicit gallbladder emptying much better than low fiber low fat diet. The intake of alcohol and estrogen has been found to reduce the gastric emptying by increasing the sphincter of Oddi tone has been proposed to explain the effect of diet and female preponderance of gallbladder cancer and gall stones [242-244]. Reduced sensitivity of gallbladder to cholecystokinin has also been reported in experimental animal [245]. Similarly somatostatin has been found to be a potent inhibitor of gallbladder contractility [246]. Orlistat (tetrahydrolipstatin) is a potent inhibitor of gastric and pancreatic lipase activity causing a diminution of free fatty acids in the intestinal lumen, as release of cholecystokinin (CCK) depends on the presence of free fatty acids in the small intestine it is proposed that CCK release and the gallbladder contractility will be decreased after Orlistat [247]. Gomez *et al*., proposed that "endogenous bile exerts a negative feedback effect on release of CCK and neurotensin induced by triglyceride and on basal plasma levels of CCK; bile is unnecessary for the stimulation of endocrine cells in the intestinal mucosa by dietary fat; and measured basal levels of CCK and neurotensin represent a real amount of circulating peptide in the fasting state, that is, the basal levels are real and not artifactual" [248]. Studies have shown upregulation of CCK receptors by leptin and enhanced gallbladder motility [249]. Various mechanism of reduction of gallbladder motility in normal gallbladder has been proposed in the literature, however, its actual effect on gallbladder carcinogenesis specially in presence of chronic cholecystitis and gall stones is not clear as they themselves can alter the gallbladder motility.

Life style

Life style factors are found to be associated with cancer. Japanese collaborative cohort study evaluating 46395 individuals who worked full time or were self employed were followed up for mean of 17 years [250]. A total of 95 biliary tract cancers were observed in this cohort including 23 cancer of the gallbladder. shift work was associated with a statistically non-significant increase in the risk of biliary tract cancer, with an HR of 1.50 (95 % CI: 0.81-2.77), among rotating shift workers. When the analysis was limited to extrahepatic bile duct cancer, a significant association appeared, with a multivariable-adjusted HR of 1.93 (95 % CI: 1.00-3.72) for rotating shift workers [250]. Brenner *et al.,* estimated 7.9% higher incidence in people with physical inactivity [251]. Booth *et al.,* also showed higher chronic illness in penitents with decreased activity including cancer [252]. It has been proposed that inactivity either because of obesity or gain in weight or by its association to other chronic illnesses like diabetes increases the risk of cancer including that of gallbladder[253]. An increase in risk of gallbladder disease with a progressive increase in pack-years of cigarette smoking, and diastolic blood pressure has been observed however there was a decrease in risk with an increase in physical activity, after controlling for the effect of other variables [254]. Diabetes has been found to be an independent risk factors for gallbladder cancer independent of body mass index and waist height ratio [255]. Panda *et al*., found association of GBC with

illiteracy [odds ratio (OR) 8.00, P=0.000], lower socioeconomic status (OR 2.45, P=0.000), and the use of nonliquefied petroleum gas cooking fuel (OR 4.17, P=0.000) [256]. Another study from India too found higher association with low socio economic status [257], other than India social and economic status has not been found association with gallbladder cancer. Education has also been found to be a risk factor. In a study from Hungary a shorter education period (< 10 years / > or = 16 years) showed higher risk of gallbladder cancer (age-adjusted OR (95%CI): 3.2 (1.2-8.7)) [258]. Similar results were also seen in an study from India where in about half of the patients with carcinoma of the gallbladder and gallstone were either illiterate or had a very low level of education (primary or below)[259]. A Hindu preponderance was seen in this study thereby suggesting that religion might also be playing a role in gallbladder carcinogenesis [259]. Ahrens *et al* failed to find any association with tobacco habits however higher incidence was seen in those consuming alcohol [260]. Higher incidence of pancreatic cancer has been seen in smokers [261], cigarette smoking, alcohol consumption has been found to be associated in literature reviews [262, 263] and study from Netherlands [264]. Another study by the same authors show that neither smoking at the time of interview (odds ratio (OR) 1.5; 95% confidence interval (CI) 0.9-2.4) nor smoking 2, 5 or 10 years before were associated significantly with the cancer [265]. Similarly current alcohol consumption (OR 1.0; 95% CI 0.6-1.5) or drinking 2, 5 or 10 years earlier too did not show significance. Interestingly, among current long-term consumers of alcohol a reduced risk (duration of use > 38 years vs < 25 years: OR 0.4; 95% CI 0.1-0.9) was observed, however, the risk was higher for late starters (starting age > 38 years vs < 21 years: OR 2.7, 95% CI 1.0-7.5) [265]. They observed a modifying effect of alcohol consumption on the smoking-cancer relationship where the risk for current smokers increased when they did not drink alcohol (OR 3.4, 95% CI 1.3-8.5) [265]. A study from Eastern India showed higher association with smoking and gallbladder cancer among males, however no association was seen in women where the incidence is higher [266]. Jain *et al*., too showed association with tobacco [OR: 4.1 (1.8-9.7); p < 0.001)] [137, 137]. CYP rs743572 genotype polymorphism has been found to be associated with increased risk of GBC in tobacco users at hetero genotype and dominant models [267]. The TCrs2486758-AGrs743572 genotypic combination was also associated with increased GBC susceptibility [267]. Another study looking at the CC genotype of CYP1A1 found significant association with gallbladder cancer (OR 2.3, 95% CI=1.1-4.5, P=0.026) [268]. In a study from Japan, a total of 113,496 participants (65,740 women) aged 40-89 years at entry were followed for 15 years, during this period, 165 gallbladder cancer deaths (95 women) were observed. Among women, the hazard ratio of current smoker was 2.00 [0.91-4.42], while among men, HR of current smoker was 2.27 [1.05-4.90] when adjusted for age and drinking. There was no clear association between alcohol consumption and the risk. HRs of those who smoked 21 cigarettes or more per day and those with 801-1,000 cigarette-years were 3.18 [1.18-8.53] and 3.44 [1.40-8.45], respectively, and positive linear associations were observed by number of cigarettes per day (p for trend = 0.007) or "cigarette-years" (p for trend = 0.012). The alcohol dose too was linearly associated with risk (p for trend = 0.004), where the HR among those who consumed 72.0 g or more of alcohol per day was 3.60 [1.29-9.85] [269]. A study from Pakistan reported higher incidence among those with prolonged fasting hours/habit of missing dinner (OR:6.8) [270]. Similar results were also reported from India where long interval between meals [OR: 1.4 (1.2-1.6); p < 0.001] was associated with gallbladder cancer [137]. Urbanization and altitude of living has been identified as risk factor for cancers in Italy [271]. The drinking-water pool in northern California contaminated with asbestos of the serpentine type has been found to be associated with increased gallbladder and lung cancer [272].

Hormones, Parity and reproductive factors

The gallbladder functions to stores and concentrates bile between meals. Gallbladder

motor function is regulated by bile acids via the membrane bile acid receptor, TGR5, and by neurohormonal signals that are linked to digestion, like, cholecystokinin and FGF15/19 intestinal hormones, that trigger gallbladder emptying and refilling that controls the flow of bile in intestine and enterohepatic circulation [273]. The gallbladder also have secretary function where in epithelium secretes bicarbonate and mucins, both provide cytoprotection against bile acids [273]. It is also to be noted that gallbladder motor function is also controlled by female hormones. It has been shown that progesterone decreases the gallbladder motor function and thus interfere with the gallbladder function and may promote gallbladder diseases like stone and may be the carcinoma. The function of estrogen is mediated through estrogen receptors and hence number of studies have evaluated the estrogen and their receptor in gallbladder cancer compared with controls. In an attempt to establish the link researches have studied the estrogen and progesterone status in gallbladder cancer. In a study from Pune studying 47 patients, receptor expression was seen in 23.4%, of these both were present in 8 patients. The expression correlated with metaplasia, dysplasia and early operable cancers [274]. In another study, ER expression was significantly high (28%) in gallbladder cancer than in chronic cholecystitis (0%; P = .012), PR expression did not differ in two groups (benign 40%, 95% CI, 21.8-61.4; malignant 52%, 95% CI, 33.5-69.9) [275], higher expression was seen in patients with metaplasia. In another study high concentrations of oestrogen in gallbladders of persons who underwent cholecystectomy for cholelithiasis [276]. In a population-based, case-control study including Swedish female Multi- and nulliparous women were found to have higher risk of biliary tract cancers including gallbladder cancer [277]. Age at first birth was not found to be associated with cancer [277]. An excess risk was found for gallbladder (OR = 3.2) in a systematically examination of the relation between HRT use and the risk of various cancers in women aged 45-79 was found using data from a framework of case-control studies conducted in Italy between 1983 and 1999 [278]. The multivariate odds ratio (OR) of 3.2 (95% confidence interval: 1.1-9.3) for gallbladder cancer risk in those who had ever used HRT and the OR tended to rise with longer duration was seen in this first study from India [279]. Baskaran *et al*., found ER in the gallbladder mucosa in all the three groups studied (9/21 in carcinoma, 4/19 in gallstones, and 1/6 normal), whereas the expression of PgR was greater in carcinomas (13/18), less in cholelithiasis (4/12), and absent in normal gallbladders [280]. PR status also correlated with better survival and early stage of the disease.

The overall higher occurrence of gallbladder carcinoma in women and bile duct cancer in men suggest a role of hormonal factors [281]. Role of female hormones in cholesterol gallstones formation is well established [282]. A case-control study within the frame work of a programme for studying risk factors in relation to cancer (SEARCH programme, Surveillance on Environmental aspects in relation to cancer in humans), established by International Agency for Research on Cancer (IARC) has shown that younger age at menarche, early age at first pregnancy, higher number of pregnancies and prolong fertility may enhance the risk of extrahepatic biliary tract malignancies [283]. The exact role of female hormones is not yet clear, however, overall increased exposure to endogenous oestrogens and progesterone continues to be a high risk factors. Indian Study has shown age of menarche less than 14 years (83%) and the age of the first child birth less than 20 years to be risk factor for gallbladder cancer [257]. Sharma *et al*., examined association of CYP1A1-MspI, CYP1A1-Ile462Val, and CYP1B1-Val432Leu with GBC susceptibility, these enzyme system is involved in activation/detoxification of environmental carcinogens and endogenous estrogens. CYP1A1-MspI [CC] and CYP1A1-Ile462Val [iso/val] genotypes (p=0.006 and p=0.03, respectively) and CYP1A1 haplotype [C-val] (p=0.006) showed a significant association with gallbladder cancer, while CYP1B1-Val432Leu failed to show any association [284].

The common genetic variants in estrogen receptor genes on the risk of biliary tract cancers and stones were studied in a population-based case-control study in Shanghai, China, six single-nucleotide polymorphisms (SNPs), four in ESR1 (rs2234693, rs3841686, rs2228480 and rs1801132) and two in ESR2 (rs1256049 and rs4986938) were categorized in this study [285]. The ESR1 rs1801132 (P325P) G allele was associated with excess risks of bile duct [odds ratio (OR) = 1.7, 95% confidence interval (CI) 1.1-2.8] compared with the CC genotype, this was apparent among men but not among women as expected [285]. ESR2 rs4986938 (38 bp 3' of STP) GG genotype was associated with a higher risk of bile duct cancer (OR = 3.3, 95% CI 1.3-8.7) compared with the AA genotype, while none of the SNP's were found to be associated with cancer [285]. The data on receptor expression was reviewed by Barreto *et al*., [286] in 2009, wherein they reviewed 11 published studies and reported expression in 9 of these. The indirect evidence for this occurrence is abound. Hormone therapy (HT) is widely used for controlling menopausal symptoms and has also been used for the management and prevention of cardiovascular disease, osteoporosis and dementia in older women, one of the complications of hormone therapy is gallbladder disorders like gall stones and also cancer. Effect of HT has been studied in numerous series. Farquhar *et al*., reviewed Nineteen trials involving 41,904 women and found that in relatively healthy women, combined continuous HT significantly increased the risk of venous thrombo-embolism or coronary event (after one year's use), stroke (after three years), breast cancer and gallbladder disease [287]. Liu *et al*., [288] reported on 1,001,391 postmenopausal women (mean age 56) recruited between 1996 and 2001 from NHS breast screening centres and followed by record linkage to routinely collected NHS hospital admission data for gallbladder disease. During follow-up 19 889 women were admitted for gallbladder disease; 17 190 (86%) had a cholecystectomy. Compared with never users of hormone replacement therapy, current users were more likely to be admitted for gallbladder disease (relative risk 1.64, 95% confidence interval 1.58 to 1.69) [288]. In EPIC-Norfolk Study 117 women developed gallstones. Women who had ever used HRT had a risk of 1.94 (95% CI = 1.17-3.22) compared with women who had never used HRT [289].

Cytochrome P450C17alpha (CYP-17) is a key enzyme involved in estrogen metabolism and polymorphisms in CYP-17 are associated with altered serum levels of estrogens. The frequency of mutant allele A2 of CYP17 MspA1 gene polymorphism has been found to be higher among cancer (OR=5.13, 95% CI+3.10-8.51, p=0.0001), stone (OR=5.69, 95%CI=3.46-9.37, p=0.0001) and cancer + stone (OR=3.54, 95%CI=1.90-6.60, p=0.0001) when compared with the control group [290]. The lipid profile and estrogen level were significantly higher however there was no significant association between genotypes of CYP17 MspA1 gene polymorphism [290]. In another study 18 single-nucleotide polymorphisms (SNPs) in nine genes involved in steroid hormone biosynthesis, metabolism and transport were studied in a population-based case-control study in Shanghai, China [291]. The CYP1A1 IVS1 + 606 (rs2606345) T allele was associated with gallbladder [odds ratio (OR) = 2.0, 95% confidence interval (CI), 1.3-3.0] and bile duct cancers (OR = 1.8, 95% CI = 1.1-3.1) [291]. CYP1A1 was significantly associated with gallbladder (P = 0.004). The effect of CYP1A1 IVS1 + 606 on gallbladder cancer was more pronounced among non-obese (body mass index < 23) (OR = 3.3, 95% CI = 1.8-6.1; P interaction = 0.001). Among women taking oral contraceptives, the effect of SHBG Ex8 + 6 (rs6259) on gallbladder cancer (OR = 6.7, 95% CI = 2.2-20.5; P interaction = 0.001) and stones (OR = 2.3, 95% CI = 1.1-4.9; P-interaction = 0.05) was statistically significant [291].

Armstrong *et al*., reviewed role of hormones in carcinogenesis and concluded that endogenous hormones probably do not initiate cancer directly but may influence carcinogenesis by facilitation or inhibition of endogenous production of carcinogens; effects on the metabolic activation or inactivation of carcinogens; alteration of the susceptibility of tissues to the initiation of cancer;

promotion of the development of clinical cancer from initiated cells; and (theoretically) alteration of the body's capacity to eliminate initiated cells [292]. They further stated that most commonly postulated mechanisms of action are alteration of the susceptibility of tissues to initiation, and promotion of the once-initiated cancer. In human beings and, to some extent, in animals it is difficult to distinguish between these two mechanisms, both of which are based on hormone-induced cell proliferation, because the time of initiation cannot be pinpointed. Environmental factors may influence carcinogenesis by effects on the production, transport, peripheral action, inactivation and excretion of endogenous hormones [292].

Obesity and body mass index

Obesity and gallstones, both are related to insulin resistance, and are linked to an elevated risk of biliary cancer. The peroxisome proliferator-activated receptors (PPARs) and the retinoid X receptors (RXRs), expressed in adipose tissue, play a key role in the regulation of obesity-related insulin sensitivity, thus genetic variants of these two receptor genes may be related to biliary cancer [293].

Seven single-nucleotide polymorphisms in the PPAR-gamma, PPAR-delta, RXR-alpha, RXR-beta and INS genes with biliary cancer and stones were studied [293]. Relative to individuals with the RXR-beta C51T (rs2076310) CC genotype, those having the TT genotype had a 1.6-fold risk for bile duct cancer [odds ratio (OR) = 1.67; 95% confidence interval (CI) = 0.99-2.84], with a more pronounced association among men (OR = 2.30; 95% CI = 1.14-4.65; P interaction = 0.07) [293]. This marker was also associated with a higher risk of gallstones among subjects with a higher body mass index (BMI) (>or=23 kg/m(2)) (OR = 1.80; 95% CI = 1.09-2.94) [293]. Association between body mass index (BMI) and hormone-dependent tumors, was studied utilizing a cohort of 21,884 Swedish twins born during 1886-1925 [294], higher risk of gallbladder cancer was not found in this cohort.

Diet

As the gallbladder cancers are associated with the gallstones and have a unique geographical distribution, it has been hypothesized that they may have an association with diet. Several studies have been conducted in gallbladder cancer to explore the association with diet and life style factors. In a study from Italy, the gallstones were found to be independently associated with increasing age, number of pregnancies, body mass index and serum triglycerides, and with decreasing total (and low-density lipoprotein) cholesterol, suggesting a role for diet in formation of stones [295]. Abedin *et al*., [296] studied the effect of feeding mice with cholesterol and observed alteration in the biliary bile acid compositions. A fall in cholic acid (CA) and the chenodeoxycholic acid (CDCA) concentrations were found to increase on feeding mice with cholestrol [296]. They also demonstrated alteration of biliary acid composition by administration of lovastatin [297], suggesting that lovastatin therapy may produce gallstones. In an European multicentric study actually failed to demonstrate any association with the life style factors in biliary tract cancer [298]. This was probably due to small number of cases in their study.

In a study on Mediterranean diet usefulness of the olive oil was studied. A diet rich in monounsaturated fatty acids provides an adequate fluidity to the biological membranes, diminishing the hazard of lipid peroxidation of polyunsaturated fatty acids leading to generation of carcinogenic substances. It is also reported that the antioxidents present in the olive oil also help in preventing the carcinogenesis [299]. Besides, it is found to enhance the gallbladder emptying thus having a special effect on gallbladder. Baggio *et al*., [300] evaluated serum lipoproteins, biliary cholesterol saturation index, and gallbladder motility in healthy volunteers after feeding diet rich in olive oil. A significant decrease of mean total cholesterol, total apo B, LDL cholesterol, and total triglycerides was observed [300]. In the animal studies, the highest reduction in the biliary

cholesterol levels have been observed in sunflower oil fed animals [301]. Further alterations in hepatic acyl-CoA cholesterol acyl transferase (ACAT) activities, lipoprotein production and turnover and/or the rate or extent of gallbladder emptying in rabbits have also been observed[302].

Erythrocyte Fatty acid composition has been studied in the gallstones and gallbladder cancer as a marker of general fatty acid composition of the body and its effect on disease. Arca *et al*., [303] evaluated the erythrocyte fatty acid composition in patients with gallstones and not with stones and found no difference in the composition.

In the Italian study exploring the role of the diet in gallstone formation, A significant negative association was found between fiber intake for females (chi2 = 5.45; P = .02), and a positive association was observed carbohydrate (chi2 = 5.95; P = .01 for males; chi2 = 9.39; P = .002 for females) and protein intake only for males (chi2 = 10.92; P = .01) [304]. A higher prevalence of stones was observed among subjects who had an overnight fasting period of over 12 hours compared with those with less than 12 hours. (RR: 1.35; 95% CI: 1.01-1.80 for males; RR: 1.28; 95% CI: 1.03-1.60 for females) [304]. In Argentina the rate of gallbladder disease is as high as 20%. A study in Argentinean patients with gallbladder disease higher intake of fat, saturated fatty acids and cholesterol and consumption of carbohydrates, calcium, niacin and fiber below the recommended quantities has been reported [305]. Benini *et al*., [306] evaluated gluten free diet and its effect on gallbladder motility in patients with celiac disease and found that slow gallbladder emptying returns to normal with gluten free diet. Incidence of N-nitrosobis-(2-oxopropyl)amine (BOP) -induced gallbladder adenocarcinoma was found to be elevated in cabbage-fed hamsters irrespective of dietary fat intake [307]. Feeding high fat diet to hamsters on the other hand results in increase in pancreatic cancer [308].

In a case-control studies conducted in northern Italy between 1983 and 1996, a 50% reduction in gallbladder cancer was found with whole grain food intake [309]. In the study from Taiwan, no meaningful associations were observed [310]. Dietary Stearic acid (18:0) significantly reduce the proportion of hydrophobic secondary bile acids, resulting in a lower hydrophobicity index of the bile, It is further suggested that it may have altered the microflora populations that synthesize secondary bile acids thus influencing the entrohepatic circulation[311]. Cafestol, a diterpene present in coffee has been found to elevate cholestrol levels and thus may be lithogenic. It is also undergo glucuronidization and show very high concentration in bile [312]. In another study the intake of green tea was found to reduce the risk of biliary tract cancers, while coffee was not found to be associated with cancer risk [313]. In the Serbian study high energy intake (OR = 9.720, p < 0.001) and overnight fasting period (12 hours and longer) (OR = 4.285, p = 0.005) were the most important predictors of gallstone disease [314]. A 1989 study in the diet of Mexican Indians women with the high intake of total fat and linoleic acid had reduced risks of gallbladder disease [315]. High levels of sucrose intake and low levels of cholesterol intake were associated with an increased risk for both sexes though the effect was not statistically significant [315].

Legume lowers serum cholesterol and increase cholesterol saturation of bile, though the mechanisms of these effects are poorly understood, in a human study, legume consumption was found to reduce LDL cholesterol, increase mean cholesterol saturation, and lowering of the absorption of bile salts [316]. Similarly, soya based vegetable proteins lower the cholesterol, decreased serum low-density lipoprotein (LDL) cholesterol but not high-density lipoprotein (HDL) cholesterol or triglyceride has been observed with soya protein [317]. ascorbic acid deficiency impairs the conversion of cholesterol to bile acid elevates plasma cholesterol levels, and predisposes to development of cholesterol cholelithiasis

However, in a study in healthy volunteers there was no effect of short term ascorbic acid deficiency on plasma cholesterol and triglycerides; plasma cholesterol in high, very low, and low density lipoprotein fractions; biliary lipid composition and saturation index of gallbladder bile; synthesis, fractional turnover, or pool size of either cholic or chenodeoxycholic acids; output of fecal acid or neutral sterols; and fecal sterol balance [318].

Fish consumption has been shown to reduce the risk of many gastrointestinal tract cancer however in a case control study no reduction in risk was observed for gallbladder cancer, despite reduction in risk of esophagus, stomach, colon and rectal cancer [319]. This was probably due to inclusion of less number of patients with gallbladder cancer in their study. An study from Tehran showed unhealthy diet as a risk factor for gallbladder cancer, the risk was found to increase by 3.7 times [320]. The difference between diet of Indians in North America has been compared with that of Caucasians and it has been found that the Indian diet had higher carbohydrate, lower protein and lower fiber content than that of Caucasian women, who derived a higher percentage of energy from protein and had a higher intake of vitamin A, niacin and ascorbic acid [321]. Overnight fast was also longer among Indian women. In the study of Jhonston *et al*., high percentage of all women reported diets that did not reach the Canadian Dietary Standard (CDS) for total energy intake in kilocalories or for calcium, iron, vitamin A, thiamin or riboflavin [321]. Kato *et al*., reported intakes of animal proteins and fats such as fish, eggs, meat, etc., as reason for higher risk and ingestion of vegetables and fruits, and taking snacks were low risk factors for gallbladder cancer [322]. Kuller *et al*., in an review reported higher risk of cancer with fat rich diet, however, they stated that risk lowering by low fat diet is not known [323]. Similarly lowering of glycemic index of the food and lower calorie intake reduces the risk of gallbladder diseases [324]. The results on nutritional study has also been reported from Chile [325].

Mishra *et al*., examined the role of argemone oil and butter yellow in gallbladder carcinogenesis in animals [326] and reported that while argemone oil intake increase risk of gallbladder cancer, the butter yellow increase risk of gallstones with no effect on carcinogenesis. A reduction in risk with vegetables (ORs 1.0, 0.7, 0.4, P value trend < 0.01) and increase in risk associated with sugar added to drinks and desserts (ORs 1.0, 1.3, 2.5; P value trend <0.01) has also been reported [327]. Hungarian hot pepper consumption has been found to be a significant independent risk factor for GBC, while in this study no association was found with any other dietary variable studied [328].

In a prospective single group study from India, majority patients with gallbladder cancer were non-vegetarians (67%) and 84% of them consumed mustard oil as predominant cooking medium [329]. Another study showed increased risk with fatty food and residence in Gangetic belt as a risk factor for gallbladder carcinoma [330]. Khan *et al*., too found subjects taking non vegetarian diet to be at higher risk for gallbladder cancer [331]. In the study of Pandey *et al*., a significant reduction in odds ratio was seen with the consumption of radish (OR 0.4; 95% CI 0.17-0.94), green chilli (OR 0.45; 95% CI 0.21-0.94) and sweet potato (OR 0.33; 95% CI 0.13-0.83) among vegetables, and mango (OR 0.4; 95% CI 0.16-0.99), orange (OR; 0.45; 95% CI 0.22-0.93), melon (OR 0.3; 95% CI 0.14-0.64) and papaya (OR 0.44; 95% 0.2-0.64) among fruits. A reduction in odds was also seen with the consumption of cruciferous vegetables, beans, onion and turnip, however the difference was not statistically significant. On the other hand, an increase in the odds was observed with consumption of capsicum (OR 2.2), beef (OR 2.58), tea (OR 1.98), red chili (OR 1.29) and mutton (OR 1.2), however the difference was statistically not significant [41]. In another study from Varanasi protective effect of vegetable consumption has been seen [332]. In this study a low consumption of vegetables showed an increase in odds ratio for gallbladder cancer for almost all the vegetables studied. A significant inverse trend was observed for green leafy

vegetables and gallbladder cancer. An inverse association was observed for amaranth with an OR of 3.45 for the low vs. high level of consumption. Observed values were 2.14 for spinach, 1.86 for bathua, 1.02 for Bengal gram leaves, 2.26 for cabbage, 3.06 for fenugreek leaves, 1.95 for mustard leaves and 1.44 for radish leaves [332]. Fenugreek seeds too have been shown to have protective role and decrease cholesterol saturation in bile [333].

In the Shanghai based study the risk of gallbladder cancer was higher in those who consumed both preserved vegetables and salted meats food (OR:1.27, 95% CI: 1.06-1.52; OR: 1.18, 95% CI: 1.02-1.37, respectively) [334]. While a recent Japanese study showed that the increased consumption of vegetable and fruit is associated with a decreased risk of extrahepatic biliary tract cancers (HR = 0.49; 95% CI: 0.29-0.81), this study did not look at gallbladder cancer in isolation [335]. A study from Nepal also showed a 2.4 times increased risk of gallbladder cancer in current smokers [336].

Larsson et al., [337] studied the effect of two dietary modification in gallbladder cancer, they used Stop Hypertension (mDASH) diet and modified Mediterranean (mMED) diet and found that there is lowering of hazard of gallblaader cancer from both the diets [0.36 (0.20-0.64); & 0.42 (0.23-0.79)] respectively. The hazard for extrahepatic biliary tract cancer other than gallbladder cancer too was reduced in their study [337].

Cost analysis for the meat intake has also been done and it's found that Direct health care costs attributable to meat consumption are +0-16.5 billion for cancer, beside +2.8-8.5 billion for hypertension, +9.5 billion for heart disease, +14.0-17.1 billion for diabetes, +0.2-2.4 billion for gallbladder disease [338].

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