A review of association of dietary factors in gallbladder cancer

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Abstract

Gallbladder cancer (GBC) is the prominent malignancy of hepato-biliary tract, being the fifth most common carcinoma for gastrointestinal tract in United States. Epidemiological studies world wide have implicated dietary factors in the development of gallbladder cancer. The ecological evidences indicate considerable geographic variation in the incidence of gallbladder cancer. However the variations in GBC incidence of different populations might be partly determined by their dietary variations. Higher intake of energy and carbohydrate possibly increase the risk of gallbladder cancer. Obesity plays an important role in the causation of GBC. Adequate intake of fruits and vegetables probably reduce the risk of GBC. This nutritional preventive effect against GBC could be attributed to high content of vitamins, carotenes and fibers. They can not be too emphatically stated as the sole determinants of GBC. It is apparently clear that a variety of essential nutrients can significantly modify the carcinogenic process. Furthermore, an attempt has been made to establish an association between dietary factors and the occurrence of gallbladder cancer.

Key Words: Diet, Nutrients, Fruits and vegetables, Gallbladder Cancer.

Introduction

Gallbladder cancer (GBC) is a well recognized malignancy of hepato-biliary tract and is the fifth most common malignancy of gastrointestinal tract in United States. Even after two centuries of its first description; the tumour remains characterized by an unfavorable prognosis due to silent progression of the clinical course and limited knowledge of its etiology and poor scientific capability for epidemiological forecasting. The incidence of gallbladder cancer varies in different parts of the world. Within the Indian population, It is much higher in the Northern cities (eg, incidence in Delhi is 3.7 per 100 000 for male and 8.9 per 100 000 for female and in Bhopal it is 1.6 and 2.5 per 100 000 for male and female respectively) compared with the Southern cities (eg, in Chennai incidence is 0.5 per 100 000 for male and 0.8 per 100 000 for female and in Bangalore incidence for male is 0.6 per 100 000 and for female it is 0.7 per 100 000 population). Its incidence has been increasing in the Ganges delta. Thus geographical medicine, ethnic differentials and cultural variation of this disease suggest major environmental influences, rendering etiology of GBC obscure and hazy. Several factors however have been suggested, although none has stood the test of time. The incidence of gallbladder cancer parallels the prevalence of gallstone disease; large and longstanding gallstones being associated with a higher risk of GBC. The risk of GBC in patients with gallstones has been reported to have increased four to seven times. GBC occurs more commonly in elderly women. The disease incidence considerably increases with age. More than 90% of the patients are above the age of 50 years. Peak incidence is between 70-75 yrs; with the male: female ratio 1:3.2. The typical statement of ‘four Fs’: “fat-fair-fertile-forty” for gallstone and the predominance of the latter for GBC arouses a logical research question to
study GBC in relation to dietary pattern. Epidemiological studies world wide have implicated dietary factors in the development of gallbladder cancer. Many factors in diet have been attributed to be either causative or protective factors in the GBC and other biliary tract cancers. An increased risk has been observed with obesity, high intake of calorie, high carbohydrate and greater preference for oily foods. Risk of GBC was associated with high consumption of red chili pepper. Smoking is also increased the risk of gallbladder cancer. Vegetables and fruits have protective effect and there has been some suggestion of inverse association with intake of fiber, vitamin C and vitamin E. In spite of high prevalence of gallbladder cancer, there is an acute scarcity of literature to emphasize the relationship of diet and gallbladder cancer. This article is thus intended to arrange information of gallbladder cancer risk factors and their association with diet, based mainly on published evidence from epidemiological studies.

Association with major food groups

Consumption of Staple diet

In India the geographical distribution indicates that GBC rates are higher in the Northern part than in the Southern part. This striking peculiarity of North-South variation in occurrence of GBC in India makes one suspect that variation in dietary habits could be an important factor related to the etiology of GBC.

Malhotra (1967), reported the variation of dietary habit in North and South parts of India. The pattern of diet and eating in North Indian are masticatory diet in nature in contrast to sloppy diets of South Indians. A potential association of masticatory diet with GBC might be that the mucus concentration in the saliva rises with masticatory meals as compared to sloppy diets of South Indians. A protective effect of masticatory diet with GBC might be that the mucus concentration in the saliva rises with masticatory meals as compared to sloppy diets of South Indians. A protective effect of masticatory diet with GBC might be that the mucus concentration in the saliva rises with masticatory meals as compared to sloppy diets of South Indians.

Consumption of vegetables and fruits

Findings in various studies on the consumption of vegetables indicate an inverse association with gallbladder cancer risk. Lower risk of GBC was also reported with frequent intake (ranging from daily to three times per week) of fruits, odds ratio (OR) = 0.30 (0.19-0.49); boiled vegetables, OR = 0.37 (0.19-0.75) and salad, OR = 0.45 (0.21-1.00). Further indications of a protective role of vegetables and fruits were found in an integrated series of case-control studies conducted in Northern Italy, in which researchers found a weak inverse association with high consumption of fruits and vegetables for GBC. Low intake of fresh fruits was associated with gallbladder cancer with OR of 6.40 (1.40-30.30) in a case-control study in Chilean population. Consumption of vegetables in higher amount has been found to be associated with a reduced risk of many epithelial cancers of the alimentary tract. A protective effect of vegetables and fruits on gallbladder cancer was also reported by Pandey et al (2002). There are many possible reasons given as how a diet with a high consumption of vegetables and fruits prevents the occurrence of cancer. A large number of potentially anti-carcinogenic agents i.e. carotenoids, vitamin C, vitamin E, selenium, folic acid, dietary fiber, indoles, phenols, flavonoids, protease inhibitors, allium compounds and plant sterols are found in these food sources. These have both complementary and overlapping mechanism of action which include the induction of detoxification of enzymes, inhibition of nitrosoamine formation, provision of substrate for formation of antineoplastic agents, dilution and binding of carcinogens in the digestive tract, alteration of hormone metabolism, stimulation of immune system, regulation of gene expression in cell proliferation and apoptosis and scavenging of oxidative agents. Further, plant-based diets have a lower calorie density and increased nutrient density which are important factors in preventing obesity epidemic.

Consumption of flesh foods and egg

A case control study of cancer of the biliary tract in Japan reported decreased risk with greater consumption...
of fresh or salted fish with odds ratio in the range of 0.1 to 0.4 (P<0.05) and eggs with OR= 0.21 (0.10-0.45). Another study in Japan reported a positive association between the mortality rate of biliary tract cancer and expenditure for foods like pork. Tavani et al (2000) demonstrated a positive relationship with consumption of red meat and several neoplasms; but no statistically significant association was found with red meat intake and risk of GBC. Strom et al (1995) suggested non-vegetarian diet as a risk factor but they emphasized more on the cooking habit; baking/roasting meat vs frying was a risk factor for GBC. In a case-control study, red meat consumption was found to be associated with increased risk of gallbladder cancer.

**Consumption of Sugar**

Sugars have been stated to be one of the risk factors for biliary tract cancer. For gallbladder cancer the association with the intake of sugar was significant (P<0.05) and there was a two fold increase in risk in the upper tertile of intake, OR= 2.38 (1.03-5.46). Specific dietary constituents like monosaccharides and disaccharides are potential risk factors for gallbladder cancer. Sugar may influence the bile composition through lipoprotein metabolism. Sugar increases caloric intake without providing any of the nutrients that reduce cancer risk. By promoting obesity and elevating insulin levels, high sugar intake may increase cancer risk. However, a case-control study conducted by Seera et al (2002) found a positive association between low intake of sugar as soft drinks with gallbladder cancer, OR=3.60 (1.30-10.10).

**Consumption of Tea and Coffee**

Researchers have proposed that tea might protect against cancer because of its antioxidant content. One of the studies has reported an inverse association with the amount of tea drunk throughout life. Coffee has been suggested to be carcinogenic due to presence of mutagens. Kratzer et al (1997) reported that regular coffee was consumed by 74.5% of the subjects and trend was seen towards slightly higher prevalence of gallbladder stones in coffee drinkers. But a study in Japan, reported a low risk of GBC with frequent intake of coffee, OR= 0.25 (0.09-0.68).

**Role of Dietary constituents**

**Energy and related factors**

**Energy intake**

A case-control study in Poland, found gallbladder cancer risk was positively associated with total calorie intake, with an odds ratio of 4.13 reported for the upper versus the lowest quartile (P<0.01). Another study in Poland also found, total energy intake was related to gallbladder cancer with an OR of 2.00 (1.10-3.70) for the highest vs the lowest quartile.

**Body Mass Index**

Higher body mass may play a role- either direct or indirect- in gallbladder cancer. In a case-control study in Poland, researchers noted an elevated risk of GBC for females with higher values of BMI, the OR for females in the highest vs the lowest quartile was 2.10 (1.20-3.80). A prospective cohort study in the USA, found that gallbladder mortality rates were associated with obesity in women. Other studies also revealed that obesity was positively associated with a higher incidence of GBC. Several reports have demonstrated a strong relationship between obesity, gallstone and gallbladder cancer.

**Carbohydrate**

In a case-control study of GBC in Poland, a weak positive effect of carbohydrate consumption was observed, although the trends in risk were not significant (OR= 1.18, P= 0.77). The intake of total carbohydrates was positively related to the disease of the biliary tract (P< 0.01). For the upper tertile of intake, total carbohydrates showed an almost fourfold increase in risk. A positive association was observed between total carbohydrate intake and GBC. The risk ratio of 11.30 (4.60-28.00) reported for the highest vs the lowest quartile (P < 0.0001).

**Fiber**

Low intake of dietary fiber has been suggested as a possible cause of a variety of disorders prevalent among western societies including cholesterol gallstones. In a case-control study in Poland, a weak inverse association with high fiber consumption, OR= 0.31 (0.09-1.10) P = 0.08 was observed. Higher intake of dietary fiber appeared to be protective for GBC. Another case-control study also showed that low fiber intake was positively associated with GBC risk.

**Fat**

Gallbladder cancer rates are higher in Japan than in the USA, even though dietary fat intake is higher in the USA. The major risk factors for gallbladder cancer include a history of gallstones and obesity. To the extent
that dietary fat contributes to either gallstone formation or obesity, it may indirectly increase the risk of gallbladder cancer. A case-control study observed no apparent trend with total fat intake and gallbladder cancer OR = 0.86 (0.23-3.22) \( P=0.91 \). Another case-control study in Japan reported increased risk for GBC with greater preference for “Oily foods”, with an odds ratio of 3.29 (1.68-6.43); this study did not find positive associations for higher intakes of high fat foods, such as meat, fried food, or milk. Still another case-control study in Chilean population, found a weakly direct association for high consumption of fried foods and gallbladder cancer. A positive association of high fat intake with GBC risk was found in a case-control study in Karachi.

### Cholesterol

A population based case-control study in Poland, found a positive association of GBC with cholesterol, an adjusted OR of 1.54 (0.51-4.65).

### Protein

In a case-control study in Poland, a weaker direct association was observed for protein consumption with an adjusted OR of 3.88 (0.92-16.30). On the other hand a study in Japan reported that intake of animal proteins was low risk factor for gallbladder cancer.

### Vitamins

**Vitamin A**

A case-control study in Karachi showed that risk of GBC was positively associated with low intake of vitamin A.

**Vitamin B**

Epidemiological studies that have investigated association of cancer risk at specific sites and diets high in vitamin B are limited in number. In a case-control study a significant reduction in risk of GBC associated with increased intake of vitamin B (pyridoxine) was observed by Zatonski et al (1997).

**Vitamin C**

Vitamin C is a potential cancer inhibiting agent. It prevents the formation of carcinogen from precursor compounds. Epidemiological evidences show a protective effect of diets high in vegetables and fruits containing vitamin C for cancer of the gallbladder. A case-control study in Poland, found an inverse association between GBC and vitamin C, which was statistically significant for the three highest consumption quartile, OR = 0.29 (0.10-0.86). Another epidemiological case-control study found an inverse association of vitamin C with GBC. Ascorbic acid deficient guinea pigs frequently develop gallstones and ascorbic acid status may also affect the risk of gallbladder disease in human.

### Vitamin E

Researchers in a study found an inverse association of vitamin E with GBC. In a case-control study in Poland, possible protective association with vitamin E intake was found, OR for the highest vs the lowest quartile of intake was 0.30 (0.09-0.96).

### Conclusion

In this review we have concluded that there is an important relation between dietary factors and gallbladder cancer. Higher intake of energy and carbohydrate possibly increase the risk of gallbladder cancer. Obesity plays an important role in the causation of GBC. Adequate intake of fruits and vegetables probably reduce the risk of GBC. Fruits and vegetables may have several potentially anticarcinogenic agents. The specific mechanism of how fruits and vegetables prevent carcinogenesis is unclear, but the cancer inhibitory effect reported for these plant foods may be attributed in part to various antioxidant constituents including micronutrients: β carotene (Provitamin A), vitamin C and vitamin E, selenium and certain carotenoids which are efficient antioxidants and can prevent damage to chromosomes, enzymes and cell membranes caused by the peroxidation of free radicals.

The importance of other factors including meat, egg, cholesterol, protein, tea and coffee is not yet clear due to insufficient evidences and inconsistent results. The limited number of studies and their inconsistent results give rise to a need of more studies in this direction to confirm the findings as well as to bring to light new facts about the relation between dietary factors and gallbladder cancer.

### References

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