Etiology of gallbladder cancer (C23–24) in Central and South America

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Although the etiology of gallbladder cancer is still not well understood, it has been linked with the following factors: a history of gallstones (hard deposits that form inside the gallbladder), diet and obesity, infections, and ethnicity [1–5].

Gallstones, infection, and chronic inflammation

A history of gallstones has been associated with an increased risk of developing gallbladder cancer [1–4, 6] that has been shown to be approximately 10-fold higher in patients with gallstones that are larger than 3 cm compared with those who have smaller gallstones [3]. However, the number, size, or the duration of the presence of gallstones have been inconsistently associated with the risk of gallbladder cancer [1, 3]. Although the role of gallstones in the development of this cancer remains poorly understood, chronic inflammation – repeated trauma to the gallbladder mucosa induced by the presence of gallstones which may or may not be accompanied by chronic *Salmonella typhi* infection – has been hypothesized to lead to dysplasia and malignant changes in the gallbladder mucosa [1]. Because only a small proportion (1–3%) of patients with cholelithiasis (presence of ≥ 1 gallstone) develop gallbladder cancer [6] and approximately 20% of patients with gallbladder cancer do not have a previous history of cholelithiasis [7], other genetic and/or environmental factors must be involved in the carcinogenic process in this organ [7, 8].

In an autopsy study conducted in Chile (Concepción, Santiago, and Valdivia), Nervi et al. [9] found that the prevalence of gallstone disease (including the presence of gallstones or removal of the gallbladder) was strongly correlated with the risk of gallbladder cancer (odds ratio [OR], 7.0). Similarly, in a multicentre case–control study conducted in Australia (Adelaide), Canada (Montreal and Toronto), the Netherlands (Utrecht), and Poland (Opole), Zatonski et al. [10] found that cases of gallbladder cancer were more likely to report having a history of gallbladder symptoms that required medical attention (i.e., gallstones or gallbladder disease) than controls (OR, 4.4; 95% confidence interval [CI], 2.6–7.5); the association was even stronger when symptoms were reported 20 years after the first gallbladder examination (OR, 6.2; 95% CI, 2.8–13.4).

In areas where *S. typhi* is endemic (i.e., Africa, Asia, the Caribbean, and Latin America), only approximately 1–4% of all infected individuals become chronic carriers [11], the likelihood of which after acute infection increases with age,

particularly among women [12]. Chronic infection with *S. typhi* has been associated with an increased risk of gallbladder cancer, although the exact mechanism of its contribution has not been elucidated [11]. In a collaborative case–control study conducted in Bolivia (La Paz) and Mexico (Mexico City), Strom et al. [13] found that typhoid fever diagnosed by a physician increased the risk of gallbladder cancer (OR, 12.7; 95% CI, 1.5–598.0). Similar findings were reported by Nagaraja and Eslick [11] in a meta-analysis of 15 case–control studies (1 in Bolivia and Mexico, 3 in Chile, 1 in China, 9 in India, and 1 in the USA) and two cohort studies (Japan and the United Kingdom), the risk of developing gallbladder cancer for chronic typhoid carriers was 4.28 (95% CI, 1.84–9.96), although statistically significant evidence of heterogeneity was detected. The strong positive association remained in a stratified analysis by *S. typhi* detection method (OR, 3.52; 95% CI, 2.48–5.00 for serum-antibody levels; OR, 4.14; 95% CI, 2.41–7.12 for culture). The use of different methods to identify infection in chronic carriers may also explain some of the differences observed across countries because most studies used culture or serological tests to detect the infection. In general, the isolation rates of *S. typhi* using the currently available detection methods are very poor, thus the development and use of novel sensitive and specific molecular techniques might help to elicit the etiological role of *S. typhi* in gallbladder cancer [14, 15].

In Chile, typhoid fever has been highly endemic since the 1930s and was associated with sewage-contaminated irrigation systems. In 1976–1985, Chile had one of the largest epidemics of typhoid fever; the rates began to decline after the 1990s due to public health interventions [16]. However, how the typhoid fever epidemic would have affected the present rates of gallbladder cancer remains unclear because only a small percentage (2–5%) of people who have acute *S. typhi* infections become chronic carriers and the latency period for the development of gallbladder cancer is long [17]. The role of *S. typhi* infection in gallbladder disease needs further research using the best available tools to identify chronic carriers of the infection and gallbladder stones.

Excess body weight

Excess body weight has been suggested to be a risk factor for gallbladder cancer because of its strong association with an increased risk of developing gallstones [18], perhaps through bile cholesterol supersaturation [6, 19]. Gallstone formation has also been highly correlated with dieting, particularly with low-energy diets and bariatric surgery, and weight cycling [19]. In a meta-analysis of eight cohort and three case–control studies, Larsson et al. [18] found that the risk of gallbladder cancer increased by 15% (95% CI, 1–30%) in people who were overweight and by 66% (95% CI, 47–88%) in those who were obese compared with people whose weight was normal. They also reported that the association between obesity and gallbladder cancer was stronger in women than in men (relative risk [RR], 1.88; 95% CI, 1.66–2.13 for women; RR, 1.35; 95% CI, 1.09–1.68 for men). Approximately 12% of the gallbladder cancers that occurred in men and 30% of those in women were attributed to excess body weight.

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) [19] summarized the scientific evidence on the effect of food and nutrients on the risk of gallbladder cancer as well as the dietary causes of gallstones.

The WCRF/AICR found that each 5 kg/m^2 increase in body mass index increased the risk of gallbladder cancer by either 23% (summary RR, 1.23; 95% CI, 1.15–1.32 in cohort studies with moderate evidence of heterogeneity detected) or 19% (RR, 1.19; 95% CI, 0.81–1.75 in 7 case–control studies with statistically significant evidence of heterogeneity). Thus the WCRF/AICR concluded that greater body fat is a probable cause of gallbladder cancer either directly or indirectly through the formation of gallstones. Consistent with the WCRF/AICR report, a meta-analysis of 11 studies by Park et al. [20] found that, for every 5 kg/m^2 increase in body mass index, the risk of developing gallbladder cancer increased by 9% (RR, 1.09; 95% CI, 1.02–1.16 in 7 cohort studies; RR, 1.09; 95% CI, 0.88–1.30 in 4 case–control studies).

Other factors

The etiology of gallbladder cancer is complex, and several other factors and environmental exposures (pesticides, water pollution, and radiation) have been suggested to play a role in its development; however, the epidemiological evidence is limited [21–23].

Hormones

The rates of gallbladder cancer are generally higher in women than in men and women are twice as likely to develop gallstones than men, suggesting that reproductive and/or hormonal factors may play a role in its development [24]. Although the mechanisms are not well understood, increased exposure to endogenous estrogen and progesterone seems to promote the formation of biliary stones [25]. High parity and the number of pregnancies have been linked with an increased risk of gallstones as well as an increased risk of gallbladder cancer with risk ratios between 1.3 and 4.2 for high parity and between 1.0 and 6.7 for the number of pregnancies [3].

In a case–control study conducted in Shanghai, China, Andreotti et al. [26] showed that, among women with biliary stones, the risk of gallbladder cancer was higher in those who had more than three children (vs 1 child), late menarche (> 17 vs 13 years), and early age at first birth than in controls (risk estimates per year increase in age, 2.1; 95% CI, 1.0–4.2; 1.8; 95% CI, 1.03–3.24; and 1.2; 95% CI, 0.99–1.6, respectively). Breastfeeding was inversely related to the risk of bile duct cancer (OR, 0.90; 95% CI, 0.74–1.0 after adjustment for parity). A stratified analysis by biliary stone status revealed that these factors were still associated with an increased risk of gallbladder cancer but not in women without stones. These results show that the mechanisms of hormonal factors need further research to elucidate their role and contribution in the development of gallbladder cancer.

Other factors

A growing body of literature has suggested that *Helicobacter* species may be implicated in the development of gallbladder cancer [27] because some have been found in the bile and tissue biopsies of the biliary tract of patients with this cancer [28]. A case–control study in men showed that *H. pylori* was found in blood samples collected up to 22 years before the diagnosis of cancer. The prevalence of *H. pylori*

at baseline was 91–100% in the gallbladder cancer samples and 88% in the controls. The reported risk estimates were 5.47 (95% CI, 1.17–25.65) for all biliary cancers combined, 7.01 (95% CI, 0.79–62.33) for cancer of the extrahepatic bile duct, and 2.21 (95% CI, 0.19–25.52) for cancer of the ampulla of Vater. All tumours of the gallbladder site were positive for *H. pylori* [29]. In a recent comprehensive review of 20 studies, de Martel et al. [27] reported that *Helicobacter* species were found more frequently in the bile of gallbladder cancer cases than in controls in four of these studies in Japan, but were also often detected in benign biliary tract diseases (gallstones or chronic cholecystitis). However, no conclusions can be drawn regarding these associations because the results are based on studies with small sample sizes using different methods of detection which could lead to potential misclassifications of the infection status.

Chronic infection with hepatitis B virus (HBV) has been associated with hepatocellular carcinoma but not with the risk of cancers of the gallbladder or ampulla of Vater [30]. Anomalous pancreatobiliary duct junction, a rare congenital malformation of the biliary tract, may also be related to gallbladder cancer because it influences the degree of pancreatic fluid regurgitation which can lead to changes in the gallbladder epithelium that can then undergo malignant transformation [6].

Epidemiological studies examining the association between cigarette smoking and the risk of gallbladder cancer have yielded mixed results [31]. A recent meta-analysis of 11 studies (10 case–control and 1 cohort) revealed that smokers had an increased risk of developing gallbladder cancer than non-smokers (summary RR, 1.45; 95% CI, 1.11–1.89), although moderate heterogeneity among studies was observed and the risk was independent of alcohol consumption and a history of gallstones [32]. Moderate alcohol consumption appears to protect against gallbladder cancer but is not associated with cancer of the ampulla of Vater [33].

New evidence has suggested that exposure to aflatoxins may increase the risk of gallbladder cancer [33, 34]. A recent pilot study conducted in Chile revealed that people with gallbladder cancer had a higher risk of having increased levels of aflatoxins in their blood than controls with gallstones or community controls (RR, 4.0; 95% CI, 1.0–78.0 for controls with gallstones; RR, 2.5; 95% CI, 1.0–16.7 for community controls) [5].

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