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GALLBLADDER CANCER: A COMPREHENSIVE REVIEW OF NAVIGATING RISK FACTORS AND ADVANCING PREVENTIVE STRATEGIES

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ABSTRACT

Gallbladder cancer (GBC), the fifth most common and aggressive gastrointestinal malignancy, with significant global incidence variation and high mortality rates. The multifactorial aetiology, identifying key risk factors encompasses age, gender, geographic location, obesity, genetic predispositions, gallstones, infections, chronic inflammation, anatomical abnormalities and environmental factors plays a role in disease occurrence. Early detection of GBC remains challenging due to its asymptomatic nature in initial stages, non-specific symptoms, late-stage presentation and rapid progression contributing to poor prognosis. Diagnostic modalities encompass ultrasonography, computed tomography, magnetic resonance imaging, and histopathological examination, which remains the gold standard. Tumor markers like CA19-9 and CEA can aid in diagnosis but lack specificity. Preventive measures, particularly prophylactic cholecystectomy for high-risk individuals, are emphasized as effective strategies to reduce GBC incidence long with dietary and lifestyle modification. Postoperative metabolic and gastrointestinal sequelae highlight the need long-term follow-up. Overall, this study emphasizes the need of further research into GBC pathogenesis through molecular research, may lead to improved diagnostic and therapeutic approaches, targeted prevention strategies and public health initiatives to mitigate the impact of gallbladder cancer, ultimately aiming to improve patient outcomes and reduce mortality associated with this lethal disease.

KEYWORDS: Gallbladder cancer (GBC), Risk factors, Cholelithiasis, Prevention, Post-cholecystectomy complications.

INTRODUCTION

Gallbladder cancer (GBC) is the fifth most common and aggressive cancer involving gastrointestinal tract originating from the epithelial lining of the gallbladder, as well as the intrahepatic and extrahepatic bile ducts, and typically appears as either a diffuse thickening of the gallbladder wall or as a mass located in the gallbladder's fundus, neck, or body.[1,2] It is the leading malignancy within the biliary tract, accounting for 80-95% of biliary tract cancers globally.[2] The incidence rate of GBC shows significant variation worldwide, reaching epidemic proportions in certain regions and among specific ethnic groups. This disparity is likely due to differences in environmental exposures and inherent genetic susceptibility to cancer development.[3] The age-standardized incidence of GBC worldwide is 2.2 cases per 100,000 people.[4] The age standardized mortality rate is 1.7 per 100,000 people.[5] GBC generally develops over a period of 5 to 15 years, progressing as metaplasia advances to dysplasia, then carcinoma in situ, and ultimately to invasive cancer.[2] Jaundice, persistent right upper quadrant pain, nausea, vomiting, weight loss and fever in case of infection are the common symptoms. Some patients present with palpable abdominal mass representing advanced disease.[6] With a less than one-year overall survival rate, gallbladder cancer is one of the

most lethal gastrointestinal cancers due to its nonspecific presentation and asymptomatic progression, leading to detection at a late stage with a poor prognosis.[7] Diagnostic technique involves ultrasound, computed tomography, positron emission computed tomography, endoscopic ultrasonography, magnetic resonance (MR) cholangiography and MR angiography. The histopathological analysis of biopsy specimens continues to be the gold standard for confirming a definitive diagnosis.[6,8] Elevated levels of tumor markers CA19-9, CEA, CA72-4, CA125 and CA242 are useful for early detection and malignancy assessment.[9]

Various conditions associated with chronic inflammation are considered risk factors for GBC, which include gallstone disease, porcelain gallbladder, gallbladder polyps, chronic *Salmonella* infection, congenital biliary cysts, and abnormal pancreaticobiliary duct junction. GBC is incidentally detected in approximately 0.5% to 1.5% of patients undergoing cholecystectomy for presumed cholelithiasis. [2] Complete cure is only possible through surgical resection.[10] Achieving a successful outcome relies on early diagnosis and surgical removal of the tumour. Even with surgery, most cases progress to metastatic disease, underscoring the need for advancements in adjuvant therapies. [2] Late-stage detection and low survival rates emphasizes the need for early detection, risk identification, and prevention strategies to address the potential risk factors and reduce disease incidence.

RISK FACTORS

Age

Gallbladder cancer demonstrates a rising incidence with increasing age. [3] This is largely due to the accumulation of damaged DNA in cells over time, which can arise from natural biological processes or long-term exposure to risk factors.[11]

Gender

Globally, gallbladder cancer shows a significant female predominance, particularly in northern India, Pakistan, and among American Indian women. The incidence is two to six times higher in women compared to men This gender disparity may be linked to female sex hormones (estrogen and progesterone).[3] The gallbladder mucosa contains estrogen and progesterone receptors, which may contribute to gallbladder stasis and stone formation that increases the duration of exposure of the gallbladder lining to bacterial and chemical toxins, which can promote further irritation and potential carcinogenic changes.[1]

Geography

The global incidence of GBC is highest in Asia with India, Japan, and China accounting for largest caseloads. Along with Latin America, such as Bolivia and Chile, as well as in parts of Southeast Asia, including Bangladesh, Pakistan, Nepal.[12] Geographic variations in GBC incidence may be partly attributed by the distribution of certain risk factors.[5] Certain ethnic groups, including Hispanic populations, American Indians, Mexican Indians, Alaskan Natives, and Asian Indians, face a higher-than-average risk of developing gallbladder cancer.[1]

Obesity

A body mass index (BMI) of greater than 30 indicates obesity, which is linked to a twofold increased risk of GBC.[1] The relative risk of GBC rises by 1.59 for women and 1.09 for men for every 5-point increase in BMI along with diabetes, hypertension and hypercholesterolaemia.[3, 5]

Parity

Higher parity is related to greater risk for GBC in both pre and postmenopausal women. A short reproductive lifespan i.e menopause at younger age is also associated with higher GBC risk. The association between GBC and parity is biologically plausible, suggesting that sex hormones may play a role in GBC development. During pregnancy, elevated estrogen levels enhance hepatic secretion of biliary cholesterol, causing bile to become supersaturated with cholesterol and more lithogenic. Increased concentrations of estrogen and progesterone are known to reduce gallbladder contractility, thereby contributing to gallbladder stasis. These physiological changes promote the development of biliary sludge and gallstones which along with associated inflammation, are considered key factors in the carcinogenesis of GBC.[13]

Genetics

Several well-known factors for GBC include the presence of microsatellite instability (MSI), abnormality in tumor suppressor genes, oncogenes, and DNA repair genes, and epigenetic alterations mainly caused by aberrant promoter methylation of gene areas. KRAS is a key regulator in a number of signalling pathways. The KRAS oncogene in tissue has been found to have several harmful alterations. The TP53 gene is a well-recognized tumor suppressor with multiple anticancer mechanisms, playing a key role in maintaining genome integrity, regulating apoptosis, ensuring genomic stability, and inhibiting angiogenesis. When TP53 function is lost, abnormal cells with genetic impairments survives, potentially leading to tumor development. *c-erbB-2*, an oncogene homologous to the epidermal growth factor receptor, encodes a protein with tyrosine kinase activity. Immunohistochemical studies have shown c-erb-B2 expression in 10%–46% of gallbladder cancer cases.[14] In 72% of GBCs and 28% of chronic cholecystitis, methylation patterns of the tumor suppressor genes p16, APC, MGMT, hMLH1, RARbeta2, hTERT, and p73 have been found.[15]

Cholelithiasis

Gallstones are a significant risk factor for GBC, found in approximately 85% of patients with the disease. The risk rises with larger stone size; stones exceeding 3 cm are associated with a tenfold increase in risk compared to

smaller stones.[3] Other factors like longer duration, multiple stones, and greater stone volume (over 6 mL) are all linked to an elevated risk of GBC. Gallstones without additional cofactors, may cause mechanical damage, which the gallbladder mucosa can typically heal through natural repair processes. However, repeated and varied types of injury can exhaust the tissue's repair mechanisms, leading to chronic inflammation, mutations and ultimately carcinogenesis.[8] Additionally, complicated gallstone conditions, such as Mirizzi's syndrome and xanthogranulomatous cholecystitis, also increases the risk of developing GBC.[1]

Smoking and Diet

Worldwide, smoking has been linked to an increased risk of GBC.[1] Tobacco is widely known risk factor.[15] Furthermore, GBC has been linked to dietary and alcohol consumption particularly total calorie intake, carbohydrate, red meat, eating fried, fatty, junk foods, vanaspati, frozen and dried fish, betel leaf, certain advanced glycation products, sucrose, glycemic load, kheer, milled mustard oil, argemone oil, puffed rice with urea, chili powder, inadequate water intake, excessive salt and having intervals of more than 8 hours between meals.[16,7,10,17,18]

Chemical exposure

Heavy metals and toxins such as copper, lead, nickel, cadmium, chromium and dichloro diphenyl trichloroethane (DDT), BCH, vinyl chloride, leather tanneries, exposure to mining, radon gas, pesticides, fertilizers, rubber industries, paint, chemicals, paper, shoe, textile, cellulose acetate fibre manufacturing and wood industries have the potential to cause GBC.[1,15,16,19] The liver excretes these conjugated toxins into the bile and accumulate in the gallbladder. The bacteria present releases the enzyme beta glucuronidase, which deconjugates the conjugated toxins and makes them harmful to the mucosa.[1] Drugs such as methyldopa, isoniazid, oral contraceptives, long term use of proton pump inhibitors may additionally increase the risk of GBC.[15,20]

Anomalous pancreaticobiliary junction

APBJ is a rare congenital malformation characterized by the union of the pancreatic and bile ducts occurring outside the duodenal wall, proximal to the ampulla of Vater. Approximately 10% of patients with gallbladder cancer exhibit this anomaly.[3] This condition has been linked to a higher risk of GBC in Japan and other East Asian countries, making prophylactic cholecystectomy advisable.[8] The regurgitation of pancreatic enzymes into the gallbladder due to absence of sphincter can cause chemical irritation of the gallbladder mucosa, leading to K-ras mutations and the development of papillary adenocarcinomas. Chronic mucosal injury from pancreatic enzymes and secondary bile acids contributes to mucosal hyperplasia and dysplasia.[1,15]

Gallbladder polyps

Gallbladder polyps are found in about 5% of adults, with the majority (95%) being non-neoplastic (inflammatory and hyperplastic) including cholesterolosis (60%), adenomyosis (25%), and inflammatory polyps (10%). Additionally neoplastic polyps include leiomyomas, fibromas, lipomas, and adenomas.[10] Benign adenomas account for <5% of all GB polyps, typically measuring 0.5-2 cm. Features suggesting neoplastic polyp include a size >10 mm, sessile or solitary appearance, presence of gallstones, older age, and rapid growth.[21] Polyps >10–15 mm is linked to malignancy in 45%–67% of cases.[16] Endoscopic ultrasound (EUS) is effective for distinguishing benign from malignant polyps, with hypoechoic, heterogeneous structure, a height-to-width ratio of 0.8, and increased vascularity indicate higher neoplastic risk.[22] If polyps appear neoplastic, are associated with gallbladder wall thickening, increasing growth on imaging or there is a family history of cancer, cholecystectomy is generally recommended. Other polyps should be monitored with imaging every 3–6 months for size progression until it attains size ~10mm.[1,15]

Sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a long-term fibroinflammatory condition that relates chronic inflammation with the development and elevate the risk of biliary cancers, including cholangiocarcinoma and GBC.[1,3] Annual surveillance for GBC is recommended for these patients, and they may benefit from prophylactic cholecystectomy if lesion size is >8cm.[22]

Chronic inflammation

Chronic inflammation plays a critical role in carcinogenesis. Persistent or recurrent inflammatory episodes can damage DNA, trigger frequent tissue proliferation, and release cytokines and growth factors, thereby increasing the likelihood of oncogenic transformation. Oncogenic mediators such as nuclear factor kappa B, reactive oxygen and nitrogen species, inflammatory cytokines, prostaglandins, and certain micro-RNAs can influence cell growth, apoptosis, mutation rates, DNA methylation, and angiogenesis. Consequently, repeated damage from gallstones resulting in chronic cholecystitis may be the pathway through which cancer eventually develops.[3]

Chronic inflammation can arise from various factors, including mechanical obstruction caused by cholelithiasis, environmental infections, polyps and adenomas, autoimmune conditions, as well as anatomical abnormalities such as pancreatobiliary variations.[16] It may also lead to calcium accumulation within the gallbladder wall.[23] As calcium deposit grows, the gallbladder turns bluish and becomes fragile and brittle, a condition known as "porcelain gallbladder".[3] Therefore, it is recommended to remove gallbladders prophylactically that have many small calcifications,

stippled calcifications, or partial calcification, those with associated wall thickness in the mucosa.[24]

Infections

Chronic bacterial cholangitis is a known risk factor for biliary tract cancers caused by pathogens namely species of Salmonella (*S. typhi*, *S. paratyphi*) and Helicobacter (*H. bilis*).[3] Approximately 6% of individuals have twelvefold increased risk of GBC due to typhoid carriers as they are antibiotic resistant and cause continuous inflammation in the gallbladder which are linked to mutagenesis because they deconjugate bile acids and metabolites, creating highly active intermediates that can bind to DNA.[1,3] H. pylori, particularly its more virulent strains, triggers a pro-inflammatory response leading to harmful immune changes in the host, thereby promoting carcinogenesis in a manner similar to the development of gastric cancer.[25] Liver flukes, specifically *Clonorchis sinensis* and *Opisthorchis viverrini*, have been associated with the development of GBC.[15]

Socio-economic status

Low socioeconomic status is linked to lower literacy rates, overcrowding, limited healthcare access, poor prognosis, inadequate sanitation, restricted access to clean drinking water, prevention of mortality due to gallbladder cancers compared to higher socioeconomic levels, greater exposure to faecal-oral infections (S. typhi, H. pylori) that could lead to GBC development.[1,16]

Autoimmune and hereditary syndromes

The link between ulcerative colitis and biliary malignancy is well established. Transplant recipients with ulcerative colitis are 10 times more prone to develop GBC compared to the general population due to chronic inflammation.[16]

Other factors

Conditions that can contribute to the development of GBC includes congenital biliary cysts, segmental gallbladder adenomyomatosis, chronic inflammatory bowel disease, polyposis coli, Mirizzi syndrome, abnormal metabolism of arachidonic acid and altered metabolites levels.[16,26] A correlation exists between GBC and biliary dysbiosis.[27]

PREVENTIVE MEASURES

Patients with symptomatic gallstones should be recommended to undergo prophylactic cholecystectomy (PC), an effective strategy for reducing mortality associated with GBC.[28,29] Histopathological examination of gallbladders removed is essential to identify incidental early-stage GBC, as gallstones are a major risk factor for its development.[28]

Post-cholecystectomy complications: Despite its effectiveness, cholecystectomy effective, poses some risk of complications. Bleeding and wound infections are the most common complication associated with cholecystectomy.[30] Port-site recurrences, may occur due to tumor cell implantation from bile spillage, necessitating port-site excision during radical reoperation.[2] Intestinal ischemia, though rare and life-threatening is caused by elevated intra-abdominal pressure. Lost gallstones are typically harmless but can be misinterpreted as peritoneal lesions or, in some cases, cause abscesses and fistulas.[31]

Bloating, diarrhea, and abdominal pain are short-term effects due to changes in bile flow which typically resolve within weeks to a few months but may persist longer with high-fat diets. Long-term can contribute to gastritis (secondary to duodeno-gastric reflux of bile acids), elevated body mass index, metabolic syndrome (dyslipidemia, T2DM, insulin resistance, metabolic dysfunction-associated steatotic liver disease), and deficiencies of fat-soluble vitamins.[32,33,34,35] Colorectal cancer, non-alcoholic fatty liver disease (NAFLD), cardiovascular disease occur potentially due to gut microbiota imbalances and prolonged intestinal exposure to bile acids. Therefore, maintaining gut microbiota stability through balanced diet is crucial for normal physiological functions and disease prevention.[36] Post-cholecystectomy syndrome (PCS) refers to a group of symptoms that may persist or recur after cholecystectomy, including upper abdominal pain, dyspepsia, nausea, vomiting, gastrointestinal disturbances, and occasionally jaundice, with or without associated fever and cholangitis. Biliary symptoms of PCS can arise due to incomplete removal of gallstones (left in the cystic duct remnant or common bile duct), bile duct damage or bile leakage. Late onset often results from inflammatory scarring strictures during clamping or ligation, recurrent calculi, or biliary dyskinesia of the sphincter of Oddi that develops after a few months to years.[37] A retained cystic duct remnant may lead to stone formation and Mirizzi syndrome.[34]

Most gallbladder cancer (GBC) cases are considered preventable, particularly those linked to metabolic conditions.[38] A diet rich in cruciferous vegetables, such as broccoli and cabbage, along with regular fruit intake, has been associated with a lower risk of developing GBC.[39] Fruits contain numerous potentially anti-carcinogenic compounds, such as carotenoids, vitamins C and E, selenium, folic acid, dietary fibres, dithiolthiones, isothiocyanates, glucosinolates, indoles, phenols, flavonoids, protease inhibitors, allium compounds, plant sterols, and limonene that exhibit complementary and overlapping actions, including the activation of detoxifying enzymes, suppression of nitrosamine formation, binding and dilution of carcinogens in the digestive system, modulation of hormone metabolism, and antioxidant properties.[40] Adopting a vegetarian diet, along with consuming foods such as potatoes, onions, garlic, eggplant, cabbage, carrots, mustard leaves, green tea, sunflower oil, butter, ghee, fish consumption more than twice a week, sea fish, packaged milk, as well as maintaining elevated levels of

zinc and selenium in serum and bile, has been identified as potentially protective factors.[18,17,40] Japanese-style breakfast, statin use, occupational physical activity, slow weight reduction, improving lipid profiles, decreasing insulin resistance, and controlling fat consumption may further aid in reducing individual risk.[41,42,43] Improving socioeconomic conditions, promoting education, discouraging the use of non-liquefied petroleum gas as a cooking fuel and addressing environmental pollution are crucial in reducing the mortality and incidence of GBC.[44,16]

CONCLUSION

Gallbladder cancer being highly fatal malignancy necessitates the deeper understanding of diverse risk factors which is essential for early identification, risk stratification and thereby implementing targeted preventive strategies. Enhancing the effectiveness of PC involves identifying molecular risk factors alongside existing risk factors, which helps predict GBC risk. Furthermore, advancement in research is required to deepen our understanding of the disease's epidemiology and molecular biology, which could result in effective approaches for prevention and treatment.[29] Understanding the pathogenesis of GBC, development of advanced diagnostic techniques and preventive strategies is essential to bridging these knowledge gaps and paving the way for improved outcomes in managing the disease.

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