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Review

Gallbladder Cancer: The Basics

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Carcinoma of the gallbladder is notoriously lethal. Complete surgical extirpation is the only effective treatment. Because early symptoms are vague and anatomically the gallbladder lacks a serosa to limit the spreading of cancer, the diagnosis of gallbladder cancer frequently occurs at an advanced stage, typically with an abysmal prognosis. Its 5-year survival rate is less than 5% for more advanced stages.[1-5] Gallbladder cancer spreads locally to the liver and adjacent organs, and it disseminates by lymphatics, blood (even directly via gallbladder veins to the liver), and the peritoneum. In patients with early gallbladder cancer, cholecystectomy offers a possible cure when the cancer is confined to the mucosa (stage I or T1/T2).[5-7] Over 80% of gallbladder cancer cases are adenocarcinomas and originate from the fundus (60%), body (30%), or neck (10%).

Despite being the most common malignancy of the biliary tract, gallbladder cancer is fortunately rare in developed countries. In the United States, gallbladder cancer accounts for only 0.5% of all gastrointestinal malignancies (placing it in fifth place); less than 5,000 cases occur yearly (1–2.5 per 100,000).[3] Worldwide, however, incidence rates among different geographic areas and ethnicities vary widely, reaching extremely high rates in North and South American Indians (particularly Chilean Mapuche Indians).[8] Mortality rates are inordinately high in these American Indians: 15.5 per 100,000 in women (vs 7.5/100,000 in men) from La Paz, Bolivia, and 11.3 per 100,000 in women (vs 4/100,000 in men) from New Mexico, United States. Among Chilean women, gallbladder cancer is the leading cause of cancer death, exceeding breast, lung, and cervical cancers.[9,10] Intermediate frequencies of 3.7–9.1 per 100,000 occur elsewhere in South Americans of Indian descent.[8] Other high-risk regions include Eastern Europe (14/100,000 in Poland), northern India (as high as 21.5/100,000 for women from Delhi), south Pakistan (11.3/100,000), Israel (5/100,000), and Japan (7/100,000).[11] The incidence is rising in China and has doubled over the past 20 years in Shanghai.[12] In these areas, gallbladder cancer is the most frequent gastrointestinal malignancy and a significant source of death. Elsewhere in the world, the occurrence of gallbladder cancer is low (<2/100,000).

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Risk factors for gallbladder cancer provide insight into the pathogenetic basis for its geographic and ethnic variances; such information, in turn, should yield strategies for the prevention and treatment of this unusual malignancy.[11] A common characteristic is the presence of gallstones and chronic gallbladder inflammation.[2-4,13] Cholelithiasis is found in approximately 85% of people with gallbladder cancer. The association between cholelithiasis and gallbladder cancer ranges from 2.3 to 34.4 in case-control studies.[11] American Indians and other people who have a high incidence of carcinoma of the gallbladder also have an inordinately high prevalence of cholesterol gallstone disease.[14] This association with cholelithiasis may explain why female gender, multiparity, or elevated body mass indices (which are also risk factors for cholesterol gallstone formation) are also associated with a higher risk of developing carcinoma of the gallbladder. The basis for the development of cancer in the setting of cholelithiasis likely occurs through chronic irritation and local production of carcinogens such as secondary bile acids, leading to epithelial dysplasia and carcinoma, the presumed dysplasia-carcinoma sequence. The larger the gallstones (>2–3 cm in diameter), the greater the association with gallbladder carcinoma.[15-18] The link appears to be contingent upon the length of time that the stones reside in the gallbladder. A long duration provides the necessary time for such chronic trauma to the mucosa to initiate a sequence of pathologic changes that culminate in cancer. This would explain the inverse correlation that exists between cholecystectomy rates and gallbladder cancer; socioeconomic issues can delay access to cholecystectomy for cholelithiasis, increasing gallbladder cancer rates.[8,19,20] The latter may also contribute to the heightened risk that occurs in patients belonging to lower socioeconomic groups. The logical consequence of a decrease in the cholecystectomy rate is an augmented number of gallstone carriers in the population and hence older stones with an increased diameter, resulting in higher incidence and mortality rates from gallbladder cancer.[20-23] Although gallstones are an associated risk factor, likely facultative rather than causative, studies of their natural history and decision analysis do not favor prophylactic cholecystectomy for clinically silent gallstones.[24-26] The exceptions are very large stones (≥3 cm), which carry a relative risk of 10.1 (4% over 20 years),[15] and perhaps elderly American Indian women with cholelithiasis.[6]

Chronic inflammation can also lead to calcium deposition in the gallbladder wall known as "porcelain gallbladder." This term derives its name from extensive calcification that produces a somewhat fragile, brittle consistency and bluish color. The frequency of such calcification is generally not common (<1% of gallbladder specimens), tending to occur in women in their sixth decade. The porcelain gallbladder is frequently (average 25%, range 12–61%) associated with gallbladder cancer in most but not all reports.[27,28] Only those with stippled calcification are premalignant; the ones with complete calcification are less likely to be associated with carcinoma.[27] The partially calcified gallbladder is thus a quite reasonable indication for prophylactic cholecystectomy.[6] Irritation and inflammation also arise from chronic bacterial infections; *Salmonella typhi* (~6% of carriers develop gallbladder cancer: a 12-fold risk increase) and *Helicobacter bilis* have been implicated in gallbladder cancer.[4,29,30] Carcinogenesis associated with bacteria may also be associated with carcinogens that result from the degradation of bile (ie, bacterial hydrolysis of bile salts and β-glucuronides), chronic inflammation itself, and/or alterations of tumor suppressor genes (such as *p53*) or proto-oncogenes (such as mutations of *K-ras*).[31,32]

Anomalous pancreaticobiliary duct junction is a rare congenital malformation of the biliary tract, in which the pancreatic duct drains into the biliary tract outside the duodenal wall. More prevalent in Asians (particularly Japanese patients), this anomaly carries a heightened risk of developing biliary tract cancer; 3–18% develop gallbladder cancer.[3,33,34] This association occurs particularly in relatively young women and is not associated with gallstones. The junction abrogates any sphincter of Oddi control, permitting pancreatic secretions to regurgitate into the biliary system and gallbladder, which causes stasis and leads to malignant change in the mucosa. Because of the high frequency of gallbladder cancer, prophylactic cholecystectomy is warranted.

Chronic inflammation of the gallbladder for 15 or more years in a genetically predisposed individual likely promotes malignant transformation, aided in some instances by exposure to carcinogens. Carcinoma of the gallbladder is a multistep process involving cumulative genetic and epigenetic alterations that include activation of oncogenes and inactivation of tumor suppressor genes.[35] A unifying hypothesis consolidates the epidemiology and molecular pathogenesis into two pathways for the development of gallbladder cancer.[4] In most cases associated with cholelithiasis, the chronic inflammation leads to missense *p53* mutations. Such loss of p53 function allows genetically damaged cells to survive inappropriately. This sequence predominates in older (>65 years) Chilean women. In the second pathway, associated with anomalous pancreaticobiliary duct junction and seemingly more common in Asian populations, the molecular aberration is a *K-ras* point mutation leading to an atypical epithelium and eventually to carcinoma. Similar malignant transformation, likely from atypical epithelium, can

also develop in congenital bile duct dilation (choledochal cysts) that may be accompanied (in 70% of cases) by an anomalous pancreaticobiliary duct.[36]

Carcinoma of the gallbladder shares with gallstone disease epidemiologic occurrences that point to environmental and genetic factors.[12,14,37] Both are a family affair. Genetic factors account for approximately 25% of gallstone formation. In cholesterol stones, the factors best identified are the genes responsible for specific biliary lipid transporters in the canalicular membrane—the ATP-binding cassette (ABC) transporters. These transporters include ABCG5/ABCG8 for cholesterol secretion, ABCB11 as the bile salt export pump, and ABCB4 for phospholipids and lecithin. Mutations in the gene *ABCG5/G8*, as the variant *D19H,* result in increased cholesterol secretion into bile, making it an important susceptibility factor.[38] Defective *ABCB4* leads to reduced lecithin secretion and stone formation. In gallbladder cancer, variants of the *APOB* gene responsible for apolipoprotein B function, which influences cholesterol handling by the liver, have been associated with an increased risk for gallbladder cancer. Yet, this is independent of the presence of gallstones.[39] One comprehensive explanation for the association of gallbladder cancer with cholesterol gallstones suggests an interdependent disposal pathway for cholesterol and environmental toxins exported into bile, linked by the activity of hepatic nuclear receptors and ABC transporter pumps.[40] This explanation also proposes that female sex hormones increase the secretion of cholesterol and xenobiotics into bile. Furthermore, prolonged gallbladder residence time (stasis due to impaired contractility) results from progesterone and the excessive cholesterol secreted in bile.[41] Such protracted exposure allows environmental carcinogens such as aflatoxin B, possibly the culprit in some endemic areas, to then cause malignant transformation, helping to reconcile the schism of nature versus nurture. In this scenario, the cancer phenotype results from gene variants that control key metabolic pathways, which then interact with environmental triggers to yield carcinogens.

Gallbladder polyps are considered a risk factor. Polypoidal masses of the gallbladder affect 5% of adults (range, 0.3–7%), depending upon the population studied.[42] The vast majority are not associated with symptoms, though they occasionally cause biliary colic. Most gallbladder polyps (over two thirds) are composed of cholesterol esters, the common composition of those under 5 mm, yet they are not particularly associated with cholesterol gallstones. Other polypoidal lesions are adenomas, leiomyomas, or inflammatory polyps. As such, the majority of these immobile hyperechoic shadows are incidental findings discovered on abdominal ultrasound performed for other purposes. Most polyps do not grow or change in size. Features predicting malignancy of polypoidal gallbladder masses include large polyps (>10 mm; one quarter are malignant); a solitary lesion; a sessile polyp; polyp growth; age over 50–60 years; or associated gallstones.[42] Features suggesting a malignant polyp, or when accompanied by gallbladder symptoms (biliary-type pain), warrant cholecystectomy. Endoscopic ultrasound quite accurately images the gallbladder, assesses the depth of tumor invasion, and offers the opportunity for fine-needle aspiration to provide histologic diagnosis. It is difficult to envision a cholesterol polyp developing into a carcinoma. More likely, both conditions represent a mass in the gallbladder; the challenge is to distinguish between them. Separation of gallbladder sludge from a potentially malignant polyp can be assisted by Doppler ultrasound, which has the ability to show blood flow in polyps. Certainly, polyps over 18 mm must be removed, as they are likely malignant.[43]

Gallbladder cancer is either discovered early, an incidental finding when cholecystectomy is performed for symptomatic cholelithiasis, or late, when the tumor has invaded the bile ducts or has metastasized. A common presentation for early-stage gallbladder cancer mimics cholecystitis with upper abdominal pain similar to biliary colic and the presence of cholelithiasis.[44] Such incidental gallbladder cancers are detected histologically after the fact in 0.3–3% of laparoscopic cholecystectomies performed for cholelithiasis; the frequency depends upon the regional prevalence of gallbladder cancer in that population.[45-48] Complete excision of such early gallbladder cancers offers a cure (termed R0 resection). If invasion is limited to the mucosa or subserosa (Tis=in situ; T1=confined to the lamina propria or muscularis), the 5-year survival rate is over 95%.[49] If the resection margins are clear in T1 disease, no further surgical intervention is required.[5] Less than 10% of cases with T1 disease have lymph node metastasis. Nevertheless, port-site recurrences can follow laparoscopic cholecystectomies in up to 17% of cases when unsuspected gallbladder cancer is discovered.[50] These are local circumscribed tumors at trocar sites or the incision. Here, accidental bile spillage presumably implants the tumor cells, a result of the contact between the carcinoma and normal tissue at the port site when the gallbladder is extracted or its bile contents spill. When preoperative diagnosis of gallbladder cancer is suspected from risk factors (eg, an irregular gallbladder wall seen on imaging studies, a large gallbladder polyp, or a congenital anomaly of the biliary tract), surgery must not be performed laparoscopically. Open exploration is indicated to allow for the option of a radical cancer operation.[5,46] The deeper the invasion, the worse the prognosis is: 5-year survival rates range from 70% with involvement of the subserosa (T2=invasion of perimuscular connective tissue) to 0% with spreading to adjacent organs (T3=penetration of the

serosa; T4=invasion of the portal vein or hepatic artery or involvement of multiple extrahepatic structures and organs). More advanced gallbladder cancers (T2 or T3) require careful preoperative assessment. Staging gallbladder cancer to determine whether the tumor is resectable requires the identification of any contiguous invasion into the liver and adjacent structures. Careful staging requires diagnostic imaging with magnetic resonance (MR) imaging (MR cholangiopancreatography or angiography), advanced computed tomography scanning, or even a staging laparoscopy. In selected cases, radical surgery aims for a curative R0 resection.[5,50-52] When gallbladder cancers are diagnosed postoperatively, some (T2 cancers) warrant a second radical procedure.[46] Late stages present with anorexia, malaise, weight loss, nausea, vomiting, or cholestatic jaundice. These features, particularly jaundice indicating bile duct involvement, carry a dismal prognosis. As yet, no truly effective adjuvant therapy exists.

Gallbladder cancer may be a rare but fatal condition in some regions, and yet, it is endemic elsewhere in the world. Originating in a small organ that functions merely for the storage of bile in anticipation of a meal, this malignancy is distinctive because of its demographic profile. Advancements that clarify the genetics of biliary tract diseases and develop unifying hypotheses to explain gallbladder cancer's unusual epidemiology not only will define its etiology but should also improve management. Secondary prevention should follow clarification of the value of prophylactic cholecystectomy in endemic areas and in patients at risk. Primary prevention will arrive once high-risk genes and environmental toxins are clearly identified.

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