Epidemiology of Gallbladder Disease: Cholelithiasis and Cancer

Laura M. Stinton and Eldon A. Shaffer

Division of Gastroenterology, Department of Medicine, Faculty of Medicine, University of Calgary, Calgary, Canada

Diseases of the gallbladder are common and costly. The best epidemiological screening method to accurately determine point prevalence of gallstone disease is ultrasonography. Many risk factors for cholesterol gallstone formation are not modifiable such as ethnic background, increasing age, female gender and family history or genetics. Conversely, the modifiable risks for cholesterol gallstones are obesity, rapid weight loss and a sedentary lifestyle. The rising epidemic of obesity and the metabolic syndrome predicts an escalation of cholesterol gallstone frequency. Risk factors for biliary sludge include pregnancy, drugs like ceftiaxone, octreotide and thiazide diuretics, and total parenteral nutrition or fasting. Diseases like cirrhosis, chronic hemolysis and ileal Crohn's disease are risk factors for black pigment stones. Gallstone disease in childhood, once considered rare, has become increasingly recognized with similar risk factors as those in adults, particularly obesity. Gallbladder cancer is uncommon in developed countries. In the U.S., it accounts for only ~5,000 cases per year. Elsewhere, high incidence rates occur in North and South American Indians. Other than ethnicity and female gender, additional risk factors for gallbladder cancer include cholelithiasis, advancing age, chronic inflammatory conditions affecting the gallbladder, congenital biliary abnormalities, and diagnostic confusion over gallbladder polyps.
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INTRODUCTION

Diseases of the gallbladder commonly manifest as gallstones and gallbladder cancer. To identify risk factors in a given population, epidemiological studies must first define the frequency of disease. Studies employing necropsy surveys or healthcare databases carry biases by their implicit nature: being postmortem or requiring biliary symptoms/complications, respectively.[1-3] Another potential measure of disease burden, the frequency of cholecystectomy, is a limited marker for the prevalence of gallstones, as the perceived threshold for surgery and patient access to care differ greatly.[4] Some epidemiological studies have been confounded by inadequate sample size or selection bias. Small sample size is open to a beta-II type error: a failure to accurately identify a true difference (i.e., a false negative result). Selection bias may lead to spurious differences (i.e., a false positive result). More reliable epidemiological studies now use transabdominal ultrasound to screen robust numbers in defined asymptomatic populations. Ultrasonography is an ideal means to quantitate the frequency of gallstone disease, being a noninvasive and safe imaging technique that accurately can detect the point prevalence of gallstones in a defined asymptomatic population.

GALLSTONE DISEASE

1. Burden of gallstone disease

Gallstones constitute a significant health problem in developed societies, affecting 10% to 15% of the adult population, meaning 20 to 25 million Americans have (or will have) gallstones.[2,5-7] The resultant direct and indirect cost of gallbladder disease represents a consumption of ~$6.2 billion annually in the U.S., constituting a major health burden that has increased more than 20% over the last 3 decades.[2,8,9] With an estimated 1.8 million ambulatory care visits each year, gallstone disease is a leading cause for hospital admissions related to gastrointestinal problems.[10] These numbers are likely an underestimate because laparoscopic cholecystectomy is often performed as a day procedure and thus not captured by hospital statistics that require overnight admission. Although the mortality rate for gallstones disease is relatively low at 0.6%, the high burden of disease imposes troubling mortality figures, such as an estimated 1,092

gallstone-related deaths for 2004 in the U.S. Fortunately, case fatality rates have steadily diminished from over 5,000 deaths in 1950, falling >50% between the years 1979 and 2004. This decline represents the greatest decrease for any digestive disease.[9]

Gallstone disease *per se* also carries inherent risks. Prospective population-based surveys have revealed an increased overall mortality, particularly from cardiovascular disease and cancer, as seen in Americans and Pima Indians with cholelithiasis.[11,12] Further, as the incidence of gallstone disease escalates, there is a concomitant increase in complications like gallstone-related pancreatitis.[13]

The number of surgical procedures for cholelithiasis has risen markedly in developed countries since 1950.[14] The introduction of laparoscopic cholecystectomy in 1989 further increased the cholecystectomy rate.[14-16] From 1990 to 1993, for example, there was a 28% escalation in the number of cholecystectomies performed.[17] The change in practice emanated from the laparoscopic surgical approach, which represented a less invasive, more cosmetically acceptable operation while providing a lower surgical risk compared to the then conventional or "open" procedure. This likely resulted in more surgeries being done in patients previously thought to be too high a risk, or in those with minimal symptoms. Although there is undoubtedly an element of overuse, cholecystectomy is now the most common elective abdominal surgery performed in the U.S., with over 750,000 operations being performed annually.[6,16,18] The cholecystectomy rate, though increased, fortunately appears to have stabilized in the late 1990s and may even be on the decline in the U.S.[19]

2. Clinical aspects of gallstone disease

1) Asymptomatic/Silent gallstones

Gallstones are common. 10% to 20% of Americans will develop stones at some time.[20] The majority will not develop symptoms: up to 80% will never experience biliary pain or complications such as acute cholecystitis, cholangitis, or pancreatitis.[21] Hence, most gallstones are clinically "silent," an incidental finding often uncovered during abdominal ultrasound being performed for another reason.[22] People with such asymptomatic cholelithiasis, however, eventually may develop symptoms (biliary pain) that require treatment,[23] but this risk is quite low averaging 2% to 3% per year,[24] 10% by 5 years.[1,23] An even lower proportion, 1% to 2% per year, develop major gallstone complications.[20,25] Therefore, expectant management is an appropriate choice for silent gallstones in the general population. The exception is patients at high risk for experiencing biliary complications:

(1) Large gallstones (>3 cm) or gallbladders crammed with stones that carry a higher risk of developing gallbladder cancer, perhaps an indication for prophylactic cholecystectomy.[26,27]

(2) Sickle cell disease is associated with the development of pigment gallstones, frequently necessitating cholecystectomy. Prophylactic cholecystectomy should be considered because stone complications is frequently difficult to distinguish from the clinical features of a sickle cell crisis or its complications such as infarction of the liver or abdominal viscera.[28] When performed early, outside the emergency setting, cholecystectomy lessens the surgical risks, but still carries a high mortality rate at 1% and postoperative complications of >30%.[29]

(3) Solid organ transplantation (heart, lung, kidney, pancreas). Although stem cell (bone marrow) transplantation carries its own problems from cholelithiasis and biliary sludge developing, more problematic is the aftermath of solid organ transplantation in which gallstones that develop frequently progress to symptoms and complications like cholecystitis, principally during the first 2 years.[30] Liver transplantation is exempt; the gallbladder is removed at the time of hepatectomy. Controversy exists in patients with asymptomatic gallstone disease who are undergoing solid organ transplantation: expectant management with routine screening ultrasonography vs prophylactic (pre-/post-transplantation) cholecystectomy.

(4) Abdominal surgery, performed for other reasons, may benefit from a simultaneous cholecystectomy in situations where the risk of gallstone formation and complications are high. Prophylactic cholecystectomy therefore should be considered in morbidly obese patients undergoing bariatric surgery.[31]

2) Symptomatic gallstone disease

Since most gallstones are asymptomatic, it is essential to define exactly which symptoms are caused by gallstones: true biliary pain and/or complications, versus nonspecific abdominal complaints including dyspepsia.[32-34] Gallstone-associated pain seems to follow a certain pattern in most patients.[35,36] Consensus groups have attempted to establish criteria for biliary pain relative to defined characteristics (e.g., episodic, steady, severe pain located in the upper abdomen and lasting more than 30 minutes) and some accompanying features (e.g., nocturnal onset; nausea and vomiting; radiating through to the back).[11] The importance for clarifying what constitutes true biliary pain is to better predict relief following cholecystectomy. Currently, cholecystectomy does not relieve biliary pain in 10% to 33% of people with documented gallstones.[37,38] Confusion with other functional gut disorders like irritable bowel syndrome (IBS) and dyspepsia will not provide a favorable outcome from cholecystectomy.[39,40] The avoidance of an unnecessary cholecystectomy becomes critically germane in an era of escalating rates of surgery.

3) Functional (acalculous) gallbladder disease

Biliary pain seemingly results from increased intraluminal pressure as the gallbladder contracts against an obstructed outlet. In gallstone disease, the obstruction is obvious: a stone in the cystic duct. In functional gallbladder disease (also termed; acalculous gallbladder disease, gallbladder dyskinesia or biliary dyskinesia), the pain mechanism may be obstruction located at

the gallbladder outlet, incoordination between gallbladder contraction and sphincter of Oddi relaxation, or visceral hypersensitivity. A clue to its existence is impaired gallbladder emptying, reliably quantitated by cholecystokinin-cholescintigraphy.[41,42] Yet the frequency and management of acalculous gallbladder disease remains unclear. Eliminating the apparent problem, the gallbladder, via laparoscopic cholecystectomy is fraught with challenges, particularly in selecting those who would most benefit. Although the exact frequency of biliary dyskinesia is unknown, any increase in the employment of cholecystectomy for such cases most certainly would impact surgical rates. Thus, there is insufficient evidence to support a role for cholecystectomy in functional gallbladder disease at this time.[43] Hence, patients with suspected functional biliary pain but whose intact gallbladder lacks ultrasonographic evidence of gallstones should be carefully evaluated to exclude other causes for their symptoms.

3. Risk factors for gallstone formation

Important risk factors have been identified as being associated with gallstones (Table 1).[2] Multiple case-control studies, comparing those with gallstones versus those without, have shown that gallstone formation is multifactorial. Some features, such as ethnicity, genetics, advancing age and female gender cannot be modified, whereas others (e.g., diet, physical activity, rapid weight loss and obesity) are modifiable.

1) Ethnicity

Geography and particularly ethnicity play an enormous role in the prevalence of gallstone disease and also the type of stone that forms: cholesterol gallstones predominate in the developed countries of the Western world; brown pigment stones in the bile ducts are more common in Asia (Table 2, Fig. 1).[44]

North American Indians have the highest reported rates of cholelithiasis, afflicting 64.1% of women and 29.5% of men.[2,45] The aboriginal populations of South America also have an exceedingly high prevalence of gallstones: 49.4% of native Mapuche Indians of Chile women and 12.6% of men harbor gallstones.[46] Mexican Americans are also at heightened risk

when compared to White Americans; however, this risk is directly related to the degree of Amerindian admixture.[47-50] White Americans have an overall prevalence of 16.6% in women and 8.6% in men.[6,47] Intermediate prevalence rates occur in Asian populations[51,52] and Black Americans (13.9% of women; 5.3% of men).[6] The lowest frequencies occur in sub-Saharan Black Africans (<5%).[53] The majority of gallstones in developed countries consist predominantly of cholesterol (>85%), whereas the remainder constitutes black pigment stones (i.e., composed of calcium bilirubinate) (Table 2).[2,7]

The situation differs in East Asia where brown pigment stones are located in bile ducts, predominately associated with parasitic infestation. In developed countries, however, these bile duct stones arise in association with the inflammation and infection that result from biliary strictures and malignancies. Brown pigment stones consist of some calcium bilirubinate (hence their dark color), fatty acid soaps (calcium palmitate and calcium stearate, hence their greasy feel), some cholesterol, and mucinous glycoproteins (a product of bacterial biofilms). They form *de novo* in the common bile duct (choledocholithiasis) or the intrahepatic bile ducts (hepatolithiasis). These primary ductal stones result from bacterial infection, biliary parasites (*Clonorchis sinensis, Opisthorchis* species, *Fasciola hepatica*) and stasis from partial biliary obstruction. Brown pigment stones are the predominant type in Asia where they can cause Oriental cholangiohepatitis: biliary obstruction with recurrent cholangitis, dilatation and stricturing of the biliary tree. In hepatolithiasis, stones are present in the intrahepatic bile ducts, regardless of any coexistent stones residing elsewhere in the biliary system (i.e., the extrahepatic ducts or the gallbladder). The brown pigment stones that arise in intrahepatic sites (hepatolithiasis) possess relatively more cholesterol and less bilirubin than those that form in extrahepatic sites, presumably due to a different mechanism for their formation. The frequency of hepatolithiasis, as a proportion of all bile duct stones, is as high as 20% in China and Taiwan, yet as low at 2% to 3% in Japan, Singapore, and Hong Kong.[54] The stone type curiously has recently shifted in developing Asian countries from pigment to cholesterol stones. The basis for this change may reflect a decreased rate of chronic

Table 1. Risk Factors for Gallstone Disease

Not modifiable	Modifiable
Family history	Obesity/metabolic syndrome/diabetes mellitus/dyslipidemia
Genetic predilection	Drugs – ceftriaxone, octreotide, thiazide diuretics, female sex hormones
Ethnic background	Reduced physical activity
Female sex	Rapid weight loss
Age	TPN
	Diet
	Underlying disease: cirrhosis, Crohn's disease

TPN, total parental nutrition.

biliary infections and consumption of a more Westernized diet.[2]

2) Family history & genetics

Genetic susceptibility is a key factor in gallstone formation.[55] Familial studies reveal an increased frequency: a nearly 5 times elevated risk in the relatives of gallstone patients. These rate are even higher in monozygotic twins at 12% and dizygotic twins at 6%.[56,57] Yet spouses of affected patients do not have any increased risk, thereby eliminating a shared environment as the basis - i.e., similar dietary and other common habits among family members as the explanation for this apparent association.[58] In a Swedish twin study, genetic effects accounted for

25%, shared environmental influences for 13% and unique environmental effects for 62% of the phenotypic variance.[59]

No mode of simple Mendelian pattern of inheritance can account for the majority of cases with gallstone disease. In fact, stone formation is a complex interaction of genes and environmental factors, particularly diet-gene interactions.[55,60] Several genes have been associated with gallstone disease.[61] Identified so far have been: the apolipoproteins E (*APOE*) and B (*APOB*),[62] cholesterol ester transporting protein (*CETP*), cholesterol 7 α-hydroxylase,[63] cholecystokinin receptor A (*CCKAR*),[64] the LDL receptor (*LDLR*)[65] and the *CETP*.[66] Genome-wide association analysis has revealed that variants for the hepatic cholesterol

Table 2. Types of Gallbladder and Biliary Tract Stones: Characteristics and Clinical Associations

|	Cholesterol gallstones	Black pigment stones	Brown pigment stones	Biliary sludge (microlithiasis)
Composition	Cholesterol (50-100%)	Calcium bilirubinate polymer	Unconjugated bilirubin, calcium soaps of fatty acids, cholesterol & mucin	Pigment (calcium-bilirubinate), cholesterol microcrystals & mucin
Location	Gallbladder ±common duct (~10%)	Gallbladder ±common duct	Bile ducts	Gallbladder
Detection	Ultrasonography	Ultrasonography	Cholangiography	Abdominal or endoscopic ultrasonography; microscopy of bile
Clinical associations	Metabolic: family history (genetic traits), obesity, female sex, aging [excessive cholesterol secretion]	Increased or altered bilirubin excretion in hemolysis, cirrhosis, cystic fibrosis, Crohn's disease, advanced age [excessive bilirubin excretion]	Infection, inflammation, infestation [stasis, strictures]	Fasting, TPN, pregnancy-possible prelude to stone formation

TPN, total parental nutrition.
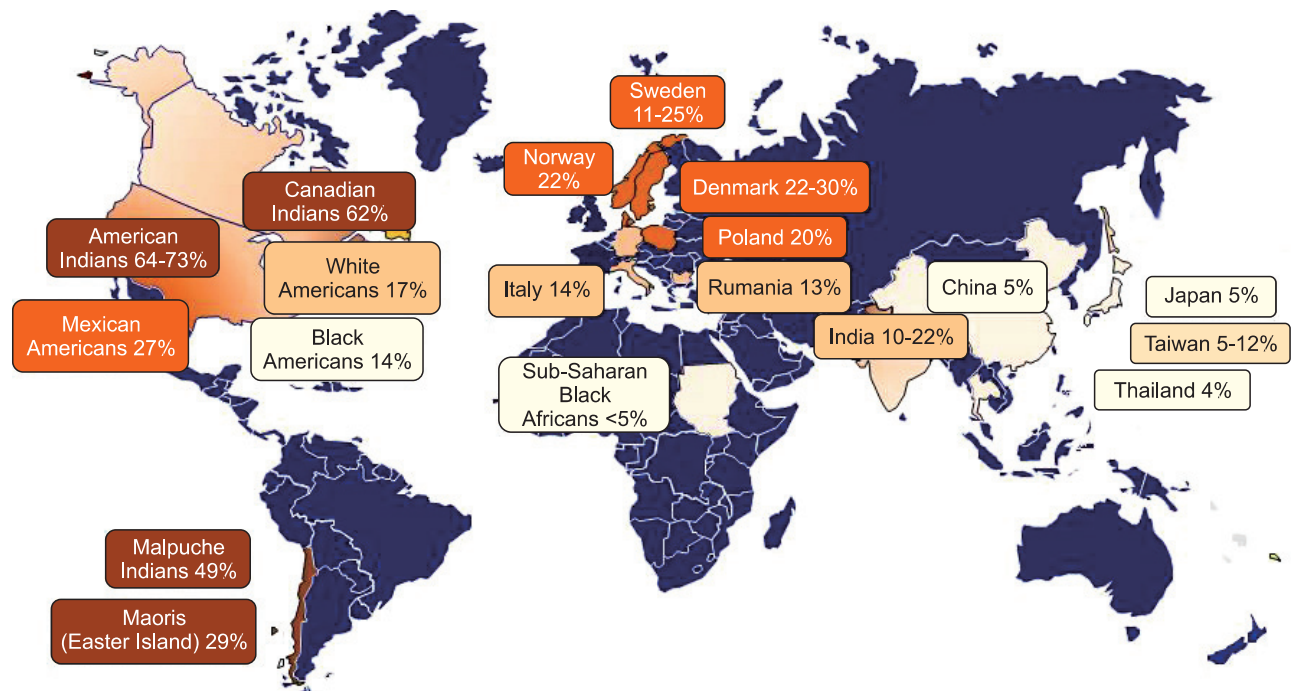
Fig. 1. Worldwide prevalence of gallstones in females based on ultrasonographic surveys varies.[45] Prevalence is inordinately high in American Indians and their admixtures, and also Northern Europeans; somewhat lower in European and American whites; intermediate in Asians and black Americans, and quite low in black Africans.

secretion (*ABCG8 19H* and *ABCB4*) represent a susceptibility factor for human gallstones.[67,68] Conferring an odds ratios of 2 to 3 for heterozygous and 7 for homozygous carriers, these variants account for 11% of the total gallstone risk. Such human susceptibility ("gallstone") genes therefore are not common and so embody a rather modest contribution. Cholelithiasis most likely is a polygenetic disease entity.

3) Age

The frequency of gallstones increases with age, escalating markedly after age 40 to become 4 to 10 times more likely in older individuals.[2,69] The stone type also changes with age: initially being composed predominantly of cholesterol (corresponding to an increased cholesterol secretion into and saturation of bile) but in late life tending to be black pigment stones. Further, symptoms and complications increase with age, leading to more frequent cholecystectomies.[70]

4) Gender and female sex hormones

The female gender has a most compelling association with gallstone disease, especially during the fertile years. Women are almost twice as likely as men to form stones; the gap narrows following menopause after which men begin to catch up.[2] The underlying mechanism is female sex hormones; parity, oral contraceptive use and estrogen replacement therapy are established risk factors for cholesterol gallstone formation.[71-73] Female sex hormones adversely influence hepatic bile secretion and gallbladder function. Estrogens increase cholesterol secretion and diminish bile salt secretion, while progestins act by reducing bile salt secretion and impairing gallbladder emptying leading to stasis. A new 4th generation progestin, drospirenone, used in some oral contraceptives may further heighten the risk of gallstone disease and cholecystectomy; however, the increased risk is quite modest and not likely to be clinically meaningful.[74]

During pregnancy when female sex hormones are endogenously raised, biliary sludge (particulate material that is composed of cholesterol, calcium bilirubinate, and mucin) appears in 5% to 30% of women. Resolution frequently transpires during the post-partum period: sludge disappears in two-thirds; small (<1 cm) gallstones (microlithiasis) vanish in one-third, but definitive gallstones become established in ~5%.[75,76] Additional risk factors for stone formation during pregnancy include obesity (prior to the pregnancy), reduced high density lipoprotein (HDL) cholesterol and the metabolic syndrome.[76,77]

5) Obesity

The exploding prevalence of obesity now reaches epidemic levels in both developed and developing nations like China.[78,79] Obesity, particularly abdominal or centripetal obesity, is a well-established risk factor for gallstone disease.[2,80-83] At least 25% of morbidly obese individuals have evidence of gallstone disease.[84] Obesity in the late teenage years carries the greatest

risk, whereas thinness protects against cholelithiasis.[2,85] Females with obesity have an even increased risk of stones formation. Women with severe obesity (body mass index [BMI] >32 kg/m^2) showed an age-adjusted relative risk of 6.0 for the development of gallstones compared with nonobese controls; their annual incidence of developing gallstones is 2%.[85] Obesity is associated with an increased activity of the rate-limiting step in cholesterol synthesis, the hepatic enzyme, 3-hydroxyl-3-methyl-glutaryl co-enzyme A (HMG-CoA) reductase, leading to increased cholesterol synthesis in the liver and its heightened secretion into bile.[80,86,87]

6) Dyslipidemia, diabetes mellitus and the metabolic syndrome

Cholesterol gallstone disease is a metabolic problem, which correlates with lipid abnormalities, diabetes mellitus and adiposity. A low HDL cholesterol[88] and hypertriglyceridemia[89,90] carry an increased risk of developing stones. In contrast, there is no definite association with hypercholesterolemia.[2,91] High homocysteine levels also may correlate with gallstone disease.[92]

The metabolic syndrome is defined by the presence of at least 3 features out of: abdominal obesity, high blood pressure, high fasting glucose, increased triglyceride levels and reduced HDL levels.[93,94] Both the metabolic syndrome and diabetes mellitus are risk factors for gallstone disease.[95] The metabolic syndrome has also been associated with stone complications.[96] Insulin resistance predisposes to cholesterol gallstone formation,[97,98] suggesting altered cholesterol and bile salt metabolism. Hepatic insulin resistance may act by enhancing hepatic cholesterol secretion, depressing bile salt synthesis and/or impairing gallbladder motility.[99-101]

7) Rapid weight loss

Low caloric diets and/or bariatric surgery with rapid weight loss are associated with gallstones developing in 30% to 71% of such individuals.[102-108] Weight loss that exceeds 1.5 kg/wk following bariatric surgery increases the risk for stone formation; these stones are most likely to become apparent during the first 6 weeks after surgery when weight loss is most profound.[109,110] Weight loss-associated gallstones are typically asymptomatic; only 7% to 16% develop symptoms, best predicted by a postoperative weight loss exceeding 25% of the body weight.[84] Even less extreme weight fluctuations create a risk for stone formation,[111] as is a history of dieting.[112]

8) Diet and total parental nutrition (TPN)

Other than a high caloric intake that leads to obesity, any importance of the dietary content is unclear and difficult to analyze.[113-115] Diets specifically high in cholesterol,[116] fatty acids,[117] carbohydrates[118,119] or legumes[120] seem to increase the risk of cholelithiasis. In contrast, unsaturated fats,[121] coffee,[122,123] fiber,[124,125] ascorbic acid (vitamin C),[126,127] calcium[114] and moder-

ate consumption of alcohol[118,124,128] reduce the risk. Certainly, the shift to a more Western diet, high in refined carbohydrates and fat (triglycerides) and low in fiber, best explains the profound increase in cholesterol gallstones amongst American Indians (unmasking their presumed genetic burden) and in European countries following World War II. This dietary change also might account for the shift from pigment to cholesterol stones in Asian countries[2,129,130] Genetic variations, especially in the genes that control cholesterol metabolism, might underscore why some respond to dietary change by developing cholesterol gallstones.[16,60]

TPN is a well-known risk factor for developing microlithiasis (biliary sludge) and gallstone disease, in addition to acute acalculous cholecystitis in critically ill patients.[131-134] In an intensive care setting, biliary sludge appears after 5 to 10 days of fasting.[17,49] After 4 weeks of TPN, half of those on TPN develop gallbladder sludge on ultrasonography; after 6 weeks all show evidence of sludge.[135] Most are asymptomatic. Fortunately, sludge resolves within 4 weeks of discontinuing TPN and resuming an oral intake, a pattern similar to sludge appearing during pregnancy and rapid weight loss and then disappearing once the inciting event resolves.[136] A possible explanation for this relates to loss of the enteric stimulation of the gallbladder in the absence of eating, leading to gallbladder stasis.[134] Additionally, ileal disorders such as Crohn's disease or ileal resection, in which TPN is frequently required, can affect the enterohepatic cycling of bile acids and so augment bilirubin absorption and subsequent hepatic excretion.[86]

9) Lifestyle factors and socioeconomic status

The exact role of socioeconomic status and gallstones is controversial.[2] A previous cross-sectional study of non-Hispanic Whites and Mexican Americans, found gallbladder disease inversely related to socioeconomic status.[137] Socioeconomic status, however, may merely be an indirect marker for other risk factors like obesity and chronic medical conditions. The role of smoking in cholelithiasis is unclear.[138]

Reduced physical activity heightens the risk of gallstone disease whereas increased physical activity helps prevent cholelithiasis, independent of its role in weight loss.[122,139] Increased endurance exercise (to 30 minutes 5 times a week) may avert symptomatic gallstones developing in men.[140]

10) Underlying chronic diseases

(1) Liver disease

Advanced cirrhosis is a well-established risk factor for gallstones, with an overall prevalence at 25% to 30%.[141-143] Usually the stones consist of the black pigment type in patients with cirrhosis.[144] This is likely related to altered pigment secretion, abnormal gallbladder motility and/or increased estrogen levels.[2] Gallstone disease is also associated with chronic hepatitis C viral infection and nonalcoholic fatty liver disease;[145-147] other factors

for this are the metabolic syndrome and obesity.[148]

(2) Crohn's disease

There is a two-three fold increased risk of developing gallstones in patients with extensive ileal Crohn's disease.[77,149] An obvious explanation for this is ileal disease or loss leading to bile acid malabsorption and depletion, reduced hepatic secretion of bile acids and bile that is supersaturated with cholesterol, leading to cholesterol stone formation. The cholesterol content in bile however can be rather normal or even low in these patients.[150] Instead, there appears to be an increased frequency of pigment stones. Failure of terminal ileal transport in Crohn's disease allows excess bile acids to escape into the colon, where these biological detergents solubilize unconjugated bilirubin and so facilitate their absorption and return to the liver. The liver then secretes excessive pigment that subsequently precipitates as gallstones.[151] Other explanations include fasting in patients with Crohn's disease, or altered bacterial colonic flora that enhance the deconjugation of bilirubin, which can then be passively absorbed; the result is an upregulated enterohepatic cycling of bile pigment.[152]

(3) Cystic fibrosis

Similar to ileal Crohn's disease, cystic fibrosis is associated with bile acid malabsorption due to its binding to undigested dietary nutrients. Gallstone prevalence in cystic fibrosis is increased 10% to 30%.[153]

(4) Other diseases

In sickle cell disease, chronic hemolysis leads to excessive bilirubin excretion with the formation of black pigment stones composed of calcium bilirubinate. These tend to be small in size, permitting some to travel into the common duct; the resultant obstruction is low-grade, not necessarily accompanied by duct dilation or cholangitis. Due to potential complications and the difficulty in distinguishing biliary-type pain from other complications of sickle cell disease, prophylactic cholecystectomy should be considered.[29]

Spinal cord injury is associated with a threefold increase in gallstone formation.[154-156] Possible explanations for this include gallbladder stasis with sludge formation and intestinal hypomotility that alters bile acid metabolism.

IBS presents with abdominal pain in addition to other features, perhaps fostering cholecystectomy as a more common operation in patients with IBS. This may reflect inappropriate surgery caused by diagnostic confusion[157] or post-surgical IBS symptoms as a consequence of the operation.[158]

11) Drugs

(1) Octreotide

Octreotide, a long-acting analogue of somatostatin that inhibits cholecystokinin release, results in decreased gallbladder motility and stasis.[159] Inhibition of cholecystokinin also depresses small intestine motility; the resultant intestinal stasis enhances the formation of secondary bile acids like deoxycho-

lic acid. Deoxycholic acid adversely influences bile formation (increasing cholesterol secretion) and augments the synthesis of gallbladder mucin (important for the precipitation of cholesterol microcrystals from bile and their subsequent growth into stones). Greater than 50% of patients receiving octreotide accordingly will develop cholelithiasis, although the majority are asymptomatic.[160,161]

(2) Ceftriaxone

Ceftriaxone, a third generation cephalosporin antibiotic, is secreted unmetabolized into bile, achieving high concentrations.[86] This can result in biliary sludge and "pseudolithiasis" in those patients, particularly children, receiving ceftriaxone. Most remain asymptomatic. Meanwhile, the sludge resolves once the medication is discontinued.[162,163]

(3) Thiazide diuretics

Thiazide treatment may increase biliary cholesterol saturation leading to gallstones developing.[164] Some case-controlled reports have suggested that thiazide use is associated with a heightened risk of acute cholecystitis.[165,166] Others have not found any association.[140] Most likely, thiazide use conveys a modest effect. In one prospective study concerning women taking thiazide diuretics, the relative risk of cholecystectomy rose 36% for past users and 57% for current users.[167]

(4) Statins

Drugs that inhibit HMG-CoA reductase seem to prevent cholesterol gallstone disease by diminishing cholesterol synthesis in the liver and decreasing its secretion into bile.[168]

12) Gallbladder disease in children

Cholelithiasis in the pediatric age group has been considered rare, historically thought to be black pigment stones related to prematurity and TPN use in infants or chronic hemolysis in adolescents. Cholesterol stones, in fact, are becoming increasingly more common in children.[169-171] In unselected pediatric populations, the prevalence rates are reported between 0.1% to 1.0%.[170,172] One explanation for this increase is greater access to and use of abdominal ultrasonography in children.[173] A more prominent factor now is obesity, accounting for some 8% to 33% of gallstones observed in children.[174,175] In obese children and adolescents, the prevalence may be as high as 2.0%.[171] Other risk factors for gallstone disease in childhood include: female gender, pregnancy and oral contraceptive use; being of Mexican-American origin; drug exposure to cephalosporins, ceftriaxone or diuretics; a history of cardiac surgery or bowel resection, and having cystic fibrosis.[149,172,173,176] In fact, the risk factors for pediatric gallbladder disease now more closely resemble those in adults.

40% to 51% of children with gallstones are asymptomatic.[173,177] Those with no symptoms have a lower rate of complications, while gallstones may resolve in 17%. Therefore conservative management is recommended in these children. Pediatric patients with symptomatic cholelithiasis are at risk for compli-

cations (18% to 28%); the most common presentation is right upper quadrant abdominal pain.[173,178] Complications include acute cholecystitis, choledocholithiasis and pancreatitis.

Laparoscopic cholecystectomy is safe and can be quite effective in children. Cholecystectomy for children with symptomatic gallstones therefore is the standard of care. Surgery is also being used more frequently for functional gallbladder disease (biliary dyskinesia), an entity that bears scrutiny given the absence of clear diagnostic criteria or effective management schemes.[169]

GALLBLADDER CANCER

Gallbladder cancer is a notoriously rare though lethal malignancy with marked ethnic and geographical variations. The presenting symptoms are typically vague so that its diagnosis commonly occurs at an advanced stage. This late diagnosis plus the anatomic feature that the gallbladder lacks a serosa culminates in a rather dismal prognosis.[179-181] The overall mean survival rate for patients with advanced gallbladder cancer is 6 months, with a 5-year survival rate of 5%.[182] Early gallbladder cancer (confined to the mucosa), though infrequent, offers the potential for a cure though cholecystectomy. Most (>80%) gallbladder cancers are adenocarcinomas that originate from the fundus (60%), body (30%), or neck (10%). The basis likely is genetic susceptibility, perhaps elicited by chronic gallbladder inflammation, often a product of cholelithiasis.[181,183,184] One reasonable hypothesis focuses on chronic irritation of the mucosa (e.g., from the physical presence of the stones and/or superimposed chronic infection such as from *Salmonella typhi*) leading to dysplasia (perhaps abetted by mutagenic secondary bile acids) and terminating in malignant change.

The risk factors for developing gallbladder cancer therefore include ethnicity, genetic susceptibility, lifestyle factors and infections. Elucidating such risk factors (Table 3) not only provides insight into its pathogenesis accounting for its geographic and ethnic variances (Fig. 2), but more importantly should yield strategies to prevent and treat this unusual malignancy.[185]

1. Ethnicity, gender, and age

Gallbladder cancer is rare in developed countries. In the U.S., it only accounts for 0.5% of all gastrointestinal malignancies, accounting for less than 5,000 cases per year (1 to 2.5 per 100,000).[183] Worldwide, gallbladder cancer has a low occurrence <2 per 100,000, but has a wide variance (Fig. 2). High annual incidence rates occur in North and South American Indians, generating an inordinate mortality, particularly amongst women: 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. Hence, carcinoma of the gallbladder is the leading cause of cancer death in Chilean women, exceeding even breast, lung and cervical cancers.[186,187] Other high-risk regions are scattered though Eastern Europe (14/100,000 in Po-

land), northern India (as high as 21.5/100,000 for women from Delhi) and south Pakistan (11.3/100,000).[185] Intermediate incidences (3.7 to 9.1 per 100,000) occur elsewhere in South Americans of Indian descent, and in Israel (5/100,000) and Japan (7/100,000).[184] The frequency is increasing in Shanghai, China and now accounts for the most frequent gastrointestinal malignancy and is a substantial cause of mortality.[188] Although the majority of the world has decreasing mortality trends in gallbladder cancer, Iceland, Costa Rica, and Korea have an increase in mortality for men.[189] There appears to be a modest decline in prevalence over the past two decades (National Cancer Institute. Surveillance, Epidemiology and End Results (SEER) Program [http://seer.cancer.gov/]).

Gender differences exist with geographic variances, generally being unfavorable for women. In those locals with the highest incidence, women have frequency rates greater than men. With age, gallbladder cancer increases.

2. Gallstones

A history of gallstones appears to carry the highest risk for gallbladder cancer, with a relative risk of 4.9.[185] Most (69% to 100%) but not all people with gallbladder cancer have cholelithiasis. Further, these 2 entities frequently co-exist in the same populations, suggesting that stones may function as a co-factor for this carcinoma.[190] American Indians, who have a quite high prevalence of cholesterol gallstone disease, also have a high incidence of carcinoma of the gallbladder; yet in other

settings, there is a low incidence of gallbladder cancer despite an overall high frequency of cholelithiasis. Increasing stone size (>3 cm),[191,192] number, volume, and weight, all are associated with an increased risk of cancer.[190] Less important is the duration of cholelithiasis.[193] Cholesterol stones seem to be more common than pigment stones in gallbladder cancer patients.[194] Further attesting to gallstones being a risk factor for gallbladder carcinoma, the incidence of this cancer rises when the cholecystectomy rate declines.[184,195] Nevertheless, consensus does not generally favor prophylactic cholecystectomy for asymptomatic stones[196,197] as cholelithiasis is too common and gallbladder can-

Table 3. Risk Factors for Gallbladder Cancer

Risk factor	Relative risk		Reference
Gallstones	3.01–23.8		218–222
Size of gallstones			
2.0–2.9 cm	2.4		191,223
>3.0 cm	9.2–10.1		
Duration of gallstones			
5–19 yr	4.9		193
>20 yr	6.2		
BMI	Men	Women	215
30.0–34.9	1.8	2.1	
Infections			
Chronic typhoid & paratyphoid carriers	12.7–167		224,225
Helicobacter bilis	2.6–6.5		206,226

Fig. 2. Incidence of gallbladder cancer worldwide (From National Cancer Institute. Surveillance, Epidemiology and End Results (SEER) Program. Available from http://seer.cancer.gov/). Carcinoma of the gallbladder is more common in certain ethnic groups: native American Indians, white Hispanics from North and South America, and those from northern India and Eastern Europe.[198] Elsewhere in the world, the incidence is low at <2/100,000.

cer too rare. Potential exceptions include large stones greater than 3 cm, which have a risk of 4% over 20 years,[27,198] and elderly American Indian females with gallstones.[199]

3. Chronic inflammation

Chronic inflammation from any cause may lead to calcium being deposited in the gallbladder wall, termed the "porcelain gallbladder" because of its bluish color and fragile, brittle consistency.[200] This entity is rare, being identified pathologically in less than 1% of gallbladder specimens. The calcium deposits can be detected on diagnostic imaging - plain abdominal radiographs, ultrasounds or computed tomography images. Controversy exists whether or not the porcelain gallbladder is truly associated with an increased risk of cancer. Some studies indicate that 25% (range, 12% to 61%) are associated with gallbladder cancer,[199,201] whereas more recent reports negate any such association.[202] Only gallbladders with partial calcification, stippled or multiple punctate calcifications in the glandular spaces of the mucosa, are premalignant and therefore should be removed prophylactically. Those with a broad continuous band of calcification in the muscularis appear not to be harbingers of gallbladder cancer.

Chronic bacterial infections also cause irritation and inflammation in the gallbladder. S. typhi carriers have an 8 to 12-fold increased risk with 6% developing gallbladder cancer.[203-205] In contrast to typhoid carriers, however, a past history of typhoid fever is not associated with the development of gallbladder cancer.[206] Helicobacter pilis is also implicated in gallbladder cancer with an odds ratio of 6.5 in Japanese patients and 5.86 in Thai patients.[206]

Primary sclerosing cholangitis (PSC) is typically associated with an increased risk of cholangiocarcinoma. As dysplasia occurs in 37% and adenocarcinoma in 14% of gallbladders from patients with PSC, their general predilection for biliary carcinoma as cholangiocarcinoma may place these individuals at heightened risk for developing gallbladder cancer.[207]

4. Congenital biliary abnormalities

An anomalous pancreaticobiliary junction is a rare congenital anomaly of the biliary tract in which the pancreatic and biliary ducts join outside the duodenal wall, forming an abnormally long channel that lies beyond the sphincter of Oddi.[208] Such an anomaly defeats sphincter of Oddi gatekeeper function, potentially allowing pancreatic secretions to regurgitate into the biliary system and gallbladder, and so leading to malignant changes in the mucosa.[209] The anomalous pancreaticobiliary junction is more prevalent in Asian (particularly Japanese) populations and carries an increased risk of gallbladder cancer at 3% to 18%.[183,210] Hence, prophylactic cholecystectomy is recommended due to the high frequency of gallbladder carcinoma.

5. Genetic factors

There are undoubtedly genetic and environmental factors that coincide to become expressed as gallbladder cancer. A family history of gallbladder cancer is clearly a risk factor.[211,212] The only responsible gene so far identified seems to be that for apolipoprotein B function (the APOB gene), which influences cholesterol handling yet is not associated with gallstones. In fact, the link between cholesterol gallstones and gallbladder cancer may relate to an interdependent disposal pathway that increases the export of both cholesterol and environmental toxins into bile. As gallbladder cancer is more common in women, such mutagenic toxins secreted reside longer in the gallbladder due to stasis from impaired contractility associated with the female hormone, progesterone. This protracted exposure allows environmental carcinogens to then cause malignant transformation, helping to reconcile the schism of seed versus soil and incorporate the predilection to the development of gallstones (also requiring some gallbladder stasis) and gallbladder cancer.[213]

6. Gallbladder polyps

Polypoidal masses of the gallbladder affect 5% of adults and may be confused with gallbladder cancer.[214] Over two-thirds of polyps are composed of cholesterol esters; the other lesions are adenomas, leiomyomas or inflammatory polyps. Although occasionally associated with biliary colic, the vast majority of gallbladder polyps are asymptomatic, being found incidentally when abdominal imaging is performed for other purposes. Features that predict malignancy are: large polyps (>10 mm), a solitary or sessile mass, associated gallstones, patient age over 50 and most importantly, rapid polyp growth. Prophylactic cholecystectomy is warranted in patients with polyps that possess such malignant-appearing features.

7. Other lifestyle factors

The association of gallstones with gallbladder cancer likely explains why some of the traditional risk factors for gallstones are also risk factors for gallbladder cancer including obesity, female gender, and multiparity. In over 84,000 men and 97,000 women included in The Cancer Prevention Study II Nutrition Cohort, the relative risk of gallbladder cancer was 1.8 (95% confidence interval [CI], 1.1 to 2.9) in obese men with a BMI of 30.0 to 34.9 compared to men with a normal BMI (18.5 to 24.9). Obese women (BMI, 30.0 to 34.9) had a relative risk of 2.1 (95% CI, 1.6 to 2.9) compared to women with a normal BMI.[215] Overall, obesity has a relative risk of 1.66 (95% CI, 1.47 to 1.88) for gallbladder cancer.[216] Other lifestyle risks involve cigarette smoking, and alcohol consumption (in men only).[217]

CONCLUSION

The prevalence of gallbladder disease at any point in time

(i.e., prevalence) has advanced with the use of ultrasonographic surveys as opposed to previous studies based on clinical or necropsy evidence.[2,3] These population surveys have better defined important risk factors, both unchangeable and modifiable. The implications of changing environmental risk factors predict an increase in the numbers of individuals with gallstones. An aging population plus the rising epidemic of obesity and the metabolic syndrome are certain to aggravate the frequency and complications of gallstone disease. Identifying risk factors that can be altered (i.e., extreme obesity, rapid weight loss, sedentary lifestyle, and key dietary factors) should provide an opportunity to prevent cholelithiasis. Several risk factors for gallstones are also implicated in the pathogenesis of gallbladder cancer. Although the frequency of gallbladder cancer is relatively low in the U.S., if the incidence of gallstones rises, gallbladder cancer most likely will also increase.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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