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 cholecystitis, advancing age, chronic inflammatory conditions affecting the gallbladder, congenital biliary abnormalities, and diagnostic confusion over gallbladder polyps.

Key Words: Gallstones; Cholecystectomy; Gallbladder polyps; Gallbladder cancer

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. 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. 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. 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. With an estimated 1.8 million ambulatory care visits each year, gallstone disease is a leading cause for hospital admissions related to gastrointestinal problems. 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.1,12 Further, as the incidence of gallstone disease escalates, there is a concomitant increase in complications like gallstone-related pancreatitis.11

The number of surgical procedures for cholelithiasis has risen markedly in developed countries since 1950.17 The introduction of laparoscopic cholecystectomy in 1989 further increased the cholecystectomy rate.24-16 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.1,22 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 are 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.29 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.\textsuperscript{31,42} 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.\textsuperscript{41} 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).\textsuperscript{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).\textsuperscript{41}

North American Indians have the highest reported rates of cholelithiasis, afflicting 64.1% of women and 29.5% of men.\textsuperscript{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.\textsuperscript{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.\textsuperscript{47-50} White Americans have an overall prevalence of 16.6% in women and 8.6% in men.\textsuperscript{54} Intermediate prevalence rates occur in Asian populations\textsuperscript{51,52} and Black Americans (13.9% of women; 5.3% of men).\textsuperscript{2} The lowest frequencies occur in sub-Saharan Black Africans (<5%).\textsuperscript{55} 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).\textsuperscript{2,57}

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 cholangiopancreatitis: 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.\textsuperscript{56} 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.35 Familial studies reveal an increased frequency: a nearly 5 times elevated risk in the relatives of gallstone patients. These rates 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.60,60 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 |
|---------------------------------------------|
| **Composition** | **Cholesterol gallstones** (50-100%) | **Black pigment stones** (Calcium bilirubinate polymer) | **Brown pigment stones** (Unconjugated bilirubin, calcium soaps of fatty acids, cholesterol & mucin) | **Biliary sludge (microlithiasis)** (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.41 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.](image)
secretion (ABCG8 19H and ABCB4) represent a susceptibility factor for human gallstones. Converting 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 polygenic disease entity.

3) Age

The frequency of gallstones increases with age, escalating markedly after age 40 to become 4 times more likely in older individuals. 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.

4) Gender and female sex hormones

The female gender has a most compelling association with gallstone disease, especially during the fertile years. Women are at least twice as likely as men to form stones; the gap narrows following menopause after which men begin to catch up. The underlying mechanism is female sex hormones; parity, oral contraceptive use and estrogen replacement therapy are established risk factors for cholesterol gallstone formation. 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 for gallstone disease; however, the increased risk is quite modest and not likely to be clinically meaningful.

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%. Additional risk factors for stone formation during pregnancy include obesity (prior to the pregnancy), reduced high density lipoprotein (HDL) cholesterol and the metabolic syndrome.

5) Obesity

The exploding prevalence of obesity now reaches epidemic levels in both developed and developing nations like China. Obesity, particularly abdominal or centripetal obesity, is a well-established risk factor for gallstone disease. At least 25% of morbidly obese individuals have evidence of gallstone disease. Obesity in the late teenage years carries the greatest risk, whereas thinness protects against cholelithiasis. Females with obesity have an even increased risk of stones formation. Women with severe obesity (body mass index [BMI] >32 kg/m²) 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%. 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.

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 and hypertriglyceridemia carry an increased risk of developing stones. In contrast, there is no definite association with hypercholesterolemia. High homocysteine levels also may correlate with gallstone disease.

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. Both the metabolic syndrome and diabetes mellitus are risk factors for gallstone disease. The metabolic syndrome has also been associated with stone complications. Insulin resistance predisposes to cholesterol gallstone formation, 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.

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. 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. Rapid 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. Even less extreme weight fluctuations create a risk for stone formation, as is a history of dieting.

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. Diets specifically high in cholesterol, fatty acids, carbohydrates or legumes seem to increase the risk of cholelithiasis. In contrast, unsaturated fats, coffee, fiber, ascorbic acid (vitamin C), calcium and moder-
ate consumption of alcohol 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. Genetic variations, especially in the genes that control cholesterol metabolism, might underscore why some respond to dietary change by developing cholesterol gallstones.

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. In an intensive care setting, biliary sludge appears after 5 to 10 days of fasting. After 4 weeks of TPN, half of those on TPN develop gallbladder sludge on ultrasonography; after 6 weeks all show evidence of sludge. 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. A possible explanation for this relates to loss of the enteric stimulation of the gallbladder in the absence of eating, leading to gallbladder stasis. 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.

9) Lifestyle factors and socioeconomic status

The exact role of socioeconomic status and gallstones is controversial. A previous cross-sectional study of non-Hispanic Whites and Mexican Americans, found gallbladder disease inversely related to socioeconomic status. 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.

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

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%. Usually the stones consist of the black pigment type in patients with cirrhosis. This is likely related to altered pigment secretion, abnormal gallbladder motility and/or increased estrogen levels. Gallstone disease is also associated with chronic hepatitis C viral infection and nonalcoholic fatty liver disease, other factors for this are the metabolic syndrome and obesity.

2) Crohn’s disease

There is a two-three fold increased risk of developing gallstones in patients with extensive ileal Crohn’s disease. 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. 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. 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.

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%.

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.

Spinal cord injury is associated with a threefold increase in gallstone formation. 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 or post-surgical IBS symptoms as a consequence of the operation.

11) Drugs

1) Octreotide

Octreotide, a long-acting analogue of somatostatin that inhibits cholecystokinin release, results in decreased gallbladder motility and stasis. Inhibition of cholecystokinin also depresses small intestine motility; the resultant intestinal stasis enhances the formation of secondary bile acids like deoxycho-
lich 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.162 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.163,164

(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.167 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.166

(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.169,174,175,176 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.177,178 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 complications (18% to 28%); the most common presentation is right upper quadrant abdominal pain.173,178 Complications include acute cholecystitis, choleclocholithiasis 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.180

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.179-184 The overall mean survival rate for patients with advanced gallbladder cancer is 6 months, with a 5-year survival rate of 5%.185 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.186,187,188 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.189

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).182 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). 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). The frequency is increasing in Shanghai, China and now accounts for the most frequent gastrointestinal malignancy and is a substantial cause of mortality. 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. 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. 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. 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), number, volume, and weight, all are associated with an increased risk of cancer. Less important is the duration of cholelithiasis. Cholesterol stones seem to be more common than pigment stones in gallbladder cancer patients. Further attesting to gallstones being a risk factor for gallbladder carcinoma, the incidence of this cancer rises when the cholecystectomy rate declines. Nevertheless, consensus does not generally favor prophylactic cholecystectomy for asymptomatic stones 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                          |               |           |
| 30.0-34.9                    | 1.8           | 215       |
| Women                        | 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. Elsewhere in the world, the incidence is low at <2/100,000.](image-url)
cancer too rare. Potential exceptions include large stones greater than 3 cm, which have a risk of 4% over 20 years, and elderly American Indian females with gallstones.

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. 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, whereas more recent reports negate any such association. 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. In contrast to typhoid carriers, however, a past history of typhoid fever is not associated with the development of gallbladder cancer. Helicobacter pylis is also implicated in gallbladder cancer with an odds ratio of 6.5 in Japanese patients and 5.86 in Thai patients.

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.

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. 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. The anomalous pancreaticobiliary junction is more prevalent in Asian (particularly Japanese) populations and carries an increased risk of gallbladder cancer at 3% to 18%. 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. 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 predisposition to the development of gallstones (also requiring some gallbladder stasis) and gallbladder cancer.

6. Gallbladder polyps

Polypoidal masses of the gallbladder affect 5% of adults and may be confused with gallbladder cancer. 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 men with a normal BMI. Overall, obesity has a relative risk of 1.66 (95% CI, 1.47 to 1.88) for gallbladder cancer. Other lifestyle risks involve cigarette smoking, and alcohol consumption (in men only).

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. 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.

**REFERENCES**

1. Gracie WA, Ransohoff DF. The natural history of silent gallstones: the innocent gallstone is not a myth. N Engl J Med 1982;307:798-800.
2. Shaffer EA. Epidemiology and risk factors for gallstone disease: has the paradigm changed in the 21st century? Curr Gastroenterol Rep 2005;7:132-140.
3. Kratzer W, Mason RA, Kächele V. Prevalence of gallstones in sonographic surveys worldwide. J Clin Ultrasound 1999;27:1-7.
4. Pedersen G, Hoem D, Andrén-Sandberg A. Influence of laparoscopic cholecystectomy on the prevalence of operations for gallstones in Norway. Eur J Surg 2002;168:464-469.
5. Schirmer BD, Winters KL, Edlich RF. Cholelithiasis and cholecystitis. J Long Term Eff Med Implants 2005;15:329-338.
6. Everhart JE, Khare M, Hill M, Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. Gastroenterology 1999;117:632-639.
7. Tazuma S. Gallstone disease: epidemiology, pathogenesis, and classification of biliary stones (common bile duct and intrahepatic). Best Pract Res Clin Gastroenterol 2006;20:1075-1083.
8. Sandler RS, Everhart JE, Donowitz M, et al. The burden of selected digestive diseases in the United States. Gastroenterology 2002;122:1500-1511.
9. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part I: overall and upper gastrointestinal diseases. Gastroenterology 2009;136:376-386.
10. Shaheen NJ, Hansen RA, Morgan DR, et al. The burden of gastrointestinal and liver diseases, 2006. Am J Gastroenterol 2006;101:2128-2138.
11. Ruhl CE, Everhart JE. Gallstone disease is associated with increased mortality in the United States. Gastroenterology 2011;140:508-516.
12. Grimaldi CH, Nelson RG, Pettitt DJ, Sampiner RE, Bennett PH, Knowler WC. Increased mortality with gallstone disease: results of a 20-year population-based survey in Pima Indians. Ann Intern Med 1993;118:185-190.
13. Lindkvist B, Appelros S, Manjer J, Borgström A. Trends in incidence of acute pancreatitis in a Swedish population: is there really an increase? Clin Gastroenterol Hepatol 2004;2:831-837.
14. Legorreta AP, Silber JB, Costantino GN, Kobylinski RW, Zatz SL. Increased cholecystectomy rate after the introduction of laparoscopic cholecystectomy. JAMA 1993;270:1429-1432.
15. Marshall D, Clark E, Hailey D. The impact of laparoscopic cholecystectomy in Canada and Australia. Health Policy 1994;26:221-230.
16. Kang JY, Ellis C, Majeed A, et al. Gallstones: an increasing problem: a study of hospital admissions in England between 1989/1990 and 1999/2000. Aliment Pharmacol Ther 2003;17:561-569.
17. Nenner RP, Imperato PJ, Rosenberg C, Ronberg E. Increased cholecystectomy rates among Medicare patients after the introduction of laparoscopic cholecystectomy. J Community Health 1994;19:409-415.
18. Russo MW, Wei JT, Thiny MT, et al. Digestive and liver diseases statistics, 2004. Gastroenterology 2004;126:1448-1453.
19. Zacks SL, Sandler RS, Rutledge R, Brown RS Jr. A population-based cohort study comparing laparoscopic cholecystectomy and open cholecystectomy. Am J Gastroenterol 2002;97:334-340.
20. Gilney EJ. Asymptomatic gallstones. Br J Surg 1990;77:368-372.
21. Sakorafas GH, Milingos D, Peros G. Asymptomatic cholelithiasis: is cholecystectomy really needed? A critical reappraisal 15 years after the introduction of laparoscopic cholecystectomy. Dig Dis Sci 2007;52:1313-1325.
22. Halldestam I, Enell EL, Kullman E, Borch K. Development of symptoms and complications in individuals with asymptomatic gallstones. Br J Surg 2004;91:734-738.
23. Thistle JL, Cleary PA, Lachin JM, Tyor MP, Hersh T. The natural history of cholelithiasis: the National Cooperative Gallstone Study. Ann Intern Med 1984;101:171-175.
24. Ransohoff DF, Gracie WA, Wolfenson LB, Neuhauser D. Prophylactic cholecystectomy or expectant management for silent gallstones. A decision analysis to assess survival. Ann Intern Med 1983;99:199-204.
25. Friedman GD. Natural history of asymptomatic and symptomatic gallstones. Am J Surg 1993;165:399-404.
26. Schirmer BD, Winters KL, Edlich RF. Cholelithiasis and cholecystitis. J Long Term Eff Med Implants 2005;15:329-338.
27. Kapoor VK. Cholecystectomy in patients with asymptomatic gallstones to prevent gall bladder cancer: the case against. Indian J Gastroenterol 2006;25:152-154.
28. Bonatsos G, Birbas K, Toutouzas K, Durakis N. Laparoscopic
cholecystectomy in adults with sickle cell disease. Surg Endosc 2001;15:816-819.
29. Ebert EC, Nagar M, Hagspiel KD. Gastrointestinal and hepatic complications of sickle cell disease. Clin Gastroenterol Hepatol 2010;8:483-489.
30. Kao LS, Kuhr CS, Flum DR. Should cholecystectomy be performed for asymptomatic cholelithiasis in transplant patients? J Am Coll Surg 2003;197:302-312.
31. Shiffman ML, Sugarman HJ, Kellum JM, Brewer WH, Moore EW. Gallstone formation after rapid weight loss: a prospective study in patients undergoing gastric bypass surgery for treatment of morbid obesity. Am J Gastroenterol 1991;86:1000-1005.
32. Jørgensen T. Abdominal symptoms and gallstone disease: an epidemiological investigation. Hepatology 1989;9:856-860.
33. Traverso LW. Clinical manifestations and impact of gallstone disease. Am J Surg 1993;165:405-409.
34. Fenster LF, Lonborg R, Thiriby RC, Traverso LW. What symptoms does cholecystectomy cure? Insights from an outcomes measurement project and review of the literature. Am J Surg 1995;169:533-538.
35. Festi D, Sottili S, Colecchia A, et al. Clinical manifestations of gallstone disease: evidence from the multicenter Italian study on cholelithiasis (MICOL). Hepatology 1999;30:839-846.
36. Berhane T, Verhues M, Hausken T, Olafsson S, Sondena K. Pain attacks in non-complicated and complicated gallstone disease have a characteristic pattern and are accompanied by dyspepsia in most patients: the results of a prospective study. Scand J Gastroenterol 2006;41:93-101.
37. Weinert CR, Arnett D, Jacobs D Jr, Kane RL. Relationship between persistence of abdominal symptoms and successful outcome after cholecystectomy. Arch Intern Med 2000;160:989-995.
38. Verhues M, Berhane T, Søreide O, Sondena K. Pain persists in many patients five years after removal of the gallbladder: observations from two randomized controlled trials of symptomatic, noncomplicated gallstone disease and acute cholecystitis. J Gastrointest Surg 2005;9:826-831.
39. Mertens MC, Roukema JA, Scholtes VP, De Vries J. Risk assessment in cholelithiasis: is cholecystectomy always to be preferred? J Gastrointest Surg 2010;14:1271-1279.
40. Thistle JL, Longstreth GF, Romero Y, et al. Factors that predict relief from upper abdominal pain after cholecystectomy. Clin Gastroenterol Hepatol 2011;9:891-896.
41. Shaffer E. Acalculous biliary pain: new concepts for an old entity. Dig Liver Dis 2003;35 Suppl 3:S20-S25.
42. DiBaise JK, Richmond BK, Zieissman HH, et al. Cholecystokinin-cholecystintigraphy in adults: consensus recommendations of an interdisciplinary panel. Clin Gastroenterol Hepatol 2011;9:376-384.
43. Gurusamy KS, Junmarkar S, Farouk M, Davidson BR. Cholecystectomy for suspected gallbladder dyskinesia. Cochrane Database Syst Rev 2009(1):CD007086.
44. Shaffer EA. Gallstone disease: epidemiology of gallbladder stone disease. Best Pract Res Clin Gastroenterol 2006;20:981-996.
45. Everhart JE, Yeh F, Lee ET, et al. Prevalence of gallbladder disease in American Indian populations: findings from the Strong Heart Study. Hepatology 2002;35:1507-1512.
46. Miquel JF, Covarrubias C, Villaroel L, et al. Genetic epidemiology of cholesterol cholelithiasis among Chilean Hispanics, Amerindians, and Maoris. Gastroenterology 1998;115:937-946.
47. Everhart JE. Gallstones and ethnicity in the Americas. J Assoc Acad Minor Phys 2001;12:137-143.
48. Diehl AK, Stern MP. Special health problems of Mexican-Americans: obesity, gallbladder disease, diabetes mellitus, and cardiovascular disease. Adv Intern Med 1989;34:73-96.
49. Maurer KR, Everhart JE, Ezzati TM, et al. Prevalence of gallstone disease in Hispanic populations in the United States. Gastroenterology 1989;96(2 Pt 1):487-492.
50. Hanis CL, Hewett-Emmett D, Kuhnsly LF, et al. An ultrasound survey of gallbladder disease among Mexican Americans in Starr County, Texas: frequencies and risk factors. Ethn Dis 1993;3:32-43.
51. Singh V, Trikha B, Nain C, Singh K, Bose S. Epidemiology of gallstone disease in Chandigarh: a community-based study. J Gastroenterol Hepatol 2001;16:560-563.
52. Chen CY, Lu CL, Huang YS, et al. Age is one of the risk factors in developing gallstone disease in Taiwan. Age Ageing 1998;27:437-441.
53. Bagi Abdel M, Arabi M, Abdel Rahim B, et al. Prevalence of gallbladder disease in Sudan: first sonographic field study in adult population. Gastroenterology 1991;100:A307.
54. Shoda J, Tanaka N, Osuga T. Hepatolithiasis: epidemiology and pathogenesis update. Front Biosci 2003;8:e398-e409.
55. Lammert F, Matern S. The genetic background of cholesterol gallstone formation: an inventory of human lithogenic genes. Curr Drug Targets Immune Endocr Metabol Disord 2005;5:163-170.
56. Sarin SK, Negi VS, Dewan R, Sasan S, Saraya A. High familial prevalence of gallstones in the first-degree relatives of gallstone patients. Hepatology 1995;22:138-141.
57. Gilat T, Feldman C, Halpern Z, Dan M, Bar-Meir S. An increased familial frequency of gallstones. Gastroenterology 1983;84:242-246.
58. van der Linden W, Westlin N. The familial occurrence of gallstone disease. II. Occurrence in husbands and wives. Acta Genet Stat Med 1966;16:377-382.
59. Katsika D, Grijibovski A, Einarsson C, Lammert F, Lichtenstein P, Marschall HU. Genetic and environmental influences on symptomatic gallstone disease: a Swedish study of 43,141 twin pairs. Hepatology 2005;41:1138-1143.
60. Rudkowska I, Jones PJ. Polymorphisms in ABCG5/G8 transporters linked to hypercholesterolemia and gallstone disease. Nutr Rev 2008;66:343-348.
61. Stinton LM, Myers RP, Shaffer EA. Epidemiology of gallstones. Gastroenterol Clin North Am 2010;39:157-169.
62. Mittal B, Mittal RD. Genetics of gallstone disease. J Postgrad Med
97. Ruhl CE, Everhart JE. Association of diabetes, serum insulin, and C-peptide with gallbladder disease. Hepatology 2000;31:299-303.
98. Nervi F, Miquel JE, Alvarez M, et al. Gallbladder disease is associated with insulin resistance in a high risk Hispanic population. J Hepatol 2006;45:299-305.
99. Biddinger SB, Haas JT, Yu BB, et al. Hepatic insulin resistance directly promotes formation of cholesterol gallstones. Nat Med 2008;14:788.
100. Twisk J, Hoekman MF, Lehmann EM, Meijer P, Mager WH, Princen HM. Insulin suppresses bile acid synthesis in cultured rat hepatocytes by down-regulation of cholesterol 7 alpha-hydroxylase and sterol 27-hydroxylase gene transcription. Hepatology 1995;21:501-510.
101. Nakabe A, Comuzie AG, Al-Azzawi H, Sonnenberg GE, Kissebah AH, Pitt HA. Insulin resistance causes human gallbladder dysmotility. J Gastrointest Surg 2006;10:940-948.
102. Everhart JE. Contributions of obesity and weight loss to gallstone disease. Ann Intern Med 1993;119:1029-1035.
103. Tsai CJ, Leitzmann MF, Willett WC, Giovannucci EL. Long-chain saturated fatty acids consumption and risk of gallstone disease among men. Ann Surg 2008;247:95-103.
104. Cueva A, Miquel JE, Reyes MS, Zanlungo S, Nervi F. Diet as a risk factor for cholesterol gallstone disease. J Am Coll Nutr 2004;23:187-196.
105. Tseng M, Everhart JE, Sandier RS. Dietary intake and gallbladder disease: a review. Public Health Nutr 1999;2:161-172.
106. Lee DW, Gilmore CJ, Bonorris G, et al. Effect of dietary cholesterol on biliary lipids in patients with gallstones and normal subjects. Am J Clin Nutr 1985;42:414-420.
107. Tsai CJ, Leitzmann MF, Willett WC, Giovannucci EL. Dietary carbohydrates and glycemic load and the incidence of symptomatic gall stone disease in men. Gut 2005;54:823-828.
108. Nervi F, Covarrubias C, Bravo P, et al. Influence of legume intake on biliary lipids and cholesterol saturation in young Chilean men. Identification of a dietary risk factor for cholesterol gallstone formation in a highly prevalent area. Gastroenterology 1989;96:825-830.
109. Tsai CJ, Leitzmann MF, Willett WC, Giovannucci EL. The effect of long-term intake of cis unsaturated fats on the risk for gallstone disease in men: a prospective cohort study. Ann Intern Med 2004;141:514-522.
110. Leitzmann MF, Willett WC, Rimm EB, et al. A prospective study of coffee consumption and the risk of symptomatic gallstone disease in men. JAMA 1999;281:2106-2112.
111. Leitzmann MF, Stampfer MJ, Willett WC, Spiegelman D, Colditz GA, Giovannucci EL. Coffee intake is associated with lower risk of symptomatic gallstone disease in women. Gastroenterology 2002;123:1823-1830.
112. Leitzmann MF, Tsai CJ, Stampfer MJ, et al. Alcohol consumption in relation to risk of cholecystectomy in women. Am J Clin Nutr 2003;78:339-347.
113. Attilli AF, Scafato E, Marchioli R, Marfisi RM, Festi D. Diet and gallstones in Italy: the cross-sectional MiCoL results. Hepatology 1998;27:1492-1498.
114. Simon JA, Hudes ES. Serum ascorbic acid and gallbladder disease prevalence among US adults: the Third National Health and Nutrition Examination Survey [NHANES III]. Arch Intern Med 2000;160:931-936.
115. Simon JA, Hudes ES. Serum ascorbic acid and other correlates of gallbladder disease among US adults. Am J Public Health 1998;88:1208-1212.
116. Simon JA, Hudes ES. Serum ascorbic acid and other correlates of gallbladder disease among US adults. Am J Public Health 1998;88:1208-1212.
117. Simon JA, Hudes ES. Serum ascorbic acid and other correlates of gallbladder disease among US adults. Am J Public Health 1998;88:1208-1212.
118. Simon JA, Hudes ES. Serum ascorbic acid and other correlates of gallbladder disease among US adults. Am J Public Health 1998;88:1208-1212.
119. Simon JA, Hudes ES. Serum ascorbic acid and other correlates of gallbladder disease among US adults. Am J Public Health 1998;88:1208-1212.
120. Simon JA, Hudes ES. Serum ascorbic acid and other correlates of gallbladder disease among US adults. Am J Public Health 1998;88:1208-1212.
121. Simon JA, Hudes ES. Serum ascorbic acid and other correlates of gallbladder disease among US adults. Am J Public Health 1998;88:1208-1212.
122. Simon JA, Hudes ES. Serum ascorbic acid and other correlates of gallbladder disease among US adults. Am J Public Health 1998;88:1208-1212.
130. Kameda H, Ishihara F, Shibata K, Tsukie E. Clinical and nutritional study on gallstone disease in Japan. Jpn J Med 1984;23:109-113.

131. Guglielmi FW, Boggio-Bertinet D, Federico A, et al. Total parenteral nutrition-related gastroenterological complications. Dig Liver Dis 2006;38:623-642.

132. Roslyn JJ, Pitt HA, Mann LL, Ament ME, DeNesten E. Gallbladder disease in patients on long-term parenteral nutrition. Gastroenterology 1983;84:148-154.

133. Baudet S, Medina C, Vilaseca J, et al. Effect of short-term octreotide therapy and total parenteral nutrition on the development of biliary sludge and lithiasis. Hepatogastroenterology 2002;49:609-612.

134. Angelico M, Della Guardia P. Review article: hepatobiliary complications associated with total parenteral nutrition. Aliment Pharmacol Ther 2000;14 Suppl 2:54-57.

135. Messing B, Borries C, Kunstlinger F, Bernier JJ. Does total parenteral nutrition induce gallbladder sludge formation and lithiasis? Gastroenterology 1983;84(5 Pt 1):1012-1019.

136. Shaffer EA. Gallbladder sludge: what is its clinical significance? Curr Gastroenterol Rep 2001;3:166-173.

137. Diehl AK, Rosenthal M, Hazuda HP, Comeaux PJ, Stern MP. Socioeconomic status and the prevalence of clinical gallbladder disease. J Chronic Dis 1985;38:1019-1026.

138. Sahi T, Paffenbarger RS Jr, Hsieh CC, Lee IM. Body mass index, cigarette smoking, and other characteristics as predictors of self-reported, physician-diagnosed gallbladder disease in male college alumni. Am J Epidemiol 1998;147:644-651.

139. Leitzmann MF, Rimm EB, Willett WC, et al. Recreational physical activity and the risk of cholecystectomy in women. N Engl J Med 1999;341:777-784.

140. Banim PJ, Luben RN, Wareham NJ, Sharp SJ, Khaw KT, Hart AR. Physical activity reduces the risk of symptomatic gallstones: a prospective cohort study. Eur J Gastroenterol Hepatol 2010;22:983-988.

141. Acalovschi M, Badea R, Dumitraçcu D, Varga C. Prevalence of gallstones in liver cirrhosis: a sonographic survey. Am J Gastroenterol 2006;101:70-74.

142. Hutchinson R, Tyrrell PN, Kumar D, Dunn JA, Li JK, Allan RN. Pathogenesis of gall stones in Crohn's disease: an alternative explanation. Gut 1994;35:94-97.

143. Brink MA, Sors JF, Keulemans YC, et al. Enterohepatic cycling of bilirubin: a putative mechanism for pigment gallstone formation in ileal Crohn's disease. Gastroenterology 1999;116:1420-1427.

144. Roti E, Minelli R, Gardini E, et al. Chronic treatment with a long-acting somatostatin analogue in a patient with intestinal carcinoid tumor: occurrence of cholecystitis. Gut 1994;35:94-97.

145. Alvaro D, Angelico M, Gandin C, Cinanni Corradi S, Capocaccia L. Physico-chemical factors predisposing to pigment gallstone formation in liver cirrhosis. J Hepatol 1990;10:228-234.

146. Loria P, Lonardo A, Lombardini S, et al. Gallstone disease in non-alcoholic fatty liver disease: prevalence and associated factors. J Gastroenterol Hepatol 2005;20:1176-1184.

147. Chen CH, Huang MH, Yang JC, et al. Prevalence and risk factors of gallstone disease in an adult population of Taiwan: an epidemiological survey. J Gastroenterol Hepatol 2006;21:1737-1743.

148. Acalovschi M, Buzas C, Radu C, Grigorescu M. Hepatitis C virus infection is a risk factor for gallstone disease: a prospective hospital-based study of patients with chronic viral C hepatitis. J Viral Hepat 2009;16:860-866.

149. Vitek L, Carey MC. Enterohepatic cycling of bilirubin as a cause of 'black' pigment gallstones in adult life. Eur J Clin Investig 2003;33:799-810.

150. Rotter KP, Larrain CG. Gallstones in spinal cord injury [SCI]: a late medical complication? Spinal Cord 2003;41:105-108.

151. Xia CS, Han YQ, Yang XY, Hong GX. Spinal cord injury and cholecystitis. Hepatobiliary Pancreat Dis Int 2004;3:595-598.

152. Kennedy TM, Jones RH. Epidemiology of cholecystectomy and irritable bowel syndrome in a UK population. Br J Surg 2000;87:1658-1663.

153. Ros E, Zambon D. Postcholecystectomy symptoms. A prospective study of gall stone patients before and two years after surgery. Gut 1987;28:1500-1504.

154. Lustgarten DE, Moertel CG, Kvols LK. Incidence and morbidity of biliary complications associated with total parenteral nutrition. Aliment Pharmacol Ther 2000;8(Suppl 2):54-57.

155. Trendle MC, Moertel CG, Kvols LK. Incidence and morbidity of biliary complications associated with total parenteral nutrition. Aliment Pharmacol Ther 2000;8(Suppl 2):54-57.

156. Apstein MD, Dalecki-Chipperfield K. Spinal cord injury is a risk factor for gallstone disease. Gastroenterology 1984;87:92-966-968.

157. Whorwell PJ, Hawkins R, Dewbury K, Wright R. Ultrasound survey of gallstones and other hepatobiliary disorders in patients with Crohn’s disease. Dig Dis Sci 1984;29:930-933.

158. Hutchinson R, Tyrrell PN, Kumar D, Dunn JA, Li JK, Allan RN. Pathogenesis of gall stones in Crohn’s disease: an alternative explanation. Gut 1994;35:94-97.

159. Alvaro D, Angelico M, Gandin C, Cinanni Corradi S, Capocaccia L. Physico-chemical factors predisposing to pigment gallstone formation in liver cirrhosis. J Hepatol 1990;10:228-234.

160. Alvaro D, Angelico M, Gandin C, Cinanni Corradi S, Capocaccia L. Physico-chemical factors predisposing to pigment gallstone formation in liver cirrhosis. J Hepatol 1990;10:228-234.

161. Alvaro D, Angelico M, Gandin C, Cinanni Corradi S, Capocaccia L. Physico-chemical factors predisposing to pigment gallstone formation in liver cirrhosis. J Hepatol 1990;10:228-234.

162. Alvaro D, Angelico M, Gandin C, Cinanni Corradi S, Capocaccia L. Physico-chemical factors predisposing to pigment gallstone formation in liver cirrhosis. J Hepatol 1990;10:228-234.

163. Alvaro D, Angelico M, Gandin C, Cinanni Corradi S, Capocaccia L. Physico-chemical factors predisposing to pigment gallstone formation in liver cirrhosis. J Hepatol 1990;10:228-234.

164. Alvaro D, Angelico M, Gandin C, Cinanni Corradi S, Capocaccia L. Physico-chemical factors predisposing to pigment gallstone formation in liver cirrhosis. J Hepatol 1990;10:228-234.

165. Alvaro D, Angelico M, Gandin C, Cinanni Corradi S, Capocaccia L. Physico-chemical factors predisposing to pigment gallstone formation in liver cirrhosis. J Hepatol 1990;10:228-234.

166. Alvaro D, Angelico M, Gandin C, Cinanni Corradi S, Capocaccia L. Physico-chemical factors predisposing to pigment gallstone formation in liver cirrhosis. J Hepatol 1990;10:228-234.

167. Alvaro D, Angelico M, Gandin C, Cinanni Corradi S, Capocaccia L. Physico-chemical factors predisposing to pigment gallstone formation in liver cirrhosis. J Hepatol 1990;10:228-234.

168. Alvaro D, Angelico M, Gandin C, Cinanni Corradi S, Capocaccia L. Physico-chemical factors predisposing to pigment gallstone formation in liver cirrhosis. J Hepatol 1990;10:228-234.
tion in healthy volunteers. Eur J Clin Pharmacol 1989;37:95-96.
165. Rosenberg L, Shapiro S, Slone D, Kaufman DW, Miettinen OS, Stolley PD. Thiazides and acute cholecystitis. N Engl J Med 1980;303:546-548.
166. Van der Linden W, Ritter B, Edlund G. Acute cholecystitis and thiazides. Br Med J (Clin Res Ed) 1984;289:654-655.
167. Leitzmann MF, Tsai CJ, Stampfer MJ, Willett WC, Giovannucci E. Thiazide diuretics and the risk of gallbladder disease requiring surgery in women. Arch Intern Med 2005;165:567-573.
168. Tsai CJ, Leitzmann MF, Willett WC, Giovannucci EL. Statin use and the risk of cholecystectomy in women. Gastroenterology 2009;136:1593-1600.
169. St Peter SD, Keckler SJ, Nair A, et al. Laparoscopic cholecystectomy in the pediatric population. J Laparoendosc Adv Surg Tech A 2008;18:127-130.
170. Palasciano G, Portincasa P, Vinciguerra V, et al. Gallstone prevalence and gallbladder volume in children and adolescents: an epidemiological ultrasonographic survey and relationship to body mass index. Am J Gastroenterol 1989;84:1378-1382.
171. Kaechele V, Wabitsch M, Thiere D, et al. Prevalence of gallbladder stone disease in obese children and adolescents: influence of the degree of obesity, sex, and pubertal development. J Pediatr Gastroenterol Nutr 2006;42:66-70.
172. Kratzer W, Walcher T, Arnold F, et al. Gallstone prevalence and risk factors for gallstone disease in an urban population of children and adolescents. Z Gastroenterol 2010;48:683-687.
173. Bogue CO, Murphy AJ, Gerstle JT, Moineddin R, Daneman A. Risk factors, complications, and outcomes of gallstones in children: a single-center review. J Pediatr Gastroenterol Nutr 2010;50:303-308.
174. Holcomb GW Jr, Holcomb GW 3rd. Cholelithiasis in infants, children, and adolescents. Pediatr Rev 1990;11:268-274.
175. Friesen CA, Roberts CC. Cholelithiasis. Clinical characteristics in children. Case analysis and literature review. Clin Pediatr (Phila) 1989;28:294-298.
176. Waldhausen JH, Benjamin DR. Cholecystectomy is becoming an increasingly common operation in children. Am J Surg 1999;177:364-367.
177. Wesporp I, Bosman D, de Graaff A, Aronson D, van der Blij F, Taminiua J. Clinical presentations and predisposing factors of cholelithiasis and sludge in children. J Pediatr Gastroenterol Nutr 2000;31:411-417.
178. Kumar R, Nguyen K, Shun A. Gallstones and common bile duct calculi in infancy and childhood. Aust N Z J Surg 2000;70:188-191.
179. Henson DE, Alhores-Saavedra J, Corle D. Carcinoma of the gallbladder. Histologic types, stage of disease, grade, and survival rates. Cancer 1992;70:1493-1497.
180. Wistuba II, Gazdar AF. Gallbladder cancer: lessons from a rare tumour. Nat Rev Cancer 2004;4:695-706.
181. Lai CH, Lau WY. Gallbladder cancer: a comprehensive review. Surgeon 2008;6:101-110.
182. Levy AD, Murakata LA, Rohrmann CA Jr. Gallbladder carcinoma: radiologic-pathologic correlation. Radiographics 2001;21:295-314.
183. Pandey M. Risk factors for gallbladder cancer: a reappraisal. Eur J Cancer Prev 2003;12:15-24.
184. Lazcano-Ponce EC, Miquel JF, Muñoz N, et al. Epidemiology and molecular pathology of gallbladder cancer. CA Cancer J Clin 2001;51:349-364.
185. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. Int J Cancer 2006;118:1591-1602.
186. Andia ME, Hsing AW, Andreotti G, Ferreccio C. Geographic variation of gallbladder cancer mortality and risk factors in Chile: a population-based ecologic study. Int J Cancer 2008;123:1411-1416.
187. Serra I, Calvo A, Csendes A, Sharp A. Gastric and gallbladder carcinoma in Chile: epidemiological changes and control programs. Rev Med Chil 1989;117:834-836.
188. Hsing AW, Bai Y, Andreotti G, et al. Family history of gallstones and the risk of biliary tract cancer and gallstones: a population-based study in Shanghai, China. Int J Cancer 2007;121:832-838.
189. Haritharan D, Sained A, Kocher HM. Analysis of mortality rates for gallbladder cancer across the world. HPB (Oxford) 2008;10:327-331.
190. Shrikhande SV, Barreto SG, Singh S, Udawadia TE, Agarwal AK. Cholelithiasis in gallbladder cancer: coincidence, cofactor, or cause? Eur J Surg Oncol 2010;36:514-519.
191. Diehl AK. Gallstone size and the risk of gallbladder cancer. JAMA 1983;250:2323-2326.
192. Csendes A, Becerra M, Rojas J, Medina E. Number and size of stones in patients with asymptomatic and symptomatic gallstones and gallbladder carcinoma: a prospective study of 592 cases. J Gastrointest Surg 2000;4:481-485.
193. Zatonski WA, Lowenfels AB, Boyle P, et al. Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH Program of the International Agency for Research on Cancer. J Natl Cancer Inst 1997;89:1132-1138.
194. Kimura W, Shimada H, Kuroda A, Moriya K. Carcinoma of the gallbladder and extraperitoneal bile duct in autopsy cases of the aged, with special reference to its relationship to gallstones. Am J Gastroenterol 1989;84:386-390.
195. Diehl AK, Beral V. Cholecystectomy and changing mortality from gallbladder cancer. Lancet 1981;2:187-189.
196. Tewari M. Contribution of silent gallstones in gallbladder cancer. J Surg Oncol 2006;93:629-632.
197. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. Int J Cancer 2006;118:1591-1602.
198. Sheth S, Bedford A, Chopra S. Primary gallbladder cancer: recognition of risk factors and the role of prophylactic cholecystectomy. Am J Gastroenterol 2000;95:1402-1410.
199. Stephen AE, Berger DL. Carcinoma in the porcelain gallbladder: a
relationship revisited. Surgery 2001;129:699-703.
200. Berk RN, Armbruster TG, Saltzstein SL. Carcinoma in the porcelain gallbladder. Radiology 1973;106:29-31.
201. Cunningham SC, Alexander HR. Porcelain gallbladder and cancer: ethnicity explains a discrepant literature? Am J Med 2007;120:e17-e18.
202. Kim JH, Kim WH, Yoo BM, Kim JH, Kim MW. Should we perform surgical management in all patients with suspected porcelain gallbladder? Hepatogastroenterology 2009;56:943-945.
203. Kumar S, Kumar S, Kumar S. Infection as a risk factor for gallbladder cancer. J Surg Oncol 2006;93:633-639.
204. Dutta U, Garg PK, Kumar R, Tandon RK. Typhoid carriers among patients with gallstones are at increased risk for carcinoma of the gallbladder. Am J Gastroenterol 2000;95:784-787.
205. Tewari M, Mishra RR, Shukla HS. Salmonella typhi and gallbladder cancer: report from an endemic region. Hepatobiliary Pancreat Dis Int 2010;9:524-530.
206. Matsukura N, Yokomuro S, Yamada S, et al. Association between Helicobacter bilis in bile and biliary tract malignancies: H. bilis in bile from Japanese and Thai patients with benign and malignant diseases in the biliary tract. Jpn J Cancer Res 2002;93:842-847.
207. Lewis JT, Talwalkar JA, Rosen CB, Smyrk TC, Abraham SC. Prevalence and risk factors for gallbladder neoplasia in patients with primary sclerosing cholangitis: evidence for a metaplasia-dysplasia-carcinoma sequence. Am J Surg Pathol 2007;31:907-913.
208. Nomura T, Shirai Y, Sandoh N, Nagakura S, Hatekeyama K. Cholangiographic criteria for anomalous union of the pancreatic and biliary ducts. Gastrointest Endosc 2002;55:204-208.
209. Babbitt DP, Starshak RJ, Clemett AR. Choledochal cyst: a concept of etiology. Am J Roentgenol Radium Ther Nucl Med 1973;119:57-62.
210. Kang CM, Kim KS, Choi JS, Lee WJ, Kim BR. Gallbladder carcinoma associated with anomalous pancreaticobiliary duct junction. Can J Gastroenterol 2007;21:383-387.
211. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. J Natl Cancer Inst 1994;86:1600-1608.
212. Hemminki K, Li X. Familial liver and gall bladder cancer: a nationwide epidemiological study from Sweden. Gut 2003;52:592-596.
213. Venneri P. Cholesterol gallstones and cancer of gallbladder (CAGB); molecular links. Med Hypotheses 2008;70:646-653.
214. Myers RP, Shaffer EA, Beck PL. Gallbladder polyps: epidemiology, natural history and management. Can J Gastroenterol 2002;16:187-194.
215. Calle EE, Rodriguez C, Jacobs EJ, et al. The American Cancer Society Cancer Prevention Study II Nutrition Cohort: rationale, study design, and baseline characteristics. Cancer 2002;94:2490-2501.
216. Larsson SC, Wolk A. Obesity and the risk of gallbladder cancer: a meta-analysis. Br J Cancer 2007;96:1457-1461.
217. Yagyu K, Kikuchi S, Obata Y, et al. Cigarette smoking, alcohol drinking and the risk of gallbladder cancer death: a prospective cohort study in Japan. Int J Cancer 2008;122:924-929.
218. Chow WH, Johansen C, Gridley G, Mellemkjaer L, Olsen JH, Fraumeni JF Jr. Gallstones, cholecystectomy and risk of cancers of the liver, biliary tract and pancreas. Br J Cancer 1999;79:640-644.
219. Ishiguro S, Inoue M, Kurahashi N, Iwasaki M, Sasazuki S, Tsugane S. Risk factors of biliary tract cancer in a large-scale population-based cohort study in Japan (JPHC study); with special focus on cholecithiasis, body mass index, and their effect modification. Cancer Causes Control 2008;19:33-41.
220. Zatonski WA, La Vecchia C, Przewoziak K, Maisonneuve P, Lowenfels AB, Boyle P. Risk factors for gallbladder cancer: a Polish case-control study. Int J Cancer 1992;51:707-711.
221. Khan ZR, Neugut AJ, Alsan H, Chabot JA. Risk factors for biliary tract cancers. Am J Gastroenterol 1999;94:149-152.
222. Hsing AW, Gao YT, Han TQ, et al. Gallstones and the risk of biliary tract cancer: a population-based study in China. Br J Cancer 2007;97:1577-1582.
223. Lowenfels AB, Walker AM, Althaus DF, Townsend G, Domellöf L. Gallstone growth, size, and risk of gallbladder cancer: an interracial study. Int J Epidemiol 1989;18:50-54.
224. Caygill CP, Hill MJ, Bradick M, Sharp JC. Cancer mortality in chronic typhoid and paratyphoid carriers. Lancet 1994;343:83-84.
225. Strom BL, Soloway RD, Rios-Dalenz JL, et al. Risk factors for gallbladder cancer. An international collaborative case-control study. Cancer 1995;76:1747-1756.
226. Murata H, Tsuji S, Tsujii M, et al. Helicobacter bilis infection in biliary tract cancer. Aliment Pharmacol Ther 2004;20 Suppl 1:90-94.