Epidemiology of gallbladder cancer

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Abstract

According to GLOBOCAN 2018 data, gallbladder cancer (GBC) accounts for 1.2% of all global cancer diagnoses, but 1.7% of all cancer deaths. Only 1 in 5 GBC cases in the United States is diagnosed at an early stage, and median survival for advanced stage cancer is no more than about a year. The incidence of the disease is increasing in the developed world. Gallstones, biliary cysts, carcinogen exposure, typhoid, and Helicobacter pylori infection, and abnormal pancreaticobiliary duct junctions are all risk factors, many of which account for its geographical, ethnic and sex distribution. Genetics also plays a strong role, as about a quarter of GBC cases are considered familial, and certain ethnicities, such as Native Americans, are at far higher risk for the neoplasm. Prevention includes weight loss, vaccination against and treatment of bacterial infections, early detection and elimination of polyps and cysts, and avoidance of oral estrogen replacement therapy.

Key words: risk factor, survival, incidence, etiology, mortality.

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Cancers of the gallbladder are nearly all adenocarcinomas, which arise from the secretory cells. The gallbladder is the most common primary cancer site among the biliary tracts. A rare form of gallbladder adenocarcinoma is papillary adenocarcinoma, which arises from papillary cells that help to promote the motility of bile in the gallbladder. While rare, papillary cancers typically have a better prognosis than other gallbladder carcinomas [3].

According to GLOBOCAN 2018 data, gallbladder cancer is the 22nd most incident but 17th most deadly cancer worldwide [2]. Gallbladder cancer is disproportionately deadly because it is rarely found before it has advanced or metastasized. In fact, in the United States (US), only about 1 in 5 gallbladder cancers are diagnosed in the early stages [4]. A better understanding of the etiology and risk factors for the disease will allow patients to make modifications to prevent the disease, and clinicians to target and diagnose populations at high risk of the deadly carcinoma.
Epidemiology

Incidence

In 2018, about 219,000 people were estimated to have been diagnosed with gallbladder cancer. This constitutes 1.2% of all cancer diagnoses [2].

Gallbladder cancer is the only digestive system cancer that is more common among women than men. In 2018, the estimated incidence was 97,000 for men and 122,000 for women. One factor behind the disparity is women's tendency to live longer. However, the age-standardized incidence rate of gallbladder cancer for women, at 2.4 (per 100,000), is still higher than that for men, at 2.2. The cumulative risk of gallbladder cancer, from birth to age 74, is 0.26% for women and 0.25% for men [2].

The incidence in the US is lower than that around the world, with a rate of 1.4 per 100,000 among women and 0.8 among men. The disparity between men and women is also greater in the US than around the world. The incidence rate in the US was highest among American Indians and Alaskan Native people (3.2/100,000), likely due to limited access to healthcare, as well as differences in genetics, diet, and lifestyle. Geographically, cancer incidence was highest in the Northeast and Midwest US Census regions [5]. Incidence rates are highest in Eastern Europe, East Asia and Latin America (Fig. 1) [6, 7].

Countries with the top five highest age-standardized incidence rates per 100,000 for males in 2018 are Bolivia (12.8), Thailand (9.0), Republic of Korea (8.4), Chile (6.6) and Nepal (6.0). Countries with the top five highest age-standardized incidence rates per 100,000 for females in 2018 are Bolivia (15.1), Chile (11.7), Bangladesh (7.3), Nepal (7.3) and Peru (6.0) [7]. The geographic differences in incidence are likely attributable to differences in environmental exposures to various chemicals, genetic predisposition and regional intrinsic risk factors that predispose to carcinogenesis [8].

Mortality

Gallbladder cancer is among the minority of cancers that present with a greater proportion of cancer mortality than incidence. While the incidence accounts for 1.2% of all cancer diagnoses, gallbladder cancer mortality accounts for 1.7% of all cancer deaths. Estimated age-standardized mortality rates (per 100,000) of other gastrointestinal cancers are colorectum (8.9), liver (8.5), stomach (8.2), esophagus (5.5) and pancreas (4.4) (Fig. 2) [2, 7]. About 165,000 people died of gallbladder cancer in 2018. Of them, about 70,000 were male and 95,000 were females. The gender disparity is about on par with the disparity in incidence. The age-standardized mortality was 1.6/100,000 for men and 1.8 for women. The cumulative risk of dying from gallbladder cancer stands at 0.17% for men and 0.19% for women [2].

About 2000 people die annually in the US from gallbladder cancer. This constitutes a rate of 0.7/100,000 among women and 0.5/100,000 among men, which is 2-3 times lower than the global average (and more disparate when it comes to gender). In fact, in the US two thirds of gallbladder cancer cases and deaths occurred among women. As with incidence, mortality in the US was highest among American Indians and Alaskan Native people and in the Northeast and Midwest regions [5].

Fig. 1. Map showing estimated age-standardized incidence rates (ASR) in 2018 for gallbladder cancer, both sexes, all ages. Created with mapchart.net. Data obtained from Globocan 2018 [7]
Around the world, gallbladder cancer age standardized mortality rates for both sexes (per 100,000) were highest in Central and Eastern Europe (Slovakia 3.2, Hungary 2.5, Poland 2.2), Eastern Asia (Republic of Korea 4.1, Japan 3.3, Cambodia 2.6), and Latin America (Bolivia 10.6, Chile 5.4, Peru 3.1). Bolivia had the highest mortality rate (Fig. 3) [2, 7]. A few countries, including Japan and South Korea, showed greater mortality among men than women, though this was a strong deviation from the norm of a female to male ratio between 1.1 and 2.6 [6].

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**Trends**

In the US gallbladder cancer incidence has decreased over the past decades among all racial and ethnic groups except non-Hispanic blacks [9]. Among this group, the incidence rate increased by 2.2% annually. Among US women, incidence rates decreased about 0.5% annually, while incidence has remained about stable for men (Fig. 4) [5, 9].

Of all the histologies, only the rate of mucinous adenocarcinoma has significantly decreased in the US since 1999. However, in 1999, mucinous adenocarcinoma was the most common gallbladder adenocarcinoma.
Papillary adenocarcinoma is now the most common, with an incidence rate of around 0.04 [5]. Gallbladder cancer mortality has decreased significantly over the past several decades in women in 80% of countries and men in more than 50% of countries. However, since the 2000s, this decrease has stalled or even reversed in many countries. While obesity has been considered the primary cause of the reversal, a case study in Greece demonstrated that the recent increase in gallbladder cancer mortality could not be fully explained by an increase in the prevalence of obesity [6].

**Survival**

Gallbladder cancer has historically had a poor prognosis due to its late diagnosis. In the US, 43% of gallbladder cancers were found after cancer had spread to regional organs or lymph nodes, while 42% were found after spreading to distant organs or lymph nodes [5]. The median survival in the US is 12-14 months for patients undergoing resection, and six months for patients treated with palliative stenting [10].

The average 5-year survival rate in the US for gallbladder cancer is 18%. For those with stage I cancer, where the cancer is confined to the gallbladder, the 5-year survival rate is 60% [9]. These rates apply to only the 1 out of 5 cases that are diagnosed prior to cancer metastasis. For those whose cancer has spread to nearby lymph nodes, the survival rate is 25%, while for those with distant metastases, the 5-year survival rate is below 2% (Fig. 5) [9, 11]. While the proportion of distant/regional metastasized diagnoses had been decreasing for decades, it has recently increased, in line with the recent spikes in incidence and mortality in the developed world [6].

Unlike most cancers, gallbladder carcinoma mortality does not show a negative association with the human development index (HDI). In fact, nations with higher HDI tend to suffer from greater mortality rates (Fig. 6) [2, 7].

**Etiology and risk factors**

As with all cancers, gallbladder adenocarcinoma is often preceded by chronic inflammation in the gallbladder that disrupts normal cell signaling and growth. The accumulation of gallstones, known as cholelithiasis, often precedes gallbladder cancer by about 20 years, resulting in chronic inflammation. However, recent increases in gallbladder cancer prevalence among those below 45 call for further investigation.
into question gallstones as the only driver of gallbladder cancer. Other major etiological factors for gallbladder cancer include age, obesity, genetics, occupational exposure to mutagens and chronic infection (Table 1).

**Age and sex**

Gallbladder cancer rates become more common with age, likely because the malignancy takes decades to develop. The average age of diagnosis in the US is 72. Gallbladder cancer is common after the age of 60 years [1]. The Surveillance, Epidemiology, and End Results (SEER) database from the US from 2015 reveals that age-adjusted incidence rates (per 100,000) in 2015 rose from 0.2 for those aged 20-49 years, to 1.6 for those aged 50-64 years, to 4.3 for those aged 65-74 years, and to 8.1 for individuals aged 75 years and older. This corresponded with mortality rates (per 100,000), which increased from 0.1 for those aged 20-49 years, to 0.7 for those aged 50-64 years and to 2.1 for those aged 65-74 years. The highest mortality rate was 4.9/100,000, for individuals aged 75 years and older [9].

Gallbladder cancer is more common in females than males [12]. Women are two to six times more commonly affected than men [13]. The female hormone estrogen is known to increase the saturation of cholesterol in bile, thus increasing the risk of gallstone formation. This pathogenesis is believed to be the primary culprit behind the greater risk of gallbladder cancer among females [14].

**Genetics and family history**

A family history of gallbladder cancer can increase a person's risk of developing gallbladder cancer [15, 16]. Reports regarding the familial risk of gallbladder cancer have been contradictory. Familial clustering of gallbladder cancer has been noted in some studies [15]. A Swedish study showed that the standardized incidence ratio (SIR) for gallbladder cancer in offspring of parents diagnosed with gallbladder cancer was 2.47 [17]. But results from the Biliary Tract Cancers Pooling Project recently did not show any association between family history of cancer and gallbladder cancer [18]. Multiple genetic mutations have been implicated among gallbladder cancer cases, including KRAS, P16, c-erb-B2, and TP53. Most are common oncogenes or tumor suppressor genes implicated in many cancers; hence, it is not clear which are driving mutations unique to gallbladder cancer. Certain mutations are associated with other cancer risk factors; for instance, gallbladder cancer in those with an anomalous pancreaticobiliary duct junction frequently presents with KRAS mutations and relatively late onset of p53 mutations, while in patients with cholelithiasis and chronic cholecystitis, KRAS mutations are rare and p53 mutations arise early [19-21].

**Gallstones**

A history of gallstones carries the highest risk for gallbladder cancer, with the relative risk (RR) being 4.9 [22]. About 85% of people who develop gallbladder cancer have cholelithiasis; however, this statistic may...
be inflated because those undergoing treatment for gallstones are more likely to be diagnosed with gallbladder cancer [23]. While gallstones are strongly associated with gallbladder cancer etiology, their role as a cause of cancer remains uncertain [24]. The common theory is that chronic irritation due to gallstones and local production of carcinogens such as secondary bile acids leads to sequential development of metaplasia/hyperplasia, dysplasia and finally carcinoma [25].

The overall incidence of gallbladder cancer in patients with gallstones was found to be 0.5% in a Swedish study recently [26]. The RR of developing gallbladder cancer in patients with gallstones ranges between 3 and 24 [27-31]. Increasing size of the gallstones is associated with increased risk for gallbladder cancer. RR of gallbladder cancer with gallstone diameters of 2.0 to 2.9 cm (vs. stone size less than 1 cm) is 2.4; for stones 3 cm or larger, the risk increases to 10.1 [32-34]. In gallbladder cancer patients cholesterol stones seem to be more common than pigment stones [35]. A high incidence of gallbladder carcinoma is seen in American Indians, who have quite a high prevalence of cholesterol gallstones [23]. High rates of gallbladder cancer incidence and gallstone prevalence are also seen in Pima Indian females, Chilean Mapuche Indian females, East Indian females and New Zealand Maori [36].

As the duration of gallstones increases the RR of gallbladder cancer increases, with RR being 4.9 for gallstones with duration of 5-19 years and RR of 6.2 for duration > 20 years [37]. In a large cohort study of 396,720 patients conducted in South Korea, the multivariable-adjusted hazard ratios for gallbladder cancer mortality comparing those with gallstones and without gallstones was 7.35 (95% confidence interval [CI] 2.60-20.8) [38]. This study showed that gallstones were significantly associated with an increased risk of gallbladder cancer and subsequent mortality.

Gallbladder calcification, also known as porcelain gallbladder due to its appearance on X-ray imaging, is a condition caused by excessive gallstones. It is especially common in middle-aged, overweight females. While porcelain gallbladder has historically been associated with gallbladder cancer (prior studies suggested sufferers of the disorder had a cancer incidence of over 60%), recent research has indicated a much lower concomitant incidence of below 6% [39]. In a study by Khan et al. the incidence of gallbladder carcinoma in porcelain gallbladder patients was found to be as low as 2% to 3% [40].

**Gallbladder polyps**

Polyps in the gallbladder have the potential to grow and become cancerous over many decades. It remains uncertain how many ultimately progress and become cancerous. Among ten studies, 1% to 23% of polyps displayed growth in the follow-up period. Malignancy is significantly more common among polyps more than 10 mm long [41]. There is currently no official recommendation regarding the follow-up schedule for asymptomatic polyps less than 10 mm in length, although studies suggest they do have the capacity to become cancerous [42].

Cholecystectomy should be strongly considered in patients with gallbladder polyps 10 mm in size or greater. Ultrasound imaging should be performed in patients with polyps less than 10 mm in size for at least 2 years until stability is documented, or if growth is documented, then the cholecystectomy option should be discussed with the patient [43].

**Primary sclerosis cholangitis**

Primary sclerosis cholangitis (PSC) is believed to be an autoimmune disease in which the bile ducts inside and outside the liver are attacked by the body’s immune system, leading to inflammation, scarring, and ultimate blockage. Certain genetic loci have been identified to predispose to the condition. Those with a first-degree relative with PSC have a 9- to 39-fold greater risk of developing the disease [44].

The build-up of bile and the inflammation can lead to gallbladder carcinogenesis. PSC is a relatively rare disorder, estimated to occur in somewhere between 6 and 16 per 100,000 people, with a male predominance. Those with PSC are at a higher risk of gallstones and inflammatory bowel disorder, which can independently predispose an individual to gallbladder cancer [44]. In a study of 286 patients with PSC, 6% were found to have gallbladder mass lesions, of which 56% were found to be gallbladder carcinoma [45]. Cholecystectomy is recommended in these patients regardless of the size of the mass lesion. Routine annual ultrasound screening of the gallbladder can be helpful in these patients [45, 46].

**Chronic infection**

Chronic infection by *Salmonella* (e.g., *S. typhi* and *S. paratyphi*) or *Helicobacter* (*H. pylori* and *H. bilis*) has been associated with gallbladder cancer [47-52]. More than 75% of patients with gallbladder cancer test positive for the stomach bacterium *H. pylori* in their bile. It is believed that the bacterium may similarly promote inflammation in the liver and bile ducts, thus increasing the odds of gallbladder carcinogenesis. In a study in Egypt, patients with chronic cholecystitis who had *H. pylori* in their gallbladder mucosa had 28% meta-
plasia of gallbladder mucosa compared to patients who did not have *H. pylori* [53]. *H. bilis* also has been implicated in gallbladder cancer [48, 49].

*Salmonella enterica* serovar Typhi, the bacterium behind typhoid fever, has likewise been associated with gallbladder cancer. One study found that those with the presence of antibodies for typhoid had a 4.6-fold increased risk of gallbladder cancer. Latin American countries such as Bolivia and Chile, where typhoid fever is endemic, also have the highest rates of gallbladder cancer around the world [54].

**Congenital biliary cysts**

Congenital biliary cysts are especially prevalent in women and in Asian populations, both of which are groups at an increased risk of gallbladder cancer. While most cases are surgically resolved in infancy, about 20% of cases are recognized in adults. Biliary cysts are usually identified via ultrasound, computed tomography (CT) scan or magnetic resonance imaging (MRI), and are usually removed surgically via Roux-Y hepaticojejunostomy. Studies suggest that biliary tract cancer, of which gallbladder cancer is the most common, occurs in 2.5–28% of those with biliary cysts. Reports indicate that gallbladder cancer can occur even if an infant has undergone radical biliary cyst removal [55].

**Anomalous pancreaticobiliary duct junction**

An anomalous junction of the pancreaticobiliary duct is a congenital malformation in which the pancreatic duct drains into the biliary tract outside the duodenal wall. An anomalous pancreatic and bile duct junction can impact the degree of pancreatic fluid regurgitation, thus increasing the risk of biliary tract malignancy. Gallbladder cancers associated with abnormal pancreaticobiliary junction occur at a younger age, have a lower incidence of associated cholelithiasis and show less female gender bias [56]. Among 29 patients treated with biliary tract cancers whose pancreaticobiliary junctions were visualized, 45% presented with an abnormal junction. In the USA, the anatomy of the pancreaticobiliary junction is rarely identified on cholangiopancreatograms. Prospective identification of this risk factor may help clinicians diagnose gallbladder cancer at an earlier stage [57]. An abnormal pancreaticobiliary junction is particularly common in the Asian population and may explain the increased burden of the disease in East Asia [58].

**Medications**

Post-menopausal women undergoing oral estrogen or estrogen-progesterone therapy are at increased risk of gallstones and gallbladder cancer [59], although the association between oral contraceptives and gallbladder cancer is unclear [33]. Further studies have suggested that transdermal estrogen replacement therapy presents with a lower risk for gallbladder diseases than oral therapy [60]. Since oral estrogen is ingested, it likely finds its way into the liver and bile in greater concentration than transdermal applications. Methyldopa and isoniazid have been implicated in biliary carcinogenesis [61, 62].

**Carcinogens**

Toxic substances that are ingested are often filtered by the liver and excreted into the bile, where they come into contact with the lining of the gallbladder. Workers in rubber plants or textile factories, or those exposed to nitrosamines, are at an increased risk of gallbladder cancer [1]. Those living in the Gangetic belt in India, an industrial region with a high load of pollutants, have a nearly 10-fold increased risk of developing gallbladder cancer relative to the average in the country [63]. Cigarette smoking has also been associated with the neoplasm [64–66]. A meta-analysis by Bagnardi *et al.* of 8 studies showed that heavy drinking (> 50 g of alcohol/day) was associated with a RR of 2.64 for gallbladder cancer [67]. Aflatoxin exposure has also been associated with an increased risk of gallbladder cancer [27].

**Obesity**

Obese people, those with a body mass index (BMI) > 30 kg/m², have an increased risk of developing gallbladder cancer [23, 68–70]. Overweight and obese individuals have a 1.15 and 1.66 RR, respectively, of developing gallbladder cancer. Potential biological mechanisms for the association include an increased concentration of hormones such as estrogen or insulin, which increases the formation of gallstones. The association is stronger among women than men, perhaps because women already have a higher level of estrogen in the circulation [71]. A meta-analysis of 15 studies with 5902 cases showed that the risk increased by 4% for each 1 kg/m² increase in BMI above 25 kg/m² [72]. In another meta-analysis of 20 studies it was found that compared with nondiabetics, diabetic individuals had 1.56 times increased risk of gallbladder cancer [73].

**Prevention**

While gallbladder cancer does have a heritable component, research indicates that about 75% of cases are acquired, and thus could be largely preventable...
factors include gallstones, which form in women more prevalent among women than men. The greatest risk and East Asia, and in almost all countries, are more especially prevalent in Latin America, Eastern Europe, section is only 12-14 months. Gallbladder cancers are survival for those with advanced cases undergoing re-

biliary cysts should seek surgical removal upon diag-
nosis, especially in infancy, as this can lessen (though not eliminate) the risk of developing gallbladder cancer. However, prevention is possible, and necessary to decrease global mortality rates. Many crucial risk factors for the neoplasm are behavioral or environmental, including obesity, exposure to carcinogens and estrogen replacement therapy. Typhoid and H. pylori infection, which are the likely culprits behind the heightened risk in Latin America, are preventable with vaccination and treatable with antibiotics. Gallbladder cancer prevention can also take the form of earlier detection via imaging technologies, or surgical removal of polyps and cysts.

Conclusions

While the gallbladder is a small organ unessential for life, adenocarcinoma of the gallbladder is a deadly and often untreatable cancer. Gallbladder cancers often do not go diagnosed until advanced stages, when virtually nothing can be done to extend life expectancy beyond several months. Only 1 in 5 gallbladder cancers in the US are diagnosed in early stages, and the median survival for those with advanced cases undergoing reection is only 12-14 months. Gallbladder cancers are especially prevalent in Latin America, Eastern Europe, and East Asia, and in almost all countries, are more prevalent among women than men. The greatest risk factors include gallstones, which form in women more often due to high estrogen levels, and an abnormal pancreaticobiliary junction, which is more common in Asian populations. Over a quarter of gallbladder cancers are considered familial, and many oncogenes and tumor suppressor genes have been linked to gallbladder cancer development. However, prevention is possible, and necessary to decrease global mortality rates. Many crucial risk factors for the neoplasm are behavioral or environmental, including obesity, exposure to carcinogens and estrogen replacement therapy. Typhoid and H. pylori infection, which are the likely culprits behind the heightened risk in Latin America, are preventable with vaccination and treatable with antibiotics. Gallbladder cancer prevention can also take the form of earlier detection via imaging technologies, or surgical removal of polyps and cysts.

Disclosure

Authors report no conflict of interest.

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1. Abou-Alfa GK, Jarnagin W, Lowery M, et al. In: Abeloff’s Clinical Oncology – Liver and Bile Duct Cancer. Niederhuber JE, Armitage JO, Doroshow JH, et al. (eds.). 5th ed. Sanders, Philadelphia 2014; 1373-1396.
2. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.
3. Nuzzo G, Clemente G, Cadeddu F, et al. Papillary carcinoma of the gallbladder and anomalous pancreatico-biliary junction. Report of three cases and review of the literature. Hepatogastroenterology 2005; 52: 1034-1038.
4. Howlader N, Noone AM, Krapcho M, et al. (eds.). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD. Available from: https://seer.cancer.gov/csr/1975_2014/. Accessed 20 December 2018.
5. Henley SJ, Weir HK, Jemal A, et al. Gallbladder cancer incidence and mortality, United States 1999-2011. Cancer Epidemiol Biomarkers Prev 2015; 24: 1319-1326.
6. Torre LA, Siegel RL, Ziegler A, et al. Worldwide burden of and trends in mortality from gallbladder and other biliary tract cancers. Clin Gastroenterol Hepatol 2018; 16: 427-437.
7. Ferlay J, Sirbu C, Cadranel S, et al. Global cancer observatory: cancer today. International Agency for Research on Cancer, Lyon, France. Available from: https://gco.iarc.fr/today. Accessed 20 December 2018.
8. Latiano Panco EC, Miuel HP, Munoz N, et al. Molecular epidemiology and molecular pathology of gallbladder cancer. CA Cancer J Clin 2001; 51: 349-364.
9. SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute. Available from https://seer.cancer.gov/explore/. Accessed December 20 2018.
10. Misra SP, Dwivedi M. Pancreaticobiliary ductal union. Gut 1990; 31: 1144-1149.
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11. American Cancer Society. Cancer Facts & Figures 2018. Atlanta, Ga: American Cancer Society; 2018. Available from https://www.cancer.org/cancer/gallbladder-cancer/about/key-statistics.html. Accessed December 02 2018.

12. Konstantinidis IT, Deshpande V, Genevay M, et al. Trends in presentation and survival for gallbladder cancer during a period of more than 4 decades: a single-institution experience. Arch Surg 2009; 144: 441-447; discussion 447.

13. Duffy A, Capanu M, Abou-Alfa GK, et al. Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC). J Surg Oncol 2008; 98: 485-489.

14. Everson GT, McKinley C, Kern F Jr. Mechanisms of gallstone formation in women. Effects of exogenous estrogen (Premarin) and dietary cholesterol on hepatic lipid metabolism. J Clin In vest 1991; 87: 237-246.

15. Hemminki K, Li X. Familial liver and gall bladder cancer: a nationwide epidemiological study from Sweden. Gut 2003; 52: 592-596.

16. Goldgar DE, Easton DF, Cannon-Albright LA, et al. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. J Natl Cancer Inst 1994; 86: 1600-1608.

17. Hemminki K, Hemminki A, Forsti A, et al. Genetics of gallbladder cancer. Lancet Oncol 2017; 18: e236.

18. Van Dyke AL, Langhamer MS, Zhu B, et al. Family history of cancer and risk of biliary tract cancers: results from the biliary tract cancers pooling project. Cancer Epidemiol Biomarkers Prev 2018; 27: 348-351.

19. Matsumoto T, Seno H. Updated trends in gallbladder and other biliary tract cancers worldwide. Clin Gastroenterol Hepatol 2018; 16: 339-340.

20. Wistuba, II, Sugio K, Hung J, et al. Allele-specific mutations involved in the pathogenesis of endemic gallbladder carcinoma in Chile. Cancer Res 1995; 55: 2511-2515.

21. Wistuba, II, Gazdar AF, Roa I, et al. Genetic analysis of gallbladder cancer. Lancet Oncol 2017; 18: e236.

22. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer world-wide: geographical distribution and risk factors. Int J Cancer 2018; 143: 592-596.

23. Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: cholecystitis and cancer. Gut Liver 2012; 6: 172-187.

24. Shrikhande SV, Barreto SG, Singh S, et al. Cholelithiasis in gallbladder cancer: coincidence, cofactor, or cause? Eur J Surg Oncol 2010; 36: 514-519.

25. Jain K, Mohapatra T, Das P, et al. Sequential occurrence of preneoplastic lesions and accumulation of loss of heterozygosity in patients with gallbladder stones suggest causal association with gallbladder cancer. Ann Surg 2014; 260: 1073-1080.

26. Muszynska C, Lundgren L, Lindell G, et al. Predictors of incidental gallbladder cancer in patients undergoing cholecystectomy for benign gallbladder disease. Results from a population-based gallstone surgery registry. Surgery 2017; 162: 256-263.

27. Koshio J, Gao YF, Dean M, et al. Association of aflatoxin and gallbladder cancer. Gastroenterology 2017; 153: 488-494.

28. Chow WH, Johansen C, Gridley G, et al. Gallstones, cholecystectomy and risk of cancers of the liver, biliary tract and pancreas. Br J Cancer 1999; 79: 640-644.

29. Ishiguro S, Inoue M, Kurahashi N, et al. Risk factors of biliary tract cancer in a large-scale population-based cohort study in Japan (JPHC study); with special focus on cholecystitis, body mass index, and their effect modification. Cancer Causes Control 2008; 19: 33-41.

30. Khan ZR, Neugut AI, Ahsan H, et al. Risk factors for biliary tract cancers. Am J Gastroenterol 1999; 94: 149-152.

31. Zatonski WA, La Vecchia C, Przeworski K, et al. Risk factors for gallbladder cancer: a Polish case-control study. Int J Cancer 1992; 51: 707-711.

32. Diehl AK. Gallstone size and the risk of gallbladder cancer. JAMA 1983; 250: 2323-2326.

33. Shaffer EA. Gallstone disease: epidemiology of gallstone disease. Best Pract Res Clin Gastroenterol 2006; 20: 981-996.

34. Lowenfels AB, Walker AM, Althaus DP, et al. Gallstone growth, size, and risk of gallbladder cancer: an interracial study. Int J Epidemiol 1989; 18: 50-54.

35. Kimura W, Shimmada H, Kuroda A, et al. Carcinoma of the gallbladder and extrahepatic bile duct in autopsy cases of the aged, with special reference to its relationship to gallstones. Am J Gas troenterol 1989; 84: 386-390.

36. Hundal R, Shaffer EA. Gallbladder cancer: epidemiology and outcome. Clin Epidemiol 2014; 6: 99-109.

37. 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.

38. Ryu S, Chang Y, Yun KE, et al. Gallstones and the risk of gallbladder cancer mortality: a cohort study. Am J Gastroenterol 2016; 111: 1476-1487.

39. Machado NO. Porcelain gallbladder: Decoding the malignant truth. Sultan Qaboos Univ Med J 2016; 16: e416-e421.

40. Khan ZS, Livingston EH, Huerta S. Reassessing the need for prophylactic surgery in patients with porcelain gallbladder: case series and systematic review of the literature. Arch Surg 2011; 146: 1143-1147.

41. Okamoto M, Okamoto H, Kitahara F, et al. Ultrasonographic evidence of association of polyps and stones with gallbladder cancer. Am J Gastroenterol 1999; 94: 446-450.

42. Wiles R, Varapandhe M, Muly S, et al. Growth rate and malignant potential of small gallbladder polyps-systematic review of the evidence. Surgeon 2014; 12: 221-226.

43. Elmasry M, Lindop D, Dunne DF, et al. The risk of malignancy in ultrasound-detected gallbladder polyps: A systematic review. Int J Surg 2016; 33 Pt A: 28-35.

44. Eaton JE, Talwalkar JA, Lazaridis KN, et al. Pathogenesis of primary sclerosing cholangitis and advances in diagnosis and management. Gastroenterology 2013; 145: 521-536.

45. Said K, Glaumann H, Bergquist A. Gallbladder disease in patients with primary sclerosing cholangitis. J Hepatol 2008; 48: 598-605.

46. Chapman R, Favery J, Kalloo A, et al. Diagnosis and management of primary sclerosing cholangitis. Hepatology 2010; 51: 660-678.

47. Gonzalez-Escobedo G, Marshall JM, Gunn JS. Chronic and acute infection of the gall bladder by Salmonella Typhi: understanding the carrier state. Nat Rev Microbiol 2011; 9: 9-14.

48. 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.

49. Fox JG, Dewhirst FE, Shen Z, et al. Hepatic Helicobacter species identified in bile and gallbladder tissue from Chilesans with chronic cholecystitis. Gastroenterology 1998; 114: 755-763.

50. Murata H, Tsuji S, Tsujii M, et al. Helicobacter bilis infection in biliary tract cancer. Aliment Pharmacol Ther 2004; 20 Suppl 1: 90-94.
51. 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.
52. Caygill CP, Hill MJ, Braddock M, et al. Cancer mortality in chronic typhoid and paratyphoid carriers. Lancet 1994; 343: 83-84.
53. Hassan EH, Gerges SS, El-Atrebi KA, et al. The role of H. pylori infection in gall bladder cancer: clinicopathological study. Tumour Biol 2015; 36: 7093-7098.
54. Koshiol J, Wozniak A, Cook P, et al. Salmonella enterica serovar Typhi and gallbladder cancer: a case-control study and meta-analysis. Cancer Med 2016; 5: 3310-3325.
55. Jablonska B. Biliary cysts: etiology, diagnosis and management. World J Gastroenterol 2012; 18: 4801-4810.
56. Sasatomi E, Tokunaga O, Miyazaki K. Precancerous conditions of gallbladder carcinoma: overview of histopathologic characteristics and molecular genetic findings. J Hepatobiliary Pancreat Surg 2000; 7: 556-567.
57. Roukounakis NE, Kuhn JA, McCarty TM. Association of an abnormal pancreaticobiliary junction with biliary tract cancers. Proc (Bayl Univ Med Cent) 2000; 13: 11-13.
58. Yamashita T, Ando H, Suyama M, et al. Japanese clinical practice guidelines for pancreaticobiliary maljunction. J Gastroenterol 2012; 47: 731-759.
59. Cirillo DJ, Wallace RB, Rodabough RJ, et al. Effect of estrogen therapy on gallbladder disease. JAMA 2005; 293: 330-339.
60. Liu B, Beral V, Balkwill A, et al. Gallbladder disease and use of transdermal versus oral hormone replacement therapy in postmenopausal women: prospective cohort study. BMJ 2008; 337: a386.
61. Broden G, Bengtsson L. Biliary carcinoma associated with methyldopa therapy. Acta Chir Scand Suppl 1980; 500: 7-12.
62. Lowenfels AB, Norman J. Isoniazid and bile duct cancer. JAMA 1978; 240: 434-435.
63. Dixit R, Shukla VK. In: Perspectives in Cancer Prevention-Translational Cancer Research - Why Is Gallbladder Cancer Common in the Gangetic Belt?. Sudhakaran P (eds.). Springer, New Delhi 2014; 145-151.
64. Sharma A, Sharma KL, Gupta A, et al. Gallbladder cancer epidemiology, pathogenesis and molecular genetics: Recent update. World J Gastroenterol 2017; 23: 3978-3998.
65. 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.
66. National Center for Health Statistics. May, 2016. Available from: https://www.cdc.gov/nchs/data/nhis/earlyrelease/earlyrelease201605.pdf. Accessed Dec 05 2018.
67. Hoffman SL, Woodward TE, Hornick RB, et al. Effective treatment and prevention of typhoid fever: updated. Trans Am Clin Climatol Assoc 1984; 95: 52-65.