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Review paper

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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Introduction

While the gallbladder is no more than an inch (2 cm) wide, cancers of the gallbladder account for about 165,000 cancer deaths annually, which is 1.7% of all global cancer deaths [1, 2]. The gallbladder is a small, pear-shaped organ tucked under the liver. Like the liver, it is found behind the right, lower ribs. Its function is to store and concentrate the bile produced by the liver before releasing it into the small intestine, where the bile aids in digestion. Bile from the gallbladder travels to the small intestine via the cystic duct, which joins with the hepatic duct (from the liver) to form the common bile duct. The common bile duct, in turn, joins with the pancreatic duct (which carries enzymes necessary for digestion) to empty into the duodenum at the ampulla of Vater [1]. The gallbladder is considered non-essential, and many lead healthy lives after having their gallbladder removed [1].

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 Americans 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]

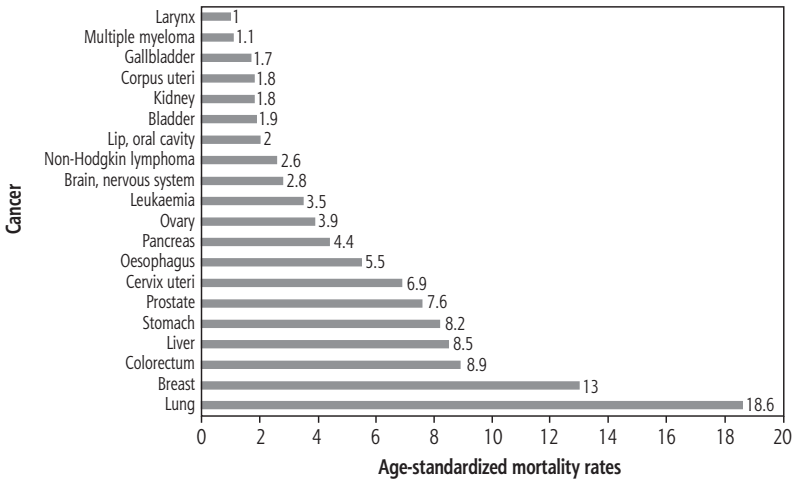

Fig. 2. Bar chart showing the estimated age-standardized cancer mortality rates (world) in 2018, worldwide, both sexes, all ages (reproduced from http://globocan.iarc.fr/ [7])

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].

Countries with the top five highest age-standardized mortality rates per 100,000 for males in 2018 are Bolivia (9.6), Thailand (7.8), Republic of Korea (5.0), Chile (4.3) and Japan (4.2). Countries with the top five highest age-standardized mortality rates per 100,000 for females in 2018 are Bolivia (11.5), Chile (6.4), Bangladesh (5.0), Thailand (5.7) and Nepal (4.9) [7].

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 adenocar-

Fig. 3. Map showing estimated age-standardized mortality rates (ASR) in 2018 for gallbladder cancer, both sexes, all ages. Created with mapchart.net. Data obtained from Globocan 2018 [7]

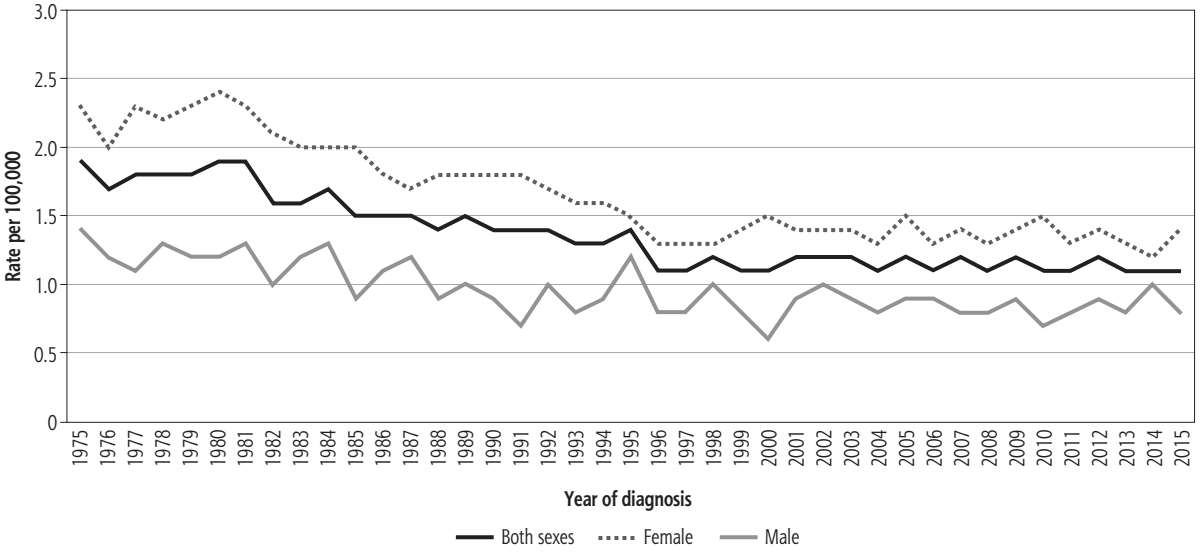

Fig. 4. Trends in gallbladder cancer incidence (1975-2015) rates by sex, US [9]

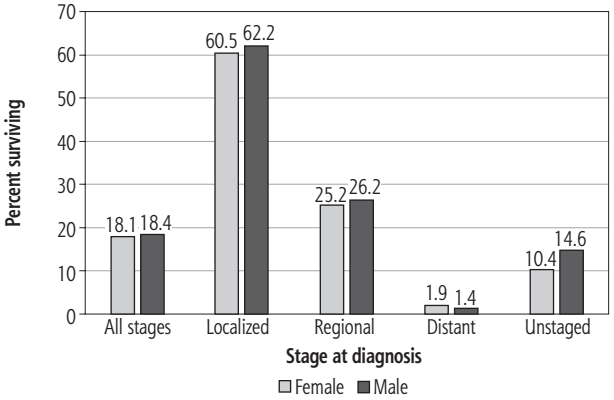

Fig. 5. Gallbladder cancer 5-year SEER relative survival rates, 2008-2014 by sex and stage at diagnosis [9]

cinoma, with an incidence of over 0.05/100,000, and today it has dropped to about 0.03/100,000 in the US. 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

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].

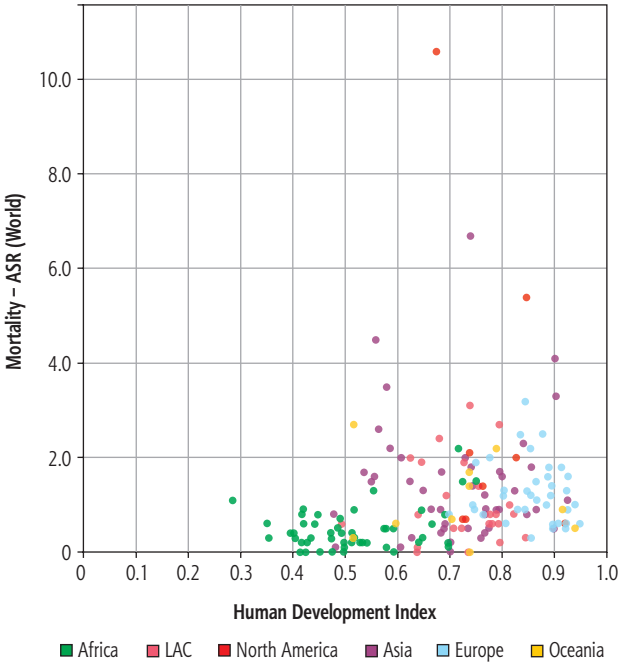

Fig. 6. Mortality – age-standardized rates (world) vs. Human Development Index, gallbladder, in 2018, both sexes, all ages (reproduced from http://globocan.iarc.fr/ [7])

Table 1. Risk factors for gallbladder cancer (adapted with permission from [23])

Risk factor	Relative risk	Reference
Gallstones	3.01-23.8	[28-31]
Size of gallstones (cm)		
2.0-2.9	2.4	[32, 34]
> 3.0	9.2-10.1	
Duration of gallstones (years)		
5-19	4.9	[37]
> 20	6.2	
Body mass index	Males Females	
30.0-34.9	1.8 2.1	[71]
Infections		
Chronic typhoid and paratyphoid carriers	12.7-167	[51, 52]
Helicobacter bilis	2.6-6.5	[48, 50]

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/m^2, 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/m^2 increase in BMI above 25 kg/m^2 [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

[19]. Some of the primary risk factors, including obesity, carcinogen exposure, and estrogen therapy, are within an individual's power to control. Those postmenopausal women undergoing estrogen therapy can reduce their risk by up to 33% by switching from oral to transdermal therapy [60].

Higher rates of obesity and physical inactivity in the developed world appear correlated with the growing gallbladder cancer incidence. The prevalence of obesity in the US has more than doubled, from 15% in 1979 to 35% in 2014 [74]. As many as 70% of Americans today are overweight or obese. However, in many developed countries, this proportion has stopped growing and is even beginning to decline. The proportion of US adults who met physical activity guidelines increased from 41% in 2006 to 50% in 2012 [75]. Further education on the benefits of healthy eating and exercise can have a serious impact in curbing gallbladder cancer.

Typhoid and *H. pylori* infection is endemic to parts of Latin America and Asia, where gallbladder cancer is especially incident. Typhoid is preventable via an oral or injectable vaccine, while both bacteria can be treated and resolved within weeks with antibiotics [55]. Better hygiene and sanitation can also prevent the spread of these bacteria, as evidenced by their eradication in the developed world [76].

Early detection can likewise prove life-saving when it comes to gallbladder cancer. Those with a history of gallstones or gallbladder polyps can practice secondary prevention by undergoing regular imaging of the gallbladder, biliary ducts, and pancreaticobiliary junction. Gallbladder polyps, especially those larger than 10 mm, ought to be removed. Those with hereditary biliary cysts should seek surgical removal upon diagnosis, especially in infancy, as this can lessen (though not eliminate) the risk of developing gallbladder cancer later in life.

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 resection 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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