



# GALLBLADDER CANCER IN THE WORLD: EPIDEMIOLOGY, INCIDENCE, MORTALITY AND RISK FACTORS

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**Abstract – Objective:** Gallbladder cancer is a highly lethal malignancy with a poor prognosis. It is the sixth digestive tract cancer and one of the most common cancers in biliary ducts. The aim of this study was to investigate the incidence, mortality, and risk factors for gallbladder cancer in the world.

**Materials and Methods:** This review study was conducted on published English studies by January 2017 through a search of PubMed, Scopus and web of science databases. The search strategy included key words “gallbladder cancer”, “epidemiology”, “incidence”, “mortality”, “risk factors”, “world”. Studies related to incidence, mortality, and causes of gallbladder cancers were also studied and included.

**Results:** The five countries with the highest incidence of kidney cancer were Chile, Bolivia, Korea, Republic of, Lao PDR and Japan. The standard incidence of gallbladder cancer in the world was 2.2 per 100000. The five countries with the highest death rates were Chile, Bolivia, Korea, Republic of, Lao PDR and Nepal. The standardized death rate for gallbladder in the world was 1.7 per 100000 people. The most important risk factors for the cancer include gallstones, porcelain gallbladder, gallbladder polyps, bacterial and salmonella infections, chronic inflammation. Fruit and vegetable consumption are known as a protective agent for this cancer.

**Conclusions:** The incidence of gallbladder cancer worldwide has a geographic variable pattern. Generally, knowledge of the stage of the disease at the time of diagnosis has a significant effect on the treatment of gallbladder cancer. It is also necessary to consider the risk factors to reduce this cancer.

**KEYWORDS:** Gallbladder cancer, Epidemiology, Incidence, Mortality and risk factor.

## INTRODUCTION

Cancer is one of the major causes of mortality in human societies<sup>1,2</sup>. One of these cancers is gallbladder cancer, a very lethal malignancy with poor prognosis<sup>3,4</sup>. This cancer is the sixth gastrointestinal tract cancer and one of the most common biliary cancers. Among various cancers of the gastrointestinal tract, it has a variety of incidence, with an annual rate of 2.2 per 100000 people

worldwide<sup>5,6</sup>. The incidence of gallbladder cancer worldwide has a geographic variable pattern; the highest incidence has been reported in India, Asia, Europe, and South America<sup>3,6</sup>. Gallbladder cancer is more in women and biliary cancers more in males<sup>7</sup>. Due to the anatomical position of the gallbladder and the non-specificity of the symptoms, diagnosis of gallbladder cancers often occurs in late stages with a poor prognosis of less than 10% so that 5-year survival in many studies is less than



5%<sup>8,9</sup>. Nearly from every five patients with cancer, four at diagnosis have advanced localized disease or metastases<sup>10</sup>. Given the importance of informing about the incidence, mortality and risk factors in prevention programs, the aim of this study was to investigate the incidence, mortality, and risk factors for gallbladder cancer in the world.

## METHODS

This review study was conducted on published English studies by January 2017 through a search of PubMed, Scopus and web of science databases. The search strategy included key words “gallbladder cancer”, “epidemiology”, “incidence”, “mortality”, “risk factors”, “world”. Studies related to incidence, mortality, and causes of gallbladder cancers were studied and included.

## NUMBER AND INCIDENCE

In 2012, there were 178101 cases of gallbladder cancer worldwide (76844 cases were male and 101,257 cases female (Sex Ratio = 0.75). The standardized incidence rate of the cancer was 2.2 per 100000. The age standardized incidence rate of the cancer was 2.3, 2.0 per 100000 people in men and 2.0, 2.4 per 100000 people in women in developed and developing countries, respectively<sup>11</sup>. The five countries with the highest standardized incidence of gallbladder cancer were Chile (9.7 per 100000), Bolivia (8.1 per 100000 people), Korea, Republic (6.5 per 100000), Lao PDR 4.8 per 100000 people and Japan 4.7 per 100000<sup>12,13</sup>. The incidence of gallbladder cancer in recent years has been rising in the advanced stage due to the time of diagnosis, often not curable. Despite the progress of information and diagnostic techniques, the disease remains deadly<sup>8</sup>. The incidence of this disease increases with age, and women are 2 to 6 times more likely to be at risk than men<sup>14</sup>. The incidence and mortality of this cancer are widespread in different geographical regions, and in different ethnic groups and ethnic groups. It is due to differences in risk factors associated with the development of gallbladder cancer and clinical manifestations during diagnosis in different areas<sup>12,14,15</sup>. The incidence of gallbladder cancer is high in many parts of the world, including Chile, Peru, Bolivia, Korea, Japan, the Czech Republic, Slovakia, Spain and India<sup>6</sup>. The basis for the difference is the difference in the distribution of risk factors, such as living environment, genetic predisposition, diet, fertility, age and gender differences (women are four to seven times more at risk than men)<sup>16,17</sup>.

## NUMBER AND MORTALITY RATE

In the whole world, in 2012, there were 142823 deaths from Gallbladder [(60339 were males and 82484 females (Sex Ratio = 0.73)]. The standardized death rate for gallbladder in the world was 1.7 per 100000. The standardized mortality rate for the cancer is 1.5 and 1.6 per 100000 per year in males, and 1.4 and 2.0 per 100000 per year in women in developed and non-developed regions<sup>11</sup>. The five countries that had the highest standardized death rates for gallbladder were Chile 7.8 per 100000, Bolivia with 7.5 per 100000, Korea, Republic with 4.8 per 100000, Lao PDR with 4.7 per 100000 and Nepal 4.1 per 100000<sup>12,13,18</sup>. The highest mortality rates in both sexes were in Latin America, East Asia, and Eastern Europe. In the recent epidemiological report in the world, the highest death and mortality rate of cancer has been in Chile and the main cause of death from cancer in women<sup>19,20</sup>. The mortality of gallbladder cancers with the diagnosis of the disease is related to stage 0 to stage IV. A 5-year survival of this cancer varies from 60% to 1% for stage 0 to stage IV of the cancer<sup>3</sup>. The highest mortality rate is for patients diagnosed in stage III<sup>21</sup>. Deaths in some countries, such as the United States, Canada, Australia, and parts of Europe (Britain and Hungary), are declining, but are increasing in some areas, including Chile and Japan<sup>17</sup>. From an epidemiological point of view, the incidence of the cancer is close to that of mortality. Countries with the highest incidence have the highest mortality rates. Lack of access to health care in some parts of the world will help to increase in these rates<sup>15</sup>.

## RISK FACTORS FOR GALLBLADDER CANCER

The most important risk factors for gallbladder cancers are summarized in Table 1. The factors are as follows.

## CHOLELITHIASIS

Many researches<sup>22-25</sup> show that cholelithiasis is considered a major risk factor for gallbladder cancer. This clinical relevance is observed in patients with symptomatic cholelithiasis, at least 20 years before the diagnosis of is gallbladder cancer described<sup>24,26</sup>. Based on studies, cholelithiasis was found in 70 to 94% of patients with gallbladder cancer<sup>6,17</sup>. Although cholelithiasis is the cause of approximately 80% to 90% of kidney cancer cases in the Western world. It does not seem that the association between the incidence of gallstone cancer is strong with a particular type of stones<sup>27</sup>. Cholelithiasis constitutes a

**TABLE 1.** Risk factors for gallbladder cancer

<i>Strength of association</i>	<i>Risk factors</i>
	Cholelithiasis
Strong	Bacterial and Salmonella infections
Strong	Porcelain gallbladder
Strong	Gallbladder polyps
Moderate to strong	Anomalous pancreatobiliary duct junction
Moderate to strong	Endogenous and exogenous estrogens
Moderate to strong	Industrial exposure to carcinogens
Moderate	Pregnancy
Moderate	Familial tendency
Weak to moderate	Segmental adenomyomatosis of gallbladder
Weak to moderate	Chronic inflammation
Weak to moderate	Polyposis coli
Weak to moderate	Mirizzi syndrome
Weak to moderate	Obesity
	Protective factor: vegetables, fruits fiber, vitamin intake

major health problem in developed societies, which affects 10 to 15 percent of the adult population. That means 20 to 25 million Americans have (or will have) cholelithiasis<sup>28-30</sup>. Increasing the number and size of cholelithiasis in patients with gallbladder cancer is not due to chemical or physical influences, but due to increased age and prolonged exposure to gallstones in the gallbladder<sup>31,32</sup>. The best epidemiological screening method for accurately determining the prevalence of cholelithiasis is ultrasonography<sup>33</sup>.

## BACTERIAL AND SALMONELLA INFECTIONS

Many cohort and case-control studies have shown a strong association between bacterial and salmonella infections and gallstone carcinogenesis, especially in endemicity areas with high levels of typhoid and bacterial degeneration<sup>23,34,35</sup>. The relationship between bacterial infection and ankylosis has been identified for a variety of cancers. The study of the role of infection in the development of this malignancy is still underway, especially in endemic areas where bile marrow cancer is more common. This mechanism involves continuous infections, leading to chronic inflammation associated with the production of toxins and metabolites that may trigger malignant epithelia in the gallbladder<sup>34</sup>. Chronic bacterial infection is also associated with gallbladder cancer, in which certain pathogens are involved<sup>34,36</sup>. Long-term studies after Aberdeen typhoid outbreaks in 1964 reported that 6% of US patients with typhoid fever have a lifetime risk of developing gallbladder cancers, and 12 times more at the risk of developing this disease<sup>23,37</sup>.

## CHRONIC INFLAMMATION

Chronic inflammation may have different causes, including: mechanical obstruction through cholelithiasis, environmental infections, polyps and adenomas, self-immune patients and also anatomical changes such as pancreatobiliary. Studies show each of these as a contributing factor to the development of gallbladder cancers<sup>38-40</sup>. The precise role of inflammation in molecular progression of the development of gallbladder cancers has been shown to weaken<sup>31</sup>.

## GALLBLADDER POLYPS AND PORCELAIN GALLBLADDER

Gallbladder and gallbladder polyps are risk factors for gallbladder cancer. Porcelain gallbladder and gallbladder polyps are present in 12.5% to 62% of patients with gallbladder cancer<sup>41,42</sup>. Cunningham et al<sup>43</sup> suggest that physicians should consider ethnicity when patients are likely to have porcelain gallbladder<sup>43</sup>. Several studies have reported the association between gallbladder polyps and the risk of gallbladder cancer. Also, approximately 45% and 67% of polyps larger than 10 and 15 mm lead to malignancy<sup>44-47</sup>. Cholecystectomy for polyps larger than 10 mm in addition to the size of the polyp is related factors such as high age<sup>45,46,48,49</sup>, clinging polyps<sup>50</sup>, having Cholelithiasis simultaneously and the symptoms of an increased risk of malignant polyps<sup>51</sup>.

## ANOMALOUS PANCREATOBILIARY DUCT JUNCTION

Another risk factor for gallbladder cancer is the Anomalous pancreatobiliary duct junction, which is found in about 17% of patients with gallbladder cancer compared with less than 3% of patients with other hepatobiliary conditions. The pancreatic water is deposited in the gallbladder and causes the gallstone, which consequently lead to inflammation and the prognosis of the bile duct<sup>26,52</sup>.

## OBESITY

Based on some study, Obesity is one of the risk factors associated with gallbladder cancer<sup>17,23</sup>. Obesity is a risk factor for gallbladder cancer, especially in women<sup>53</sup>, based on a meta-analysis on 20 studies, the relative risk for obese people was equal to 1.56 and overweight was 1.14 compared to the normal weight group, and the severity of the relationship was higher in women<sup>54</sup>. In other studies, this relationship has also been observed<sup>55,56</sup>. However, in some studies,



overweight in men did not show a significant relationship with increased risk of with gallbladder cancer<sup>57</sup>. Weiderpass et al<sup>58</sup> also noted that weight gain significantly reduced the risk of gallbladder cancer.

## **FOOD DIET, TOBACCO USAGE, ALCOHOL**

The risk factors associated with this cancer include diet, tobacco and alcohol consumption<sup>59</sup>. Red meat and tobacco increase the risk of this cancer, while vegetables and fruits have a protective role<sup>60</sup>. In addition, gallbladder cancer is associated with total calories, fiber and vitamin intake can also be associated with reduced risk<sup>61</sup>. The exact role of smoking and alcohol in the etiology of this cancer is not well defined<sup>12,62</sup>. Cigarette smoking is associated with increased chances of gallbladder cancer<sup>63</sup>, current finding supports a positive relationship between cigarette smoking and risk of gallbladder cancer, but this relationship needed more investigation<sup>64</sup>. In a study alcohol dose was linearly associated with risk of gallbladder cancer, but there was no clear association between alcohol consumption and the risk<sup>65</sup>.

## **INDUSTRIAL EXPOSURE TO CARCINOGENS**

Exposure to carcinogens plays an important role in the development of gallbladder cancers<sup>34,35</sup>. Retrospective studies have shown that chemical pollution through pesticides, excessive exposure to heavy metals, radiation, and vinyl chloride as industrial / occupational coatings (e.g. tires, fabrics, oil, and shoe factories) increases the incidence of gallbladder cancer. A review in California on 1808 cases of gallbladder cancer has pointed to the association of gallbladder cancer among workers in the rubber, automotive, and furniture industries<sup>66</sup>. The results of a study in the United States showed that 27.6% of patients with gallbladder cancers were rubber workers<sup>67</sup>. The risk of gallbladder cancers increased with some drugs (including isoniazid and oral contraceptives)<sup>68</sup>.

## **AUTOIMMUNE AND HEREDITARY SYNDROMES**

The association between ulcerative colitis and biliary malignancy has been well documented. transplant patients with ulcerative colitis are 10 times more likely to have gallbladder cancer than the general population<sup>69,70</sup>. Although the marked colitis has an active role in the development of gallbladder cancer, inflammation as a major cause of malignancy progresses in the gallbladder<sup>71</sup>.

## **ENDOGENOUS AND EXOGENOUS ESTROGENS**

Increasing estrogen levels with multiple mechanisms, including reduced gallstones, leads to an increase in the formation of biliary stones and the risk of infection and inflammation in the biliary system<sup>72,73</sup>.

## **PREGNANCY**

Fertility and the number of births are associated with gallbladder cancers<sup>62,74</sup>. Pregnancy increases the risk of gallstones, but is less associated with gallbladder cancer<sup>17,23</sup>. Another study has shown that the gestational age as well as the age of menarche are factors affecting gallbladder cancer. This is due to the role of female hormones in the pathogenesis of gallbladder cancers<sup>75,76</sup>.

## **SEGMENTAL ADENOMYOMATOSIS OF GALLBLADDER, CHRONIC INFLAMMATORY BOWEL DISEASE, POLYPOSIS COLI**

Segmental gallbladder adenomyomatosis, Chronic inflammatory bowel disease, Polyposis coli, and Mirizzi syndrome may lead to gallbladder cancer<sup>77,78</sup>.

## **MIRIZZI SYNDROME**

Mirizzi syndrome is a rare complication in kidney stone disease. The association between Mirizzi syndrome and gallbladder cancer is not well defined<sup>78</sup>. Only a few limited reports have reported the association of Mirizzi syndrome and gallbladder cancer<sup>79-82</sup>. The incidence of Mirizzi syndrome varies from 0.2% to 2.7% in patients with biliary stones<sup>78,79,83-86</sup>.

## **FAMILIAL TENDENCY AND GENETIC FACTORS**

Some reports have suggested familial tendencies toward gallbladder cancer, though they are very low based on the number of patients<sup>87</sup>. Genetic factors can also be considered as a risk factor for this cancer<sup>59</sup>. Information on genetic changes associated with gallbladder cancers is limited. However, Wistuba et al<sup>88</sup> reported that in most cases of gallbladder cancer, the loss of the chromosomal 3p loss of heterozygosity (LOH) and the locus of the suppressor of the fragile histidine triad (FHIT) tumor in the 3p14.2 is detected. Family history of gallstones is associated with an increased risk of gallbladder cancer<sup>74</sup>.

## AGE AND SEX

The incidence of this disease increases with age, and women are 2 to 6 times more likely at risk than men. According to previous studies, gallbladder cancer has been reported in the eighteenth and seventeenth years of life as an illness in elderly women with an increased incidence. Women can be at increased risk of developing this cancer due to fertility, pregnancy and hormonal factors<sup>63,89</sup>. A study in India also showed that the disease occurs mainly in women, in the fourth decade of life later because of a lower life expectancy<sup>14</sup>. The reason for the low age of the onset of gallbladder cancer in Indian women can be genetic factors in this population<sup>90,91</sup>.

## SOCIOECONOMIC STATUS

According to previous studies, the exact role of socioeconomic status and gallstone is discussed<sup>92</sup>. Studies have shown that gallstones and low socioeconomic status are independent factors for early onset and mortality of gallbladder cancer<sup>93</sup>. Low socioeconomic status indirectly affects low education and illiteracy, resulting in unemployment and inability to provide living expenses and the prevention of mortality of gallbladder cancers<sup>94</sup>. In general, improving the socioeconomic status along with controlling environmental pollution and education to increase awareness plays an important role in preventing the incidence and mortality of gallbladder cancers<sup>35</sup>. In some studies, after adjustment for age, there was no significant relationship between the risk of cancer and the socioeconomic class and education level<sup>95</sup>. The survival of this cancer is higher in higher socioeconomic classes and education level<sup>96</sup>. The aim of this review study was to determine the incidence and mortality rate of gallbladder cancer in the world and the association between environmental risk factors and incidence of gallbladder cancers. The findings of this study showed that the standardized incidence of gallbladder cancer in the world was 2.2 per 100000 and the standardized mortality rate for gallbladder cancer was 1.7 per 100000. The most important risk factors for the cancer were bile marrow, porcelain gallbladder and gallbladder polyps, bacterial and salmonella infections, and chronic inflammation. Fruit and vegetables and obesity have been known as a protective agent for this cancer. Most studies in this area focus more on clinical challenges and therapeutic strategies for managing gallbladder cancer.

## CONCLUSIONS

The incidence of gall bladder cancer worldwide has a geographic variable pattern. Generally, knowl-

edge of the stage of the disease at the time of diagnosis has a significant effect on the treatment of gallbladder cancer. It is also necessary to consider the risk factors for this cancer to reduce this cancer.

## CONFLICT OF INTEREST:

The Authors declare that they have no conflict of interests.

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