Special Article

Risk of Gall bladder Cancer in India's Gangetic Plains- A Review

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Abstract :

Gallbladder Cancer (GBC) is a global health concern known for its poor prognosis, late diagnosis, and limited treatment options. It ranks as the 23rd most common cancer worldwide, with higher prevalence in certain regions, including Northern India, Pakistan, and Latin American countries. Gender disparity exists, with higher risk in women. Age, genetic mutations (in genes like PIK3CA, KRAS, CTNNB1 and TP53), family history, lifestyle choices (like diet, smoking, obesity), and environmental factors (like arsenic exposure, heavy metal contamination) and pre-existing conditions like gallbladder inflammation and Salmonella infection contribute to the risk of developing the disease. The Gangetic plain exhibits unusually high GBC rates, attributed to factors like gallstones, water pollution (from agricultural run-offs, sewage and industrial pollutants), poor sanitation, dietary habits (including consumption of contaminated mustard oil), and socio-economic disparities. Tobacco use and, possibly, oral contraceptive usage further elevate susceptibility in this region. Efforts to mitigate this high incidence of GBC in the Gangetic plains should focus on improving healthcare access, promoting healthy lifestyles, reducing pollution, supporting genetic screening, and raising awareness. Further research is needed to uncover additional risk factors and develop targeted interventions for this region which can help reduce the burden of GBC in the Gangetic plain.

Keywords : Gall Bladder Cancer, India, genetic mutation, enbironment

INTRODUCTION

Gallbladder Cancer (GBC), a malignant neoplasm originating in the gallbladder, represents a significant global health concern. This aggressive form of cancer has been recognized for its poor prognosis, late-stage diagnosis, and limited therapeutic options, which collectively contribute to its high lethality [1]. In recent years, researchers have directed their attention towards understanding the complex web of factors contributing to GBC, shedding light on various etiological aspects and risk factors associated with this malignancy.

GBC predominantly manifests as adenocarcinoma and arises from the glandular epithelial cells lining the gallbladder. It remains a relatively rare malignancy compared to other gastrointestinal cancers, yet its insidious onset often leads to late-stage detection, reducing the chances of curative intervention [2]. It has been observed that this form of gastrointestinal cancer displays notable geographic variations in incidence rates. Certain regions of the world exhibit a disproportionately high prevalence of this cancer, with the Gangetic plain in South Asia emerging as one such hotspot [3]. Thus, understanding GBC within the context of the Gangetic plain population holds immense significance. The demographic diversity, environmental factors and distinct dietary and lifestyle practices prevalent in this region present a unique set of risk factors that contribute to the elevated incidence of this cancer [4]. Understanding these factors is pivotal for the development of targeted prevention and intervention strategies.

Through this review, we aim to comprehensively examine the existing body of research on the risk of GBC in individuals from the Gangetic plain. We seek to elucidate the epidemiological patterns of GBC and analyse the risk factors associated with gallbladder carcinoma, emphasising those that are particularly pertinent to the population of the Gangetic plain. Also, we aim to assess disparities in GBC incidence, including socio-economic and healthcare disparities, within this geographic region, thereby, providing insights that can inform targeted healthcare strategies and policies in this high-risk region.

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EPIDEMIOLOGY AND PREVALENCE OF GBC

GBC is the 23rd most common cancer worldwide, with an estimated 115,949 new cases in 2020 and 84,695 deaths in the same year [5]. It is the sixth most prevalent cancer of the gastrointestinal system but the most prevalent cancer of the biliary tract [6]. GBC is one of those unique cases that presents with a greater proportion of cancer mortality (1.7% of all cancer deaths) than incidence (1.2% of all cancer diagnoses).

There are regional variations in prevalence of GBC. Northern India, Pakistan, Japan, Korea, Poland and Latin American countries like Chile, Bolivia, and Ecuador have significantly higher than average rates of occurrence of GBC [7].This regional variation coincides with high rates of gallstones or *Salmonella* infection, which are known to increase the risk of GBC [8]. Gender disparity is also prevalent in incidence of gallbladder cancer. A study has noted that the cumulative risk of gallbladder cancer (from birth to age 74) is higher in women (0.26%) than in men (0.25%). Additionally, the cumulative risk of dying from gallbladder cancer stands at 0.17% for men and 0.19% for women [9]. Age also plays a significant role in the prevalence of gallbladder cancer. It's predominantly a disease of older adults, with the risk increasing from 30 years of age [10].

The Gangetic plain, situated in the northern part of India and encompassing parts of neighbouring countries, has garnered special attention due to its unusually high incidence of GBC. Recent research in this region has highlighted unique demographic characteristics, including a higher proportion of females affected, compared to Western populations, possibly linked to hormonal factors. Also, the high prevalence of gallstone disease has been identified as a significant contributor to the elevated GBC risk in the Gangetic plain [11]. The region's unique geology, characterised by high levels of nickel, cadmium and chromium in groundwater, has also been explored as a potential environmental risk factor [12]. Dietary habits play a crucial role in GBC epidemiology, and the Gangetic plain is no exception. Recent studies have highlighted the consumption of specific foods, including mustard oil, as potential risk factors [13].

RISK FACTORS ASSOCIATED WITH GBC

Gallbladder cancer is influenced by numerous factors. Recent studies have identified specific genetic mutations which contribute to an increased risk of gallbladder cancer. For instance, variations in genes like PIK3CA, KRAS, CTNNB1 and TP53 have been linked to a higher risk of developing this cancer in India [14]. Some authors have also shown that certain mutations in IDH1, IDH2, and KMT2C genes could result in greater susceptibility to developing GBC [15]. Moreover, these authors also found that mutations in genes CCTNNB1, ELF3, ERBB2, ARID2, ERBB3, STK11, SMAD4, ARID1A, KRAS, EHF, PIK3CA, BRAF, ACVR2A, PSIP1, NFE2L2, CHRM3, ZNF107, SMARCA4, APC, NF1, KAT8, MAP2K4, and HIST1H2AG were also present in patients suffering from GBC [16]. Additionally, family history of gallbladder cancer can be a strong indicator ,suggesting that genetic predisposition plays a role in GBC susceptibility [17].

Furthermore, the importance of lifestyle and dietary choices in gallbladder cancer risk cannot be left unnoticed. High consumption of red meat and low intake of fruits and vegetables have been associated with an increased risk of gallbladder cancer [18]. Smoking or chewing tobacco have been found as an independent risk factor for GBC [11]. Moreover, obesity is also a significant risk factor for gallbladder cancer [18]. However, in a large population based case control study held in India involving 333 patients with GBC, BMI showed an inverse relationship with GBC [19]. This might be due to a micronutrient and antioxidant deficiency, causing reduced immunity and increased chances of inflammation, which can ultimately lead to malignancy[11].

Exposure to environmental factors can also contribute to gallbladder cancer risk. One notable factor is chronic exposure to certain chemicals and pollutants. Recent studies have suggested that chronic arsenic exposure in drinking water at low-moderate levels and high levels of nickel, cadmium and chromium in groundwater may elevate the risk of gallbladder cancer [12,20]. These pollutants are not detoxified by the liver, rather they are excreted in conjugated form into the bile and are concentrated by the gallbladder (during concentration of bile). The enzyme beta glucuronidase, secreted by bacteria, deconjugates the toxins, thereby allowing them to act on the mucosa of gallbladder [11]. Furthermore, as mentioned earlier, geographical variations in gallbladder cancer incidence point to potential environmental factors involved in developing GBC.

Chronic conditions and infections have also been linked to an increased risk of gallbladder cancer. Recent studies have highlighted the role of chronic gallbladder inflammation in gallbladder cancer development [21]. Additionally, chronic infections, especially chronic Salmonella typhi and non-typhoid Salmonella infection, have been associated with a higher risk of gallbladder cancer [22,23]. S. typhi releases a cytolethal distending toxin. These toxins are coded by three genes , i.e, CdtA, CdtB, and CdtC, of which CdtB gene is responsible for carcinogenic activity. CdtB forms covalently-linked unique triplet structures with pertussis toxin (CdtB-PltA-PltB), enters into the target cell nucleus location and damages the host cell DNA, eventually leading to cell cycle inhibition [24]. Additionally, S. typhi releases certain effector protein molecules in the host cell, like Salmonella outer protein E (SopE), Salmonella outer protein E2 (SopE2), and Salmonella outer protein B (SopB), which allows the bacteria to survival in the host cell and enhance their MAPKinase and Akt activity, thereby enhancing the expression of proto-oncogenes [25]. Moreover, production of cyclic guanosine

monophosphate and adenosine monophosphate, through the cGAS-STING pathway for enhanced inflammation as an innate immunity, lead to DNA damage [26,27]. These events finally lead to the development of GBC.

It has been noted that conditions like Mirrizi's syndrome, xanthogranulomatous cholecystitis, common bile duct stone, cholecystitis and so on, is associated with increased risk of GBC [28]. Studies have noted that, in India, about 70–90% of patients with GBC have shown the presence of gallstones [11]. Also, higher parity and postmenopausal status is associated with increased risk with GBC in women. [19,29]. Furthermore, 75% of patients with GBC, in India, belong to lower-middle or lower socio-economic class. This might be due to lower literacy rate, overcrowding, lack of proper diet, poor access to health care, poorer sanitation and poorer access to clean drinking water, all of which contribute to greater susceptibility and poor prognosis of the disease.[30]

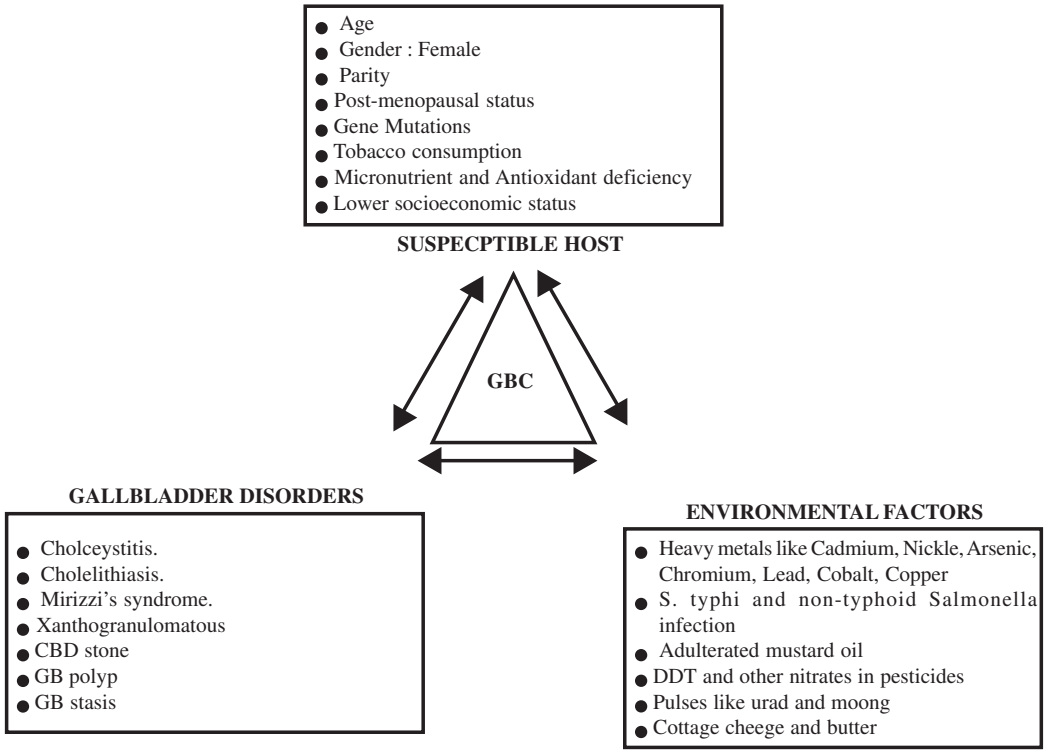

Figure (1) showing the epidemiological triad of Gallbladder Cancer in India

GANGETIC PLAIN: A HOTSPOT OF GBC IN INDIA

The Gangetic Plain, also known as the Indo-Gangetic Plain, spans over 320,000 square kilometres in India, covering the states of Uttar Pradesh, Bihar, West Bengal, and parts of Haryana, Punjab, and Rajasthan. It also extends into neighbouring countries, including Nepal and Bangladesh, making its total extent exceed 700,000 square kilometres. Epidemiological studies conducted in the Gangetic plain have reported an unusually high incidence of GBC. As mentioned earlier, they have highlighted unique demographic, environmental and behavioural characteristics that contribute to this high GBC susceptibility.

Water pollution in the Gangetic plain has been a subject of concern due to its potential association with GBC. A major portion of the plains is supplied by the Ganges, Yamuna and Brahmaputra which arise from the Himalayan glaciers , flow through the plains and in their course accumulate untreated sewage, run-offs from agricultural fields and industrial pollutants [31]. Run-offs from agricultural fields contain high amounts of heavy metals and nitrates which have been identified as carcinogenic and a study has shown that patients with GBC have a significant amount of these pesticides and nitrates in their bile [32]. Also, the leather tanneries in cities like Kanpur release heavy metal, like Chromium, Cadmium, Lead, Nickel, Arsenic, Cobalt, Copper, and so on, into the flowing river. The concentration of pollutants and faeco-orally transmitted pathogens, like *S. typhi*, increase steadily as the Ganges flows towards east, which may explain the high prevalence of GBC in this region [33]. Also, the soil and water in states like Bihar and Uttar Pradesh had significant levels of heavy metals and Dichloro diphenyl trichloroethane (DDT) which, as previously mentioned, contributes to the high incidence of GBC [31,34].

The relationship between GBC and dietary patterns have been thoroughly studied. The prevalence of consumption of urad

dal, moong dal, milk, cottage cheese and butter in this region increases the risk of GBC [19]. Furthermore, mustard oil, widely used in this region for cooking, is often adulterated with carcinogenic butter yellow. As we know, the majority of individuals living in the Gangetic plain come from poor socioeconomic backgrounds, they are forced to consume cheaper adulterated mustard oils (containing carcinogens like sanguinarine and diethyl nitrosamine) as branded, non-contaminated oils are unaffordable for them. A significant level of these adulterants, found in loose mustard oil, have been observed in blood and tissue samples of GBC patients. Moreover, mustard oil itself has tumour-inducing properties. Thus, the use of mustard oil in diet contributes to gallstones formation which may ultimately lead to GBC development [35].

Apart from genetics and dietary choices, high prevalence of consumption of tobacco, either by smoking or in non-smoking forms, in this region also contributes to the susceptibility to GBC. Also, a study from Lucknow observed that 87% of the GBC cases were oral contraceptive users [36]. However, further investigations are required to draw conclusive evidence between GBC and use of oral contraceptives. Moreover, with a significant proportion of the population living in lower-middle or lower socio-economic status, Gangetic plain, therefore, becomes more prone to GBC than the rest of India. [30]

CONCLUSION

In conclusion, the Gangetic plain has become a hotspot for GBC within the Indian subcontinent due to a complicated interaction of demographic, environmental, and behavioural characteristics. Also, predisposing factors like presence of gallstone disease, environmental factors such as water pollution, heavy metal contamination, and dietary choices like consumption of urad dal, moong dal, adulterated mustard oil and so on have significant contributions in the development of GBC in this region. Apart from genetic predisposition due to specific gene mutations, lifestyle choices, like consumption of tobacco, contribute to the susceptibility of GBC in the Gangetic plain. Furthermore, the socio-economic conditions of the majority of inhabitants of this region, characterised by lower literacy rates, limited access to healthcare and clean drinking water, further complicate the management and prevention of this disease.

Efforts to mitigate this high incidence of GBC in the Gangetic plain must have a versatile approach. They should aim at improving healthcare access and running campaigns to promote healthy dietary choices and reduce tobacco consumption. Additionally initiatives must be taken to reduce water pollution and heavy metal contamination. Since this belt has one of the highest incidences of GBC in the world, data on natural history of asymptomatic gallstones must be collected from patients of this area that shall aid in guiding government policies for supporting genetic screening and early diagnosis of the disease.[37]

Moreover, as gallstones are one of the predisposing factors, selective prophylactic cholecystectomy can be offered if patients with asymptomatic gallstones who are most vulnerable to GBC can be recognised by laboratory investigations identifying the type of stone, tumour markers and genetic markers.[38] Prophylactic cholecystectomy has shown to reduce GBC mortality in young healthy women, from the Gangetic plains, who were diagnosed to have asymptomatic gallstones, although further observational studies are required for generating more evidence.[39] Furthermore, patients with symptomatic gallstones should always be advised to undergo early cholecystectomy and the gallbladder, after the procedure, must undergo histopathological examination to allow early detection of gallbladder cancer.[40]

Therefore, it can be concluded that understanding these unique risk factors associated with gallbladder cancer in the Gangetic plain can assist in developing targeted healthcare interventions that can help reduce the burden of this cancer in this high-risk region. Further research into this topic is essential to discover and establish the contribution of other unknown factors that play a significant role in the development of GBC in this geographical area.

REFERENCES

1. Dwivedi AN, Jain S, Dixit R. Gall bladder carcinoma: Aggressive malignancy with protean loco-regional and distant spread. World J Clin Cases 2015;3(3):231-44. https://doi.org/10.12998/wjcc.v3.i3.231.

2. Andrén-Sandberg A. Diagnosis and management of gallbladder cancer. N Am J Med Sci 2012;4(7):293-9. https://doi.org/10.4103/1947-2714.98586.

3. Sharma A, Sharma KL, Gupta A, Yadav A, Kumar A. Gallbladder cancer epidemiology, pathogenesis and molecular genetics: Recent update. World J Gastroenterol 2017;23(22):3978-98. https://doi.org/10.3748/wjg.v23.i22.3978.

4. Gupta S, Kori C, Kumar V, Misra S, Akhtar N. Epidemiological Study of Gallbladder Cancer Patients from North Indian Gangetic Planes—a High-Volume Centre's Experience. J Gastrointest Cancer 2016;47(1):27-35. https://doi.org/10.1007/s12029-015-9781-5.

5. Rao HL, Chen JW, Li M, Xiao YB, Fu J, Zeng YX, et al. Increased intratumoral neutrophil in colorectal carcinomas correlates closely with malignant phenotype and predicts patients' adverse prognosis. PLoS One

2012;7(1):e30806.https://doi.org/10.1371/journal.pone.0030806.

6. Nemunaitis JM, Brown-Glabeman U, Soares H, Belmonte J, Liem B, Nir I, et al. Gallbladder cancer: review of a rare orphan gastrointestinal cancer with a focus on populations of New Mexico. BMC Cancer 2018;18(1):665. https://doi.org/10.1186/s12885-018-4575-3.

7. Halaseh SA, Halaseh S, Shakman R. A Review of the Etiology and Epidemiology of Gallbladder Cancer: What You Need to Know. Cureus. 2022 Aug 22;14(8):e28260.https://doi.org/10.7759/cureus.28260.

8. Lazcano-Ponce EC, Miquel JF, Muñoz N, Herrero R, Ferrecio C, Wistuba II, et al. Epidemiology and molecular pathology of gallbladder cancer. CA Cancer J Clin 2001;51(6):349-64. https://doi.org/10.3322/canjclin.51.6.349.

·9. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394-424. https://doi.org/10.3322/caac.21492.

10.` Malhotra RK, Manoharan N, Shukla NK, Rath GK. Gallbladder cancer incidence in Delhi urban: A 25-year trend analysis. Indian J Cancer 2017;54(4):673-7. https://doi.org/10.4103/ijc.IJC_393_17.

11. Dutta U, Bush N, Kalsi D, Popli P, Kapoor VK. Epidemiology of gallbladder cancer in India. Chin Clin Oncol 2019;8(4):33.https://doi.org/10.21037/cco.2019.08.03.

12. Unisa S, Jagannath P, Dhir V, Khandelwal C, Sarangi L, Roy TK. Population-based study to estimate prevalence and determine risk factors of gallbladder diseases in the rural Gangetic basin of North India. HPB (Oxford) 2011;13(2):117-25. https://doi.org/10.1111/j.1477-2574.2010.00255.x.

13. Mhatre S, Rajaraman P, Chatterjee N, Bray F, Goel M, Patkar S, et al. Mustard oil consumption, cooking method, diet and gallbladder cancer risk in high- and low-risk regions of India. Int J Cancer 2020;147(6):1621-8. https://doi.org/10.1002/ijc.32952.

14. Kumari N, Corless CL, Warrick A, Beadling C, Nelson D, Neff T, et al. Mutation profiling in gallbladder cancer in Indian population. Indian J Pathol Microbiol 2014;57(1):9-12. https://doi.org/10.4103/0377-4929.130849.

15. Mishra SK, Kumari N, Krishnani N. Molecular pathogenesis of gallbladder cancer: An update. Mutat Res 2019;816-8.https://doi.org/10.1016/j.mrfmmm.2019.111674.

16. Pérez-Moreno P, Riquelme I, García P, Brebi P, Roa JC. Environmental and Lifestyle Risk Factors in the Carcinogenesis of Gallbladder Cancer. J Pers Med 2022;12(2):234. https://doi.org/10.3390/jpm12020234.

17. Jain K, Sreenivas V, Velpandian T, Kapil U, Garg PK. Risk factors for gallbladder cancer: a case-control study. Int J Cancer 2013;132(7):1660-6. https://doi.org/10.1002/ijc.27777.

18. Pandey M, Shukla VK. Diet and gallbladder cancer: a case-control study. Eur J Cancer Prev 2002;11(4):365-8. https://doi.org/10.1097/00008469-200208000-00008.

·19. Tyagi B, Manoharan N, Raina V. Risk factors for gallbladder cancer/: A population based case-control study in Delhi. Indian J Med Paediatr Oncol 2008;29(29):16-26.https://doi.org/10.4103/0971-5851.51442.

20. Shridhar K, Krishnatreya M, Sarkar S, Kumar R, Kondal D, Kuriakose S, et al. Chronic Exposure to Drinking Water Arsenic and Gallbladder Cancer Risk: Preliminary Evidence from Endemic Regions of India. Cancer Epidemiol Biomarkers Prev 2023;32(3):406-14. https://doi.org/10.1158/1055-9965.EPI-22-0926.

21. Bojan A, Foia LG, Vladeanu MC, Bararu Bojan I, Plesoianu C, Plesoianu A, et al. Understanding the mechanisms of gallbladder lesions: A systematic review. Exp Ther Med 2022;24(3):604. https://doi.org/10.3892/etm.2022.11541.

22. Koshiol J, Wozniak A, Cook P, Adaniel C, Acevedo J, Azócar L, et al. Gallbladder Cancer Chile Working Group. Salmonella enterica serovar Typhi and gallbladder cancer: a case-control study and meta-analysis. Cancer Med 2016;5(11):3235-310. https://doi.org/10.1002/cam4.915.

23. Iyer P, Barreto SG, Sahoo B, Chandrani P, Ramadwar MR, Shrikhande SV, et al. Non-typhoidal Salmonella DNA traces in gallbladder cancer. Infect Agent Can-

cer 2016;11:12. https://doi.org/10.1186/s13027-016-0057-x.

24. Di Domenico EG, Cavallo I, Pontone M, Toma L, Ensoli F. Biofilm Producing Salmonella Typhi: Chronic Colonization and Development of Gallbladder Cancer. Int J Mol Sci 2017;18(9):1887. https://doi.org/10.3390/ijms18091887.

25. Scanu T, Spaapen RM, Bakker JM, Pratap CB, en Wu L, Hofland I, et al. Salmonella manipulation of host signaling pathways provokes cellular transformation associated with gallbladder carcinoma Cell Host Microbe 2015;17(6):763-74. https://doi.org/10.1016/j.chom.2015.05.002.

26. Li T, Chen ZJ. The cGAS-cGAMP-STING pathway connects DNA damage to inflammation, senescence, and cancer. J Exp Med 2018;215(5):1287-99. https://doi.org/10.1084/jem.20180139.

27. Tao J, Zhou X, Jiang Z. cGAS-cGAMP-STING: The three musketeers of cytosolic DNA sensing and signaling. IUBMB Life 2016;68(11):858-70. https://doi.org/10.1002/iub.1566.

28. Kapoor VK, McMichael AJ. Gallbladder cancer: an 'Indian' disease. Natl Med J India 2003;16(4):209-13. PMID: 14606770.

29. 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(3):784-7. https://doi.org/10.1111/j.1572-0241.2000.01860.x.

30. Dubey A, Rawat K, Pathi N, et al. Carcinoma of gall bladder: Demographic and clinicopathological profile in indian patients. Oncol J India 2018;2(1):3 https://doi.org/10.4103/oji.oji_1_18.

31. Gupta SK, Singh SP, Shukla VK. Copper, zinc, and Cu/Zn ratio in carcinoma of the gallbladder. J Surg Oncol 2005;91(3):204-8. https://doi.org/10.1002/jso.20306.

32. Shukla VK, Prakash A, Tripathi BD, Reddy DC, Singh S. Biliary heavy metal concentrations in carcinoma of the gall bladder: case-control study BMJ. 1998;317(7168):1288-9. https://doi.org/10.1136/bmj.317.7168.1288.

33. Pandey M, Vishwakarma RA, Khatri AK, Roy SK, Shukla VK. Bile, bacteria, and gallbladder carcinogenesis. J Surg Oncol 1995;58(4):282-3. https://doi.org/10.1002/jso.2930580417.

34. Unisa S, Jagannath P, Dhir V, Khandelwal C, Sarangi L, Roy TK. Population-based study to estimate prevalence and determine risk factors of gallbladder diseases in the rural Gangetic basin of North India. HPB (Oxford). 2011;13(2):117-25. https://doi.org/10.1111/j.1477-2574.2010.00255.x.

35. Shukla Y, Arora A. Enhancing effects of mustard oil on preneoplastic hepatic foci development in Wistar rats. Hum Exp Toxicol 2003;22(2):51-5. https://doi.org/10.1191/0960327103ht338oa.

36. Dwivedi S, Madeshiya A, Singh D, et al. Gall Bladder Cancer and some epidemiological factors: A cross sectional study. Biomed Res 2013;24(1):83-87.
https://www.researchgate.net/publication/288049788_Gall_Bladder_Cancer_and_some_epidemiological_factors_A_cross_sectional_study

37. Behari, A., Kapoor, V.K. Asymptomatic Gallstones (AsGS) – To Treat or Not to?. Indian J Surg 2012;74:4–12. https://doi.org/10.1007/s12262-011-0376-5 .

38. Kapoor VK. Cholecystectomy in patients with asymptomatic gallstones to prevent gall bladder cancer—the case against. Indian J Gastroenterol 2006;25(3):152-4. PMID: 16877831.

39. Mohandas KM, Patil PS. Cholecystectomy for asymptomatic gallstones can reduce gall bladder cancer mortality in northern Indian women. Indian J Gastroenterol. 2006;25(3):147-51. PMID: 16877830.

40. Kapoor, V.K. (2021). Prevention of Gall Bladder Cancer. In: Kapoor, V.K. (eds) A Pictorial Treatise on Gall Bladder Cancer. Springer, Singapore. https://doi.org/10.1007/978-981-15-5289-2_16