Article published online: 2025-05-27

Could Microplastics Be the Reason for the High Gallbladder Cancer Incidence in Northern India?

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Ind J Med Paediatr Oncol

Abstract

India accounts for more than 15% of all gallbladder cancer (GBC) diagnosed worldwide, with around 21,000 new cases diagnosed in 2022. However, a large proportion of these cases are concentrated along the banks of river Ganges flowing through northern and northeastern parts of India. GBC incidence in the Gangetic belt is around 10 times more than the rates reported from the rest of the country. In our article, we evaluated the various factors responsible for this geographic disparity and propose microplastic contamination of the river Ganges as the possible etiology for increased GBC prevalence along the Gangetic belt. Here, we attempted to describe existing literature on the harmful effects of microplastics particularly focusing on its carcinogenic potential. Although no proven association exists between GBC and microplastics, we believe there is strong circumstantial evidence to support this claim. However. extensive studies on the role of microplastics in GBC pathophysiology should be performed before any conclusion can be made on its carcinogenic potential.

Keywords
- cancer
- gallbladder cancer
- microplastics

India is among the leading countries for incidences of gallbladder cancer (GBC) globally, with around 21,000 new cases diagnosed in 2022 accounting for >15% of the total cases worldwide.[1] However, there is a wide geographic disparity in its distribution with the age-standardized rates of the Northern and Eastern parts of the country being nearly 10 times that of South India.[2] The incidence of GBC is especially high along the Gangetic belt.[2]

Residence along the Gangetic belt was found to be an important risk factor for the development of GBC with an odds ratio ranging from 1.72 to 3.3 across studies.[3,4] The Ganga along with its tributaries originate in the Himalayas and flow through major cities like Varanasi, Patna, Prayagraj, Kolkata, and Rishikesh before eventually emptying into the Bay of Bengal. It is the longest river in the country and the river basin with the highest population density in the world.[5] More than 400 million Indians depend on it for their daily activities.[5] As it flows through the Indian subcontinent, the river gets heavily contaminated with untreated domestic sewage, industrial effluents, and agricultural runoff, making it one of the most polluted rivers across the globe. It has been reported that the Ganges is responsible for more than 70% of India's total gray water output.[6]

There are a few studies that have attempted to explain the increased prevalence of GBC and its uneven distribution in India. Possible etiologies proposed for rising GBC incidence along the Gangetic belt: infection with *Helicobacter pylori* and *Salmonella typhi*; contamination of Ganga with carcinogens like pesticides, nitrates, and heavy metals; increased concentration of arsenic in groundwater; and use of adulterated mustard oil for cooking (that is especially popular among the northern and northern-eastern parts of the country) have been proposed as possible etiologies for rising GBC incidence along the Gangetic belt.[7–11]

A case–control genome-wide association study to evaluate the genetic susceptibility to GBC was performed and

DOI https://doi.org/10.1055/s-0045-1809374.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

consisted primarily of patients from northern and northeastern parts of India.[12] This study reported that the common variations in the ABCB1 and ABCB4 genes were linked with the development of GBC.[12] ABCB1 gene codes for a glycoprotein linked with resistance to anticancer drugs, while ABCB4 codes for a membrane protein responsible for transporting phospholipids into the bile.[12] Phospholipids in bile protect against the emulsifying actions of bile salt and its insufficient secretion due to mutations in the ABCB4 gene results in injury to the biliary tract. Studies performed in mice reported that the absence of this gene was associated with a higher risk of carcinogenesis on exposure to chemical carcinogens in addition to the production of reactive oxygen species (ROS) and DNA damage.[12] In humans, mutations in the same gene were found to increase susceptibility to cholestasis, cholelithiasis, liver cirrhosis, and hepatobiliary carcinoma.[12]

While a lot of these are explored as possible causative factors, pollution could be the most pertinent one. But how does pollution cause GBC? And, why in regions in low- and middle-income countries (LMICs) with heavily polluted water bodies? The answer could lie in the famous statement from the movie, The Graduate–"I want to say one word to you. Just one word: Plastics."[13]

Microplastics are produced when plastic polymers are broken down into minute particles of size less than or equal to 5 mm.[13] They are essentially nonbiodegradable, ubiquitous, and persistent in the environment. They can enter the human body following ingestion after they accumulate in the food chain, through inhalation from the atmosphere, or through direct skin contact.[13] Microplastics in the body are excreted primarily through the liver either by the reticuloendothelial system through phagocytosis or by the biliary system as part of fecal matter.[13] A small fraction is also removed by the kidney through the urine.

The exact effects of microplastics on the human body are not yet completely understood. However, they are reported to bring about unwanted immune responses and inflammatory reactions, increase oxidative stress, alter the gut microbiome, and interfere with lipid metabolism.[14] There is a dearth of studies assessing the direct carcinogenic potential of microplastics; however, multiple studies conducted in vitro and in vivo have shown their association with genotoxicity, oxidative stress, and inflammatory reactions, suggesting a possible association between the two.[15] Comprehensive studies are required before the role of microplastics in carcinogenesis can be clearly understood.

Hepatotoxicity caused by a common microplastic polymethyl methacrylate (PMMA) was studied in a highly sensitive liver injury model by Boran et al in 2023.[16] They reported that PMMA was associated with a notable release of ROS, increased oxidative stress, the production of inflammatory cytokines such as tumor necrosis factor-α and interleukin-6, and decreased antioxidant activity.[16] Oxidative stress can often lead to DNA damage and 8-OHdG is a biomarker used to assess oxidative DNA damage.[16] The study also reported a concentration-dependent increase of 8-OHdG following PMMA application, highlighting the potential of microplastics to produce DNA damage.[16]

Global plastic production as of 2019 was around 460 million tonnes.[17] The Ganga–Brahmaputra–Meghna River ranks 6th among the top 10 rivers dumping microplastics into the sea.[18] It has been reported that 1 microplastic particle is present for every 20 L of water in the Ganga. This river along with its tributaries dumps nearly 1 to 3 billion microplastics into the Bay of Bengal every day.[19,20] Rayon (54%) was the predominant polymer detected with acrylic (23%) occupying the second rank.[19] We propose that the increased incidence of GBC in the Gangetic belt could be attributed to the high concentration of microplastics in the river.

Although there is no established association between the two, there exists strong circumstantial evidence to support this claim. Continued ingestion or exposure to water from Ganga could result in microplastic accumulation in the liver and biliary tract over time. Accumulated microplastics may then produce oxidative stress, and release ROS in the region, eventually resulting in the development of GBC. Given that millions of Indians utilize water from the Ganga for their livelihood, this could explain the high prevalence of GBC in the Gangetic belt.

Other regions with elevated GBC incidence also have rivers that are highly contaminated with microplastics. Among the top 10 rivers responsible for dumping nearly 90% of the total microplastics into the sea, around 5 of them flow through eastern Asia.[18] This region also has the highest incidence of GBC in the world with an estimated 46,000 cases recorded in 2022 compared with 5,000 in Northern America.[1]

The rising incidence of GBC in LMICs along with its low prevalence in developed nations also points toward the possibility of an environmental factor like microplastics in GBC. This potential association has not been given the due importance it deserves and ours is one of the few papers on this topic. We believe the circumstantial evidence presented in our perspective would encourage further research in this area. However, currently, we do not have any direct concrete evidence linking GBC with microplastics, which is the major limitation of our article. Correlation does not necessarily mean causation and we feel extensive studies evaluating the role of microplastics in the pathogenesis of GBC are essential before any conclusions can be reached on its carcinogenic role.

Authors' Contributions

A.M. conceptualized and designed the study. J.M.B. and A.M. were involved in the data collection, analysis, and interpretation of results. J.M.B. and A.M. prepared the draft manuscript. Both authors reviewed the results and approved the final version of the manuscript.

Patient's Consent

Patient consent was not required.

Funding

None.

Conflict of Interest
None declared.

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