



## Gallbladder Carcinoma: A Reason to Worry in North and North-Eastern India

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### Editorial

Gallbladder carcinoma is a highly aggressive malignancy with very poor survival rate but luckily it has been recorded with very low incidence in various literatures from the west [1]. However, the data from India has shown wide variation in the incidence when compared between Northern and Southern parts of India. Data shows that it is one of the five most common gastrointestinal neoplasms in northern and north-eastern India [2]. So does the river water from Ganges and Brahmaputra which is the prime source of drinking water and irrigation, got a role in increased incidence of this malignancy? According to the data from GLOBOCAN, it is estimated that in 2025 India will alone represent 9.76% males and 11.15% females of the total gallbladder carcinoma burden [3]. The National Cancer Registry Program (NCRP) under the aegis of Indian Council of Medical Research (ICMR) had published in 2013 the Population Based Cancer registries (PBCR) of three years from 2009-2011 which shows the Age Adjusted Rate (AAR) comparison based on PBCR in India with rest of the world [4]. The AAR for Gallbladder carcinoma for females was 14.0 and was just below Chile (which is also along the banks of a river) and Valdivia. The Indian PBCR had shown a very high incidence of gallbladder carcinoma in river valleys (north and north-eastern states) compared to sea valleys (Chennai and Mumbai). The established risk factors for gallbladder carcinoma are multifactorial and broadly categorized into patients' demography, gallbladder abnormalities, exposures to environmental factors and infections [5]. If environmental factors need to be considered it has been seen that the incidence of gallbladder carcinoma is high in regions situated near the major river like the Ganges. Interestingly the incidence is rare in the upper reaches of these rivers where they originate from. The water of these major rivers become highly polluted in its middle course with not only agricultural effluents and domestic sewage but also with an alarming amount of industrial wastes which are being disposed of routinely in these rivers. The water contains pollutants like pesticides; heavy metals like chromium, lead and cadmium; and industrial wastes like aromatic hydrocarbons and nitrosamines, nitrates and nitrites [6].

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A study by Shukla et al. [7] had found presence of heavy metals in very high concentrations in carcinoma of gallbladder in comparison to patients of gallstones and healthy controls. These metals were present in drinking water of such regions thus confirming the hypothesis of carcinogenesis. India being predominantly an agriculture based country, in recent years there has been increased use of nitrate based fertilizers for cultivation. This has led to increased intake of nitrates through vegetables and water. High biliary concentration of nitrate was seen in cases of gallbladder carcinoma in comparison to cholelithiasis [8]. This nitrate in bile is converted to nitrite and nitrosamines and is known to initiate gallbladder carcinogenesis. It is well established that pesticides used in crop protection has a crucial role in carcinogenesis. An interesting study done in the Gangetic belt has shown that there is a significantly higher concentration of BHC and DDT pesticides in gallbladder carcinoma when compared to cases with cholelithiasis [9]. Chronic presence of bacteria in bile causes conversion of primary bile acids to secondary bile acids and may have a role in tumorigenesis. Studies have shown higher bile culture positivity and concentration of deoxycholate in cases of gallbladder carcinoma [10]. Gallbladder disease including carcinoma is common in north and north-eastern parts of India and so also Salmonella typhi infection and chronic carrier typhoid state. The risk of developing gallbladder carcinoma in culture positive typhoid carriers is 8.47 times higher than non-carriers [11].

Another interesting association was found for increased incidence of gallbladder carcinoma with use adulterated mustard oil in cooking mostly in eastern and northeastern parts of the country. Edible mustard oil is often adulterated with argemone oil because both the seeds and colour of the oil resemble closely [12]. Sanguinarine and diethylnitrosamine are present in argemone and are known to be carcinogenic and responsible for DNA damage and hepatocarcinogenesis respectively. A recent

study has shown that the concentration of both these compounds were high in patients with gallbladder carcinoma in comparison to cases with cholelithiasis [13]. As this mysterious cancer plagues the upper reaches of India, a novel case control Genome-Wide Association Study (GWAS) was carried out in a leading oncology institute of India to identify common genetic susceptibility alleles for gallbladder carcinoma in Indian descent. Three of the most significant single-nucleotide polymorphisms (SNP) in the replication cohort were studied. They reported common genetic variation conferring gallbladder cancer risk at genome-wide significance. A strong replicated association was found at chromosome7q21.12 which harbors ATP binding cassette subfamily B genes ABCB1 and ABCB4 [14]. Like gallbladder carcinoma, gallstones are common in north and north-eastern parts of India. A study from eastern India showed that out of 198 diagnosed gallbladder carcinoma cases 86% patients had gallstones [15]. However, data from West indicate that the risk of cancer from asymptomatic gallstones is negligible and does not warrant prophylactic cholecystectomy. So the question arises whether these Western recommendations are extrapolated to Indian settings where the incidence of gallbladder is so high. In view of the clinical scenario of gallbladder cancer in north and north-eastern India and the proven safety of laparoscopic cholecystectomy there is pressing evidence from various studies to justify prophylactic cholecystectomy in selected group of asymptomatic gallstones patients [16].

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