Relation of Gallbladder Cancer, Gallbladder Stones and Breast Cancer with Polluted Rivers – A Case Control Study in the Indo-Gangetic Plains

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ABSTRACT

BACKGROUND
Gallbladder cancer and breast cancer are two common malignancies seen along the Ganges River and the Indo-Gangetic plains of northern India, especially in the states of Uttar Pradesh and Bihar. Some of the postulated aetiologies include cholelithiasis (gallstones), typhoid carrier state, dietary factors, genetic predisposition and chemical carcinogens. Studies have also linked gallbladder cancer and breast cancer to carcinogens in polluted rivers. We undertook this study to investigate as to whether these conditions and gallstones were more prevalent in populations living close to polluted rivers. We also wanted to investigate as to whether there is any association between gallbladder cancer, gallstones and breast cancer with river pollution.

METHODS
This was a case-control study carried out in the Department of Oncology of a tertiary level defence hospital between 2018 and 2020. Patients who were diagnosed as having gallbladder cancer, gallstones or breast cancer in this tertiary institute, and were permanent residents of Uttar Pradesh or Bihar were included in the study.

RESULTS
In this study, we found that patients with gallbladder cancer, gallstones and breast cancer had their home closer to the river at a distance of around 53.9, 54 and 39.1 Kms. respectively compared to controls whose homes were at a distance of 76.7 Kms.

CONCLUSIONS
This study suggests that proximity to polluted rivers is one more factor in the aetiology of aforementioned diseases. Governmental agencies must consider monitoring and controlling the release of pollutants from the industries into the local nearby rivers.

KEYWORDS
Gallbladder Neoplasms, Drinking Water, Gallstones, Public Health

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DOI: 10.18410/jebmh/2021/129

How to Cite This Article:
Sreen A, Singh HP, Guleria V, et al. Relation of gallbladder cancer, gallbladder stones and breast cancer with polluted rivers – a case control study in the Indo-Gangetic plains. J Evid Based Med Healthc 2021;8(12):657-661. DOI: 10.18410/jebmh/2021/129

Submission 12-08-2020,
Peer Review 24-08-2020,
Acceptance 29-01-2021,
Published 22-03-2021.

BACKGROUND

The International Agency for Research on Cancer has estimated that the global cancer burden has risen to 19.3 million cases and 10 million deaths in the year 2020 and is projected to rise to a staggering 30.2 million new cases by 2040.[1] A previous study has similarly estimated the rise in the incidence of cancers to 1.8 million new cases by 2026 which will make cancer the second most common cause of mortality due to non-communicable causes, after cardiovascular diseases.[2]

Cancer is primarily an environmental disease with 90 - 95 % of the cases attributed to environmental factors and 5 - 10 % of the cases attributed to genetics. Common environmental factors that contribute to cancer deaths include tobacco (20 - 25 %), diet and obesity (25 - 30 %), infections (20 %), radiation (both ionizing and non-ionizing, up to 10 %), stress, lack of physical activity, and environmental pollutants. It is nearly impossible to prove a single aetiology that caused a malignancy to develop in any individual, because most cancers have multiple possible aetiologies. Substances and exposures that lead to malignant transformation of cells are called carcinogens. The International Agency for Research on Cancer monographs,[3] the Centre for Disease Control (CDC)[4] and the U.S. Department of Health and Human Services, Public Health Service National Toxicology Program[5] have identified a list of carcinogens.

Polluted rivers are known to cause cancer through exposure to certain carcinogens (Table 1). The Kishon River in Israel[6] and the Nile River[7] in Egypt are heavily polluted with carcinogens and have been linked to a high incidence of cancer in their geographical regions. Polluted rivers have also been linked to gallbladder cancer [4 is 6]. A wide variety of carcinogens[8,9,10] have been implicated in the origin of gallbladder cancer (GBC) especially from organochlorines, high biliary concentrations of benzene hexachloride, dichlorodiphenyltrichloroethane (DDT), cadmium, chromium and lead. The carcinogens in rivers have been found to cause unique patterns of mutation in both oncogenes KRAS and tumour suppressor genes p53 mutations.[8]

The incidence of gallbladder cancer varies widely across the world but it is one of the common gastrointestinal malignancies seen and reported in India. It has a high prevalence mainly along the Indo-Gangetic plains of northern and eastern India especially in the states of Uttar Pradesh and Bihar.[11] The reasons for high incidence in this population are not well-understood. Some of the postulated aetiologies include cholelithiasis, typhoid carrier state, dietary factors, genetic predisposition, chemical carcinogens and river pollution.

The geographical variations of gallbladder cancer occurrence in the states of Uttar Pradesh and Bihar suggest local and regional environmental risk factors. Owing to spatial variations in the incidence of gallbladder cancer, additional risk factors required further investigation. This study hypothesizes that there is a link between disease risk and pollution sources suspected to be environmentally contaminated. Based on this hypothesis, the following research question was formulated by the researchers: Are there any environmental contaminants in the plains of the Ganges River that have a potential to cause gallbladder cancer, gallstones and breast cancer in the at-risk population?

METHODS

This was a case-control study carried out in the Department of Oncology of a tertiary level defence hospital between the years 2018 and 2020. Patients who were diagnosed as having gallbladder cancer, gallbladder stones or breast cancer in this tertiary institute, and were permanent residents of Uttar Pradesh and Bihar living within 100 km from banks of river Ganges (Ganga) were included in the study. (They will henceforth be referred to as study subjects).

This study was conducted to investigate whether there is any association between these cancers (gallbladder cancer and breast cancer) and river pollution affecting the Ganges river. Therefore, the distance of the homes of the study subjects from the river Ganga was noted.

Cancer patients were compared with controls. 778 healthy, age-matched adults above 50 years of age with no history or evidence of gallbladder cancer, gallstones or breast cancer who belonged to the same geographical area and also had their homes within a similar range of distance from the river were included in the study as controls. The distance of their homes from the river was also noted.

All statistical analysis was performed using the latest Statistical Package for the Social Sciences (SPSS) software package.

The comparative mean distances of homes from the polluted river were analysed using the independent sample t-test. A probability value < 0.05 was considered significant.

RESULTS

A total number of 97 patients diagnosed with gallbladder cancer were included in this study. The average age of the patients at the time of diagnosis was 66 years. Women (64 %) were more commonly affected than men. The shortest distance between the villages of these patients from river Ganga was documented in kilometres and compared to 100 healthy controls. Patients with gallbladder cancer (N = 97) lived at an average distance of 53.9 (+ / - 5.4) kms. from the river. On the other hand, the controls (N = 100) lived at an average distance of 76.7 (+ / - 8) kms. from the river Ganges (P = 0.029). This shows that the difference in distances is highly significant.

61 patients diagnosed with breast cancer were included in this study. All were females with an average age of 56 years, at the time of diagnosis. It was observed that the patients with breast cancer lived at a distance of 39.1 (+ / - 6.2) km. 60 age and gender matched controls were studied and it was seen that the controls (N = 60) lived at an average distance of 66.4 (+ / - 10.6) km from Ganga river

(P = 0.006). This shows that the difference in distance is highly significant.

A total of 151 patients were diagnosed with gallbladder stones. The average age at the time of diagnosis was 52 years. Women (61 %) were more commonly affected than men. It was found that the patients with gallstones lived at a distance of 54 (+ / - 11) kms. from the Ganga river while the controls lived at an average distance of 76.7 (+ / - 12.8) kms from the river (P = 0.007). This shows that the difference in distances is highly significant.

Sl. No.	Year	Country	Polluted Rivers	Carcinogens	Cancer
1	1981	USA [13]	Mississippi River	Not reported	Rectal and urinary cancer
2	1999	Japan [10]	Shinano and Agano	Not reported	Tongue, colon, rectum, gallbladder etc.
3	2003	Israel [4]	Kishon River	Aromatic hydrocarbons, xylene phenols, alcohols, chlorinated alkylbenzenes, trichlorethylene, cresols, styrene, viny chlorides, uranium, radium.	haematolymphopoietic, central nervous system, gastrointestinal, and skin cancer;
4	2006	Egypt [12]	Nile River	Cadmium	Pancreatic cancer
7	2000	Finland [15]	Kymijoki	Polychlorinated phenols, catechols, guaiacols, diphenyl ethers & mercury.	Breast, uterine cervix, gallbladder, and nervous system, basal cell carcinoma

Table 1. Rivers Linked to Cancer in Different Countries

Sl. No	Type of Cancer	Patients (n)	Age (Years)	Distance of Home from the River (Cases)	Distance of Home from the River (Controls)	P Value
1	Gall bladder cancer	97	66 (+ / - 8)	53.9 (+ / - 8.4) Km	76.7 (+ / - 8) Km	0.029
2	Breast cancer	61	56 (+ / - 10)	39.1 (+ / - 6.2) Km	66.4 (+ / - 10) Km	0.006
3	Gall bladder stones	151	52 (+ / - 14)	54 (+ / - 11) Km	76.7 (+ / - 12.8) Km	0.007

Table 2. Distance of Homes of Gallbladder Cancer, Breast Cancer and Gallstones Patients from River Ganges

DISCUSSION

This study examined the spatial relationship between a river which has been subjected to industrial and man-made pollution for the last several decades with the incidence of gallbladder cancer and breast cancer among residents of UP and Bihar. Cancer is caused by changes in a cell's DNA. Some of these changes may be inherited, while others may be caused by environmental factors. Substances and exposures that lead to cancer are called carcinogens. The International Agency for Research on Cancer monographs[3] and the Centre for Disease Control (CDC),[4] have identified various environmental factors like chemicals, complex mixtures, occupational exposures and physical agents that can increase the risk of human cancer. It has been found that carcinogens in polluted rivers[12] are directly linked to various cancers in different parts of the world (Table 1). The present study has found that gallbladder cancer, gallbladder stones and breast cancer are more common in residents of UP and Bihar who have their homes closer to river Ganga.

The Kishon River is a 70-km-long perennial stream in Israel and is considered as the most polluted river there. A study conducted to evaluate the risk for cancers in divers with prolonged underwater exposures in the river suggested that the increase in risk for cancer resulted from direct contact with and absorption of multiple toxic compounds.[6]

Another study was conducted in Niigata, Japan where drinking water was obtained from the rivers of Shinano and Agano and their down-stream rivers. A significant relationship was found between the source of drinking water and standardised incidence ratios of malignant neoplasms. The following cancer sites were correlated with the source of drinking water; tongue, colon, rectum, gallbladder, prostate, kidney etc.[12]

The northeast Nile Delta in Egypt is similarly a heavily polluted region and has a high incidence of pancreatic cancer. It is mainly polluted with heavy metals, pesticides and hydrocarbons because of the increasing discharge of untreated industrial by-products and wastes. A study suggested that there was clustering of pancreatic cancer cases in the northeast Nile delta region and that this clustering may be related to water pollution.

Our study was designed to see if the higher incidence of gallbladder cancer and breast cancer could be linked to increasing pollution levels in the local rivers in states of Uttar Pradesh and Bihar. Gallbladder cancer is one of the common gastrointestinal malignancies seen in India. It has a high prevalence mainly along the Indo-Gangetic plains[11] of northern India especially in the states of Uttar Pradesh and Bihar. A study conducted by the Regional Cancer Centre at the Indira Gandhi Institute of Medical Sciences in Patna, the capital of the state of Bihar, has found that the districts situated along the Ganga river and districts with higher arsenic levels in the soil had a higher risk of reporting gallbladder cancer as compared to the districts situated away from the river.[13]

The American Cancer Society[14] has identified several risk factors for breast cancer. About 5 to 10 percent of breast cancers are inherited, due to strong genetic factors. Other possible risk factors include increasing age, personal history of breast cancer, long-term use of hormone replacement therapy, obesity, low physical activity and alcohol consumption.[15] At the same time, recent research showed an emerging evidence of an association between breast cancer risk and environmental pollution.[16,17] In one study, the close proximity to a river was associated with a high risk of breast cancer.[18]

Previous studies have also observed a higher risk of gallbladder diseases among the population consuming water from unsafe sources such as open wells or polluted rivers.[19]

The present study also found a significant relationship between patients of breast cancer and distance of their homes from the banks of polluted rivers. The present study has found that gallbladder cancer and breast cancer are more common among the residents of Uttar Pradesh and Bihar who have their homes closer to river Ganga.

Governmental agencies may consider monitoring and controlling the release of pollutants from the industrial

wastes into the local nearby rivers. Public health measures may be suitably strengthened and awareness among the local health officials regarding the higher incidence of these conditions in the local population should be increased. These findings may also be valuable for manufacturers to avoid or minimize releasing the identified carcinogenic chemicals into the environment. Soil and water testing should also be regularly carried out to check for high levels of implicated pollutants and alternative safe drinking water resources should ideally be provided to the high-risk populations to reduce the consumption of polluted drinking water. Finally, community health outreach should be encouraged and the local population in the high-risk districts should be educated about the safe drinking water practices.

Alongside these measures the government must continue to focus on river cleaning projects to reduce pollution levels in the rivers. India's rivers are the source of drinking water for a vast majority of the country's population and among them, the Ganga River is considered as a lifeline for the millions of inhabitants along its banks.

All these measures may help in reducing the burden of gallbladder diseases including gallbladder malignancies and breast cancer in the affected regions of the country.

CONCLUSIONS

This study provides further evidence of the association between environmental pollution and risk for gallbladder cancer, gallbladder stones and breast cancer. There is an urgent need to identify the carcinogens and more importantly, the industries which are polluting our rivers and drinking water sources. These findings are useful to researchers and governmental agencies for risk assessment, regulation and control of environmental contamination in the Indo-Gangetic plains and the Ganges River. We plan to extend this research to study the incidence of other cancers, hypothyroidism, congenital malformations and chronic renal failure and the association of these diseases with environmental pollution.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

REFERENCES

[1] NEW - GLOBOCAN 2020: New Cancer Data, UICC. Uicc.org. 2020 [cited 22 December 2020]. https://www.uicc.org/news/globocan-2020-new-cancer-data
[2] D'Souza NDR, Murthy NS, Aras RY. Projection of cancer incident cases for India-till 2026. Asian Pac J Cancer Prev 2013;14(7):4379-4386.
[3] IARC monographs on the identification of carcinogenic hazards to humans – International Agency for Research on Cancer. 2020 [cited 23 December 2020]. Monographs.iarc.fr. http://monographs.iarc.fr/index.php
[4] Carcinogen List - Occupational Cancer, NIOSH, CDC. Cdc.gov. 2020 [cited 22 December 2020]. http://www.cdc.gov/niosh/topics/cancer/npotocca.html#a
[5] Report on Carcinogens. Public Health Service National Toxicology Program. 12th edn. U.S. Department of Health and Human Services. 2011. http://ntp.niehs.nih.gov/ntp/roc/twelfth/roc12.pdf
[6] Richter ED, Friedman LS, Tamir Y, et al. Cancer risks in naval divers with multiple exposures to carcinogens. Environ Health Perspect 2003;111(4):609-617.
[7] Soliman AS, Wang X, Stanley JD, et al. Geographical clustering of pancreatic cancers in the Northeast Nile Delta Region of Egypt. Arch Environ Contam Toxicol 2006;51(1):142-148.
[8] Soliman MS, An-Chi Lo, Banerjee M, et al. Differences in K-ras and p53 gene mutations among pancreatic adenocarcinomas associated with regional environmental pollution. Carcinogenesis 2007;28(8):1794-1799.
[9] Shukla VK, Rastogi AN, Adukia TK, et al. Organochlorine pesticides in carcinoma of the gallbladder: a case-control study. Eur J Cancer Prev 2001;10(2):153-156.
[10] Shukla VK, Prakash A, Tripathi BD, et al. Biliary heavy metal concentrations in carcinoma of the gall bladder: case-control study. BMJ 1998;317(7168):1288-1289.
[11] Batra Y, Pal S, Dutta U, et al. Gallbladder cancer in India: a dismal picture. Journal of Gastroenterology and Hepatology 2005;20(2):309-314.
[12] Yamamoto M, Endoh K, Nakadaira H, et al. Ecological correlation studies on standardized incidence ratios of malignant neoplasms contracted from different sources of drinking water supply. Nihon Eiseigaku Zasshi 1999;54(3):526-533.
[13] Madhawi R, Pandey A, Raj S, et al. Geographical pattern of carcinoma gallbladder in Bihar and its association with river Ganges and arsenic levels: Retrospective individual consecutive patient data from regional cancer centre. South Asian J Cancer 2018;7(3):167-170.
[14] ACS (American Cancer Society). Cancer Facts & Figures 2008. Atlanta: American Cancer Society, 2008.
[15] Brody JG, Rudel RA, Michels KB, et al. Environmental pollutants, diet, physical activity, body size and breast cancer: where do we stand in research to identify opportunities for prevention? Cancer 2007;109(Suppl 12):2627-2634.
[16] Nie J, Beyea J, Bonner MR, et al. Exposure to traffic emissions throughout life and risk of breast cancer: The Western New York Exposures and Breast Cancer (WEB) Study. Cancer Causes Control 2007;18(9):947-955.
[17] Bonner MR, Han D, Nie J, et al. Breast cancer risk and exposure in early life to polycyclic aromatic hydrocarbons using total suspended particulates as a proxy measure. Cancer Epidemiology Biomarkers and Prevention 2005;14(1):53-60.

[18] Gallagher LG, Vieira VM, Ozonoff D, et al. Risk of breast cancer following exposure to tetrachloroethylene-contaminated drinking water in Cape Cod, Massachusetts: reanalysis of a case-control study using a modified exposure assessment. Environ Health 2011;10:47.

[19] Unisa S, Jagannath P, Dhir V, et al. 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):117-125.