Cholangiocarcinoma in Rhode Island: Incidence Trends and Risk Profile Over the Last Decade

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ABSTRACT

The incidence of cholangiocarcinoma, a fatal disease of bile ducts, is increasing at unsettling rates in the Northeast United States, including Rhode Island. The cause of this region-specific increase in incidence of cholangiocarcinoma is unknown. This is a review of the literature on cholangiocarcinoma in conjunction with cancer data from the 1995–2018 Rhode Island Cancer Registry. The goal of this paper is to discuss the potential etiologies of the increased incidence in cholangiocarcinoma and identify populations in Rhode Island most at risk. Rhode Island residents have specific environmental and occupational exposures, which may contribute to the increased rate of cholangiocarcinoma. The Rhode Island Hispanic population has the highest incidence of cholangiocarcinoma and is diagnosed at younger ages. In order to evaluate and address this fatal disease, further research is needed and would be best evaluated by creation of a statewide database to track potential risk factors.

KEYWORDS: Cholangiocarcinoma; Rhode Island; disparities

INTRODUCTION

Cholangiocarcinoma, a silent and aggressive cancer of the bile ducts, casts an unsettling shadow over the United States. While it is classified as a rare malignancy, with approximately 5,000 cases diagnosed annually,[1] its incidence is not only rising but accelerating – particularly for intrahepatic cholangiocarcinoma (ICC).[2] This alarming trend is especially pronounced in Rhode Island, where the rates of this disease surpass national averages, prompting urgent questions about the underlying causes and potential risk factors that may be unique to this region.[3]

In Rhode Island, the incidence of cholangiocarcinoma is not merely a statistic; it represents a growing public health concern that affects families, communities, and healthcare systems. As we delve deeper into this issue, we find a troubling narrative: the state's historical industrial activities, particularly around the Blackstone River, have left a legacy of pollution that may be silently contributing to the rising rates of this deadly disease. The river, once celebrated as a vital artery of commerce and industry, has transformed into a symbol of environmental neglect, with its waters historically tainted by the effluents of textile mills, metalworking facilities, and other industrial operations.

Research indicates that the increase in cholangiocarcinoma cases is primarily driven by ICC, which has seen a staggering rise of 350% in incidence over the past few decades. This is striking, especially when juxtaposed with a modest increase in extrahepatic cholangiocarcinoma (ECC).[4] As we examine these trends, exploring the potential environmental and occupational exposures that may be at play becomes essential. Could the pollutants that have contaminated the Blackstone River, including industrial solvents and heavy metals, be linked to the health of Rhode Islanders?

Moreover, the prognosis for cholangiocarcinoma remains grim, with median survival rates of four to eight months.[4] Many patients remain asymptomatic until the disease has progressed significantly, complicating early detection efforts. This highlights the critical need for awareness and targeted research to identify at-risk populations in Rhode Island and understand the specific factors contributing to such high incidence rates.

This review aims to unravel the complex interplay between historical environmental exposure and the rising incidence of cholangiocarcinoma in Rhode Island. By delving into the epidemiological data, examining known risk factors, and considering the implications of industrial pollution, we seek to illuminate the path forward for research and public health interventions. As we stand at this crossroads, it is imperative to ask: what can we learn from the past, and how can we leverage this knowledge to protect future generations from the devastating impacts of cholangiocarcinoma?

UNDERSTANDING CHOLANGIOCARCINOMA

Cholangiocarcinoma is a malignancy of the bile ducts, defined based on location. ICC arises within the liver, comprising less than 10% of cholangiocarcinoma diagnoses. ECC includes cancers of the hilum, which make up 50% of cholangiocarcinoma cases, and the distal common bile duct, which makes up 40% of all cholangiocarcinoma cases. ICC and ECC are most often adenocarcinomas. Surgical resection and adjuvant chemotherapy are the preferred treatment combination for resectable tumors.[5] Cholangiocarcinoma is a fatal disease with unresectable tumors having a median

survival of less than one year. The mortality rate for cholangiocarcinoma has increased by 39%.[5] This increased mortality is related to the increased incidence of ICC.[5] ICC in the United States has increased over threefold while ECC rates have increased to a lesser extent.[3]

The incidence of cholangiocarcinoma varies based on ethnicity, gender, and region. ICC has the highest incidence in the Northeast, while ECC has the highest rates in the Northeast and Pacific regions.[6] When looking specifically at Rhode Island, the incidence of cholangiocarcinoma has more than doubled in a decade. In 1995–1999, the age-adjusted rate per 100,000 individuals was 1.10, while from 2015–2019 it was 2.18.[3] Since 1992, Rhode Island's overall cancer age-adjusted incidence has increased while the nation's cancer age-adjusted incidence has declined.[7] The questions we aim to discuss are what drives this unsettling increase in cholangiocarcinoma, and is there anything unique to the Rhode Island population contributing to this increase?

RHODE ISLAND ENVIRONMENT

The Blackstone River Valley, running from the Massachusetts border through Woonsocket, Central Falls, and Pawtucket, Rhode Island, has a long history of water pollution.[7] The river was once known as the "world's busiest river" during the 19th and 20th centuries. During this time, there was a rapid expansion of textile mills and wire, rubber, and metal factories.[8,9] Slater's Mill in Pawtucket, RI, was the nation's first textile mill, which processed cotton and dyed it.[10] Multiple dams provided hydropower for the operation of textile mills and factories.[11]

The 19th and 20th centuries were a time of rapid expansion of mills and factories employing many Rhode Islanders at the expense of the surrounding environment. Many hazardous materials in textile manufacturing involve industrial solvents that are required for printing on the textiles, weaving them, and cleaning the machinery. These chemicals, including trichloroethylene, benzene, and ethylene dichloride, were discharged directly into the Blackstone River.[12] Workers were also at risk of exposure to these chemicals as part of their occupation. Metalworking facilities produced heavy metal waste, polluting the soil and water. As industrial activity grew, human settlements proliferated along the river in the 19th century, and untreated wastewater was discharged into the river.[11]

The rapid pace of industrialization and rapid population growth through the 20th century allowed the contamination in the river from the disposal of sewage, wastewater, heavy metals, and chemical waste to reach unprecedented levels.[13] The Clean Water Act of 1972 provided water contamination standards that had to be met by 1987; however, achieving these goals in the Blackstone River has been difficult given the size and scope of the contamination. The multiple dams in the river cause contaminants to accumulate in sediment for many years.[14] By 1990, the Blackstone River had the dubious distinction of being named "America's most polluted river" by the EPA.[13]

RHODE ISLAND AND CHOLANGIOCARCINOMA

A history of occupational exposure to industrial chemicals and environmental exposure to contaminated water renders residents of Rhode Island at risk. Environmental exposure directly from polluted waters can occur with immersion or ingestion. Although there is no current evidence that drinking water quality standards are significantly breached in any significant capacity in the state, the history of pollution and occupational exposures is a risk specific to Rhode Islanders. Other studies have similarly evaluated water pollution and occupational exposure to the increasing incidence of cancers in Rhode Island. This has been thought to contribute to Rhode Island having the highest incidence of bladder cancer in the nation.[15]

Although environmental and occupational risks unique to Rhode Island may contribute to increasing the incidence of cholangiocarcinoma, there are other potential contributors to the high incidence. Males have a higher incidence of cholangiocarcinoma than females in Rhode Island, with an increase of 5.1% each year on average versus a 3.6% increase each year on average for females [**Figure 1**]. Males are more likely to be diagnosed at a younger age [**Figure 2**]. Other studies have shown that men have a higher incidence

Figure 1. Trend of Cholangiocarcinoma incidence rate from 1995 to 2018

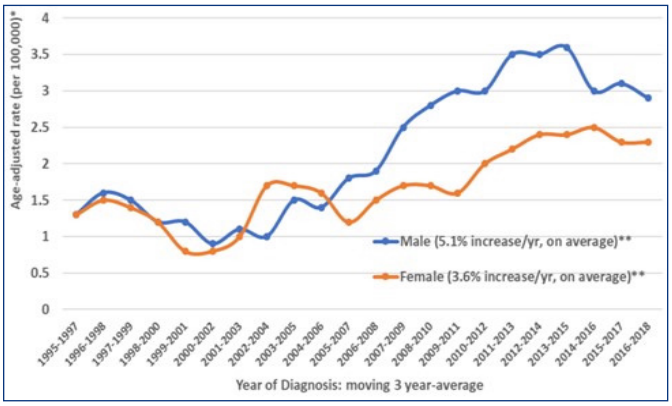


Figure 2. Age at diagnosis of Cholangiocarcinoma by sex from 1995 to 2018

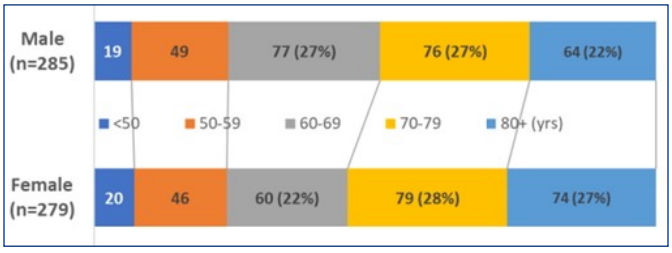


Figure 3. Incidence (rate) by sex and race/ethnicity from 1995 to 2018

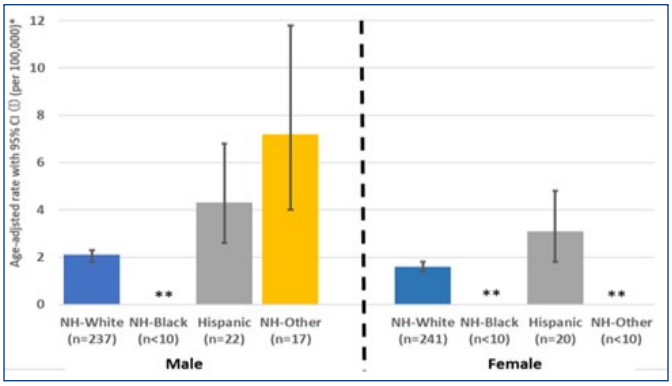
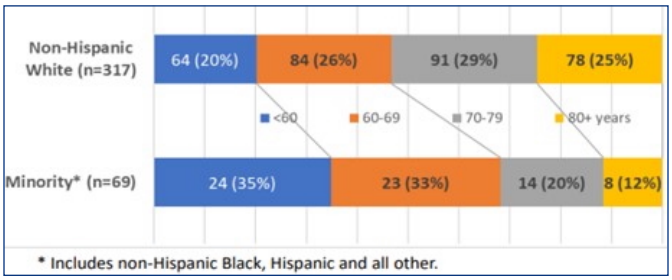


Figure 4. Age at cholangiocarcinoma diagnosis by race/ethnicity from 2007 to 2018



than women, with ratios of 1:1.2–1.5, which is in line with our data.[16,17]

In Rhode Island, age-adjusted cancer incidence rates in Hispanic people are more than double the cancer incidence rates in the non-Hispanic White population for both males and females from 1995 to 2018 [**Figure 3**]. Not only are overall cancer incidence rates higher in the Hispanic population, but incidence rates of hepatobiliary cancers, including cholangiocarcinoma, are also increasing more dramatically in the Hispanic and other minority populations in more recent years. Minority populations are also more likely to be diagnosed at younger ages [**Figure 4**]. The young age at diagnosis and the increasing incidence in the Hispanic population suggest a genetic predisposition to the diagnosis of cholangiocarcinoma.

Though genetic predisposition may contribute, the cause of increased incidence in hepatobiliary cancers in minority populations in Rhode Island is likely a multifactorial issue. Hepatitis C, HIV infection, smoking, alcohol use, and diabetes increase the risk of ICC within the United States.[1] ECC and ICC may have differing risk factors, but additional studies are needed to elucidate this further. Primary sclerosing cholangitis, choledochal cysts, and parasitic infections with the hepatobiliary flukes *Opisthorchis viverrini* and *Chlonorchis sinensis* are also associated with the diagnosis of cholangiocarcinoma. Thorotrast, a contrast agent used in the mid-1950s, is a known toxin associated with a 300-fold increase in cholangiocarcinoma.[17] To our knowledge, there is no data to determine whether these risk factors are more prevalent in the Rhode Island population than in the nation.

Social determinants of health provide another layer of complexity to the increased incidence of cholangiocarcinoma in minority populations in Rhode Island. Previous studies have demonstrated that minorities have lower education and income levels, and a lack of private insurance, which may delay their diagnosis. With delayed diagnosis, minority populations have been shown to have greater nodal involvement and higher tumor stage and are more likely to be diagnosed with metastatic disease.[18] This may be a trend seen with cholangiocarcinoma in Rhode Island minority populations as well. A study on hilar cholangiocarcinoma and treatment delay showed no impact on resectability, tumor stage, or survival, which lacks relevance to our population as this was a Danish study that did not evaluate socioeconomic determinants of health.[19-21]

More research is needed to assess the relationship between environmental pollution, occupational exposure, and genetic predisposition leading to increased cholangiocarcinomas in Rhode Island. Future studies focusing on Rhode Island residents and their proximity to the Blackstone River and occupational history are needed. This would allow us to determine if cholangiocarcinoma is higher in those with the most exposure to potential pollutants in the Blackstone River or specific occupations. Biomonitoring studies may also provide some information on past exposure to toxins and the risk of developing cholangiocarcinoma when exposed. A Rhode Island statewide database to track the incidence of cholangiocarcinoma, potential risk factors, and disparities is the next step to improve the state's outcomes in cholangiocarcinoma. The dataset would allow us to identify risk factors for the Rhode Island population and allow for directed mitigation efforts.

CONCLUSION

Cholangiocarcinoma is a highly fatal disease that uniquely impacts the Rhode Island population. This disease remains uncontrolled and unimproved in Rhode Island and nationwide due to poor comprehension of the relationship between environmental and occupational exposures, lifestyle factors, and genetic predisposition. Minorities in Rhode Island are being diagnosed at increasing rates, and national mortality rates are skyrocketing. It is time to methodically examine this disease process with continued research and efforts to improve public awareness. Policy changes are integral to mitigate environmental and occupational risks and improve access to healthcare for populations most at risk.

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Disclosures

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