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REVIEW

Obesity and cholangiocarcinoma

Mansour A Parsi

Mansour A Parsi, Center for Endoscopy and Pancreatobiliary Disorders, Digestive Disease Institute, Cleveland Clinic, Cleveland, OH 44195, United States
Author contributions: Parsi MA is the sole contributor to this manuscript.
Correspondence to: Mansour A Parsi, MD, MPH, Center for Endoscopy and Pancreatobiliary Disorders, Digestive Disease Institute, Cleveland Clinic, Cleveland, OH 44195, United States. parsim@ccf.org
Telephone: +1-216-4454880 Fax: +1-216-4446284
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Abstract

It is estimated that about half of the population in developed countries are either overweight or obese. In some developing nations obesity rates have increased to surpass those seen in Western countries. This rate increase in obesity has many implications as obesity has been associated with numerous negative health effects including increased risks of hypertension, diabetes, cardiovascular disease, stroke, liver disease, apnea, and some cancer types. Obesity is now considered to be one of the major public health concerns facing the society. Cholangiocarcinomas (bile duct cancers) are malignant tumors arising from cholangiocytes inside or outside of the liver. Although cholangiocarcinomas are relatively rare, they are highly lethal. The low survival rate associated with cholangiocarcinoma is due to the advanced stage of the disease at the time of diagnosis. Prevention is therefore especially important in this cancer type. Some data suggest that the incidence of cholangiocarcinoma in the western world is on the rise. Increasing rate of obesity may be one of the factors responsible for this increase. Determining whether obesity is a risk factor for cholangiocarcinoma has significant clinical and societal implications as obesity is both prevalent and modifiable. This paper seeks to provide a summary of the current knowledge linking obesity and cholangiocarcinoma, and encourage further research on this topic.

Key words: Cholangiocarcinoma; Obesity; Epidemiology; Bile ducts; Cancer

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INTRODUCTION

Obesity is increasing worldwide and affects a large portion of the population in developed[1-5] and some developing nations[6-13]. In many countries obesity and its comorbidities have become a major public health concern[1,14-16]. Recently, obesity-associated cancer has attracted great attention. Epidemiological studies have provided strong evidence that obesity can increase the incidence of many cancer types[17] including colon[18,19], breast[20,21], liver[22], endometrium[23,24], kidney[25], esophagus[26], stomach[27] and pancreas[28].

Cholangiocarcinomas (bile duct cancers) are malignant tumors arising from cholangiocytes inside or outside of the liver. Traditionally cancers arising from the cholangiocytes inside the liver were grouped together with hepatic cancers and classified as primary liver tumors, while those arising from the cholangiocytes outside the liver were grouped together with cancers of the gallbladder and the ampulla of Vater and classified as biliary cancers[29]. More recently, the term cholangiocarcinoma has been used to refer to cancers arising from cholangiocytes irrespective of their location[29].

Intrahepatic cholangiocarcinomas originate from cholangiocytes lining the small intrahepatic ductules while extrahepatic cholangiocarcinomas arise from cholangiocytes lining the larger bile ducts (right and left hepatic ducts, common hepatic duct, and common bile duct)[30]. The distinction between intrahepatic and extrahepatic cholangiocarcinomas is important, as the incidence and risk factors associated with each may be different[31-33].

In Western countries established risk factors for cholangiocarcinoma are age, sex, primary sclerosing cholangitis, and bile duct cysts. Less-established potential risk factors include cirrhosis, diabetes, obesity, alcohol, and smoking. Some data suggest that the incidence of cholangiocarcinoma in the Western world is on the rise. Increasing rate of obesity may be one of the factors responsible for this increase.

Although cholangiocarcinomas are rare in Western countries, they are highly lethal[34]. Annual mortality associated with cholangiocarcinoma is virtually identical to its incidence throughout the world, underscoring the high case fatality rate of this cancer type[35]. The low survival rate associated with cholangiocarcinoma is due to the advanced stage of the disease at the time of diagnosis[36]. Prevention is therefore especially important in this cancer type. Determining whether obesity is a risk factor for cholangiocarcinoma has significant clinical and societal implications as obesity is both prevalent and modifiable.

EPIDEMIOLOGY

Obesity prevalence

Obesity is considered to be among the most alarming health concerns in the United States. It has been estimated that each year, more than 300 000 Americans die from illnesses related to overweight and obesity[37]. The Centers for Disease Control and Prevention (CDC) defines obesity based on the body mass index (BMI). BMI is the ratio of weight in kilograms (kg) to height in meters squared (m^2). Per CDC criteria, a BMI of 18.5-25 kg/m^2 is normal, 25-30 kg/m^2 is overweight and $\geqslant$ 30 kg/m^2 is obese[38]. The most recent statistics from the National Health and Nutrition Examination Surveys using BMI as a measure of overweight and obesity indicate that 35.7% of adults 20 years or older were obese in 2009-2010[39]. Compared with the statistics for 1976-1980 this reflects a 2-fold increase in the prevalence of adult obesity[40,41]. This rate increase in obesity has many implications as obesity has been associated with numerous negative health effects including increased risks of hypertension, diabetes, cardiovascular disease, stroke, liver disease, apnea, and some cancer types possibly also cholangiocarcinoma. Therefore, as a potentially modifiable risk factor, a reduction in the prevalence of obesity among adults could have a substantial impact on morbidity, mortality, and incidence of various cancers.

Cholangiocarcinoma incidence

The available epidemiologic data on incidence and prevalence of cholangiocarcinoma are difficult to interpret because of differing classifications and diagnostic criteria across studies[29,32,42]. For instance, some studies group intrahepatic cholangiocarcinomas with liver cancers while others group extrahepatic cholangiocarcinomas with gallbladder cancers and cancers of the ampulla of Vater. Furthermore, some studies misclassify types of cholangiocarcinomas. For example, Klatskin tumors (a type of extrahepatic cholangiocarcinoma), at times, have been misclassified as intrahepatic cholangiocarcinoma[29,30]. Finally, some studies use histology as the only diagnostic criterion while others accept other forms of diagnosis such as clinical evaluation or imaging studies.

Despite these shortcomings, the available data suggest a highly variable incidence in different parts of the world, with the highest incidence in Southeast Asia and lowest in Australia[43,44]. The incidence of cholangiocarcinoma has been reported to be as high as 96 cases per 100 000 in men and 38 per 100 000 in women in northeast Thailand[43]. In Australia, the reported incidence is 0.2 per 100 000 among Australian men and 0.1 per 100 000 among Australian women[43]. In other Western countries including the Unites States the incidence is close to 1 case per 100 000 population[43]. In Western countries, approximately 80% of cholangiocarcinomas are extrahepatic[45]. Differing exposure to risk factors is thought to account for the varying geographic incidences, with parasitic infections and hepatolithiasis being more prevalent in Asia[46-48].

Recent data show that the incidence of intrahepatic cholangiocarcinoma is increasing around the world, while the incidence of extrahepatic cholangiocarcinoma has been largely stable or even decreasing[32,43,49]. Although the exact underlying mechanism for this discrepancy is not known, it suggests that intrahepatic and extrahepatic cholangiocarcinomas may be biologically different[32,49,50].

Finally, there is evidence suggesting under-diagnosis of cholangiocarcinoma. For example among patients transplanted for liver cirrhosis of various etiologies, an incidental cholangiocarcinoma was found in approximately 12% of explanted livers[51]. This suggests that the true incidence of cholangiocarcinoma may be higher than previously reported.

Obesity as a risk factor for cholangiocarcinoma

Data assessing the association of obesity and cholangiocarcinoma are limited. So far, four epidemiologic studies have tried to assess the link between obesity and cholangiocarcinoma (Table 1). Three of these studies were specifically designed to identify risk factors for cholangiocarcinoma[52-54].

One of those studies using the Surveillance, Epidemiology, and End Results database that links cancer registry data and Medicare enrollment and claims files, reported a significant association between obesity and intrahepatic cholangiocarcinoma, but not between obesity and extrahepatic cholangiocarcinoma[52]. That study however, has several limitations. The study only included patients 65 years of age and older, therefore the findings might not be generalizable to a younger population. Furthermore, because Medicare data are collected for billing rather than research purposes, completeness and accuracy of the Medicare data on prevalence of obesity and cholangiocarcinoma can be questioned. Finally, the possibility of diagnostic bias cannot be excluded because obese people with different medical conditions are more likely to undergo testing and thus have more diagnoses than other people.

Another population-based study conducted in Denmark did not find any significant association between

Table 1 Epidemiologic studies assessing obesity as a potential risk factor for cholangiocarcinoma

Ref.	Study design	Type of CC	Study findings	Study limitations
Welzel *et al*[52]	Case-control	ICC and ECC	Positive association between obesity and ICC; no association between obesity and ECC	Only included age ⩾ 65 yr; database limitations; possible diagnostic bias
Welzel *et al*[53]	Case-control	ICC	No association between obesity and ICC	ECC not included
Grange *et al*[54]	Case-control	NS	Positive association between obesity and cholangiocarcinoma	Type of CC not specified; diagnosis subject to misclassification
Oh *et al*[55]	Cohort	NS	Positive association between obesity and cholangiocarcinoma	Does not distinguish ECC and ICC; included only males; database limitations

CC: Cholangiocarcinoma; ECC: Extrahepatic cholangiocarcinoma; ICC: Intrahepatic cholangiocarcinoma; NS: Not stated.

obesity and intrahepatic cholangiocarcinoma[53]. That study used a fairly accurate and complete national registry. Another strength of that study was histological confirmation of cholangiocarcinoma diagnosis in all cases. Extrahepatic cholangiocarcinoma, however, was not studied.

The third study, conducted in the United Kingdom by Grainge *et al*[54], found that obese patients (BMI ⩾ 30 kg/m^2) had 1.5 times the risk of cholangiocarcinoma compared with those with BMI < 25 kg/m^2. In that study the type of cholangiocarcinoma (intrahepatic versus extrahepatic) was not specified. Another limitation of that study was that the diagnosis was not based on histology and therefore subject to misclassification.

Aside from studies looking specifically to identify risk factors for cholangiocarcinoma, a South Korean population-based study tried to assess the effect of excess weight on incidence of various cancers including cholangiocarcinoma[55]. The study found that compared to the reference group (BMI 18.5-23 kg/m^2), increasing BMI was associated with an increase in the relative risk for development of cholangiocarcinoma[55]. That study, however, did not distinguish between intrahepatic and extrahepatic cholangiocarcinomas, included only males, and the database used was not inclusive of the entire population.

In summary, the epidemiologic data available on obesity as a risk factor for cholangiocarcinoma show conflicting results and are too limited to make any conclusions.

BIOLOGIC MECHANISMS FOR POSITIVE ASSOCIATION BETWEEN OBESITY AND CHOLANGIOCARCINOMA

Obesity is an excess of adipose tissue. Adipose tissue is a biologically active organ which in addition to adipocytes contains multiple other cell types such as pre-adipocytes, endothelial cells, macrophages and other immune cells[56]. Adipose tissue secretes molecules into the bloodstream, which signal to other metabolic organs or to the brain to coordinate responses to altered metabolic demands[57]. Some of these molecules, known as adipokines, have a role in modulating the risk of cancer development. Among adipokines, some of the most studied are leptin, adiponectin and pro-inflammatory molecules.

Leptin is a hormone that is primarily secreted by the adipose tissue[58]. It acts on the hypothalamus to regulate food consumption and caloric homeostasis[58,59]. Although the major physiological site of leptin action is in the central nervous system, leptin receptors are also expressed at lower levels in peripheral tissues[60]. Two studies have shown presence of leptin receptors on cholangiocytes[61,62]. Circulating serum leptin is increased in obesity, and has been suggested as a risk factor for cholangiocarcinoma[62]. A recent study showed that normal and malignant intrahepatic cholangiocytes express leptin and leptin receptors[62]. The investigators of that study also showed that leptin stimulates growth and migration, and prevents apoptosis of intrahepatic cholangiocarcinoma cells *in vitro*[62]. They also showed that genetic ablation of leptin-mediated signaling inhibits cancer development and growth in an animal model of cholangiocarcinoma[62].

Adiponectin is another adipokine that may be involved in cancer development[63]. It acts on a number of tissues to regulate glucose and lipid metabolism. Adiponectin levels are reduced in obesity. Several basic and epidemiological studies have suggested that adiponectin has antitumor effects[63,64]. Although the link between adiponectin and cholangiocarcinoma has not been studied, there is convincing evidence for an inverse association between adiponectin levels and cancer risk for several cancer types[59,63,65-67].

Several pro-inflammatory cytokines are secreted by monocytes and other immune cells that infiltrate adipose tissues in obesity[68,69]. Among these cytokines, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) have been found to have a role in development of cholangiocarcinoma[70]. A growing body of evidence suggests that the inflammatory environment in the obese state is linked to the development of cancer through various mechanisms[71]. IL-6 seems to have an important role in the pathogenesis and growth of cholangiocarcinoma and has been shown to act by both an autocrine and paracrine manner stimulating several intracellular pathways involved in survival and growth of malignant cholangiocytes[36,72-74]. TNF-α is a mediator of inflammation with actions directed towards both tissue destruction and recovery[70]. Evidence suggests that TNF-α may act as an endogenous tumor promoter in addition to its role in immune responses[75,76]. Overexpression of TNF-α receptor genes has been observed in cholangiocarcinoma associated with hepatolithiasis[75-78].

Although not specifically linked to cholangiocarcino-

ma, there are multiple other substances that have directly or indirectly been linked to cancer in general[57]. Research on the role of different substances on development and progression of different cancers including cholangiocarcinoma is evolving.

DISCUSSION

It is estimated that about half of the population in developed countries are either overweight or obese[79]. In some regions of the world overweight and obesity affects more than two-thirds of the population[80]. By 2008, an estimated 1.5 billion adults globally were overweight and 500 million adults were obese[81]. Because of such high prevalence, establishing a clear link between excess body weight and cholangiocarcinoma can have significant effect on prevention of cholangiocarcinoma. Establishing a link may also encourage further research on identification of underlying pathophysiologic mechanisms that can potentially lead to discovery of better treatment options.

Research on obesity and cholangiocarcinoma risk should be encouraged through a variety of activities, including large cooperative initiatives, database resources, epidemiologic studies, basic science studies, and increase in funding resources.

If a link between excess weight and cholangiocarcinoma is established, multiple new questions will emerge that will need to be answered. Does reversal of obesity affect the risk for cholangiocarcinoma? Are there any differences between different modes of weight reduction (calorie restriction, exercise, drugs, bariatric surgery) in terms of cholangiocarcinoma risk reduction? Can the link between obesity and cholangiocarcinoma be somehow disrupted in the absence of weight loss (which for many individuals is a difficult task)?

Answers to these and other questions that will surely follow require well-designed studies that incorporate molecular, genetic, metabolic and nutritional factors.

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