Screening strategy for gastrointestinal and hepatopancreatobiliary cancers in cystic fibrosis

Brett Hoskins, Paul Wasuwanich, Ann O Scheimann, Wikrom Karnsakul

Brett Hoskins, Ann O Scheimann, Wikrom Karnsakul, Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, MD 21287, United States

Paul Wasuwanich, Department of Medicine, University of Florida College of Medicine, Gainesville, FL 32610, United States

Corresponding author: Wikrom Karnsakul, MD, Associate Professor, Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, The Johns Hopkins University School of Medicine, 600 North Wolfe Street, Baltimore, MD 21287, United States. wkarnsa1@jhmi.edu

Abstract

Based on systematic review and meta-analysis, the risk for developing cancers in patients with cystic fibrosis (CF) is known to be significantly greater than in the general population, including site-specific cancers of the esophagus, small bowel, colon, liver, biliary tract, and pancreas. An even higher risk has been found in patients who have severe CF transmembrane conductance regulator (*CFTR*) genotypes or who have undergone organ transplantation and are immunosuppressed. The risk continues to rise as life expectancies steadily climb due to advancements in medical care and treatment for CF. The colorectal cancer risk is at such a high level that CF has now been declared a hereditary colon cancer syndrome by the Cystic Fibrosis Foundation. The *CFTR* gene has been strongly-associated with the development of gastrointestinal (GI) cancers and mortality in the CF population. Even CF carriers have shown an increased rate of GI cancers compared to the general population. Several limitations exist with the reported guidelines for screening of GI and hepatopancreatobiliary cancers in the CF population, which are largely universal and are still emerging. There is a need for more precise screening based on specific risk factors, including *CFTR* mutation, medical co-morbidities (such as gastroesophageal reflux disease, distal intestinal obstruction syndrome, and diabetes mellitus), familial risks for each cancer, gender, age, and other factors. In this review, we propose changes to the guidelines for GI screening of patients with CF. With the development of *CFTR* modulators, additional studies are necessary to elucidate if there is an effect on cancer risk.

Key Words: Colorectal cancer; *CFTR* gene; Cystic fibrosis; Gastrointestinal cancer; Hepatopancreatobiliary cancer; Screening

Core Tip: Patients with cystic fibrosis are at a significantly elevated risk for gastrointestinal tract and hepatopancreatobiliary cancers when compared to the general population, especially in those with severe cystic fibrosis transmembrane conductance regulator (*CFTR*) mutations or who have undergone organ transplantation. As life expectancies continue to increase with *CFTR* modulators and improved care, cancer screening will become increasingly important. Screening recommendations are largely universal and still emerging. Given the financial burden of universal screening, there is a need for more precise screening based on specific risk factors. In this review, we propose changes to the guidelines for gastrointestinal screening of patients with cystic fibrosis.

INTRODUCTION

As medical care and treatment for patients with cystic fibrosis (CF) continually improve over the decades, the life expectancies for these patients have steadily increased as well. Respiratory/cardiorespiratory failure remains the leading cause of mortality in this population; however, that percentage is shrinking, decreasing from 68.1% in 2013 to 62.9% in 2019 in the United States[1,2]. This corresponds with the median age of death increasing from 27.5 years to 32.4 years in the same period[1,2]. The median predicted survival age of a newborn born in 2019 was 48.4 years (95%CI, confidence interval: 45.9-51.5)[2]. With the approval of the drug Trikafta®, a cystic fibrosis transmembrane conductance regulator (*CFTR*) gene modulator, in 2019 by the United States Food and Drug Administration, life expectancies are predicted to increase further in the CF population. However, because of the improvements in survival, cancer and other slowly progressing diseases are emerging as causes of mortality in this population.

In the CF population, the risk of developing cancer is known to be greater than in the general population, and the average age of cancer diagnosis is lower[3,4]. Of those cancers, gastrointestinal (GI) cancers are typically the most common malignancies faced by individuals with CF[3,5]. As such, physicians have increasingly considered screening their CF patients for these cancers in the hopes of improving the prognosis of these patients. In 2018, recommendations on colorectal cancer screening were published in *Gastroenterology*[6]. However, these recommendations were relatively arbitrary and recommendations on other GI cancers, such as pancreatic cancer, are lacking. In this review, we discuss the epidemiology, options for screening, the benefits and risks of screening, as well as future directions of screening for the GI cancers.

EPIDEMIOLOGY

Globally, over 72000 individuals are estimated to be currently living with CF[7]. Overall, the incidence of cancer in the CF population is low; however, the risk of GI cancers in particular are increased[3]. Of the GI cancers, colon cancer has the greatest incidence rate of 39 per 100000 CF individuals per year; however, small bowel cancer had the greatest increase in risk compared to the general population with a standardized incidence rate of 18.94 (95%CI: 9.37-38.27)[5]. In descending order, incidence rates per 100000 CF individuals per year are 39 for colon cancer, 13 for small bowel cancer, 5.1 for biliary tract cancer, and 1-5.8 for pancreatic cancer[5,8]. Data on the incidence rates of rectal, gastric, and esophageal cancers are lacking. The standardized incidence ratios are 18.94 (95%CI: 9.37-38.27) for small bowel cancer,

17.87 (95%CI: 8.55-37.36) for biliary tract cancer, 10.91 (95%CI: 8.42-14.11) for colon cancer, 6.18 (95%CI: 1.31-29.27) for pancreatic cancer, 4.5 (95%CI: 1.2-12.3) for gastric cancer, 2.8 (95%CI: 0.1-13.8) for esophageal cancer, and 0.5 (95%CI: 0.0-2.6) for rectal cancer[3,5]. The insignificant difference in esophageal cancer and rectal cancer risk in the CF population is potentially due to the low number of cases reported, only one each in Maisonneuve *et al*[3]. Pancreatic cancer is uncommon in the general population as well as in the CF population. By 2018, only 12 cases of pancreatic cancer in individuals with CF have been published in the literature[8]. The incidence rates and risks of GI cancers in CF are summarized in Table 1.

The overall frequency of cancer typically increases with age in the general population, and this remains true in the CF population. However, in a study by Maisonneuve *et al*[3], the difference in cancer risk of the colon and small bowel between the CF and general population appears to decrease with age from standardized incidence ratio of 23.3 in the 0-19 age group to 5.6 in the 50+ age group. Still, cancer risk in the CF population remains greater than in the general population in every age group and every other demographic[3]. There is increased risk of developing cancer of the colon and small bowel in males compared to females. Additionally, individuals with severe CF genotypes (*i.e.*, one or more class I, class II, or class III mutation in the *CFTR* gene) are at increased risk of developing colon and small bowel cancer as well[3]. In CF patients who receive solid organ transplant, predominately lung in studies, the risk of cancer in general is increased, particularly GI cancers[3,9].

NATURAL HISTORY

The natural history of cancer in individuals with CF is unique to each type of cancer, but there are many similarities. Exposure begins at conception with either the inheritance or spontaneous formation of defective *CFTR* genes. Individuals with either homozygous or even heterozygous defective *CFTR* genes are at increased risk of cancer[10]. While the most severe complications of CF occur in the lungs, *CFTR* is expressed in a variety of extra-pulmonary regions including the GI tract and the accessory organs of digestion[11-3]. *CFTR* controls the movement of chloride ions, and thus, the movement of water. In the lungs, defects in *CFTR* result in increased viscosity of mucosal secretions, leading to the classic lung-related complications of CF. In the GI tract, a similar mechanism results in increased viscosity of the luminal secretions, causing mucosal obstruction and inflammation of the epithelium due to bacterial contact[14,15]. The resulting chronic inflammation leads to damage of epithelial cells and bacterial dysbiosis which further increases inflammation, causing cell turnover to increase which in turn increases the risk of cancer cell formation[16]. This chronic inflammation has been confirmed in both humans and mice models[17,18]. Chronic increased GI epithelial cell turnover has been reported in individuals with CF, beginning in infancy and early childhood, potentially explaining the relatively early occurrence of cancer in the CF population[19,20].

RATIONALE FOR SCREENING OF GI AND HEPATOPANCREATOBILIARY CANCERS

GI tract

Colorectal cancer (CRC) is a major site of malignancy in the GI tract and is associated with significant morbidity and mortality. An estimated 1.8 million new cases of CRC occur worldwide each year with about 900000 associated deaths[21]. The annual incidence of CRC in the United Stated was predicted to be nearly 150000 cases with more than 50000 deaths in 2020[22]. When compared to the general population, adults with CF have a 5-10 times greater risk for CRC, which further rises to a 25-30 times greater risk after solid organ transplantation[6]. Endoscopic studies have revealed that up to 50% of patients with CF will develop adenomas by age forty with 25% developing advanced and aggressive adenomas[23]. Early detection and removal of adenomatous polyps is known to reduce mortality from CRC, making surveillance of dire importance. While a broad consensus exists for colonoscopy screening of the general population based on risk factors, specific recommendations for patients with CF are not as robust and are still emerging[24].

Table 1 Epidemiology of gastrointestinal cancers in the cystic fibrosis population

Type of cancer	Incidence rate (per 100000 CF per year)	Odds ratio (95%CI)	Standardized incidence ratio (95%CI)	Ref.
Colorectal				
Colon	39	-	10.91 (8.42-14.11)	Yamada *et al*[5]
Rectum	-	-	0.5 (0.0-2.6)	Maisonneuve *et al*[3]
Pancreatic	1-5.8	31.5 (4.8-205)	6.18 (1.31-29.27)	Neglia *et al*[4], Yamada *et al*[5], Maisonneuve *et al*[8]
Liver				
Biliary tract	5.1	-	17.87 (8.55-37.36)	Yamada *et al*[5]
Stomach	-	-	4.5 (1.2-12.3)	Maisonneuve *et al*[3]
Esophagus	-	14.3 (1.4-148)	2.8 (0.1-13.8)	Maisonneuve *et al*[3], Neglia *et al*[4]
Small bowel	13	-	18.94 (9.37-38.27)	Yamada *et al*[5]

Odds ratio and standardized incidence ratio are comparing cancers in cystic fibrosis versus cancers in the general population. CF: Cystic fibrosis; CI: C interval.

Genetic susceptibility and inheritance are known to play a role in the development of CRC with at least one third to one half of cases involving some form of familial susceptibility. Many well-known CRC hereditary syndromes exist, such as familial adenomatous polyposis and Lynch syndrome, which are associated with CRC in up to 5%-10% of cases[15,25,26]. Importantly, the full extent of the genes involved in CRC and the precise mechanisms of action are not yet fully understood. An association between CF and a familial CRC syndrome was recently found, in which high susceptibility to early and aggressive CRC was discovered in patients with homozygous inactivating mutations in the *CFTR* gene[24]. Findings like these led to CF being considered a CRC hereditary syndrome by the Cystic Fibrosis Foundation[6].

CFTR's relation to GI cancer development is likely due to the key role throughout the entirety of the GI tract, where disruption of *CFTR* leads to alterations in the composition of gut microbiota, maintenance of the barriers that protect the epithelium, and homeostasis of both the adaptive and innate immune responses[15]. Studies have also identified *CFTR* as a tumor suppressor gene in the GI tract with deficiency of *CFTR* resulting in intestinal tumors in > 60% of mice after 1 year[18]. Additionally, *CFTR* silencing has been shown to promote growth of tumors and invasion of cancer cells in mice[27]. In another study, stem cell proliferation was seen in *CFTR* knockout mice[28]. In humans with CRC, loss of *CFTR* expression has been associated with poor disease-free survival rates[18].

While the colorectal region is the most common site for GI tract malignancy with CF, all areas of the GI tract may be affected. Gastroesophageal junction and esophageal adenocarcinoma (EAC) are more prevalent among patients with CF. The exact mechanisms are not fully understood, though gastroesophageal reflux disease (GERD) is quite common with CF and is known to be the strongest modifiable risk factor for EAC. In fact, GERD is reported in up to 80% of CF patients, who are noted to have a greater degree of proximal esophageal reflux[29]. Furthermore, patients with CF have higher rates of delayed gastric emptying (up to 33%) and increased duodenogastroesophageal reflux, which may contribute to more severe GERD[30]. Prolonged exposure of the esophageal mucosa to both stomach acid and bile acid may result in a premalignant lesion to EAC, known as Barrett's esophagus (BE)[29,31,32]. Multiple studies have shown an increased risk for BE with CF[33], especially after liver transplantation[29,34]. One study demonstrated a 3-fold increased risk for BE and related neoplasia in adults with CF, which developed at earlier ages than the general population[29]. Development of BE has additionally been seen in children with CF [33]. The *CFTR* gene itself has been strongly linked with BE and EAC in several studies [27,29,35], including a meta-analysis of all genome-wide association studies of BE and EAC[36]. This meta-analysis identified a significantly associated risk variant in the *CFTR* gene with data suggesting a pathophysiological connection between CF, GERD, BE, and EAC[36]. At this time, recommendations for BE and EAC screening in the CF population are lacking.

Hepatopancreatobiliary system

The relation of *CFTR* and development of other GI cancers, including the hepatopancreatobiliary system, has been elucidated as well. CF liver disease (CFLD) has a prevalence around 23% with a range from 2%-62%, increasing linearly with age from 3.7% at age 5 to 32.2% at age 30[37,38]. A significant proportion of CF patients develop cirrhosis by the second decade of life, meaning that by the time a patient has reached their third or fourth decade of life, they could have developed cirrhosis for 20-30 years. CFLD has become an increasingly important finding as patients with CF are living longer due to excellent pulmonary care, antimicrobial regimens, improved nutrition, and the clinical use of *CFTR* modulators[37,38]. The pathogenesis of CFLD involves expression of abnormal *CFTR* on the biliary epithelium, leading to thicker and less alkaline bile that accumulates in the biliary system. This further leads to fibrosis and subsequent cirrhosis, occurring over a period of years. Longstanding cirrhosis is a risk factor for development of hepatocellular carcinoma (HCC)[39,40] one of the most common malignancies worldwide with an incidence of up to 600000 yearly cases[41]. Chronic hepatitis B and C infections account for up to 80% of HCC cases[39]. Statistically, HCC in CFLD is a relatively uncommon finding, but has been described in some case reports with a poor prognosis[39,40,42,43].

Early detection and diagnosis of HCC is primarily completed with use of imaging. Ultrasonography remains the first-line screening tool for HCC with recommendations for bi-annual liver ultrasounds from both the European Association for the Study of the Liver and the American Association for the Study of Liver Disease. Ultrasound is cost-effective and easy to perform; however, studies have revealed around 60% sensitivity, 90% specificity, and a positive predictive value of 70%[40,44]. Bi-annual monitoring of serum alpha-fetoprotein (AFP) levels have also been suggested in patients with CF[39,40], though official statements do not exist regarding this recommendation. Serum AFP is a widely used biomarker for prognostication of HCC and has even been shown to be a strong predictor of mortality in patients with cirrhosis and HCC. In patients with cirrhosis, systematic reviews have demonstrated sensitivities and specificities ranging from 41%-66% and 80%-94%, respectively. This indicates that the monitoring with serum AFP alone may not be sufficient for HCC screening; however, it is likely beneficial when combined with ultrasonography[45].

Pancreatic cancer is considered one of the most lethal and difficult to treat malignancies with a poor prognosis[46]. While the risk of pancreatic cancer remains low, this risk is increased 6-fold in patients with CF compared to the general population. Still, only 12 cases of pancreatic cancer in CF patients have been published in the literature as of 2018[8,46-53]. The majority of pancreatic cancers are thought to be sporadic, though up to 10% may be attributed to genetic factors. Chronic pancreatitis has a clear association with neoplastic transformation related to long-standing inflammation. Absence of the *CFTR* protein results in impaired secretion of bicarbonate and chloride. Mutation in the *CFTR* gene is a strong risk factor for development of chronic pancreatitis, increasing the risk for pancreatic adenocarcinoma [46].

Screening for malignancies of the biliary tree and pancreas may be difficult in patients with CF. Fortunately, cholangiocarcinoma and pancreatic cancer are rare with about 5.1 cases and 1-5.8 cases per 100000 CF cases, respectively[5,8]. Carbohydrate-19-9 antigen (CA-19-9) is generally considered a sensitive marker for several GI malignancies, including cholangiocarcinoma and pancreatic cancer[54]. Some CF recommendations advocate for hepatopancreatobiliary cancer screening every 1-3 years after 40 years of age depending on if organ transplantation has been completed. Screening may include laboratory testing (serum CA-19-9) or imaging studies (abdominal or endoscopic ultrasound and magnetic resonance cholangiopancreatography (MRCP)[5]. Patients with CF have shown to experience non-specific elevations in serum CA-19-9 levels, with volumes up to 500 U/mL (reference range 0-37 U/mL) [55-58]. Some sources have linked increased serum CA-19-9 Levels with active CF-related liver disease[54] and pulmonary exacerbation[57,59-61]. CA-19-9 has a 20% false-positive rate as a screening test and the serum level may also be elevated with other conditions, including an increased production of sputum, diabetes, chronic kidney failure, and infections. For these reasons, an elevated CA-19-9 Level alone may not be enough to justify additional expensive and unnecessary investigations[56]. The false-positivity rate, financial burden of testing, and unknown age to begin the screening has made the surveillance for pancreaticobiliary malignancies more difficult in the CF population.

CFTR carriers

Approximately 3%-4% of the United States population (10 million people) are heterozygous carriers of *CFTR* gene mutations. Though these patients do not have CF, they see somewhat similar changes with an increased risk for malignancies and other CF-related conditions[15]. One study found that the prevalence of GI cancers in CF carriers was increased by 44% when compared to the general population, including cancer of the stomach, GI tract, pancreas, and other GI organs[10,15]. These findings indicate that deficiency in *CFTR* likely has a large impact on malignancies and may affect first-degree relatives who are heterozygous carriers. Additional studies are required to further elucidate the association between *CFTR* and malignancy, in addition to the effect of *CFTR* modulators on this risk.

GUIDELINES FOR SCREENING OF GI CANCERS

The reported guidelines for GI cancer screening in the CF population mostly stem from a 20-year-long epidemiological study using the US CF Registry data. The risk of all types of GI cancers was increased, including a 6-fold increase in CRC compared with the predicted age-adjusted risk in the general population[3]. A more recent systematic review and meta-analysis study from 2018 demonstrated even higher standardized incidence ratios for these cancers and found that those with CF who had received a solid organ transplantation had a 2-5 times increased risk of GI cancer development compared to those who did not[5]. Furthermore, larger and more aggressive colonic polyps were found in individuals with CF[5]. The risk is also increased for cancers of the gastroesophageal junction, biliary tract, and small intestine. Table 2 highlights the current strategy for screening the GI system for cancer in patients with CF. The age at the time of cancer diagnosis was often not known in these CF cases, making implementation of the data for screening more challenging. Above all, these studies were performed before use of *CFTR* modulators was initiated.

GI CANCER SCREENING

The majority of epidemiologic studies reported the incidence of cancer in the colon more than any other GI site. Early colon screening in adult individuals with CF demonstrated that, by their fourth decade, approximately 50% had developed adenomas, half of which were already aggressive and advanced[23,24]. In fact, adenocarcinoma of the colon was present in 3% of the study population. The risk is even greater in the CF population who have undergone solid organ transplantation. In non-transplanted CF cases, the risk for small intestinal and colon cancer was particularly elevated in patients reported to have previously had distal intestinal obstruction syndrome (9 observed *vs* 0.8 expected; SIR = 11.2, 95%CI = 5.5-20.5). The diagnosis of distal intestinal obstruction syndrome preceded that of bowel cancer on average by 9 years[3]. For other prior GI conditions or CF complications, including GERD, gallbladder disease, liver disease, CF-related diabetes, or nasal polyps, the risk of developing intestinal cancers was not higher. The risk of bowel cancer following transplantation was higher in CF patients, particularly those with a homozygous F508del mutation and those with more severe *CFTR* genotypes. The transplantation data was analyzed for two separate time periods because more post-transplant cancers were reported during the period from 2000 to 2009 than during the period from 1990 to 1999. When comparing these two time periods, no difference in standardized incidence ratios was reported.

Colonoscopy is currently the preferred CRC screening method compared to imaging studies, such as virtual colonoscopy, or fecal occult blood testing. In addition, tumors were more frequently detected in the right colon in both non-transplanted and transplanted CF cases than in the general population. Therefore, flexible sigmoidoscopy is an inappropriate method for screening. Colonoscopy should be recommended in all patients with CF by age 40 with 5-year screening and 3-year surveillance intervals (unless a shorter interval is indicated by individual findings). In immunocompromised or transplanted patients, CRC screening should be initiated by age 30[3,6], within 2 years of transplantation, given the additional risk for CRC associated with immunosuppression[6].

Table 2 Proposed screening strategy for organ-specific gastrointestinal cancers in the cystic fibrosis population

Tumor location	Potential risks for cancer development[1]	Methods or screening	Proposed age at time of screening	Screening interval
Colon cancer[3,5, 62]	Solid organ transplantation; Immunosuppressive therapy; Severe *CFTR* mutations; Familial adenomatous polyps; Hereditary cancer syndromes; (*e.g.*, lynch syndrome); Inflammatory bowel disease	Colonoscopy	Non-transplanted: 40 yr; Transplanted: 30 yr and older (begin screening within 2 yr of transplant; unless negative colonoscopy in previous 5 yr)	Non-transplanted: Every 5 yr; Transplanted (or previous colonoscopy positive for adenomatous polyps): Every 3 yr after transplant (or polyps found)
Biliary tract cancer [5,63-67]	Solid organ transplantation; Immunosuppressive therapy; Severe *CFTR* mutations; Chronic biliary tract inflammation: (1) Primary sclerosing cholangitis; (2) Choledochal cysts; (3) Chronic cholelithiasis, choledocholithiasis; and (4) Hepatolithiasis. Chronic viral and non-viral liver diseaseInfections; (*i.e.*, HIV, *Helicobacter pylori*, certain parasites); Obesity;Other genetic conditions (*i.e.*, lynch syndrome, multiple biliary papillomatosis, BAP1 tumor predisposition syndrome)	Abdominal ultrasound, MRCP, or endoscopic ultrasonography; Measurement of CA-19-9	Non-transplanted: 40 yr; Transplanted: 30 yr (or within 2 yr after transplant)	Non-transplanted: Every 2-3 yr; Transplanted: Every 1-2 yr after transplant
Pancreatic cancer [6]	Solid organ transplantation; Immunosuppressive therapy; Severe *CFTR* mutations; Family history of pancreatic cancers (hereditary pancreatitis); Chronic pancreatitis; Frequent exposure to radiation (*i.e.*, X-rays and computed tomography scans)	Abdominal ultrasound, MRCP, or endoscopic ultrasonography; Measurement of CA-19-9	Non-transplanted: 40 yr; Transplanted: 30 yr (or within 2 yr after transplant)	Non-transplanted: Every 2-3 yr; Transplanted: Every 1-2 yr after transplant
Small bowel cancer [29]	Distal intestinal obstruction syndrome; Solid organ transplantation; Immunosuppressive therapy; Severe *CFTR* mutations	Terminal ileal intubation at time of colonoscopy (efficacy and safety of capsule endoscopy or balloon endoscopy need to be determined)	Non-transplanted: 40 yr; Transplanted: 30 yr (or within 2 yr after transplant)	Non-transplanted: Every 5 yr; Transplanted: Every 3 yr after transplant
Barrett's esophagus and esophageal adenocarcinoma [29]	Long standing GERD; Solid organ transplantation; Immunosuppressive therapy; Severe *CFTR* mutations;	Upper endoscopy	N/A[2]; 50 yr in non-CF population	N/A[2]
Hepatocellular carcinoma[39]	Cirrhosis	Abdominal ultrasound; Measurement of AFP	N/A[2]	N/A[2]

[1]Risk factors should be considered on an individual basis, based on the clinician's judgment of screening strategies.

[2]Data is not currently available in the literature. MRCP: Magnetic resonance cholangiopancreatography; CA-19-9: Carbohydrate-19-9 antigen; CF: Cystic fibrosis; N/A: Not available.

HEPATOPANCREATOBILIARY CANCER SCREENING

The risks of biliary tract and pancreatic cancers were reported to be slightly increased in CF cases compared with the general population. For example, there was an increase in biliary tract cancer (4 observed *vs* 0.4 expected; SIR = 11.4, 95%CI = 3.6-27.4)[3]. A screening strategy for pancreatobiliary cancer would include magnetic resonance cholangiopancreatography, endoscopic ultrasound, or abdominal ultrasound and measurement of a tumor marker level (CA-19-9) (Table 2). This screening method has been applied from the experience of screening cholangiocarcinoma in patients with primary sclerosing cholangitis and pancreatic cancer in individuals with a history of hereditary pancreatic cancer.

The recommendation for screening is suggested to start at age 40 with 2-3 year screening intervals (Table 2). The cost-effectiveness of these approaches needs further investigation before implementation[6,14]. Due to the increased risk for biliary tract and pancreatic cancers following transplantation, screening of these organs should be initiated. Further assessment is needed to determine whether or not to begin screening CF cases who are on immunosuppression following transplantation at a younger age (*i.e.*, 30 years), like with CRC screening. However, since decreased immune surveillance may increase cancer risk, the Cystic Fibrosis Foundation Task Force specifies that screening for colorectal cancer should begin within 2 years of transplant or even before transplant to ensure that additional surgical comorbidities exist. The pathogenesis of pancreatobiliary cancer in patients with CF cases remains unclear, but multiple

hypotheses exist, including gut dysbiosis. Other risks to consider include medical history of inflammatory bowel disease or primary sclerosing cholangitis, family history of pancreatic cancers (hereditary pancreatitis), and frequent exposure to radiation (*i.e.*, X-rays and computed tomography scans).

CONCLUSION

Increased risks of digestive tract cancer are site-specific and variable with pre-existing history or risk factors. The risk is specifically greater in individuals with severe *CFTR* genotypes and in those with immunosuppression following organ transplantation. Although many case reports of cancers in children and young adults exist, there is currently no evidence for screening of GI cancers in children with CF or before their fourth decade of life without definite risk factors. The role of precision screening may be reasonable, considering the financial burden of universal screening. The development of *CFTR* modulators, mainly to treat CF pulmonary disease, has also shown beneficial effects on other organs affected by dysfunction of *CFTR* protein and perhaps may reduce GI cancer risks. The impact of the longer life expectancy and *CFTR* modulator usage needs further collaborative research studies to develop strategic cancer screening in the CF population.

REFERENCES

1   **Cystic Fibrosis Foundation Patient Registry**. 2013 Annual Data Report to the Center Directors. Bethesda: 2014. [cited 28 Feb 2021]. Available from: https://www.cff.org/2013_CFF_Annual_Data_Report_to_the_Center_Directors.pdf

2   **Cystic Fibrosis Foundation Patient Registry**. 2019 Annual Data Report. Bethesda: 2020. [cited 28 Feb 2021]. Available from: https://cff.org/Research/Researcher-Resources/Patient-Registry/2019-Patient-Registry-Annual-Data-Report.pdf

3   **Maisonneuve P**, Marshall BC, Knapp EA, Lowenfels AB. Cancer risk in cystic fibrosis: a 20-year nationwide study from the United States. *J Natl Cancer Inst* 2013; **105**: 122-129 [PMID: 23178438 DOI: 10.1093/jnci/djs481]

4   **Neglia JP**, FitzSimmons SC, Maisonneuve P, Schöni MH, Schöni-Affolter F, Corey M, Lowenfels AB. The risk of cancer among patients with cystic fibrosis. Cystic Fibrosis and Cancer Study Group. *N Engl J Med* 1995; **332**: 494-499 [PMID: 7830730 DOI: 10.1056/nejm199502233320803]

5   **Yamada A**, Komaki Y, Komaki F, Micic D, Zullow S, Sakuraba A. Risk of gastrointestinal cancers in patients with cystic fibrosis: a systematic review and meta-analysis. *Lancet Oncol* 2018; **19**: 758-767 [PMID: 29706374 DOI: 10.1016/S1470-2045(18)30188-8]

6   **Hadjiliadis D**, Khoruts A, Zauber AG, Hempstead SE, Maisonneuve P, Lowenfels AB; Cystic Fibrosis Colorectal Cancer Screening Task Force. Cystic Fibrosis Colorectal Cancer Screening Consensus Recommendations. *Gastroenterology* 2018; **154**: 736-745.e14 [PMID: 29289528 DOI: 10.1053/j.gastro.2017.12.012]

7   **Jackson AD**, Goss CH. Epidemiology of CF: How registries can be used to advance our understanding of the CF population. *J Cyst Fibros* 2018; **17**: 297-305 [PMID: 29275954 DOI: 10.1016/j.jcf.2017.11.013]

8   **Maisonneuve P**, Lowenfels AB, Hadjiliadis D, Khoruts A, Marshall BC. Gastrointestinal cancers in patients with cystic fibrosis. *Lancet Oncol* 2018; **19**: e368 [PMID: 30102218 DOI: 10.1016/S1470-2045(18)30485-6]

9   **Meyer KC**, Francois ML, Thomas HK, Radford KL, Hawes DS, Mack TL, Cornwell RD, Maloney JD, De Oliveira NC. Colon cancer in lung transplant recipients with CF: increased risk and results of screening. *J Cyst Fibros* 2011; **10**: 366-369 [PMID: 21664882 DOI: 10.1016/j.jcf.2011.05.003]

10   **Miller AC**, Comellas AP, Hornick DB, Stoltz DA, Cavanaugh JE, Gerke AK, Welsh MJ, Zabner J, Polgreen PM. Cystic fibrosis carriers are at increased risk for a wide range of cystic fibrosis-related conditions. *Proc Natl Acad Sci USA* 2020; **117**: 1621-1627 [PMID: 31882447 DOI: 10.1073/pnas.1914912117]

11   **Wilschanski M**, Novak I. The cystic fibrosis of exocrine pancreas. *Cold Spring Harb Perspect Med* 2013; **3**: a009746 [PMID: 23637307 DOI: 10.1101/cshperspect.a009746]

12   **De Lisle RC**, Borowitz D. The cystic fibrosis intestine. *Cold Spring Harb Perspect Med* 2013; **3**: a009753 [PMID: 23788646 DOI: 10.1101/cshperspect.a009753]

13   **Castellani C**, Assael BM. Cystic fibrosis: a clinical view. *Cell Mol Life Sci* 2017; **74**: 129-140 [PMID: 27709245 DOI: 10.1007/s00018-016-2393-9]

14   **Elborn JS**. Cystic fibrosis. *Lancet* 2016; **388**: 2519-2531 [PMID: 27140670 DOI: 10.1016/S0140-6736(16)00576-6]

15   **Scott P**, Anderson K, Singhania M, Cormier R. Cystic Fibrosis, CFTR, and Colorectal Cancer. *Int J Mol Sci* 2020; **21** [PMID: 32326161 DOI: 10.3390/ijms21082891]

16   **Arthur JC**, Perez-Chanona E, Mühlbauer M, Tomkovich S, Uronis JM, Fan TJ, Campbell BJ,

Abujamel T, Dogan B, Rogers AB, Rhodes JM, Stintzi A, Simpson KW, Hansen JJ, Keku TO, Fodor AA, Jobin C. Intestinal inflammation targets cancer-inducing activity of the microbiota. *Science* 2012; **338**: 120-123 [PMID: 22903521 DOI: 10.1126/science.1224820]

17   **Werlin SL**, Benuri-Silbiger I, Kerem E, Adler SN, Goldin E, Zimmerman J, Malka N, Cohen L, Armoni S, Yatzkan-Israelit Y, Bergwerk A, Aviram M, Bentur L, Mussaffi H, Bjarnasson I, Wilschanski M. Evidence of intestinal inflammation in patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 2010; **51**: 304-308 [PMID: 20512061 DOI: 10.1097/MPG.0b013e3181d1b013]

18   **Than BL**, Linnekamp JF, Starr TK, Largaespada DA, Rod A, Zhang Y, Bruner V, Abrahante J, Schumann A, Luczak T, Walter J, Niemczyk A, O'Sullivan MG, Medema JP, Fijneman RJ, Meijer GA, Van den Broek E, Hodges CA, Scott PM, Vermeulen L, Cormier RT. CFTR is a tumor suppressor gene in murine and human intestinal cancer. *Oncogene* 2016; **35**: 4179-4187 [PMID: 26751771 DOI: 10.1038/onc.2015.483]

19   **Garg M**, Leach ST, Pang T, Needham B, Coffey MJ, Katz T, Strachan R, Widger J, Field P, Belessis Y, Chuang S, Day AS, Jaffe A, Ooi CY. Age-related levels of fecal M2-pyruvate kinase in children with cystic fibrosis and healthy children 0 to 10years old. *J Cyst Fibros* 2018; **17**: 109-113 [PMID: 28754328 DOI: 10.1016/j.jcf.2017.07.011]

20   **Pang T**, Leach ST, Katz T, Jaffe A, Day AS, Ooi CY. Elevated fecal M2-pyruvate kinase in children with cystic fibrosis: a clue to the increased risk of intestinal malignancy in adulthood? *J Gastroenterol Hepatol* 2015; **30**: 866-871 [PMID: 25376228 DOI: 10.1111/jgh.12842]

21   **American Cancer Society**.   Global Cancer Facts & Figures 4th Edition. Atlanta: 2018. [cited 28 Feb 2021]. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/global-cancer-facts-and-figures/global-cancer-facts-and-figures-4th-edition.pdf

22   **American Cancer Society**.   Cancer Facts and Figures 2020. Atlanta: 2020. [cited 28 Feb 2021]. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf

23   **Billings JL**, Dunitz JM, McAllister S, Herzog T, Bobr A, Khoruts A. Early colon screening of adult patients with cystic fibrosis reveals high incidence of adenomatous colon polyps. *J Clin Gastroenterol* 2014; **48**: e85-e88 [PMID: 24275715 DOI: 10.1097/MCG.0000000000000034]

24   **Niccum DE**, Billings JL, Dunitz JM, Khoruts A. Colonoscopic screening shows increased early incidence and progression of adenomas in cystic fibrosis. *J Cyst Fibros* 2016; **15**: 548-553 [PMID: 26851188 DOI: 10.1016/j.jcf.2016.01.002]

25   **Burt R**. Inheritance of Colorectal Cancer. *Drug Discov Today Dis Mech* 2007; **4**: 293-300 [PMID: 19043597 DOI: 10.1016/j.ddmec.2008.05.004]

26   **Syngal S**, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW; American College of Gastroenterology. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol* 2015; **110**: 223-262; quiz 263 [PMID: 25645574 DOI: 10.1038/ajg.2014.435]

27   **Li W**, Wang C, Peng X, Zhang H, Huang H, Liu H. CFTR inhibits the invasion and growth of esophageal cancer cells by inhibiting the expression of NF-κB. *Cell Biol Int* 2018; **42**: 1680-1687 [PMID: 30358020 DOI: 10.1002/cbin.11069]

28   **Strubberg AM**, Liu J, Walker NM, Stefanski CD, MacLeod RJ, Magness ST, Clarke LL. Cftr Modulates Wnt/β-Catenin Signaling and Stem Cell Proliferation in Murine Intestine. *Cell Mol Gastroenterol Hepatol* 2018; **5**: 253-271 [PMID: 29675451 DOI: 10.1016/j.jcmgh.2017.11.013]

29   **Knotts RM**, Solfisburg QS, Keating C, DiMango E, Lightdale CJ, Abrams JA. Cystic fibrosis is associated with an increased risk of Barrett's esophagus. *J Cyst Fibros* 2019; **18**: 425-429 [PMID: 30473189 DOI: 10.1016/j.jcf.2018.11.005]

30   **Pauwels A**, Blondeau K, Mertens V, Farre R, Verbeke K, Dupont LJ, Sifrim D. Gastric emptying and different types of reflux in adult patients with cystic fibrosis. *Aliment Pharmacol Ther* 2011; **34**: 799-807 [PMID: 21793864 DOI: 10.1111/j.1365-2036.2011.04786.x]

31   **Zhang C**, Shen Y, Wang J, Zhou M, Chen Y. Identification of key pathways and genes in Barrett's esophagus using integrated bioinformatics methods. *Mol Med Rep* 2018; **17**: 3069-3077 [PMID: 29257318 DOI: 10.3892/mmr.2017.8274]

32   **Eisen GM**, Sandler RS, Murray S, Gottfried M. The relationship between gastroesophageal reflux disease and its complications with Barrett's esophagus. *Am J Gastroenterol* 1997; **92**: 27-31 [PMID: 8995932]

33   **Hassall E**, Israel DM, Davidson AG, Wong LT. Barrett's esophagus in children with cystic fibrosis: not a coincidental association. *Am J Gastroenterol* 1993; **88**: 1934-1938 [PMID: 8237944 DOI: 10.1016/0022-3468(94)90032-9]

34   **Oezcelik A**, Kaiser GM, Dechêne A, Treckmann JW, Sotiropoulos GC, Reinhardt R, Saner FH, Paul A. Progression to adenocarcinoma in Barrett's esophagus after liver transplantation. *Transplantation* 2011; **91**: 1250-1253 [PMID: 21464795 DOI: 10.1097/TP.0b013e31821841a0]

35   **Alexander CL**, Urbanski SJ, Hilsden R, Rabin H, MacNaughton WK, Beck PL. The risk of gastrointestinal malignancies in cystic fibrosis: case report of a patient with a near obstructing villous adenoma found on colon cancer screening and Barrett's esophagus. *J Cyst Fibros* 2008; **7**: 1-6 [PMID: 17766191 DOI: 10.1016/j.jcf.2007.07.005]

36   **Gharahkhani P**, Fitzgerald RC, Vaughan TL, Palles C, Gockel I, Tomlinson I, Buas MF, May A, Gerges C, Anders M, Becker J, Kreuser N, Noder T, Venerito M, Veits L, Schmidt T, Manner H, Schmidt C, Hess T, Böhmer AC, Izbicki JR, Hölscher AH, Lang H, Lorenz D, Schumacher B, Hackelsberger A, Mayershofer R, Pech O, Vashist Y, Ott K, Vieth M, Weismüller J, Nöthen MM;

Barrett's and Esophageal Adenocarcinoma Consortium (BEACON); Esophageal Adenocarcinoma GenEtics Consortium (EAGLE); Wellcome Trust Case Control Consortium 2 (WTCCC2), Attwood S, Barr H, Chegwidden L, de Caestecker J, Harrison R, Love SB, MacDonald D, Moayyedi P, Prenen H, Watson RGP, Iyer PG, Anderson LA, Bernstein L, Chow WH, Hardie LJ, Lagergren J, Liu G, Risch HA, Wu AH, Ye W, Bird NC, Shaheen NJ, Gammon MD, Corley DA, Caldas C, Moebus S, Knapp M, Peters WHM, Neuhaus H, Rösch T, Ell C, MacGregor S, Pharoah P, Whiteman DC, Jankowski J, Schumacher J. Genome-wide association studies in oesophageal adenocarcinoma and Barrett's oesophagus: a large-scale meta-analysis. *Lancet Oncol* 2016; **17**: 1363-1373 [PMID: 27527254 DOI: 10.1016/S1470-2045(16)30240-6]

37 **Wasuwanich P**, Karnsakul W. Cystic fibrosis-associated liver disease in children. *Minerva Pediatr* 2020; **72**: 440-447 [PMID: 32418413 DOI: 10.23736/S0026-4946.20.05895-8]

38 **Karnsakul W**, Wasuwanich P, Ingviya T, Vasilescu A, Carson KA, Mogayzel PJ, Schwarz KB. A longitudinal assessment of non-invasive biomarkers to diagnose and predict cystic fibrosis-associated liver disease. *J Cyst Fibros* 2020; **19**: 546-552 [PMID: 32482593 DOI: 10.1016/j.jcf.2020.05.002]

39 **McKeon D**, Day A, Parmar J, Alexander G, Bilton D. Hepatocellular carcinoma in association with cirrhosis in a patient with cystic fibrosis. *J Cyst Fibros* 2004; **3**: 193-195 [PMID: 15463908 DOI: 10.1016/j.jcf.2004.04.006]

40 **O'Donnell DH**, Ryan R, Hayes B, Fennelly D, Gibney RG. Hepatocellular carcinoma complicating cystic fibrosis related liver disease. *J Cyst Fibros* 2009; **8**: 288-290 [PMID: 19473889 DOI: 10.1016/j.jcf.2009.05.002]

41 **Wang X**, Wang Q. Alpha-Fetoprotein and Hepatocellular Carcinoma Immunity. *Can J Gastroenterol Hepatol* 2018; **2018**: 9049252 [PMID: 29805966 DOI: 10.1155/2018/9049252]

42 **Kelleher T**, Staunton M, O'Mahony S, McCormick PA. Advanced hepatocellular carcinoma associated with cystic fibrosis. *Eur J Gastroenterol Hepatol* 2005; **17**: 1123-1124 [PMID: 16148560 DOI: 10.1097/00042737-200510000-00018]

43 **O'Brien C**, Ramlaul N, Haughey A, Nolan N, Malone DE, McCormick PA. Hepatocellular carcinoma in cystic fibrosis liver disease: a cautionary tale. *QJM* 2019; **112**: 693-694 [PMID: 31214693 DOI: 10.1093/qjmed/hcz150]

44 **Williams SG**, Evanson JE, Barrett N, Hodson ME, Boultbee JE, Westaby D. An ultrasound scoring system for the diagnosis of liver disease in cystic fibrosis. *J Hepatol* 1995; **22**: 513-521 [PMID: 7650330 DOI: 10.1016/0168-8278(95)80444-7]

45 **Rich N**, Singal AG. Hepatocellular carcinoma tumour markers: current role and expectations. *Best Pract Res Clin Gastroenterol* 2014; **28**: 843-853 [PMID: 25260312 DOI: 10.1016/j.bpg.2014.07.018]

46 **Cazacu IM**, Farkas N, Garami A, Balaskó M, Mosdósi B, Alizadeh H, Gyöngyi Z, Rakonczay Z Jr, Vigh É, Habon T, Czopf L, Lazarescu MA, Erőss B, Sahin-Tóth M, Hegyi P. Pancreatitis-Associated Genes and Pancreatic Cancer Risk: A Systematic Review and Meta-analysis. *Pancreas* 2018; **47**: 1078-1086 [PMID: 30134356 DOI: 10.1097/MPA.0000000000001145]

47 **Oermann CM**, Al-Salmi Q, Seilheimer DK, Finegold M, Tatevian N. Mucinous cystadenocarcinoma of the pancreas in an adolescent with cystic fibrosis. *Pediatr Dev Pathol* 2005; **8**: 391-396 [PMID: 16010483 DOI: 10.1007/s10024-005-4114-5]

48 **Prost à la Denise J**, Hubert D, Gaudric M, Scatton O, Soubrane O. Pancreatic mucinous cystadenoma in an adult with cystic fibrosis. *Clin Res Hepatol Gastroenterol* 2011; **35**: 759-761 [PMID: 21856266 DOI: 10.1016/j.clinre.2011.06.011]

49 **Meier F**, Oltmanns A, Brandmaier P, Wittekind C. [Case report about a 35 year old patient with cystic fibrosis and metastatic pancreatic cancer]. *Z Gastroenterol* 2014; **52**: 55-57 [PMID: 24420800 DOI: 10.1055/s-0033-1356225]

50 **Tsongalis GJ**, Faber G, Dalldorf FG, Friedman KJ, Silverman LM, Yankaskas JR. Association of pancreatic adenocarcinoma, mild lung disease, and delta F508 mutation in a cystic fibrosis patient. *Clin Chem* 1994; **40**: 1972-1974 [PMID: 7522998 DOI: 10.1093/clinchem/40.10.1972]

51 **Hanna T**, Abdul-Rahman Z, Greenhalf W, Costello E, Neoptolemos JP. Pancreatic mass in a young CFTR carrier with a heterozygous p.R117H CFTR gene mutation and homozygous 7T. *Pancreas* 2015; **44**: 343-345 [PMID: 25675422 DOI: 10.1097/MPA.0000000000000244]

52 **Petrowsky H**, Schuster H, Irani S, Schäfer M, Jochum W, Schmid C, Boehler A, Clavien PA. Pancreatic cancer in cystic fibrosis after bilateral lung transplantation. *Pancreas* 2006; **33**: 430-432 [PMID: 17079951 DOI: 10.1097/01.mpa.0000236724.49543.f3]

53 **Platt KD**, Sondhi AR, DiMagno MJ. Pancreatic Cancer: A Rare Cause of Abdominal Pain in Severe Cystic Fibrosis. *Pancreas* 2019; **48**: e3-e4 [PMID: 30531246 DOI: 10.1097/MPA.0000000000001162]

54 **Bettinardi N**, Felicetta I, Tomasi PA, Colombo C. Carbohydrate 19-9 antigen is not a marker of liver disease in patients with cystic fibrosis. *Clin Chem Lab Med* 2003; **41**: 311-316 [PMID: 12705340 DOI: 10.1515/CCLM.2003.050]

55 **Duffy MJ**, O'Sullivan F, McDonnell TJ, FitzGerald MX. Increased concentrations of the antigen CA-19-9 in serum of cystic fibrosis patients. *Clin Chem* 1985; **31**: 1245-1246 [PMID: 3859384 DOI: 10.1093/clinchem/31.7.1245]

56 **Denis JA**, Mazzola A, Nguyen G, Lacorte JM, Brochet C, Larsen AK, Conti F. Transient increase of CA 19-9 serum concentrations in a liver transplant recipient with cystic fibrosis and hepatic abscess: a case report and brief literature review. *Clin Biochem* 2019; **64**: 53-56 [PMID: 30342018 DOI: 10.1016/j.clinbiochem.2018.10.009]

57 **Augarten A**, Berman H, Aviram M, Diver-Habber A, Akons H, Ben Tur L, Blau H, Kerem E, Rivlin

J, Katznelson D, Szeinberg A, Kerem BS, Theodor L, Paret G, Yahav Y. Serum CA 19-9 Levels as a diagnostic marker in cystic fibrosis patients with borderline sweat tests. *Clin Exp Med* 2003; **3**: 119-123 [PMID: 14598187 DOI: 10.1007/s10238-003-0014-z]

58   **Kane RE**, Penny J, Walker K, Rubin BK, Wu J. Changes in the CA 19-9 antigen and Lewis blood group with pulmonary disease severity in cystic fibrosis. *Pediatr Pulmonol* 1992; **12**: 221-226 [PMID: 1614747 DOI: 10.1002/ppul.1950120405]

59   **Gronowitz E**, Pitkänen S, Kjellmer I, Heikinheimo M, Strandvik B. Association between serum oncofetal antigens CA 19-9 and CA 125 and clinical status in patients with cystic fibrosis. *Acta Paediatr* 2003; **92**: 1267-1271 [PMID: 14696845 DOI: 10.1080/08035250310006052]

60   **Robinson CB**, Martin WR, Ratliff JL, Holland PV, Wu R, Cross CE. Elevated levels of serum mucin-associated antigen in adult patients with cystic fibrosis. *Am Rev Respir Dis* 1993; **148**: 385-389 [PMID: 8342902 DOI: 10.1164/ajrccm/148.2.385]

61   **Wu JT**, Olson J, Walker K. Tumor markers CA 19-9 and CA 195 are also useful as markers for cystic fibrosis. *J Clin Lab Anal* 1992; **6**: 151-161 [PMID: 1506983 DOI: 10.1002/jcla.1860060310]

62   **Maisonneuve P**, FitzSimmons SC, Neglia JP, Campbell PW 3rd, Lowenfels AB. Cancer risk in nontransplanted and transplanted cystic fibrosis patients: a 10-year study. *J Natl Cancer Inst* 2003; **95**: 381-387 [PMID: 12618503 DOI: 10.1093/jnci/95.5.381]

63   **Khaderi SA**, Sussman NL. Screening for malignancy in primary sclerosing cholangitis (PSC). *Curr Gastroenterol Rep* 2015; **17**: 17 [PMID: 25786901 DOI: 10.1007/s11894-015-0438-0]

64   **Perdue DG**, Cass OW, Milla C, Dunitz J, Jessurun J, Sharp HL, Schwarzenberg SJ. Hepatolithiasis and cholangiocarcinoma in cystic fibrosis: a case series and review of the literature. *Dig Dis Sci* 2007; **52**: 2638-2642 [PMID: 17443409 DOI: 10.1007/s10620-006-9259-1]

65   **Chapman RW**. Risk factors for biliary tract carcinogenesis. *Ann Oncol* 1999; **10** Suppl 4: 308-311 [PMID: 10436847 DOI: 10.1093/annonc/10.suppl_4.S308]

66   **Welzel TM**, Mellemkjaer L, Gloria G, Sakoda LC, Hsing AW, El Ghormli L, Olsen JH, McGlynn KA. Risk factors for intrahepatic cholangiocarcinoma in a low-risk population: a nationwide case-control study. *Int J Cancer* 2007; **120**: 638-641 [PMID: 17109384 DOI: 10.1002/ijc.22283]

67   **Khan SA**, Toledano MB, Taylor-Robinson SD. Epidemiology, risk factors, and pathogenesis of cholangiocarcinoma. *HPB (Oxford)* 2008; **10**: 77-82 [PMID: 18773060 DOI: 10.1080/13651820801992641]