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Association between cholangiocarcinoma and liver flukes: review of epidemiological studies

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ABSTRACT

According to official medical statistics, liver fluke infections caused by Opisthorchis felineus, *Opisthorchis viverrini* and *Clonorchis sinensis*, are reported annually in the Southeast Asia, European countries and the Russian Federation. These infections are the main cause of digestive system diseases in the population of endemic regions. The aim of the review is to analyze the findings of epidemiological studies and to assess the relationship between liver and bile duct cancer and *Opisthorchiidae* liver fluke infections.

Materials and methods. The authors reviewed original studies published in 1974–2019 via the MEDLINE databases and the eLIBRARY scientific digital library.

Results. The studies have shown that cholangiocarcinoma is a significant medical and social problem in the trematode-endemic areas of Southeast Asia due to the absence of specific symptoms, long asymptomatic course, resistance to therapy and high mortality of patients. Long-term infection caused by trematodes *Opisthorchis viverrini* and *Clonorchis sinensis* is associated with a significant risk of developing cholangiocellular cancer. An epidemiological multicenter study is required to establish the relationship between the *Opisthorchis felineus* infection and cholangiocarcinoma in the population of endemic regions in the Russian Federation.

Key words: cholangiocarcinoma, *Opisthorchis viverrini, Clonorchis sinensis, Opisthorchis felineus,* liver cancer, review, epidemiological study.

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Анализ эпидемиологических исследований взаимосвязи холангиокарциномы и печеночных трематодозов

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РЕЗЮМЕ

Согласно официальной медицинской статистике, случаи инвазии, вызываемые печеночными трематодами Opisthorchis felineus, *Opisthorchis viverrini* и *Clonorchis sinensis*, ежегодно регистрируются как в регионах Юго-Восточной Азии, так и в европейских странах, в Российской Федерации, являясь причиной заболеваний органов пищеварительной системы у населения эндемичных регионов. Цель обзора – анализ результатов эпидемиологических исследований, посвященных оценке взаимосвязи злокачественных новообразований гепатобилиарной системы и печеночных трематодозов, вызванных гельминтами семейства *Opisthorchiidae*.

Изучены оригинальные исследования, опубликованные за период 1974– 2019 гг. и размещенные в базах данных MEDLINE и научной электронной библиотеки eLIBRARY. Проведенные исследования свидетельствуют, что холангиокарцинома является значимой медико-социальной проблемой в эндемичных по трематодозам регионах Юго-Восточной Азии ввиду отсутствия специфических симптомов, длительного бессимптомного течения, резистентности к терапии и высокой смертности пациентов. Длительная персистенция в организме печеночных трематод *Opisthorchis viverrini* и *Clonorchis sinensis* ассоциирована со значительным риском развития холангиоцеллюлярного рака. Требуется проведение эпидемиологического многоцентрового исследования для установления взаимосвязи инвазии *Opisthorchis felineus* и холангиокарциномы у населения эндемичных регионов Российской Федерации.

Ключевые слова: холангиокарцинома, *Opisthorchis viverrini*, *Clonorchis sinensis*, *Opisthorchis felineus*, рак печени, обзор, эпидемиологическое исследование.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

At present, helminthiases are spread worldwide, causing significant medical and social damage [1]. According to official medical statistics, cases of infection caused by liver flukes *Opisthorchis felineus (O. felineus), Opisthorchis viverrini (O. viverrini)* and *Clonorchis sinensis (C. sinensis)* are reported annually in the hyperendemic regions of Southeast Asia (Thailand, Vietnam, China, Korea), and in European countries (Greece, Italy, Spain, Portugal, Germany, Poland), being the cause of diseases of the digestive system in 40 million people [2–5]. Moreover, more than 600 million people are at risk of infection each year [6–8].

Based on studies conducted in Southeast Asia, the International Agency for Research on Cancer (IARC) has included hepatic trematodes *O. viverrini* and *C. sinensis* in the registry of biological carcinogens. The mentioned studies have shown a relationship between *O. viverrini-* and *C. sinensis-caused infection and cholangiocarcinoma* (CCA) [9–11].

CCA is one of the most unfavourable diseases in relation to the prognosis of malignancies [12]. The high incidence of bile duct cancer is observed in Northeast Thailand, as well as in China and South Korea [13–15].

In the Russian Federation, the study of the liver fluke infections caused by *O. felineus* and associated chronic diseases remains relevant. Over the past 20 years, there has been a significant increase in the incidence of opisthorchiasis in the endemic regions of Western Siberia and spread of invasion in several other regions due to increased population migration [16, 17].

The aim of this review was to analyze the results of epidemiological studies on the relationship between malignancies of the hepatobiliary system and hepatic trematodoses.

DATA SOURCES

The authors analyzed epidemiological studies on the relationship of malignant neoplasms of the hepatobiliary system and hepatic trematodoses caused by *Opisthorchiidae* family worms *(C. sinensis, O. viverrini and O. felineus)* from publications in the MEDLINE databases via the PubMed electronic search engine (https://www.ncbi.nlm.nih.gov/pubmed/) and the scientific electronic library eLIBRARY (https://elibrary.ru/). The review used original articles published over the period from January 1, 1974 to December 31, 2019, grouped according to the following algorithm.

Keyword preliminary search. To search for foreign publications in the PubMed database, the keywords "epidemiological study, *Opisthorchis viverini* infection, *Clonorchis sinensis infection, Opisthorchis felineus* infection, cholangiocarcinoma, liver cancer, malignant diseases" were used. In the eLIBRARY electronic library, the same following terms in Russian were studied. Also, search for studies corresponding to the above-mentioned terms was carried out among the references in the selected publications. In total, 889 publications from PubMed and 4 papers from the scientific electronic library eLIBRARY were studied.

Abstract analysis (summary) of the selected publications. This stage excluded experimental studies, review publications that are not epidemiological studies, as well as articles lacking required data in the text of the abstract. All in all, 374 publications were analyzed, of which 48 were selected.

Analysis of full-text publications. The publications studied had to have the following features as a selection criteria: original epidemiological study, completeness of the description of the study design, including the size and characteristics of the sample, selection criteria; open access to the full text of the article; compliance with the criteria for the diagnosis of "cholangiocarcinoma" (histological examination of the tumor); and description of the diagnostic method for verification of infection. The exclusion criteria were the absence of the required data in the text of the article (sample size, description of the diagnostic method for CCA and opisthorchiasis).

As a result, 14 full-text publications met the inclusion criteria and were included in this review.

EPIDEMIOLOGICAL CHARACTERISTICS OF CHOLANGIOCARCINOMA

CCA is a heterogeneous group of liver tumors characterized by damage to the intra- and / or extrahepatic bile ducts, high mortality due to its aggressiveness, the absence of specific symptoms and / or prolonged asymptomatic course, and resistance to therapy [12, 13, 18]. CCA is the second most common type of liver tumor and the most common cause of death from cancer. It also accounts for about 3% of all neoplasms of the digestive system. The incidence increases with age; with women developing CCA more often than men [19, 20].

According to the anatomical classification, CCA is divided into intrahepatic, perihilar and distal. It is believed that intrahepatic CCA ac-

counts for about 10% of cases of primary liver cancer, of which 50% are Klatskin tumors, 40% of them are distally localized tumors, and intrahepatic lesions occur in 10% of cases. CCA has a poor prognosis, with the median survival of 24 months. The only treatment methods are first-line (Gemcitabine, Cisplatin) and second-line (Oxaliplatin, Fluorouracil according to the FOLFOX scheme) chemotherapy, targeted therapy with pembrolizumab in the presence of MSI-H / dMMR and / or surgical intervention in the early stages of the disease [21–23].

The incidence of CCA in the world is about 5.9 cases per 100 thousand people annually. The highest incidence is recorded in Northern Thailand (more than 80 cases per 100 thousand population), China (more than 7.5 cases per 100 thousand population) and South Korea (more than 8 cases per 100 thousand people). On the contrary, the incidence rates of CCA in the European countries or Americas do not exceed 0.7-3.36 and 0.3-1.67 per 100 thousand, respectively [24].

The average incidence of CCA in the Russian Federation is about 4.8 per 100 thousand annually. According to the official medical statistics for 2011-2013, in the Russian Federation, the highest incidence of CCA was noted in the Republic of Sakha and Tomsk Region (14.5 and 9.3 per 100 thousand population, respectively) [17, 25].

It is important to note that in Europe, America and Africa, hepatocellular carcinoma dominates in the histological profile of liver cancers, while in regions endemic for liver flukes, cholangiocellular cancer predominates (more than 80 cases per 100 thousand in Northern Thailand) [26]. The highest incidence of hepatocarcinoma (more than 20 per 100 thousand) is recorded in China, Mongolia, Southeast Asia, as well as in countries of West and East Africa, located south of the Sahara Desert [12, 26].

CCA refers to multifactorial diseases, the development of which involves many risk factors, including genetic, infectious, environmental, and epidemiological ones. The significant risk factors include primary sclerosing cholangitis / ulcerative colitis, chronic viral hepatitis C and B, long persistence of the Epstein-Barr virus, non-alcoholic fatty liver disease, cholelithiasis and / or malformation of the biliary system, and deposition of radiopaque substances (Thorotrast) in the bile ducts [27, 28]. There is experimental evidence that N-dinitrosodimethylamine can serve as an inducer of carcinogenesis in the bile ducts [29, 30].

One of the most important and significant risk factors for CCA is prolonged persistence in the body of liver flukes *O. viverrini* and *C. sinensis*, included in the register of Group 1 biological carcinogens with proven oncogenicity for humans based on the results of studies conducted in Southeast Asia [11]. According to the 2019 report of IARC, *O. felineus* is still a biological agent with unproven carcinogenicity in humans (Group 3) due to the insufficient number of meaningful epidemiological multicenter studies [31–34].

ASSOCIATION BETWEEN CHOLANGIOCARCINOMA AND *O. VIVERRINI* INFECTION

We reviewed eight full-text articles on epidemiological relationship between CCA and *O. viverrini* infection (table).

O. viverrini infection is a significant public health problem in the Mekong River Basin countries of Southeast Asia such as Thailand, the Lao People's Democratic Republic, Vietnam and Cambodia [35–37]. According to official medical statistics, Thailand (north-eastern province) has the highest prevalence of *O. viverrini* infection, where at least 6 million people are infected by opisthorchiasis. It also has the highest rates of bile duct cancer and cholangiocarcinoma (more than 90 cases per 100,000 men and 38.3 cases per 100,000 women) [14, 38–40].

The first significant study conducted in Northeast Thailand (table 1) showed that patients with *O. viverrini* (stool and/or bile microscopy) had significantly higher frequency of CCA diagnosis than non-infected individuals [41].

The case-control study conducted in 1987–1988 found a statistically significant association between CCA and the presence of antibodies to *O. viverrini* in serum. The results showed that men and regular users of betel nut (mostly women) had higher risk of CCA development. A possible mechanism is increased exposure to nitrosamines [42].

In the case-control study conducted in 1990–1991 in 85 villages of Northeast Thailand, 12,311 people aged 24 years and over were screened for *O. viverrini* (microscopy of stool). Ultrasonography of the hepatobiliary system was performed in individuals with different intensity of invasion, 15 patients were diagnosed with CCA. The highest prevalence of CCA was found in the group with the highest intensity of *O. viverrini* infection [43].

The case-control population study conducted in 1999–2001 showed that increasing antibodies to

O. viverrini was the most significant risk factor for CCA development. Eating fermented fish, alcohol consumption and smoking increased the risk of CCA. The role of alcohol may be explained by its influence on the metabolic pathways of endogenous and exogenous nitrosamines [44].

The case-control study conducted as part of a cohort study in 1990–2001 showed significant relationship between development of CCA and detection of *O. viverrini* eggs in stool samples. Also the study found that individuals who consumed fruits and vegetables 3–4.6 times a day had significantly lower risk of CCA. Nevertheless, eating meat more often than 0.45 times per day significantly increased the risk of CCA [45].

The case-control study conducted in 1999–2001 showed that risk of CCA in patients with high levels of antibodies to *O. viverrini* and chronic viral hepatitis B and/or C was significantly higher [46].

The case-control study conducted in 2011 established that consumption of alcohol, raw freshwater fish and beef sausages increased the risk of CCA, while fruits and/or vegetables consumption reduced this risk. A relationship between a decrease in the MTHFR gene expression and consumption of raw freshwater fish infected with *O. viverrini* and meat was identified. These dietary items are source of nitrosamines, folates and antioxidants that may cause carcinogenesis along with *O. viverrini* infection [47].

In the case-control study conducted in 2009–2012, the data on increased risk of CCA in patients who had family history of cancer and increased level of immunoglobulin G to *O. viverrini* were obtained again. The consumption of alcohol more than three times a week and uncooked meat (beef, pork) also increased risk of CCA [48].

It is important to note that according to the U.S. government data, more than 700 Vietnamese war veterans were diagnosed with CCA over the past 15 years. In analysis of 50 serum samples, antibodies to *O. viverini* were found in 20% of them. Infection may be linked with consumption of heat- untreated river fish during a stay in the endemic region of South-East Asia. The long-term asymptomatic course of liver fluke infection resulted in development of bile duct cancer diagnosed at the last stage of the disease [49, 50].

Association between cholangiocarcinoma and *C. sinensis* infection

We reviewed six full-text publications on epidemiological relationship between CCA and *C. sinensis* infection (table).

According to the medical statistics, infection caused by *C. sinensis* is the most common in Asia, especially in China, Taiwan, Korea, Japan and Vietnam: more than 15 million people are infected, and 200 million are at constant risk of infection [51]. China has the highest incidence of clonorchiasis with more than 13 million people, accounting for 85% of the total number of cases [52, 53].

The first meaningful epidemiological studies carried out in South Korea (table 1) showed an increased risk of CCA in patients with positive status of *C. sinensis* infection [54, 55].

The case-control study carried out in 1990–1993 showed that the detection of *C. sinensis* eggs in samples of stool and alcohol overuse were the most significant risk factors for CCA [56].

According to the case-control study carried out in 2000-2004 in Seoul, *C. sinensis* infection was significantly related to intrahepatic CCA. The important risk factors for CCA also include chronic viral hepatitis B, liver cirrhosis, alcohol consumption, diabetes mellitus, and choledochal cysts [57].

The case-control study conducted in 2003–2004 in the same region found that eating raw freshwater fish and positive antibodies to *C. sinensis* in the serum were associated with an increased risk of CCA. Significant risk factors for distal CCA were the radiological signs of *C. sinensis* and history of raw freshwater fish consumption [58].

In the case-control study conducted in 2011 in China, association between intrahepatic CCA and *C. sinensis* infection as well as cholelitiasis, chronic viral hepatitis B and liver cirrhosis was detected [15].

ASSOCIATION BETWEEN CHOLANGIOCARCINOMA AND *O. FELINEUS* INFECTION

At present, there is deficiency of significant epidemiological multicenter studies in the Russian Federation to establish the relationship between CCA and *O. felineus* infection. According to the pilot analysis of official medical statistics data, the incidence of liver and bile duct cancer in Russia is about 4.8 cases per 100,000 population annually. Our pilot analytical study of official medical statistics data in all regions of the Russian Federation in 2011–2013 showed a significant relationship between the incidence of *O. felineus* infection and malignancies of the hepatobiliary system. Thus, the incidence of hepatobiliary malignancies is

significantly higher in regions with high level of opistorchiasis among the population (≥ 50 cases per 100,000) [17].

At present, the results of some domestic studies based on autopsy materials and surgical protocols demonstrating carcinogenic potential of *O. felineus* have been published.

This way, among patients that underwent surgery at the Tomsk Hepatology Surgery Centre from 1980 to 2000, 13% (n =152) of 1170 patients with *O. felineus* infection suffered from hepatic, pancreatic and duodenal cancer: liver or bile ducts – in 61 cases, pancreas – in 66 cases, gallbladder – in 15 cases and major duodenal papilla – in 10 patients [34].

In the analysis of autopsy materials of 44 individuals who died of liver cancer, CCA was established in 80% and hepatocellular carcinoma in 20% of cases [59].

In 2019, two cases of CCA in patients with *Opisthorchis felineus* infection have been published. Patients lived in the endemic rural area, practiced fishing and undercooked cyprinoid fish consumption. They had been infected by liver fluke *Opisthorchis felineus* for a long time and did not receive antihelminthic treatment. Both cases presented unspecific symptoms at the onset of the disease at the stage when already severe pathological changes had occurred, and patients died of multiorgan dysfunction syndrome during six months after CCA diagnosis verification [60].

CONCLUSION

Liver trematodes *Opisthorchis viverrini* and *Clonorchis sinensis* are significant biological carcinogens associated with a significant risk of developing cholangiocellular cancer. *O. felineus* is still a biological agent with unproven carcinogenicity in humans (Group 3) due to insufficient epidemiological data. However, current experimental and clinical data indicate significant carcinogenic potential of *O. felineus*. An epidemiological multicenter study is required to establish the relationship between the *Opisthorchis felineus* infection and cholangiocarcinoma in the population of endemic regions of the Russian Federation. The study results are necessary for elaborating guidelines on screening programs for early CCA diagnosis as well as for preventing and treating hepatobiliary cancer, which is socially important in endemic regions for opisthorchiasis in the Russian Federation.

Table

Epidemiological studies assessing the risk of cholangiocarcinoma development in *O. viverrini* and *C. sinensis* infection

Author, year	Country	Study design	Study sample (n)	Risk of CCA development
Study of *O. viverrini* infection				
Kurathong et al., 1985 [41]	Thailand	Case-control	551	OR = 1.21 95% CI: 0.36–4.06
Parkin et al., 1991 [42]	Thailand	Case-control	206	OR = 5.0
Haswell-Elkins et al., 1994 [43]	Thailand	Cross-sectional	12 311	OR =14.1
Honjo et al., 2005 [44]	Thailand	Case-control	258	OR = 27.09
Poomphakwaen et al., 2009 [45]	Thailand	Case-control	216	OR = 2.99 95% CI: 1.04–8.62
Srivatanakul et al., 2010 [46]	Thailand	Case-control	212	OR = 25.04 95% CI: 5.81–07.91
Songserm et al., 2011 [47]	Thailand	Case-control	657	OR = 2.0 95% CI: 1.14–3.48
Manwong et al., 2013 [48]	Thailand	Case-control	146	OR = 3.09 95% CI: 1.04–9.16
Study of *O. sinensis* infection				
Kim Y. et al., 1974 [54]	Korea	Cross-sectional	1402	OR = 6.5 95% CI: 3.5–112.04
Chung C. et al., 1976 [55]	Korea	Case-control	595	OR = 6.0 95% CI: 2.82–12.04
Shin H.R. et al., 1996 [56]	Korea	Case-control	609	OR = 2.7 95% CI: 1.13–6.46
Lee T. et al., 2008 [57]	Korea	Case-control	2488	OR = 13.6 95% CI: 6.1–30.31

End of table

Author, year	Country	Study design	Study sample (*n*)	Risk of CCA development
Choi D., Lim J.H., Lee K.T. et al., 2006 [58]	Korea	Case-control	244	OR = 8.62 95% CI: 5.05–16.06
Peng N.F., Li L.Q., Qin X. et al., 2011 [15]	Korea	Case-control	294	OR = 3,55 95% CI: 1.6–7.89

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