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Diabetes mellitus: Possible risk and promoting factors of cholangiocarcinoma
Association of diabetes mellitus and cholangiocarcinoma

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ABSTRACT

The highest incidence of Cholangiocarcinoma (CCA), a malignancy of bile duct epithelia, is in the Northeast of Thailand. The liver fluke, *Opisthorchis viverrini*, is the known risk factor for CCA development in this region. Approximately 1% of *O. viverrini* infected individuals develop CCA. There could be other factors that influence the cholangiocarcinogenesis particularly in the *O. viverrini* infected individuals. The global epidemiological studies of risk factors for CCA in non-*O. viverrini* related patients indicated diabetes mellitus (DM) as a risk factor of CCA. The molecular studies in many cancers indicated that high levels of glucose, insulin and an obese condition directly and indirectly enhanced growth of cancers. For *O. viverrini* associated CCA, there is limited information related to DM and CCA development. High mortality rates of CCA and DM, however, were reported in the same geographical areas of northeastern Thailand. Whether DM is a factor that enhances CCA development in *O. viverrini* infected individuals or promotes CCA progression are discussed in a perspective of epidemiological and molecular studies.

1. Introduction

Diabetes mellitus (DM), a disease characterized by hyperglycemia, is highly prevalent in both industrialized and developing countries. In 2011, an estimated 347 million people worldwide suffered from DM [1] and more than 80% of diabetic deaths are in low and medium income countries [2]. The World Health Organization (WHO) has projected DM to be the 7th global leading cause of death in 2030. DM is also an important health problem in Southeast Asia with an age-standardized death rate of DM at 25.96 per 100,000. The diabetic patients usually suffer from mild to serious complications, e.g., retinopathy, neuropathy and nephropathy which can cause high morbidity and mortality rates. The other complication from the indirect effects of diabetic conditions is low immunity leading to a high susceptibility to infections. DM does not only cause the commonly mentioned complications, but is also the risk factor for other non-communicable diseases including cardiovascular disease and cancer [3–5].

Cholangiocarcinoma (CCA) is a malignancy that arises from bile duct epithelia and is anatomically classified as extra- or intrahepatic. CCA is a rare disease in the western countries but there is concern that its incidence is increasing globally. Several factors, including primary sclerosing cholangitis, hepatitis B virus infection and parasitic infections are highly associated with CCA development [6,7]. Compared with the incidence in western countries, the incidence of CCA in Southeast Asia is very high and especially the highest in the Northeast of Thailand [8,9]. Infection with the liver fluke, *O. viverrini*, is a major causative factor of CCA in Thailand and countries in the Greater Mekong sub-region such as Laos and Cambodia, whereas *Clonochis sinensis* which is endemic in East Asia is found to be a cancer promoter for CCA in China and Korea. It is hypothesized that chronic infections of parasites probably initiate the carcinogenesis by parasite factors such as the mitogenic substances of excretory–secretory antigens together with the immunological response of the host which promotes prolonged inflammation, causing DNA damage and finally CCA development [10,11].

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The association of *O. viverrini* infection and CCA has been strongly proven in the experimental animal model. Hamsters infected with *O. viverrini* and supplemented with sub-carcinogenic doses of dimethylnitrosamine developed CCA whereas those infected with *O. viverrini* alone or supplemented with the carcinogen doses alone did not [12]. The infection of *O. viverrini* per se may not produce CCA, but other carcinogens or risk factors may also be required to induce CCA development. In a hospital based prospective, case–controlled study of 227 hepatobiliary disease patients with *O. viverrini* infection, 8 patients (3.5%) developed CCA within 2 years of the follow up period [13]. Recently, in the community study, based on ultrasound screening of 4154 subjects resident in the northeast Thailand, only 0.5% were suspected to be CCA [14].

The national prevalence of *O. viverrini* in Thailand was reported to be 14% in 1981 [15] and decreased to 9.4% in 2001 [16]. Approximately 6 million people in Thailand remain infected with *O. viverrini*. It should be noted here that the prevalence of *O. viverrini* infection has a regional variation. A high prevalence of *O. viverrini* infection of 22.7% was reported in the upper Northeast of Thailand, with the highest record of 40.9% in Nakhon Phanom province [17]. Even though *O. viverrini* infection is strongly associated with cholangiocarcinogenesis of people in the endemic areas, in fact, fewer than 1% of *O. viverrini* infected people develop CCA [14]. This indicates that other not yet identified factors may influence the minor group of infected persons who develop CCA. Recently there are several studies that reported that common factors, such as smoking, alcoholic consumption, obesity and DM as risks of CCA in non-*O. viverrini* related CCA [18]. DM has been reported as a risk factor of cancer development in various cancers review in [5]. Herein, is a review of the epidemiological studies that have reported that DM is a risk of CCA. The molecular mechanisms by which DM may enhance cancer development as well as the possibility of DM to be a factor which promotes CCA development in *O. viverrini* infected persons are elaborated.

2. Epidemiological studies revealed DM as a risk factor of CCA

The association of DM and cancer has been reported in various cancers. DM can increase the risk of cancer in many organs such as pancreas, liver, breast, thyroid, urinary bladder and endometrium (review in [5]). DM, however, was shown to reduce risk of prostate cancer [4,5,19–21]. For CCA, many epidemiological studies indicated DM as a risk of CCA (Table 1). The meta-analysis of 10 case–control and 5 cohort studies showed that DM increased the risk of CCA with an overall relative risk (RR) of 1.60 (95% CI: 1.38–1.87) [22]. DM increased the risk of extrahepatic CCA with a RR of 1.63 (95% CI: 1.29–2.05) and the risk became greater for intrahepatic CCA with a RR of 1.97 (95% CI: 1.57–2.46). In addition, Palmer and Patel [18] reported the meta-analysis of 11 case–control studies in areas with both a high and low prevalence of intrahepatic CCA. Some common factors, e.g., smoking, alcoholic use, obesity and type 2 DM (T2DM) increased risk of CCA to different degrees. Among these, alcohol consumption gave the highest risk with an odds ratio (OR) 2.81 (95% CI: 1.52–5.21) while DM ranked second with an OR 1.89 (95% CI: 1.74–2.07).

A recent case–control study carried on in the United States on 612 CCA patients and 594 controls revealed that DM increased risk of CCA with an adjusted odds ratio (AOR) 3.60 (95% CI: 2.30–5.50) [23]. The benefit of using metformin, an anti-diabetic drug, was also demonstrated in this study. DM patients who used metformin as DM treatment had a significantly decreased risk of CCA development with an OR 0.40 (95% CI: 0.20–0.90) [23]. The benefit of using metformin for chemoprevention of CCA was suggested. Metformin has been used as an anti-cancer drug and is now in a clinical trial in patients of several cancers [24].

For extrahepatic CCA, a meta-analysis on DM and biliary tract cancer was performed by Ren et al. [25]. In this study, DM increased the risk of extrahepatic CCA and gall bladder cancer with a summary RR 1.43 (95% CI: 1.18–1.72), however, the association of DM and cancer of the ampulla of Vater was not found. That DM increased the risk of extrahepatic CCA was supported by a meta-analysis of four case–control and five cohort studies [26]. In this meta-analysis, DM increased the risk of extrahepatic CCA with a RR 1.61 (95% CI: 1.14–2.29). The data from several epidemiological studies strongly indicate that DM is a risk factor of both intrahepatic and extrahepatic CCA.

Many epidemiological studies emphasized DM as a considerable common risk factor for various cancers including CCA. Even though the positive association of DM and CCA was unveiled, there are many factors that should be considered before making a conclusion. First, the limitation of each epidemiological study may provide a biased result, such as in the case–control studies, they were unable to define whether DM or CCA occurred first. Secondly, DM patients have more frequent health checkups in the clinic than healthy people who hardly ever see a doctor. This may increase the chance of cancer detection in DM patients compared to non-DM persons. Thus the hospital based studies are likely to be biased by reviewing the medical records. To strongly support DM increasing the risk of CCA, the molecular mechanism linking DM to CCA is ultimately needed.

3. A possible molecular linkage of DM and CCA

The molecular mechanisms by which DM increases risk of cancer have been studied in many cancers, however, studies are limited for CCA. Since DM increases the risk of cancer in several

Table 1
Meta-analysis indicates an increased risk of CCA in DM patients.

Type of biliary tract malignancy	Increased risk	Number of recruited studies	References
CCA	1.60 (1.38–1.87)[a]	10 case–control 5 cohort	Jing et al. [22]
Intrahepatic CCA	1.97 (1.57–2.46)[a]	10 case–control 5 cohort	Jing et al. [22]
	1.89 (1.74–2.07)[b]	11 case–control	Palmer and Patel [18]
Extrahepatic CCA	1.63 (1.29–2.05)[a]	10 case–control 5 cohort	Jing et al. [22]
	1.61 (1.14–2.29)[a]	4 case–control 5 cohort	Zhang and Zhao [26]
Extrahepatic CCA and CA gall bladder	1.43 (1.18–1.72)[a]	8 case–control 13 cohort	Ren et al. [25]

[a] Relative risk.
[b] Odds ratio.