CURRENT TREND

Cholangiocarcinoma: Descriptive epidemiology and risk factors

Cholangiocarcinomes : épidémiologie descriptive et facteurs de risque

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Summary  In theory, the term of cholangiocarcinoma is reserved for the tumours originating from the intrahepatic bile ducts. The problems of classification of the most frequent hilar tumours and the absence of histopathological confirmation in a large percentage of cases in cancer registries from many countries show the difficulty of establishing the specific epidemiologic behaviour of intrahepatic cholangiocarcinoma (ICC). There are clearly two types of ICC: the first one is the consequence of the recurrent infection of the biliary ducts by the parasites Opisthorchis viverrini and Clonorchis sinensis, and is only seen in the areas of Southeast Asia where liver flukes are endemic. In these areas, incidence and mortality rates of ICC are extremely high. Both parasites have been classified class I carcinogens by the International Agency for Research on Cancer. The other type of ICC is a cancer much rarer but present in the whole world. Some risk factors have been well-established (chronic inflammation of biliary ducts, hepatitis, thorotrast, etc) but many patients do not have any of these factors. An increase in incidence and mortality of this second type of ICC has been seen in recent years, mostly in developed countries. There is an ongoing discussion in the literature about its authenticity and potential causes.

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Résumé  En théorie, le terme de cholangiocarcinome est réservé aux tumeurs issues des voies biliaires intrahépatiques. Les problèmes de classification des fréquentes tumeurs hilaires et l’absence de diagnostic histopathologique de confirmation dans un large pourcentage de cas
recensés dans les registres de cancers montrent la difficulté à établir le comportement épidémiologique spécifique du cholangiocarcinome intrahépatique (CCI). Il y a clairement deux types de CCI : l’un est la conséquence de l’infection et la réinfection permanente de certaines populations par les parasites *Opisthorchis viverrini* et *Clonorchis sinensis*, et se voit uniquement dans les régions d’Asie du Sud-Est où la distomatose est endémique. Dans ces régions circonscrites, les taux d’incidence et de mortalité du CCI sont extrêmement élevés. Les deux parasites ont été classés carcinogènes de classe I par le Centre international de recherche sur le cancer. L’autre type de CCI est un cancer beaucoup plus rare mais présent dans l’ensemble du monde. Certains facteurs de risque sont bien établis (inflammation chronique des voies biliaires, hépatite, thoreast, etc.), mais la vaste majorité des patients atteints ne possèdent aucun de ces facteurs. Une augmentation de l’incidence et de la mortalité de ce second type de cancer a été observée au cours des années 1990 et alimente une discussion dans la littérature internationale à propos de son authenticité et de ses causes.

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Introduction

Definition

The definition of cholangiocarcinoma has varied with time and among countries, and there is still no clear consensus. According to the etymology of the world, cholangiocarcinoma originates in the bile ducts (from the Greek words "chole", which means bile and "angeion", which means vessel) whatever the precise anatomical location. Nevertheless, according to the classification of the tumours by the World Health Organization (WHO)[1], the term cholangiocarcinoma is reserved for the tumours originating in the intrahepatic bile ducts (Fig. 1), and this is the terminology we will use in this chapter. It should be noted however that in the recent literature, the name sometimes extends to all the tumours derived from the biliary epithelial cells and thus also includes extrahepatic biliary tract tumours [2].

Figure 1. Anatomic location of biliary tract cancers. From ref [4].

The particular case of hilar tumours (or Klatskin tumours)

Like many other junctional sites, hilar tumours (also called Klatskin tumours) pose a particular problem of classification, which has been discussed in several recent articles [3,4]. The WHO classification of tumours unambiguously states "cholangiocarcinoma arising from the right and left hepatic duct at or near their junction is called hilar cholangiocarcinoma and is considered an extrahepatic lesion" [1]. However, in practice, hilar tumours are often misclassified as intrahepatic tumours because of their tendency to quickly invade the liver [5]. Table 1 shows the evolution of the international classification of disease for oncology (ICD-O) and illustrates well the persistent confusion [4]. Klatskin tumours were not mentioned in version 1 of ICD-O. In version 2, a specific histological code (8162/3) was assigned to them; this code, as well as the alphabetical index ("Klatskin"), were cross-referenced to the topographic code C22.1, that of the intrahepatic tumours. Version 3, which is the most recent, indicates a double cross-reference to the codes C22.1 and C24.0, thus leaving the choice between intra- or extrahepatic tumours. Lastly, in versions 2 and 3, a note in the topographic section C24 suggests that the tumours overlapping the intra- and extrahepatic location, or in which a point of origin cannot be determined, constitute a sub-type of the extrahepatic tumours and should be coded C24.8.

These variations and subtleties of classification would be trivial if hilar tumours did not represent the majority of the tumours of the biliary tract. Furthermore, a few articles have shown that the two types of tumours (intra- and extrahepatic) may to have the same epidemiology. A correct interpretation of aetiology data would therefore require a clear and consensual definition and deserves, in this context, special caution.

Sources of epidemiologic data

The problems of classification mentioned above show the difficulty of establishing the specific epidemiologic behaviour of cholangiocarcinoma by comparing data from different studies, a fortiori during various time periods,
Intrahepatic cholangiocarcinoma

There are clearly two types of intrahepatic cholangiocarcinoma (ICC): the first one is the consequence of the recurrent infection of some populations by the parasites *Opisthorchis viverrini* (*O. viverrini*) and *Clonorchis sinensis* (*C. sinensis*), and is only seen in the areas of Southeast Asia where liver fluke is endemic. In these circumscribed areas, incidence and mortality rates of ICC are extremely high. The other type of ICC is much rarer but present worldwide. An increase in incidence and mortality of this second type of ICC has been seen during the nineties, mostly in developed countries. There is an ongoing discussion in the literature about its authenticity and potential causes.

**Incidence and geographical distribution**

In terms of frequency, ICC is the second primary liver tumour after hepatocellular carcinoma and represents approximately 15% of liver cancer, with great geographical variations. As noted by Parkin and al. [7], this global percentage has only limited utility, because the frequency of ICC varies inversely with the frequency of HCC, which is known to vary widely in different parts of the world.

It is thus more interesting to consider the incidence rate, i.e. the number of new cases of cancer diagnosed every year, adjusted for the age of the population. The most recent version of Cancer Incidence in Five Continents (CI5-IX) published in 2007 on the Website of the International Agency for Research on Cancer (IARC) shows incidence data from cancer registries all around the world. In the liver cancer category (C22), the incidence data are presented by histological sub-type, making it possible to distinguish ICC from HCC. In 30% to 50% of the cases however, histological confirmation of the diagnosis is missing. The data should thus be interpreted with caution, but it appears that overall, ICC is a rare tumour. In industrialized countries, its incidence is generally lower than two per 100,000 inhabitants with a slight male predominance (sex ratio man/woman between 1 and 1.5) [8]. This is the case for example in the United States where data from the 14 cancer registries in the Surveillance Epidemiology and End Results (SEER) program show an incidence rate of 0.6/100,000, with a sex ratio of 1.4. The ICC is hardly more frequent in developing countries.

The exception, as noted above, is seen in certain areas of South-East Asia (South Korea, South-East China and Thailand). In these areas, the incidence rate reaches four per 100,000 inhabitants [8]. An extremely high peak of incidence of primary liver cancer (up to 118 per 100,000 inhabitants in Khon Kaen [9]) was observed in certain parts of the North-East and the East of Thailand (Fig. 2) [10]. Histological verification shows that in 85% of the cases, these liver cancers are indeed ICC [11]. A very clear geographical correlation with liver flukes (due to the parasites *O. viverrini* in

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**Table 1** Topographic classification of the biliary tract tumours and ICD-O codes.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Intrahepatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic, unspecified</td>
<td>155.0</td>
<td>C22.0</td>
<td>C22.0</td>
</tr>
<tr>
<td>Intrahepatic cholangiocarcinoma</td>
<td>155.1</td>
<td>C22.1</td>
<td>C22.1</td>
</tr>
<tr>
<td>Hilary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klatskin tumour*</td>
<td>Unspecified</td>
<td>C22.1</td>
<td>C22.1</td>
</tr>
<tr>
<td>Extrahepatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallbladder</td>
<td>156.0</td>
<td>C23.9</td>
<td>C23.9</td>
</tr>
<tr>
<td>Cancer of the extrahepatic bile ducts</td>
<td>156.1</td>
<td>C24.0</td>
<td>C24.0</td>
</tr>
<tr>
<td>Ampulla of Vater</td>
<td>156.2</td>
<td>C24.1</td>
<td>C24.1</td>
</tr>
<tr>
<td>Overlapping tumours (intra- and extrahepatic)</td>
<td>156.8</td>
<td>C24.8</td>
<td>C24.8</td>
</tr>
<tr>
<td>Tumour of the biliary tract, unspecified</td>
<td>156.9</td>
<td>C24.9</td>
<td>C24.9</td>
</tr>
</tbody>
</table>

*In classifications ICD-O-2 and ICD-O-3, Klatskin tumours received a single histological code (8162/3). This code was used in cross-reference with the topographic code C22.1 in version 2, and with the code C22.1 or C24.0 in version 3.*

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and in countries with different health care systems. Most published data come from surgical series or autopsies, and only a few large case-control studies are available. The data collected by cancer registries are often limited by the absence of histopathological confirmation of the diagnosis, generally because the cancer is too advanced for surgical treatment. In addition, with the development of powerful imaging techniques (for example cholangiography by magnetic resonance), a growing number of tumours of the bile duct are diagnosed without systematic recourse to biopsies [6]. Moreover, in the case of advanced cancers, the distinction between cholangiocarcinoma and other liver tumours is not always obvious. In the absence of histopathology or precise site of origin, it is probable that a good number of tumours are classified C22.0 or C22.1 (hepatic tumours or of the bile ducts, respectively, without another specification) and do not appear in the statistics specific to each cancer.

Lastly, due to the extremely poor prognosis of biliary tract cancers, incidence and mortality figures are almost identical, and mortality rates are often used by epidemiologists as valid indicators for the estimate of the incidence rates.

**Descriptive epidemiology**

**Intrahepatic cholangiocarcinoma**

The exception, as noted above, is seen in certain areas of South-East Asia (South Korea, South-East China and Thailand). In these areas, the incidence rate reaches four per 100,000 inhabitants [8]. An extremely high peak of incidence of primary liver cancer (up to 118 per 100,000 inhabitants in Khon Kaen [9]) was observed in certain parts of the North-East and the East of Thailand (Fig. 2) [10]. Histological verification shows that in 85% of the cases, these liver cancers are indeed ICC [11]. A very clear geographical correlation with liver flukes (due to the parasites *O. viverrini* in

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Figure 2. Incidence rate of cholangiocarcinoma (CCA) and Opisthorchis viverrini (OV) infection prevalence in Thailand (2004). From ref [10].

Thailand and C. sinensis in Korea and China) has been shown and is not disputed anymore [9,12]. It should however be noted that in certain registries, the proportion of tumours with unspecified origin remains very high.

Variation in time

Mortality data
Two independent reviews of mortality data collected by WHO were published in 2002. Both showed an increase in mortality due to ICC in most studied countries between 1979 and 1997 [13,14]. This increase was seen in all the areas of the world except for Africa, for which reliable epidemiologic data are lacking. The areas showing the strongest increase include North America (the United States and Canada), Oceania (Australia and New Zealand) and Western Europe (France, Germany, Ireland, Portugal and Spain). In separate publications, mortality data in England and in Wales have shown the same tendency, which seems to continue after the year 2000. For instance, between 1968 and 2001, the mortality rate due to ICC increased from 0.11 to 1.33 per 100,000 in men and from 0.09 to 1.06 per 100,000 in women. Notably, among women, ICC was the most frequent primary liver cancer in England at the end of this period [16]. In Scotland, incidence data between 1968 and 1997 show a similar increase, from 0.12 to 1.53 per 100,000 in men and from 0.17 to 1.24 per 100,000 in women [17]. It should be noted however that the proportion of histological verification in Scotland for the same period decreased from 80% to less than 40%, probably as a consequence of a greater confidence in imaging technologies for the diagnosis of cancer [17]. The American data collected in the larger SEER program confirm this increase: the standardized incidence rate of ICC increased between 1977 and 1997 from 0.4 to 1.06 per 100,000 in men and from 0.27 to 0.69 per 100,000 in women [18].

More detailed analyses of the SEER data later showed that this increase mostly took place after the year 1985 was more pronounced in men than in women and concerned particularly people aged over 65 years of age (Fig. 3) [19].

A discordant note however came from Denmark in a recent publication [20]. According to the Danish cancer registry, whose quality is internationally recognized, but

Incidence data
According to the cancer registry of England and Wales, incidence data show the same trend as mortality data, with a standardized incidence rate increasing between 1971 and 2001 from 0.11 to 1.33 per 100,000 in men and from 0.09 to 1.06 per 100,000 in women. Notably, among women, ICC was the most frequent primary liver cancer in England at the end of this period [16]. In Scotland, incidence data between 1968 and 1997 show a similar increase, from 0.12 to 1.53 per 100,000 in men and from 0.17 to 1.24 per 100,000 in women [17]. It should be noted however that the proportion of histological verification in Scotland for the same period decreased from 80% to less than 40%, probably as a consequence of a greater confidence in imaging technologies for the diagnosis of cancer [17]. The American data collected in the larger SEER program confirm this increase: the standardized incidence rate of ICC increased between 1977 and 1997 from 0.4 to 1.06 per 100,000 in men and from 0.27 to 0.69 per 100,000 in women [18].

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which only relates to the small population of Denmark, the incidence rate of ICC has decreased between 1978 and 2002 from 1.27 to 0.46 per 100,000 inhabitants (both sexes together).

Klatskin tumours

Because of the difficulties of classification mentioned in introduction, Klatskin tumours are split in an unequal and unpredictable way between four possible ICD-O topographic codes: C22.1 (intrahepatic cholangiocarcinoma), C24.0 (tumours of the extrahepatic bile ducts), C24.8 or C24.9 (overlapping or unspecified tumour sites). In fact, it is risky to rely only on cancer registries to study the epidemiology of hilar tumours. The specific histological code dedicated to Klatskin tumours 8162/3 in versions ICD-O 2 and 3 does not solve the problem since other possibilities of histological coding (i.e. adenocarcinoma) exist and are probably used [4]. Klatskin tumours, which are by definition extrahepatic, were probably more often coded as being intrahepatic during the period when version 2 of the ICD-O code was in use (Table 1), because of the single cross reference with the topographic code C22.1. This misclassification could partly, but probably not completely, explain the increase in ICC incidence noted in many parts of the world during the years 1990–2000.

Adding to the problem, it seems that the hilar localization is the most frequent cancer of the bile duct. In a series of 560 patients surgically treated over 31 years in the John Hopkins hospital in the USA, hilar tumours comprised 50% of the tumours of the bile ducts, the remainder being 8% intrahepatic and 42% extrahepatic distal tumours [21,22].

Risk factors

**Opisthorchis viverrini and Clonorchis sinensis**

In South-East Asia, the major risk factor for cholangiocarcinoma is a chronic or recurrent infection with a parasite of the class of the trematodes, *O. viverrini* in Thailand, Laos and Kampuchea, and *C. sinensis* in Korea, China and Taiwan [23]. The relative risk for ICC associated with a positive serology for *O. viverrini* is estimated between 5 and 30, according to several case-control studies, the most recent adjusting its results for alcohol consumption, smoking, age, sex and place of residence of the participants [24,25]. The magnitude of risk is comparable for *C. sinensis* in Korea and China, with odds ratios (ORs) estimated between 3 and 13 depending on methods of diagnosis. In 1994 a group of international experts convened by IARC classified *O. viverrini* as carcinogenic to humans [23]. A second IARC working group in March 2009 also classified *C. sinensis* as carcinogenic to humans [26]. Both parasites have a complex natural cycle requiring several intermediate hosts (molluscs and fish). The infection is contracted during the consumption of raw or under-cooked fish, and the adult parasites find their final location in the intrahepatic bile ducts where they lay their eggs. It is the chronic inflammation caused by the recurring presence of the parasite and its eggs in the bile ducts, which leads to malignant transformation [9,27].

**Overall picture of the other risk factors for ICC**

Outside the endemic zones for *O. viverrini* and *C. sinensis*, many other factors have been associated with the develop-
Another group predisposed to the development of ICC is Congenital biliary diseases, approximately 1.5% per year\cite{46}. In regard to chronic inflammation of the bile duct, gallstone disease, alcoholic disease and cirrhosis, whatever its origin. Some of these risk factors deserve to be described in more detail.

**Other infectious agents**

Hepatitis B and C viruses (HBV and HCV) have also been classified as carcinogenic to humans by IARC for their role in the genesis of HCC\cite{34}. The two viruses may also have a role in the occurrence of ICC, but the epidemiologic data are not yet sufficient to conclude with certainty that there is a causal relationship.

The results of human epidemiologic studies (all case-control studies and mostly carried out in Asia) on the association between HCV infection and cancers of the biliary tract were reviewed by an IARC working group in March 2009\cite{26}. Five studies specifically looked at ICC, and three of them showed a statistically significant OR, suggesting a risk of ICC at least five times higher among anti-HCV positive subjects\cite{35—37}.

The same five case-control studies also examined the presence of hepatitis B surface antigen in serum with regard to the risk of ICC. All in all, the risk of ICC was higher for HBV carriers, with an OR ranging between 1.8 and 8.9. However, only two of the five studies (the ones not having shown a higher risk for anti-HCV positive subjects) showed a statistically significant difference\cite{38,39}.

A large and well-conducted population-based study was recently carried out in China. Although it only studied extrahepatic biliary tract cancers, it also showed a significant association with HBV, but no association with HCV\cite{40}.

In conclusion, for these two viruses, the limited number of studies available to date, and the absence of a statistically significant association in some of them led the IARC working group to conclude that there was only limited epidemiological evidence for a causal association between HBV and HCV and ICC\cite{26}.

**Primary sclerosing cholangitis**

Primary sclerosing cholangitis is one of the most studied risk factors for ICC\cite{41—43}. This disease, the aetiology of which is still poorly understood, is characterized by a chronic inflammation of the intra- or extrahepatic bile ducts evolving toward fibrosis. It affects relatively young subjects, generally of male gender, and HLA groups A1-B8-DR3, DR6 and DR2 (whereas group DR4 seems protective). In two-thirds of the cases, another chronic inflammatory disease of the digestive tract, such as inflammatory bowel disease, is also present\cite{44,45}. For a patient with primary sclerosing cholangitis, the risk of developing cholangiocarcinoma is approximately 1.5% per year\cite{46}.

**Congenital biliary diseases**

Another group predisposed to the development of ICC is comprised of patients with congenital malformation of the bile ducts, namely choledochal cyst, Caroli’s disease or syndrome, and congenital hepatic fibrosis. In the absence of a preventive surgical resection, the lifetime risk of ICC could reach 10% in patients with Caroli’s syndrome, and is estimated between 2.5 and 28% for patients with choledochal cyst\cite{47—49}. One has to keep in mind however that such congenital malformations are rare diseases and thus are rare causes of ICC.

**Toxic agents**

Certain toxic agents have been identified as being strong risk factors for the development of liver tumours, including ICC. The best example is that of Thorotrast, which was the commercial name of an X-ray contrast medium, a colloidal solution of thorium dioxide and dextrin, formerly used for cerebral angiography and liver scans. It is estimated that between 1930 and 1970, around 100,000 people were exposed to Thorotrast worldwide. Approximately 60% of the injected dose remained trapped in the liver, slowly diffusing radioactive alpha-particles at the rate of approximately 25 rad per year\cite{50}. It was shown that the exposure to Thorotrast generally induces angiosarcoma but also ICC, hepatocarcinoma, gallbladder cancers and cancers at many other sites. The latency period between the exposure and the development of cancer was evaluated between 16 and 45 years, but may be longer. Thorotrast is regarded as one of the most carcinogenic substance ever described in humans\cite{51,52}.

**Other factors**

Among the other factors having been associated with the occurrence of ICC, one can cite diabetes mellitus and tobacco smoking\cite{29,53}, which have both been suspected, along with HCV, to at least partially explain the recent increase in case of ICC in industrialized countries. The explanation is not entirely satisfactory however, and the increase of ICC remains poorly understood as of today.

**Conclusion**

ICC is still badly understood in terms of its temporal trends and risk factors. There are three reasons for this, the first being a persistent confusion over its classification, the second its relative rarity over industrialized countries and the last its late diagnosis and consequently poor prognosis, which makes epidemiological research difficult. Under these circumstances prevention measures that are known to be effective are extremely important. One example is preventive surgery in patients with congenital malformations of the bile duct. Another key prevention measure is education: cooking of fish in the area endemic for *O. viverrini* and *C. sinensis* would be enough to destroy the parasite and should thus prevent a considerable number of cancers. This message, as simple as it is, is difficult to implement in the field as it goes against long established food habits.

The recent increase in incidence and mortality of ICC certainly requires further study, bearing in mind that it could merely be the consequence of changes in classification or diagnostic practices. It might also partly be explained by...
changes in risk factors whose impact is still poorly known, for instance infections agents like HCV infection. Financed by the "Fondation innovations en infectiologie" (F1NOV1).

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