



Mini-review

Liver cancer: Descriptive epidemiology and risk factors other than HBV and HCV infection

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ABSTRACT

The incidence of liver cancer is high in all low-resource regions of the world, with the exception of Northern Africa and Western Asia. The estimated worldwide number of new cases of liver cancer in 2002 is 600,000, of which 82% are from developing countries. Given the poor survival from this disease, the estimated number of deaths is similar to that of new cases.

Hepatocellular carcinoma (HCC) is the main form of liver cancer. A part from chronic infections with Hepatitis B and Hepatitis C viruses, which are the main causes of HCC, contamination of foodstuff with aflatoxins, a group of mycotoxins produced by the fungi *Aspergillus flavus* and *Aspergillus parasiticus*, is an important contributor to HCC burden in many low-income countries. Alcoholic cirrhosis is an important risk factor for HCC in populations with low prevalence of HBV and HCV infection, and the association between tobacco smoking and HCC is now established. Diabetes is also related to an excess risk of HCC and the increased prevalence of overweight and obesity likely contributes to it.

The second most important type of liver cancer is cholangiocarcinoma, whose main known cause is infestation with the liver flukes, *Opisthorchis viverrini* and *Clonorchis sinensis*, which is frequent in some areas in South-East Asia. Angiosarcoma is a rare form of liver cancer whose occurrence is linked to occupational exposure to vinyl chloride.

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1. Descriptive epidemiology

The epidemiology of liver cancer is made complex by the large number of secondary tumours, which are difficult to separate from primary liver cancers without histological verification. The most common histological type of liver malignant neoplasm is hepatocellular carcinoma (HCC). Other forms include: (i) childhood hepatoblastoma, and (ii) adult cholangiocarcinoma (originating from the intrahepatic biliary ducts) and (iii) angiosarcoma (from the intrahepatic blood vessels). Primary liver cancer is the sixth most common cancer in the world and the third most

common cause of cancer mortality [1]. The estimated worldwide number of new cases of liver cancer in 2002 is 600,000, of which 82% are from developing countries. China alone accounts for 55% liver cancer death worldwide [2]. The incidence of liver cancer is high in all low-resource regions of the world, with the exception of Western Asian and Northern African countries other than Egypt. The highest rates (above 40/100,000 in men and above 10/100,000 in women) are recorded in Thailand, Japan, Korea, and certain parts of China. In most high-resource countries, age-standardized rates are below 5/100,000 in men and 2.5/100,000 in women. Intermediate rates (5–10/100,000 in men) are observed in areas of Southern and Central Europe [3]. The 5-year survival rate was 8% in the United States during 1988–2001 [4], 9% in Europe during 1995–1999 [5], and 5% in developing countries in 2002 [1].

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Table 1

Overall age-adjusted (world standard population) mortality rates from hepatocellular carcinoma (HCC) per 100,000 men and women in selected European countries in 1990–1994 and 2000–2004 (unless mentioned in parentheses), and the corresponding change in rates.

	Men				Women			
	1990–1994	2000–2004	Number of deaths	% Change 2000–2004/1990–1994	1990–1994	2000–2004	Number of deaths	% change 2000–2004/1990–1994
Austria	3.71	4.24	301	14.3	0.85	0.92	88	8.2
Croatia	0.88	1.24	47	40.9	0.29	0.37	25	27.6
Czech Republic	3.45	2.76	222	–20.0	1.45	0.99	106	–31.7
Denmark (2000–2001)	0.88	1.49	72	69.3	0.58	0.41	19	–29.3
Finland	3.67	2.69	121	–26.7	2.24	0.91	54	–59.4
France (2000–2003)	6.91	6.79	3313	–1.7	1.02	0.96	704	–5.9
Germany	2.49	2.89	2385	16.1	0.92	0.75	892	–18.5
Greece	0.77	1.55	162	101.3	0.17	0.30	49	76.5
Ireland	0.61	0.78	26	27.9	0.16	0.30	11	87.5
Italy (2000–2002)	8.14	6.72	3601	–17.4	2.49	1.92	1650	–22.9
Lithuania	1.32	1.40	23	6.1	0.44	0.39	23	–11.4
The Netherlands	1.09	1.05	118	–3.7	0.44	0.33	51	–25.0
Norway	0.76	0.96	23	26.3	0.37	0.43	13	16.2
Portugal (2000–2003)	2.12	2.71	236	27.8	0.64	0.68	72	6.3
Spain	4.42	4.92	2130	11.3	1.28	1.53	853	19.5
Sweden (2000–2002)	2.26	0.68	67	–69.9	1.31	0.27	37	–79.4
UK	1.17	1.38	791	17.9	0.38	0.36	244	–5.3
<i>Countries whose data did not allow distinction between HCC and other liver cancers</i>								
Estonia	4.88	5.36	49	9.8	2.16	2.26	34	4.6
Hungary (2000–2003)	8.21	7.72	626	–6.0	3.77	2.92	361	–22.5
Latvia	4.10	5.09	97	24.1	2.11	1.87	42	–11.4
Poland	6.22	4.15	1027	–33.3	4.47	2.65	970	–40.7
Russian Federation	5.56	5.66	4575	1.8	2.43	2.52	3595	3.7
Switzerland	5.60	5.93	374	5.9	1.50	1.75	176	16.7

Number of deaths in the more recent year available.

Within Europe, male overall mortality from HCC increased in Austria, Germany, Switzerland, while decreased in recent years in France and Italy, which showed upward trends up the mid 1990s (Table 1). In the early 2000s the highest HCC rates in men were in France (6.8), Italy (6.7) and Switzerland (5.9), while the lowest ones were in Norway (1.0), Ireland (0.8) and Sweden (0.7). In women, a moderate increase in HCC mortality was observed in Spain and Switzerland, while mortality decreased in several European countries, particularly since the mid 1990s. In the early 2000s, female HCC mortality rates were highest in Italy (1.9/100,000), Switzerland (1.8) and Spain (1.5), and lowest in Greece, Ireland and Sweden (0.3) [5]. Incidence and mortality from liver cancer have been rising among middle age men in the USA [6].

The male to female ratio in liver cancer incidence is about 2.4 and the difference is stronger in high- incidence than in low-incidence areas.

The epidemiology of liver cancer is linked to the incidence and mortality rates from liver cirrhosis, since a large proportion of HCCs develop from cirrhotic liver [7]. The improved survival and reduced mortality from cirrhosis, due to improvements in the prevention and treatment of this condition, have in fact increased the possibility of developing HCC in cirrhotic patients. Of some importance are also the improvements in diagnosis, mainly due to widespread use of ultrasound and measurement of α -fetoprotein since the early 1980s, which led to more frequent detection of neoplastic liver in cirrhotic patients.

The established risk factors for hepatocellular carcinoma include Hepatitis B or C viruses (HBV and HCV) infec-

tion, alcohol drinking, tobacco smoking, and aflatoxin. The suspected risk factors for liver cancer include diet, obesity, diabetes and insulin resistance, use of oral contraceptives, iron overload [7]. In the following, we will review risk factors other than infections with HBV and HCV, which are discussed in a companion paper.

2. Aflatoxin

Ecological studies have shown that the incidence of HCC correlates not only with HBV and HCV infection, but also with contamination of foodstuff with aflatoxins, a group of mycotoxins produced by the fungi *Aspergillus flavus* and *Aspergillus parasiticus*, which cause liver cancer in many species of experimental animals [8]. Contamination originates mainly from improper storage of cereals, peanuts and other vegetables and is prevalent in particular in Africa, South-East Asia and China. The investigation of the carcinogenic role of aflatoxins in humans has been complicated by the inadequacy of traditional methods of exposure assessment (e.g., questionnaires). During the last decades, however, prospective studies have shown a strong association between biological markers of aflatoxin exposure in serum or urine and risk of subsequent liver cancer. A carcinogenic role of aflatoxins, in particular of aflatoxin B₁ (AFB₁), has therefore been confirmed and shown to be independent from – and to interact with – that exerted by HBV infection [7]. AFB₁ frequently induces G:C to T:A transversions at the third base in codon 249 of P53. HBV alone does not affect the mutation rate while the coexistence of AFB₁ exposure was associated with in-

creased mutation prevalence [9]. In area where HBV infection is prevalent, AFB₁ exposure is usually also a problem [7]. HBV infected persons might be benefited by eliminating AFB₁ exposure.

3. Alcohol drinking

Alcohol drinking is associated with an increased risk of liver cancer [10]. A meta-analysis has shown a dose response relationship between alcohol intake and liver cancer with relative risks (RRs) of 1.19 (95% CI = 1.12–1.27), 1.40 (95% CI = 1.25–1.56), and 1.81 (95% CI = 1.50–2.19) for 25, 50, and 100 g of alcohol intake per day, respectively [11]. It is believed that there is no “safety threshold” for the effects of alcohol on liver [12].

The most probable mechanism of alcohol-related liver cancer is through the development of liver cirrhosis [9,13]. In a Swedish cohort study [13], the risk of liver cancer among alcoholisms was 2.3 (95% CI = 2.0–2.7). Among patients who were diagnosed with alcoholism and cirrhosis, the risk increased to 16.5 (95% CI = 12.7–21.2). In addition, HCV infection appeared to accelerate the course of alcoholic liver disease [14] and to cause the development of HCC at a younger age among drinkers than among non-drinkers [15]. Donato et al. [16] examined the association between alcohol intake and HCC among 464 cases and 824 hospital controls. They found that for each level of alcohol intake, the highest risks were observed among subjects with HCV infection, followed by those with HBV infection, and finally by those without hepatitis virus infection, with parallelism between the curves. Furthermore, synergistic interactions between alcohol intake and smoking, obesity and diabetes had been observed [7]. The population attributable risks in Mediterranean area to liver cancer were 28.8% for alcohol, 21.6% for HCV, and 16.2% for HCV and alcohol combined [12]. Alcoholic cirrhosis is probably the most important risk factors for HCC in populations with low prevalence of HBV and HCV infection and low exposure to aflatoxins, such as North America and Northern Europe [17].

The reduction in *per capita* alcohol consumption observed since the 1970s in various countries of southern Europe has likely contributed to the decrease in cirrhosis incidence and mortality in those countries during the last decade, with a consequent impact on HCC mortality, too.

4. Tobacco smoking

Tobacco smoking is causally associated with liver cancer [18]. A meta-analysis on smoking and liver cancer [19] concluded an overall OR of 1.56 (95% CI = 1.29–1.87) comparing current-smokers to never-smokers and of 1.49 (95% CI = 1.06–2.10) comparing former smokers to never-smokers. The associations among current smokers appeared to be consistent with the overall RR regardless of region, study design, study sample size, and publication period.

The synergistic interaction between tobacco smoking and HBV/HCV are inconsistent. A Taiwanese study found a higher RR of tobacco smoking among HBV negative than

among HBV positive subjects [20], while another Japanese study found a higher RR among HBV positive subjects [21], and an Italian study reported an interaction between tobacco smoking and infection with HBV and HCV [22].

5. Dietary factors

Several data have been reported on a potentially favorable effect of coffee on liver function and liver diseases, including liver cancer [23]. Data on coffee and liver cancer are based on at least 10 studies, 6 case-control (from Greece, Italy and Japan) and 4 cohort investigations (all of these from Japan). Overall, the pooled relative risk (RR) was 0.54 (95% confidence interval, CI, 0.39–0.76) for case-control studies, and 0.64 (95% CI 0.56–0.74) for cohort studies [14]. Such an inverse relation may however be spurious, and due to the fact that subjects with a broad spectrum of digestive tract disorders, liver diseases or cirrhosis may reduce their coffee consumption. Indeed, caffeine metabolism is impaired in patients with cirrhosis, who could therefore reduce coffee intake in order to avoid side effects of caffeine. Thus, bias due to reduction of coffee drinking in unhealthy subjects cannot be excluded [23]. The inverse association between long-term coffee consumption and type 2 diabetes was also suggested [24]. It is interesting to investigate the main or joint effect of coffee drinking on the risk of liver cancer with or without the presence of other risk factors.

Green-yellow vegetables were associated with a reduction in liver cancer mortality among Japanese atomic-bomb survivors (RR = 0.81, 95% CI = 0.67–0.97 for “2–4 times per week” and RR = 0.75, 95% CI = 0.60–0.95 for “daily or almost daily” comparing to “once per week or less”, *p* for trend = 0.0092) [25]. However, no evidence has been found in Greece that vegetable intake may reduce the risk of HCC [26]. Nonetheless, a marginally inverse association was implied between milk and dairy products and HCC risk (OR = 0.70, 95% CI = 0.49–1.01). In another case-control study in Italy, investigators observed protective effect from milk and yoghurt (OR = 0.28, 95% CI = 0.13–0.61), white meats (OR = 0.44, 95% CI = 0.20–0.95), eggs (OR = 0.31, 95% CI = 0.14–0.69), and fruits (OR = 0.48, 95% CI = 0.22–1.05) [27]. In conclusion, there is limited suggestive protective effect from fresh fruits; while the evidence for other dietary factors is not conclusive [14]. Most of the evidence on diet and liver cancer is based on case-control studies, and the retrospective assessment of diet is particularly problematic in studies involving chronically ill individuals such as liver cancer patients.

6. Obesity and diabetes

Obesity is now widely recognized as a significant risk for the development of many types of cancers. A meta-analysis [28] found that the relative risks (RR) for liver cancer were 1.17 (95% CI = 1.02–1.34) for those who were overweight (BMI = 25–30) and 1.89 (95% CI = 1.51–2.36) for those who were obese (BMI ≥ 30).

Diabetes, a condition closely associated with obesity, has been proposed as a risk factor for both chronic liver

disease and HCC. A case–control study [29] conducted in Italy found an odds ratio (OR) for liver cancer of 2.1 (95% CI = 1.4–3.2) after adjustment for age, sex, area of residence, alcohol and tobacco consumption, history of hepatitis and liver cirrhosis, BMI, and family history of liver cancer in first-degree relatives.

It is well known that patients with various forms of liver disease can be predisposed to impaired glucose tolerance [30] and suggested that the relationship between diabetes and HCC is a result of HCV infection [31]. However, a cohort study [32] in high hepatitis virus infection area (Taiwan) found that the effect of type 2 diabetes was higher in those with HCV negative than in those with HCV positive (incident HCC cases, adjusted hazard ratio (HR) = 2.08 (95% CI = 1.03–4.18) and 0.62 (95% CI = 0.22–1.76) for HCV negative and positive, respectively). A population-based case–control study [33] conducted in Los Angeles, CA, USA on non-Asian population found an increased risk of HCC among diabetic patients free of HBV/HCV (OR = 3.2, 95% CI = 1.5–6.7) and an interaction with HBV/HCV (OR_{int} = 4.8, 95% CI = 2.7–6.9 on an additive scale). Interaction with drinking (>4 drinks per day) was also observed in the study (OR_{int} = 4.2, 95% CI = 2.6–5.8 on an additive scale).

The potential mechanism from obesity and diabetes to HCC may be through fatty liver or non-alcoholic fatty liver disease (non-alcoholic steatohepatitis, NASH) [34]. However, NASH is usually asymptomatic and difficult to identify until liver cancer or cirrhosis is established. The most important issue now is the temporal ambiguity between diabetes and chronic liver diseases. Whether diabetes is a result of cirrhosis, which in turn predisposes the subject to HCC, or an independent risk factor for HCC, is still under debate. In addition, the effect of duration and treatment of diabetes on the risk of HCC might be worthwhile to investigate.

7. Oral contraceptives

Use of combined estrogen–progestogen oral contraceptives (OC) greatly increases the risk of liver adenomas, and is associated with the risk of HCC, although the absolute risk is likely to be small and has been shown in populations at low HBV risk [35]. Case reports have associated use of anabolic steroids with development of liver cancer, but the evidence is not conclusive at present. A recent meta-analysis was failed to link the use of oral contraception and the risk of HCC due to the huge variation among studies [36]. Future investigations on the duration, intermittency, recency of OC use, effect modification by HBV/HCV, and other reproductive factors might help to improve the knowledge on this aspect.

8. Iron overload

An increase in iron storage in the body is a likely cause of HCC: the evidence comes from studies of patients with hemochromatosis (HH) or other disorders of iron metabolism. Iron was observed to be associated with HCC in a group of patients in their end stage of liver diseases other than HH as well (none: reference; mild: OR = 1.59, 95%

CI = 1.07–2.38; excess: OR = 2.10, 95% CI = 1.25–3.52) [37]. The effect of iron overload seems to be independent from development of cirrhosis and may interact with alcohol and HBV/HCV infections. Most of the HH is associated with HFE gene mutation. HFE mutation seems to be associated with iron overload in patients with end-stage liver diseases and might accelerate hepatic fibrosis in patients with chronic hepatitis C infection [38]. However, results from small studies considering HFE mutations in HCC patients are conflicting, showing either no increased HCC risk [39] or a positive association of iron overload only in the presence of viral or alcohol induced liver damage or cirrhosis [40–42].

9. Types of liver cancer other than HCC

9.1. Hepatoblastoma

Hepatoblastoma is the most common childhood hepatic tumor [7]. It represented 1% of malignancies for children younger than 20 years old with a peak incidence of 11.2/1,000,000 during infancy [46]. The etiology of hepatoblastoma is still unknown. Current knowledge on the cause include Beckwith–Wiedemann syndrome, hemohypertrophy, familial adenomatous polyposis, and Gardner's syndrome. Evidences for parental occupational exposures are not consistent and limited [43].

9.2. Cholangiocarcinoma

Intrahepatic cholangiocarcinoma is the second most frequent type of liver cancer and accounts for about 3% of gastrointestinal cancers worldwide [44]. In most regions of the world the incidence in the range 0.2–2/100,000; the incidence is much higher in areas where liver fluke infestation is common, such as North-East Thailand [7]. During the last decades the incidence has increased in many high-income countries; the reasons of this trend are not known [44]. Infestation with the liver flukes, *Opisthorchis viverrini* and *Clonorchis sinensis*, is the main known cause of this form of malignancy. Infection occurs via consumption of improperly cooked fish. Liver cirrhosis, chronic HCV infection, heavy alcohol consumption [45], obesity, and gallstones [46] were reported to be associated with the malignancy. Other risk factors include inflammatory bowel disease, primary sclerosing cholangitis, and α 1-antitrypsin deficiency [7,44]. Exposure to thorotrast, a contrast medium containing radioactive thorium used for angiography in Europe and Japan during 1930–1955, resulted in an increase of cholangiocarcinoma and of liver angiosarcoma [9].

9.3. Angiosarcoma

Hepatic angiosarcoma is a rare mesenchymal tumor of the liver which usually presents in elderly men [47]. The estimated incidence was about 0.14–0.25/1,000,000 in the USA [48]. Workers exposed to vinyl chloride, a monomer used in the chemical industry for production of the plastic polymer, polyvinyl chloride, experience an increased risk of angiosarcoma. The identification of clusters

of cases of liver angiosarcoma in these workers has led to a drastic reduction in occupational exposure to vinyl chloride.

10. Prevention

The more important way to prevent liver cancer is control of HBV and HCV infection, as discussed in a companion paper. Control of aflatoxin contamination of foodstuffs represents another important preventive measure. While this is easily achieved in high-income countries, its implementation is limited by economic and logistic factors in many high-prevalence regions. Control of alcohol drinking and tobacco smoking represents additional primary preventive measures.

Since about half of HCC, but not normal adult liver, secrete the fetal antigen α -fetoprotein, the detection of this marker has been proposed as a screening method, but its effectiveness has not been demonstrated. No population-based studies are currently available showing a decreased mortality from liver cancer in screened populations.

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