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Hepatic Cancers in Man: Quantitative Perspectives[1,2]

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INTRODUCTION

This report will present a survey of the worldwide distribution and incidence of the various types of malignant hepatic tumors, followed by a discussion of the etiologic factors involved, including consideration of possible approaches to the prevention of these tumors. Finally, speculation will be offered about possible reasons for peculiarities in the incidence of some specific etiologies. It should be noted at the outset that the quantitative data base for hepatic malignancies is even more inaccurate than that for many other types of malignancies. This inaccuracy arises from the fact that incidence rates in the United States are relatively low for the more common tumors which occur frequently in developing countries, where the fragmentation of data yields estimations rather than hard data. Nevertheless, environmental factors seem to play a major role in the production of all hepatic malignancies, although genetic predisposition cannot be excluded.

TYPES AND INCIDENCE OF HEPATIC MALIGNANT TUMORS

Hepatocellular Carcinoma

This is the most common hepatic tumor and one of the most common fatal malignancies worldwide. It has a characteristic geographical distribution (1) in that it is most frequent in Subsaharan African Blacks, with the highest incidence reported in Mozambique (98.2/100,000/year) (2), where in the Shangaans the high incidence of this tumor has inexplicably decreased in the last decade (3). The second highest rate of hepatocellular carcinoma seems to occur in Mainland China, with increasing incidence from the north to the south, and similarly Taiwan has a high rate. Next follow South East Asia, Japan, and India, then, Southern Europe, Greece, Spain, and also Italy, with the lowest incidence in South America, Central and Northern Europe, and the United States. Within these areas there are peculiar geographic pockets of higher incidence, such as, for instance, Vienna (4) and Geneva (5). The rate of occurrence of these tumors is also high in the Oriental population of the United States (6), although this rate is still significantly lower than that found in the countries of their ancestors. The Atlas of Cancer Mortality in the United States (7) indicates a higher incidence of cancer of the biliary passages and liver, unfortunately, not separated from each other, in areas where certain types of industrial plants aggregate. The geographic distribu-

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tion suggests an environmental causation although genetic factors doubtlessly play a role.

In general, the higher the regional incidence, the younger the age group, the more rapid is the evolution of the disease, and the higher is the fraction of this tumor in the allover cancer mortality. About 75% of all hepatocellular cancers worldwide are associated with cirrhosis. The tumor shows male predominance and occurs in almost any age groups. Hepatocellular carcinoma is often multicentric (8) and preferentially invades the portal veins. α-Fetoprotein titers in the serum are high and paraneoplastic features such as hypoglycemia are common. Although this tumor is primarily composed of hepatocytes, ductular carcinomatous features may be present.

Hepatoblastoma

This tumor of the early years of life (9) may consist, in addition to cancerous hepatocytes, of primitive mesenchymal cells. Cirrhosis is absent and metastases occur late. Etiologic factors are difficult to identify.

Intrahepatic Bile Duct Carcinoma

This tumor, which resembles the carcinoma of the extrahepatic biliary passages (10), is less common than hepatocellular carcinoma. It has almost equal sex distribution with questionable female predominance, and little relation to cirrhosis. It is usually unicentric, hard, and desmoplastic and consists of circumscribed white hypovascular nodules within the liver or on its hilus and may produce mucus. The tumor does not invade portal veins and does not cause elevated α-fetoprotein levels. There are rare papillary cystadenocarcinomas which are slowly growing. Intrahepatic bile duct carcinoma seems to be more frequent in the Far East than in Western countries although there is some indication that its incidence has recently increased in the United States. The best known etiologic correlation is with *Clonorchis sinensis* infection in the Far East (11) and it has also been anecdotically associated with isoniazid therapy (12). There is a claimed, but rare, association between tumors of this type and intrahepatic gallstones and cysts. Childhood tumors have been related to maternal exposure (13).

Hepatic Angiosarcoma

This tumor (14) of hepatic endothelial cell origin is usually multicentric. It occurs only rarely in man, but is more common in domestic and experimental animals. In its presence, α-fetoprotein is not increased. A specific etiology (see later) has been established in about 20% of the cases reported in recent surveys in the United States (14) and Great Britain (15).

ETIOLOGIC FACTORS AND APPROACHES TO PREVENTION

The relative frequency of hepatocellular carcinoma among hepatic malignancies and its characteristic geographical distribution facilitate considerations of its etiology and its prevention. Although early detection of this tumor has been made possible by immunologic procedures, particularly the determination of serum α-fetoprotein levels, and by radiologic techniques such as angiography (16), its treatment by surgery and chemotherapy is still unsatisfactory. For this reason, determination of means for the prevention of hepatocellular carcinoma is particularly important.

Frequent Etiologic Factors

Three major etiologic factors seem to account for, or are associated with, the vast majority of the cases of hepatocellular carcinoma.

The first is *hepatitis B infection*, found in highest incidence in the same geographic areas which have the highest incidence of hepatocellular carcinoma (17–19). Hepatitis B infection is indicated by a high frequency of serum markers, either of the surface component of the hepatitis B antigen (s) or of antibodies to the core component (c), reflecting persistent virus replication. In Mozambique, 92.1% of all patients with hepatocellular carcinoma have these markers, in contrast to 34.6% of control subjects (18). This higher frequency of serum markers in patients with hepatocellular carcinoma holds true in all areas of the world, even those where the rate of hepatitis B infection is low. Although conspicuous chronic active hepatitis is occasionally followed by hepatocellular carcinoma (20, 21), in the majority of cases the clinical manifestations of the hepatitis B infection are mild or absent (16, 22, 23). Usually carcinoma develops in asymptomatic hepatitis B carriers, often without biochemical evidence of liver injury; e antigen, a marker of activity, is absent, as a rule (24, 25).

The majority of hepatocellular carcinomas seem to develop in carriers infected by either vertical transmission at birth or in early childhood, when low immune reactivity interferes with the clinical expression of hepatitis. In Africa, high rates of hepatitis B markers in the mothers of patients with carcinoma have been observed, while the fathers were found to have a lower rate of antibodies to HBsAg than the rest of the population (26), suggesting a peculiar immunologic situation. Genetic factors in hepatitis B evolution have also been stressed and were indeed the initial lead to the discovery of the Australia antigen by Blumberg.

The parallel between the hepatitis B carrier rate and the rate of hepatocellular carcinoma appears to be worldwide, and occurs even in specific regions in Greece which vary in carcinoma rates (27). Thus it has been claimed (28) that the risk of hepatocellular carcinoma is the same for the hepatitis B carrier in high-incidence and low-incidence areas, including the United States. This claim is important in view of the estimated almost 200 million hepatitis carriers in the world. The fact that the vast majority of hepatitis B-associated cancers are accompanied by cirrhosis, mainly of the macronodular type, suggests that hepatitis B carriers, despite the low-grade clinical hepatitis, are also at risk to develop cirrhosis, probably in higher incidence than carcinoma (29).

The carriers, particularly those suspected of having been infected by vertical transmission, have large amounts of HBsAg in their hepatocytic cytoplasm, which has a ground-glass appearance (30), and relatively little HBcAg, the marker of the virion, in their hepatocytic nuclei (19, 31). An oncogenic role of the hepatitis B virus can thus be postulated, for which at least two possible mechanisms have to be considered. One of these mechanisms is the incorporation of viral DNA into hepatocytic DNA, the common explanation of viral carcinogenesis (18). So far, however, such incorporation has not been convincingly established for hepatitis B. The second possible mechanism is an epigenetic effect of the excess HBsAg in the hepatocytic smooth endoplasmic reticulum (32), the site of microsomal biotransformation, also acting on chemical carcinogens. This epigenetic effect might alter the response to such carcinogens, putting these cells at risk of carcinomatous

transformation, as suggested by their conspicuous histologic reaction for α-fetoprotein (33).

Experimental observations do suggest an epigenetic effect of other viruses in carcinogenesis (34). Indeed, the epidemiologic evidence for coexistent exposure to aflatoxin has been considered to support the theory of cocarcinogenesis (26). Although marmosets with viral hepatitis (type A or related) appear to be particularly susceptible to aflatoxin-induced hepatocellular carcinoma (35), such an animal model for hepatitis B does not exist. However, regardless of the precise mechanism of hepatitis B-associated hepatocarcinogenesis, the avoidance or elimination of hepatitis B infection is indeed the most promising approach to the prevention of hepatocellular cancer. This purpose might be one of the first applications of the hepatitis B vaccine, now far advanced in development (36). A second approach to the prevention of hepatocellular carcinoma is the inhibition of vertical infection by hyperimmune γ-globulins. This has been attempted repeatedly (37), and also in Taiwan, where the purpose is indeed to prevent cancer (38).

Hepatitis non-A–non-B, for which no markers exist so far, has, unlike hepatitis A but like hepatitis B, a high tendency to chronicity and to a carrier stage, as demonstrated by studies of the transmission of hepatitis non-A–non-B to chimpanzees (39). It is therefore a serious candidate for favoring development of hepatocellular cancer (40).

The second major factor in causation of hepatocellular carcinoma is the *association with chronic alcohol abuse*, which is particularly frequent in areas which have a low hepatitis B carrier rate, such as North America as well as Central and Northern Europe. The cancer related to alcohol abuse is not necessarily associated with cirrhosis (41), which develops in about 15% of chronic alcoholics. However, the incidence of cancer in alcoholic cirrhosis is claimed to be on the increase, particularly among reformed alcoholics (42). This increase might be explained by the longer survival of alcoholic cirrhotics as a result of better medical management. Data in the United States based on autopsy observations (43, 44), reporting an 8–15% incidence of hepatic carcinomas accompanying cirrhosis, are not reliable. Cohort studies in alcoholics (45, 46) have not supported the association between carcinoma and cirrhosis. Data in Europe (47), allowing for variations in age, sex, and autopsy rate, suggest a higher incidence. A study in Malmö (48), uniformly covering an entire city, reported a 15% rate of cancers occurring in conjunction with cirrhosis, but with equal frequency in alcoholics and nonalcoholics. Also, in spite of the higher susceptibility of females to alcoholic liver injury, carcinoma in alcoholics is far more frequent in males. In Chile, peculiarly, high incidence of alcoholic cirrhosis is not associated with high rate of hepatocellular carcinoma; only 50% had cirrhosis and 63% were positive for HBsAg (48a).

The pathogenesis of hepatocellular carcinoma in alcoholics has not been established. In addition to ethanol, other contaminants in alcoholic beverages may be responsible. The cirrhosis itself may favor carcinoma formation either by altering cellular regeneration or by creating higher susceptibility to ubiquitous carcinogens (49). Ethanol, which alters the microsomal biotransformation system, may increase the amount and life span of an ultimate carcinogen derived from other

substances as it enhances the necrotizing effects of carbon tetrachloride (50). Finally, ethanol may be metabolized to carcinogenic free radicals. Evidence for the mutagenicity of ethanol has been presented (51). Carcinomas occur in alcoholics in the pharynx, larynx, and esophagus as well as in the stomach, although the tumors at these sites may be associated with smoking as additional factor. However, because no experimental model exists so far, all explanations of pathogenesis are hypothetical. Even if such links were easily demonstrable, prevention would require changes in life style of the population difficult, if not impossible, to enforce.

The third etiologic or associated factor are mycotoxins, particularly *aflatoxin*, the most potent hepatocarcinogen per unit weight in many species of animals, including primates, but not in adult mice. The metabolic basis of the carcinogenesis of aflatoxin has been well worked out, particularly with respect to specific ultimate carcinogens (52). The human liver is able to metabolize aflatoxin (53), and the causal relationship between aflatoxin exposure and human cancer is strongly suggested but the evidence for that relationship is still as circumstantial as for the other two major factors. That evidence is based on the parallelism of hepatic cancer rates and the aflatoxin content of food contaminated by molds of *Aspergillus flavus* and *parasiticus*, which form the mycotoxin. Quantitative data are available from Thailand, Uganda, Swaziland, Kenya, and Mozambique (54, 55). They also suggest that there is a dose–response relationship between aflatoxin ingestion and hepatocellular carcinoma. Moreover, acute liver injury from aflatoxin has been reported in Taiwan, Uganda (55), and possibly India (56). In addition, a children's disease resembling Reye's syndrome has been reported in Thailand (55). The danger of aflatoxin contamination of food is most acute in hot, moist climates. Because many of the developing countries are in regions where such a climate prevails, prevention of aflatoxin contamination is a formidable hygienic and technologic problem. Evidence for the hepatocarcinogenicity of other mycotoxins, such as sterigmatocystin in South Africa (57) and luteoskyrin in Japan (58), is, so far, restricted to animals. This is also true of plant poisons, such as pyrrolizidine alkaloids (59) and cycads. Malnutrition (except for contaminants) appears not to be a primary cause of cirrhosis and hepatocellular carcinoma (8).

Rare Etiologic Factors

In contrast to the three factors mentioned, seemingly accounting for the vast majority of human hepatocellular carcinomas in the world, but without unassailable proof of causation, there are two groups of etiologic factors for most of which the causal relation to hepatic tumors appears well established. Although the incidence of tumors in those exposed to these groups of factors may be relatively high, these tumors constitute a quantitatively insignificant portion of the total number of hepatic malignancies in man.

1. Sex steroids. The first such group is hepatocellular tumors related to the intake of sex steroids. The administration of relatively large doses of *anabolic steroids* to men and women, primarily for the treatment of aregeneratory anemia, has sometimes been followed by the appearance of benign and, more frequently, by the development of malignant hepatocellular tumors (60, 61). The incidence of

these malignancies has appeared to be highest in children with Fanconi anemia (62). All this suggests a strong causal relation in a relatively small number of patients.

The relationship between the intake of *contraceptive steroids* and the development of hepatic tumors is less convincing (63, 64). Several hundred cases of benign hepatic adenomas in women on contraceptive drugs have been described in the literature and about 700 have been estimated to have occurred; that means about 100 per year (65). This also includes a smaller number of cases of focal nodular hyperplasia (66). This is a very small percentage of the large number of women taking these drugs. Moreover, not all adenomas have been associated with the intake of contraceptive drugs or with pregnancy (67). This is particularly true of focal nodular hyperplasia, which has a female predominance. Nevertheless, geographic considerations suggest a causal association between the use of contraceptive steroids and hepatic adenomas. In Japan, where contraceptive drugs are outlawed, no adenomas have been reported, in spite of a high incidence of hepatocellular cancers. In Central Europe, hepatic adenomas were almost unknown until 3 years ago. These tumors are now observed in relatively high numbers, and their occurrence has paralleled the widespread use of contraceptives in that area in recent years (68). Malignant transformation of adenomas has not been reported. On the contrary, these tumors apparently undergo regression after discontinuation of exposure to the steroids (69). However, in the center of at least one adenoma a carcinoma has been found (70), and the number of hepatocellular carcinomas in women on contraceptive drugs appears to be somewhat higher than expected (71).

Characteristically, all sex steroid-related tumors have developed in the absence of cirrhosis. α-Fetoprotein does not appear to be elevated. An experimental model exists (72).

2. *Industrial and medicinal factors.* The second group with strong causal association but low total number worldwide shows a characteristic morphologic and clinical sequence, best studied in workers exposed to gaseous *vinyl chloride* during its polymerization to the plastic, polyvinyl chloride (14). The entire morphologic sequence of the vinyl chloride-induced human lesion has been duplicated in rodents, mainly by Maltoni in Bologna (63, 73). These observations represent to date the best morphologic correlation between man and experimental animals in the entire sequential development of hepatic malignancy. Indeed, Maltoni's report on the angiosarcoma in rodents was made at about the same time that the association between vinyl chloride exposure and angiosarcoma in plastics workers was recognized (74).

The initial lesion produced in man and rodents by exposure to vinyl chloride is a focal hyperplasia of hepatocytes. This lesion progresses to a circumscribed mixed hyperplasia of hepatocytes and sinusoidal cells, as well as an increased reticulum framework (14). In man, this precursor stage, which is often accompanied by sinusoidal dilatation, may also be associated with portal hypertension and all its consequences. Eventually, the histologic precursor stage progresses to classical angiosarcoma, initially associated with persistent hyperplasia of the hepatocytes. Exposure of newborn rats to vinyl chloride has also induced hepatocellular car-

cinoma (75). A few cases of carcinoma have been reported in man following vinyl chloride exposure (76). Guided by the doses found to be effective in experimental animals, the vinyl chloride concentration permissible in the ambient air of factories has been reduced by regulatory action to levels which should avoid initiation of additional angiosarcomas or their precursor lesions. Because of the long period of promotion in carcinogenesis in general and particularly in factories where low-grade but still dangerous levels of vinyl chloride existed, it is still possible that additional cases of hepatic angiosarcoma will occur in the foreseeable future. To date, 64 angiosarcomas following vinyl chloride exposure in man are on record (77).

The same morphologic and clinical sequence has been observed in a small number of cases following exposure to *inorganic arsenic*, either in Fowler's solution (78, 79) used for the long-term treatment of psoriasis and asthma, or in pesticides applied in vineyards, particularly in Germany (80), where use of arsenic-containing pesticides has been discontinued. In the latter group, carcinoma has been reported. But an experimental counterpart of the arsenic-induced hepatic malignancy does not exist. Possibly, excess arsenic exposure in industrial settings or in drinking water may account for cases of human angiosarcoma without established etiology (81). Such cases may constitute approximately three-fourths of all cases of human angiosarcoma.

The same morphologic sequence, including carcinoma, mainly cholangiocarcinoma, has also been observed in some individuals years after the administration of *thorium dioxide* for radiologic visualization, especially of brain lesions (82, 83). Again, worldwide this sequence represents only a small fraction of all hepatic malignancies, with fewer than 100 known cases. Thorium dioxide administration produces angiosarcoma in animals (84). Other forms of radiation rarely seem to produce hepatic tumors in man (85).

The entire group of tumors induced by sex steroids and environmental agents (the latter causing the sequence terminating usually in angiosarcoma) appears characterized by a relatively small number of cases. However, the strong causal relationship between the etiologic factors and hepatic malignancy is reflected both in animal models and the absence of cirrhosis. In cases of angiosarcoma this relationship is further supported by the rarity of these tumors in the general population. Prevention of both medicinal and industrial exposure appears to be easy and seems, to a great extent, to have been accomplished.

In passing it should be mentioned that a quantitatively small group of hepatocellular carcinomas are associated with *metabolic alterations* (8). Within this group, the most frequent association is with iron overload disease of the type of hemochromatosis. A less common association occurs between hepatocellular carcinoma and porphyria, α_1-antitrypsin deficiency, Wilson's disease, and tyrosinemia (the latter in children).

PECULIARITIES OF HUMAN HEPATIC MALIGNANCIES

Ever since the 1930s, when Yoshida and Kinosita produced hepatocellular carcinoma in rats by chemical agents, an increasing number of such agents have been shown to produce the tumor, often preceded by a nodular lesion, in experimental

animals, including primates (86). The long list of chemical agents known to have hepatic carcinogenic potential in animals includes food additives (such as safrole and ponceau red), pesticides, industrial agents, such as polyhalogenated biphenyls, dioxan, phenobarbital in mice, and many others, which have been listed in many excellent reviews (87, 88). The carcinogenic potential of these agents in animals has led to the assumption that chemical factors cause also hepatocellular carcinoma in man. However, a review of the literature reveals a dearth of information about substantiated carcinomas in man by the large number of these agents (89). For instance, in one case of hepatocellular carcinoma recorded years after injury from carbon tetrachloride, alcoholism was also present (90). The same lack of substantiated information applies to production of human cirrhosis (as a precursor of carcinoma) by these agents and by other industrial compounds. One apparent exception to this are compounds like trinitrotoluene, which have been associated with hypersensitivity reactions (89). Table 1 correlates the rate of incidence, certainty of association, animal models, and approaches to the prevention of different human hepatic malignancies. A reliable estimate as to the total yearly number of cases of hepatocellular carcinoma in the world is impossible. A conservative assumption based on a 5/100,000/year incidence worldwide would account for at least 150,000 cases per year which are presumably induced by the three common factors discussed. This contrasts with at most 30 cases per year worldwide by the known industrial and therapeutic factors.

It should be emphasized that the two apparently most important carcinogens incriminated in human cancer in other organ sites have not been unequivocally associated with hepatocellular carcinoma in man, even though they are metabolized in the human liver. Specifically, polycyclic hydrocarbons do not produce hepatic tumors in any species, and there is no evidence that nitrosocompounds, potent hepatocarcinogens in many species, including primates (86), cause human

TABLE 1
ETIOLOGIC FACTORS IN HUMAN HEPATIC MALIGNANCIES

"Carcinogens"	Incidence	Animal model	Certainty of association	Prevention
Hepatitis B	Highest	0	+	Vaccine Immunoglobulin
Alcoholism	High	0	+	Life style change??
Aflatoxin	High	+	++	Technologic?
Anabolic steroids	Very low	+	+++	Possible
Contraceptive steroids	Very low	+	±	Possible
Vinyl chloride	Very low	++	+++	Possible
Inorganic arsenic	Very low	0	++	Possible
Thorotrast	Very low	+	+++	Possible
Common hepato carcinogens in experimental animals (87, 88)	?	+++	?	

hepatocellular carcinoma. This peculiar protection of the human liver, particularly in adults, can possibly be explained by its biochemical and biological characteristics (91). The liver is rich in hydratases, which can remove ultimate carcinogens; it has high activity of endonucleases, which excise altered DNA; and the turnover of hepatocytes favoring carcinogenic transformation is particularly low.

This does not exclude the possibility that these substances, many of which are stored for a long time in human fat tissue, have effects on hepatic metabolism which are detrimental. In animals, the vast majority of these substances enhance the enzymatic action of the microsomal biotransformation system, which potentially increases both the amount and the life span of the ultimate bioactive carcinogen, which binds to macromolecules, particularly to DNA. This "induction" of the biotransformation occurs in man, but its long-term effects in man are not known except in relation to adverse drug reactions (92). Induction in epileptics as a result of specific drug therapy has not resulted in an increased incidence of tumors which cannot otherwise be explained (93). However, both the establishment of induction in man and its epidemiologic consequences as far as carcinogenesis in the liver and in other organ sites is concerned require further study.

CONCLUSIONS

The geographic distribution of human hepatic malignancies strongly suggests a causative role of environmental factors. The vast majority of malignancies in all areas of the world are usually associated with cirrhosis and one of three factors: hepatitis B infection, alcoholism, or aflatoxin exposure. The greatest chance for the prevention lies in limiting hepatitis B infection. Although they constitute only a very small number of all hepatic malignancies, some tumors not associated with cirrhosis have been caused by industrial and therapeutic factors and prevention of these tumors is being accomplished. However, the correctable environmental, including industrial, burden is small. A large number of common carcinogens in experimental animals, many of them environmental and industrial agents, have so far not been proven to produce hepatic malignancies in man. Nevertheless, these substances may alter the hepatic metabolism with consequences for the liver and other organs which still require establishment. As long as the consequences of exposure to these agents remain unproven, there can be no justification for any relaxation of vigilance.

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