PRIMARY CARCINOMA OF THE LIVER AND ITS ASSOCIATION WITH CIRRHOSIS

A REVIEW OF 54 DEATHS

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It is a common observation that primary carcinoma of the liver is relatively rare among Westerners but is quite frequent among Orientals like the natives of Malaya, Java, China, Japan, India and the Philippines, and also among the Bantu natives of South Africa (5, 6, 8, 9, 10, 11, 12, 13, 29, 31). This striking difference in racial and geographic distribution is of great interest and opens a field for further study that may lead to the elucidation of some factor or factors possibly concerned in the etiology of primary liver carcinoma. The purpose of this paper is to contribute what little it can to the vast knowledge that has already been advanced, to reemphasize the frequent occurrence among Orientals, the Filipinos in particular, of primary liver carcinoma, and to furnish additional evidence of its high frequency of association with cirrhosis.

MATERIAL

The necropsy files of the Department of Pathology, College of Medicine, University of the Philippines covering a four-year period from April 1953 to April 1957 were reviewed. Out of 4,539 autopsies of infants, children and adults, 54 deaths with primary carcinoma of the liver were found, or a percentage of 1.12.

FREQUENCY IN VARIOUS GEOGRAPHIC AREAS

The opening statement that liver carcinoma is more common among Orientals is attested to by the figures in Table 1. These autopsy data may not represent the actual occurrence in

living patients but they are more exact than those obtained from the clinics. Statistics from American and European countries give a range of 0.19 to 0.36 per cent frequency of primary liver carcinoma among necropsied cases. In Asia and Africa it is 0.98 per cent. Our study which consisted of 52 Filipinos and 2 Chinese deaths yielded a higher percentage — 1.12. In 1926, Smith (33) reviewed 872 autopsies of Filipinos and found 12 cases of primary carcinoma of the liver; this gave a higher percentage of 1.4 compared to 1.12 of the present report. The percentage of 0.036 to 0.76 given by Lichtman is the usual range quoted by several authors who have made studies on both Occidental and Oriental populations.

Table 1. COMPARISON OF FREQUENCY OF PRIMARY CARCINOMA, LIVER, AMONG NECROPSIES IN VARIOUS GEOGRAPHIC AREAS

	No. of necropsies	No. with primary Ca, liver	Percentage
Edmondson and Steiner (12) (Los Angeles County Hospital)	48,900	100	0.20
Hoyne and Kernohan (19) (Mayo Clinic)	16,303	31	0.19
Gustafson (15) (Bellevue Hospital)	24,400	62	0.254
Hermosilla et al (17) (South America)	4,337	16	0.36
Literature (American and European) cited by Hoyne and Kernohan (19)	159,144	339	0.227
Lichtman (23) (quotes numerous authors)			0.036-0.76
Literature (Asia and Africa) cited by Hoyne and Kernohan (19)	47,292	465	0.983
Pirie (29) (South Africa)	3,900	36	0.923
Smith (33) (Philippines)	872	12	1.4
Barrera and Dalmacio-Cruz (Philippines)	4,539	54	1.124

ASSOCIATION WITH LIVER CIRRHOSIS

The association of liver carcinoma with a chronic degenerative and regenerative disease of the liver (cirrhosis) is definitely acknowledged and established by numerous authors (2, 5, 12, 19, 20, 21, 25, 28). Table 2 compares the statistics given by different investigators of the incidence of primary carcinoma of the liver associated with cirrhosis. Between the two types of liver carcinoma, the table shows that cholangiocarcinoma or bile duct carcinoma has less association with cirrhosis, the range given by various authors is 18.2 to 52.7 percent in contrast to a greater association with cirrhosis of hepato-carcinoma or liver cell carcinoma, which ranged from 74.1 to 90 per cent. Our study conforms to the above pattern and gave 20 and 89.8 per cent for cholangiocarcinoma and hepato-carcinoma, respectively.

Table 2. ASSOCIATION OF PRIMARY CARCINOMA, LIVER, WITH CIRRHOSIS

	No. of cases of carcinoma, liver	No. of cases associated w/cirrhosis	Percentage
Berk and Lieber (5) (Collected from literature)	Hepato Ca-351		74.1
	Cholangio Ca-131		52.7
Hoyne and Kernohan (19) (Mayo Clinic)	Hepato Ca-20		18.2
	Cholangio Ca-11		75
Anderson (2)	Hepato Ca-		90
	Cholangio Ca-		37-50
Moore (25)	Hepato Ca-		90
	Cholangio Ca-		50
Jaffé and Lafvendahl (20)			90
Edmondson and Steiner (12)	Hepato Ca-		89.2
	Cholangio Ca-		23.5
Peller (28)	41	20	48.8
Barrera and Dalmacio-Cruz (Philippines)	54	45	83.3
	Hepato Ca-49	44	89.8
	Cholangio Ca-5	1	20

From the necropsies which were covered by our study, 155 were found with cirrhosis of different types — Laennec's postnecrotic, parasitic (due to schistosomiasis) and biliary cirrhosis. Table 3 gives a breakdown of the 155 necropsies with cirrhotic livers. It appears that postnecrotic cirrhosis is most closely associated with liver carcinoma. It is perhaps the greater tempo of proliferative and regenerative activity in this type of cirrhosis, exceeding the boundary line of physiological hyperplasia, which predispose to actual neoplastic growth (4, 24, 30).

Table 3. FREQUENCY OF OCCURRENCE OF PRIMARY CARCINOMA OF THE LIVER IN 155 CASES OF CIRRHOSIS

Type of cirrhosis	No. of cirrhosis cases	No. of cases with carcinoma	Percentage
1. Laennec's cirrhosis	71	32	45.07
2. Postnecrotic cirrhosis	19	10	52.64
3. Parasitic cirrhosis (schistosomiasis)	41	3	7.31
4. Biliary cirrhosis	24	—	0.00
Total	155	45	29.03

Table 4 presents a comparison of the frequency of occurrence of carcinoma in cirrhotic livers, given by different investigators. It is interesting to note that our survey gives the highest percentage of 29.03 of cirrhotic liver associated with carcinoma. The range given by foreign authors is only from 3 to 7.5 per cent. Why do a greater proportion of cirrhosis necropsies in the Philippines show liver carcinoma? Dr. Hans Smetana (32) of the Armed Forces Institute of Pathology, Washington, D.C., who came over for a visit to the Philippines, was struck by this significant finding. He examined the slides of several of the cases which were materials for this study and he commented that most of the cases of Laennec's cirrhosis here have some points of difference from Laennec's cirrhosis abroad; cases in the Philippines show more unrest of regenerating liver

cells and larger regenerative nodules. The histopathological picture reminded him very much of the changes in the livers of experimental mice induced by the feeding of butter yellow. Can it be that a substance whose action is analogous to the effects of feeding butter yellow to experimental mice might possibly be invoked as the factor in the production of both the cirrhosis as well as the primary carcinoma of the liver in humans? This is just a casual speculation and exhaustive research is needed, especially about the diet of Filipinos. Sufficient casein and riboflavin in the diet of mice and rats have been found to prevent the development of the hepatic cancer which can be induced by a diet containing azo dyes such as butter yellow (11). Rice and fat in the diet seem to favor the production of hepatic tumors by butter yellow (27). Thus, certain dietary factors appear to predispose the liver to cancerous change, although the actual carcinogenic agent is unknown (11, 14, 18, 21). Al-

Table 4. ASSOCIATION OF CIRRHOSIS WITH PRIMARY CARCINOMA, LIVER, AS FOUND BY VARIOUS WORKERS

	No. of cases of cirrhosis	No. of cases with Ca. liver	Percentage
Berk and Lieber (5) (Collected from literature)	1,989	90	4.5
Sheldon (1935) (31)	Cases of hemochromatosis	—	7.1
Binford, Laurence and Wollenweber (8)	387 cases of hemochromatosis	29	7.5
Anderson (2)	—	—	3 - 7
Moore (25)	—	—	3 - 6
Counseller and McIndoe (10)	127	—	4
Blumenau (9)	198	—	3.5
Peller (28)	—	—	3.29
Barrera and Dalmacio-Cruz (Philippines)	155	45	29.03

though the hepatomagen butter yellow is said not to be widely used in human foodstuff, other azo dyes have wider use and one of these, "oil orange E" (benzeneazo B naphthol), used in coloring margarine in Great Britain has induced hepatomas in mice (22).

FREQUENCY BY SEX AND AGE

The observation in different countries by different authors (2, 6, 10, 12, 13, 15, 16, 25) that liver carcinoma is more common in males than in females has also been seen in our survey and appears to be even more striking. Table 5 shows the sex distribution of liver carcinoma, as associated with the different types of cirrhosis and also the age distribution. The uncorrected sex ratio of male to female is 5.8 to 1. However, it should be noted that for liver carcinoma not associated with cirrhosis, the male to female ratio is reversed and is 1 to 2. Four out of the 6 females with liver carcinoma without cirrhosis, had cholangio-carcinoma, and only 2 had hepato-carcinoma. This is in agreement with the greater number of carcinomas of the extra-hepatic bile ducts and the gall bladder in women. Three of the 4 females with cholangio-carcinoma had a concomitant chronic biliary tract infection, in the form of chronic cholecystitis and/or choledocholithiasis. These factors bring about some etiological implications with regards to occurrence of cholangio-carcinomas.

Primary liver carcinomas occur at all ages, from newborn infants to the very old. The recent review by Bigelow and Wright (7) concludes that 95 acceptable cases in infancy and childhood are now recorded in literature. In adults, the average age in a series of reported cases varies with the total frequency of liver carcinoma in the population. Where the frequency is low, as in Europe and North America, the average age is in the sixth decade as in many other carcinomas; in populations where frequency is high, the average age is lower (12). This observation also holds true in our material in which the average age in both sexes is 37.7 years. The highest average age is in those liver carcinomas associated with Laennec's cirrhosis which is 44.4 years; the lowest in those associated with parasitic cirr-

hosis, 26.6 years. The average age for females is 38.1 years, almost five years younger than the average age for males, which is 42.4 years.

Table 5. SEX AND AGE DISTRIBUTION OF 54 NECROPSIES WITH CARCINOMA, LIVER

	Associated w/Laennec's cirrhosis	Post-necrotic cirrhosis	Parasitic cirrhosis	Without cirrhosis	Total No.	Total Percentage
Number of cases	32 (1 Chinese)	10 (1 Chinese)	3	9	54	100
Sex incidence:						
Male	30	10	3	3	46	85.2
Female	2	—	—	6	8	14.8
Age range:	22-72 yrs.	20-55 yrs.	16-42 yrs	24-67 yr	16-72 yrs.	
Age distribution:						
Below 20 years	—	—	1	—	1	
20-30 years	6	3	1	2	12	
31-40 years	5	4	—	3	12	
41-50 years	7	2	1	2	12	
51-60 years	11	1	—	1	13	
61-70 years	2	—	—	1	3	
Above 70 years	1	—	—	—	1	
Average age	44.4 yrs.	38.3 yrs.	26.6 yrs.	41.3 yrs.	37.7 yrs.	

In an analysis of malignant tumors among Filipinos seen in the U.P. — P.G.H. Medical Center during ten years, 1947 to 1956, primary carcinoma of the liver was 27.11 per cent (ranked No. 1) and 6.73 percent (ranked No. 6) of all carcinomas in autopsy materials in males and females, respectively (3).

QUESTIONABLE CO-CARCINOGENS

Many factors such as malnutrition, (11, 14, 18, 21), parasitism, (29), alcoholism, (11, 21), malaria (21), and viral infections of the liver (24) have been invoked but have not been definitely established to be factors in carcinogenesis. However,

these factors undoubtedly contribute to the total integrity of the liver functionally and structurally, and are significant determinants of how the liver components will react to further injury of whatever sort.

Table 6 gives the results of recorded inquiry into the personal and social histories, and past diseases of some of the 54 patients. A history of birth and/or residence for sometime in an endemic area for schistosomiasis, as Samar, Leyte, Sorsogon, and Mindoro have been recorded in 9 cases. In one of the 3 patients who were verified to have parasitic cirrhosis, a history of endemicity was not elicited, possibly due to failure of the historian to inquire. Inquiry into the history of alcoholism was made only in 18 cases. Twelve cases or 22.2 per cent of the 54 patients were alcoholics. Six patients were definitely non-alcoholics. The determination of whether one's diet is nutritionally sufficient or not is very difficult, especially on the part of the patients. Thus, even with detailed inquiry into the dietary regimen of every patient, data will not be reliable. In this study, there were only 2 with strongly positive history of dietary insufficiency — one from a patient who was a guerilla for five years during World War II, and the other from a beggar. A positive history of malaria in the past, ranging from 1 to 37 years ago was present in 16 cases, or 29.6 per cent of the 54 cases. A history of probable liver disease, possibly hepatitis, sometime in the past, from 8 to 36 years age was elicited in 4 cases. In the 10 cases of postnecrotic cirrhosis, there were only 2 where positive history of probable hepatitis in the past was elicited. It is to be noted that no factor in Table 6 gives a percentage of 50 or more, allowing due consideration for the probable failure of inquiry into the histories of some of the cases. It is indeed accepted that the pattern of organization of the liver, like that of any other gland structure, is not automatically maintained but is dependent on a hierarchy of continuously operating, coordinated stimuli, including those arising from the diet, from the liver itself, and through its secretions, as well as from various endocrine glands (14).

Table 6. PERTINENT DATA ABOUT PERSONAL, SOCIAL HISTORY AND PAST DISEASES OF 54 PATIENTS WITH PRIMARY CARCINOMA, LIVER

	Associated with			Without cirrhosis	Total No. of cases	Per cent of Total
	Portal cirrhosis	Postnecrotic cirrhosis	Parasitic cirrhosis			
Number of Cases	32	10	3	9	54	100
Resided for sometime in endemic area for schistosomiasis	3	2	2	2	9	16.7
Inquiry into history of alcoholism:	12	4	1	1	18	33.3
(+) for alcoholism	7	3	1	1	12	22.2
(−) for alcoholism	5	1	—	—	6	11.1
Definite evidence of dietary deficiency	1	—	—	1	2	4.7
(+) history of malaria in past	12	3	—	1	16	29.6
(+) history of "liver disease" with jaundice 6 or years.	2	2	—	—	4	7.4

COMMENTS

The frequency of cirrhosis as an associated lesion and its role as an etiological factor in liver carcinogenesis is of considerable importance. It is the general impression by nearly everyone (2, 5, 12, 19, 20, 25, 28) who has written on the subject that the frequency of association of cirrhosis with hepatocarcinomas is 75 to 90 per cent and in cholangio-carcinomas, 20 to 25 per cent. The majority (5, 31, 8, 12) believe that cirrhosis precedes and influences the development of carcinoma, while a few (35) believe that cirrhosis is secondary to the carcinoma. In experimental production of hepatic carcinoma by selenium, cirrhosis has been found to precede the development of the cancer (26). Karsner (21) in his personal experience has never seen liver carcinoma without some degree of cirrhosis. Roth and Duncan (30) reported a case of hepato-carcinoma in a two year-old infant following a "giant cell hepatitis" with

subsequent postnecrotic cirrhosis. Wegelin (35), on the other hand, advanced the concept that cirrhosis follows cancer, explaining that as the result of the newgrowth, the liver parenchyma undergoes atrophy and necrosis, thus giving rise to scar tissue formation. A third group (15) believe that cirrhosis and liver carcinoma may have the same provocative factors. Could the high degree of association of liver carcinoma with cirrhosis in our series be explained by this third concept? It is very apparent that the high frequency of liver carcinoma, specifically hepato-carcinomas, in males is due to the fact that cirrhosis is also more frequent in males. Likewise, the fact that cholangio-carcinomas are more frequently found in females is because it is not as frequently associated with cirrhosis as hepato-carcinomas.

However, although it is generally believed that cirrhosis regardless of its course antedates primary carcinoma of the liver, it must always be kept in mind that there are also cases of primary carcinoma which do not develop on a cirrhotic liver.

SUMMARY

1. Fifty four cases of primary carcinoma of the liver were noted among 4,539 necropsies at the Department of Pathology, College of Medicine, University of the Philippines, a percentage of 1.124. Forty nine were hepato-carcinomas, and five were cholangio-carcinomas.

2. Out of the 54 primary liver carcinomas, 45 were associated with cirrhosis, giving a percentage of 83.3 which is not in discrepancy with those reported by different authors abroad. Hepato-carcinoma has a higher frequency of association with cirrhosis than cholangio-carcinoma, 89.8 and 20 per cent, respectively.

In 155 cases of cirrhosis of different types, 45 cases had superimposed carcinoma, giving a percentage of 29.03 per cent which is significantly high in comparison with the figures given by foreign authors.

3. The uncorrected ratio of males to females was 5.8:1 for liver carcinoma in general, but is 1:2 for those liver carcinoma not associated with cirrhosis; more than half of the latter cases

were cholangio-carcinoma. This indicates differences in the etiological factors for these different varieties of tumor.

4. The average age of the patients with liver carcinoma was 37.7 years; this is about 15 years younger than those reported abroad, and is in accord with the observation that in populations where the frequency is high, the average age is lower.

5. No significant data regarding the roles played by schistosoma infection, alcoholism, dietary deficiency, malaria, and previous viral infection of the liver were obtained, although these factors are supposed to play predisposing if not exciting influences in liver carcinogenesis.

6. The possibility of a carcinogen in the diet of Filipinos, the effects of which in the liver are similar to the changes produced by butter yellow in experimental mice, is entertained.

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