A CLOSE ASSOCIATION OF HEPATOCELLULAR CARCINOMA WITH CIRRHOTIC CHANGES AMONG 275,857 PATHOLOGICAL AUTOPSY CASES IN JAPAN DURING 16 YEARS FROM 1958 TO 1973

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Based on the registered autopsy cases since 1958, the association of hepatocellular carcinoma with cirrhotic changes was studied on the 275,857 autopsy cases carried out in Japan during 16 years from 1958 to 1973.

1. The incidence of hepatocellular carcinoma among autopsies has been fairly high compared with Western countries, amounting 2.5 percent (3.5 percent in male and 1.2 percent in female).

2. The incidence of cirrhotic changes among these autopsies was 6.3 percent in male and 4.3 percent in female. Presumably, the majority of cirrhosis in Japan is of multilobular thin septal pattern, which has been popularly called as B type cirrhosis of Nagayo-Miyake's classification or posthepatitic type of Gall's classification.

3. The association of hepatocellular carcinoma with cirrhotic changes is found as 70.0 percent in male and 53.3 percent in female (66.8 percent in total). On the other hand, cirrhotic changes, particularly those above mentioned, are closely associated with hepatocellular carcinoma, and it was found that 23.3 percent of cirrhotic changes (27.2 percent in male and 12.9 percent in female) were associated with hepatocellular carcinoma.

4. Cholangiocellular carcinoma is also associated with cirrhosis to the less extent than hepatocellular carcinoma (20.7 percent in male and 10.7 percent in female), and cirrhotic changes are not associated with cholangiocellular carcinoma.

5. Age incidences of hepatocellular carcinoma, B type cirrhosis and cirrhosis NOS are presented. The peaks are at 55 years old, 60 and 60 respectively.

INTRODUCTION

Based on scanty autopsy cases up to 1940 in Japan, Berman (Berman, 1951) included Japan among the countries showing suspected high incidence of liver cancer in 1950. This high incidence, however, has been repeatedly

confirmed by many pathologists in Japan although their autopsy numbers were comparatively limited (Miyaji et al, 1960; Miyaji, 1965; Miyaji, 1970), Segi and Kurihara (Segi and Kurihara, 1972) have also repeatedly described the high incidence of hepatic malignancies in Japan among 24 countries based on the

cancer mortality. As the matter of fact, the Japanese holds the highest incidence in males and the third in females among these countries. The present report deals with a close association of hepatocellular carcinoma with cirrhotic changes in Japan based on registered autopsy cases during 16 years from 1958 to 1973 inclusive.

MATERIAL AND METHOD

Since 1958, the Annual of the Pathological Autopsy Cases in Japan has been published as a registry of autopsies, and it covers more than 95 percent of the pathological autopsies in Japan each year. From 16 volumes of the Annuals published by the Japanese Pathological Society from 1958 to 1973 each year, every registered cases was recorded on an IBM-type card following a disease code comprising 1,036 pathological findings in addition to age, sex, year of autopsy, source and autopsy number. The cards were counted and assorted with a mark system selector (Tanac).

RESULTS

1. Frequent malignancies among autopsy cases

Six years' autopsy cases from 1968 to 1973 inclusive, 82,871 males and 55,953 females altogether, revealed that the most frequent malignancies were gastric carcinoma followed by leukemia, bronchogenic carcinoma, hepatocellular carcinoma and so on as shown in Table 1. Fig. 1 shows the sites of these malignancies according to sex, and cervical carcinoma was added. As described by Segi and Kurihara (Segi and Kurihara, 1972), malignant neoplasm of the stomach in Japan holds the highest in-

TABLE 1
Frequent malignancies among autopsies in Japan during 6 years from 1968 to 1973

Malignancies	Total number
1 Stomach	20,253
2 Leukemia	9,786
3 Lung	9,149
4 Liver	4,178
5 Malignant lymphoma	3,272
6 Pancreas	3,151
7 Esophagus	2,140
8 Colon	1,770
9 Gallbladder	1,517
10 Rectum	1,480
11 Extrahepatic bile duct	1,361
Uterine cervix	2,341

Fig. 1 Frequent malignancies among autopsies in Japan during 6 years from 1968 to 1973.

cidence among 24 countries, and has been the most frequent one in the Vital Statistics in Japan. These are also reflected on the autopsy cases, and it is noteworthy that the hepatocellular carcinoma ranks the fourth among the frequent malignancies.

2. *Number of total autopsy cases, hepatocellular carcinoma and cirrhosis in comparison with those in the Vital Statistics*

During 16 years from 1958 to 1973, the number of autopsy cases registered were 275,857 in total as shown in Table 2. The number of autopsies reached the peak with 25,407 a year in 1968, and then decreased in 1969 when student riots started at universities almost all over Japan. The number of sex-unknown

cases decreased sharply since 1966 as the author made inquiry whenever sex-unknown or cases of ambiguous pathological findings were found, although the majority of sex-unknown were stillbirths and newborns amounting 33 and 24 percent respectively.

During these 16 years, 7,002 hepatocellular carcinomas and 15,136 cirrhotic changes which were not associated with hepatocellular carcinoma nor cholangiocellular carcinoma were found among autopsies as shown in Tables 3 and 8. These cases were enumerated as such irrespective of lesions of the liver which were described as manifest or latent, and primary or accessory. It did show a gradual increase in number of hepatocellular carcinoma with year more marked in male than in female.

On the other hand, total deaths and

TABLE 2

Number of autopsy cases in Japan during 16 years from 1958 to 1973

Year	Male	Female	Sex unk.	Total
1958	5,231	3,233	150	8,614
1959	5,275	3,571	180	9,026
1960	5,933	3,770	202	9,905
1961	6,951	4,495	206	11,296
1962	7,311	5,074	214	12,599
1963	8,407	5,495	195	14,061
1964	8,900	5,831	245	14,976
1965	10,283	6,565	170	17,018
1966	10,657	7,222	47	17,926
1967	12,558	8,395	97	21,050
1968	15,138	10,199	70	25,407
1969	14,202	9,638	64	23,904
1970	13,034	8,842	83	21,959
1971	13,031	8,750	123	21,904
1972	13,568	9,057	91	22,716
1973	13,898	9,467	131	23,496
Total	164,017	109,572	2,268	275,857

Based on the Annuals of Pathological Autopsy Cases in Japan

TABLE 3

Total number of autopsied hepatocellular carcinoma in Japan (1958-73)

Year	Male	Female	Sex unk.
1958	118	30	1
1959	126	30	0
1960	149	43	0
1961	176	52	0
1962	194	30	0
1963	221	45	1
1964	261	76	2
1965	288	60	0
1966	346	62	0
1967	386	97	5
1968	545	116	0
1969	510	117	0
1970	543	113	0
1971	584	136	0
1972	645	139	2
1973	568	162	0
Total	5,660	1,331	11

deaths due to "malignant primary neoplasm of the liver (ICD 155.0)" and "cirrhosis of the liver (ICD 571)" obtained from the Vital Statistics of the Ministry of Health and Welfare during the same 16 years are shown in Tables 4, 5 and 6. It is clear that only 2.75 percent of male and 2.16 percent of female deaths were autopsied and registered in the Annual of Pathological Autopsy Cases during these 16 years. Assuming that all the clinical diagnoses of hepatocellular carcinoma and cirrhosis were correct as these were listed in the Vital Statistics, it appears as if patients with hepatocellular carcinoma

TABLE 4

Total number of deaths listed in vital statistics and autopsies in Japan during 16 years from 1958 to 1973

	Male	Female
Deaths	5,964,251	5,082,993
Autopsies	164,017	109,572
Ratio	2.75%	2.16%

TABLE 5

Number of hepatocellular carcinoma among vital statistics and autopsies in Japan during 16 years from 1958 to 1973

	Male	Female
Deaths	10,978	6,726
Autopsies	5,660	1,331
Ratio	51.56%	19.79%

TABLE 6

Number of cirrhosis among vital statistics and autopsies in Japan during 16 years from 1958 to 1973

	Male	Female
Deaths	114,600	57,368
Autopsies	10,395	4,741
Ratio	9.07%	8.26%

were autopsied in the ratio of 51.6 percent in male and 19.8 percent in female, and patients with cirrhosis 9.1 percent in male and 8.3 percent in female. These marked discrepancies between autopsy cases and the Vital Statistics are not easily explained, although it is well known that autopsy cases are biased and patients with severe diseases such as hepatocellular carcinoma or cirrhosis are likely to be treated at large and well-organized hospitals, and autopsied when they pass away.

The above figures among autopsy cases do also include hepatocellular carcinoma as well as cirrhosis, which were not recognized or diagnosed clinically. As it will be mentioned later, most of hepatocellular carcinoma in Japan are associated with cirrhosis, and are liable to be covered by clinical symptoms of cirrhosis. In other words, hepatocellular carcinoma are often underdiagnosed, particularly when they are associated with cirrhosis, although the determination of alpha-fetoprotein has made the diagnosis more accurate in recent years (Hirai, 1975). Consequently, it was considered that the number of deaths due to hepatocellular carcinoma would have been higher than that appeared in the Vital Statistics.

3. Association of hepatocellular carcinoma and cholangiocellular carcinoma with cirrhosis

Since Nagayo in 1914 (Nagayo, 1914), a morphological classification of cirrhosis based on the width of septum surrounding pseudolobules has been carried out in Japan. Wide septal cirrhosis as shown in Photo 1 was called as A type cirrhosis, and narrow septal cirrhosis as shown in Photo 2 as B type. The transitional type between A and B type was named as A' type cirrhosis.

Photo 1 A type cirrhosis of Nagayo-Miyake's classification (postnecrotic cirrhosis): Pseudolobules are surrounded by wide septa with fibrosis and cellular infiltration of mainly mononuclear cells.

Photo 2 B type cirrhosis of Nagayo-Miyake's classification (posthepatic or macronodular cirrhosis): Large or multilobular pseudolobules are surrounded by thin septa, and this is the predominant cirrhosis most frequently associated with hepatocellular carcinoma in Japan.

Miyake (Miyake, 1960) added later a transitional type between fibrosis and B type cirrhosis, in which the septum surrounding pseudolobules is not completed, and named it as B' type cirrhosis. Although these classifications do not identify whether it is macronodular, micronodular or mixed, they do correspond well with popular classifications such as Gall's as shown in Table 7.

TABLE 7
Correspondence of Nagayo-Miyake's to Gall's Classification of cirrhosis

Nagayo-Miyake	Gall
B type	Posthepatic
Fatty cirrhosis*	Nutritional
A type	Postnecrotic
A' type	Mixed

* Without fatty change, could be classified as B type.

TABLE 8
Fibrosis and cirrhosis associated with hepatocellular carcinoma among autopsy cases in Japan during 16 years from 1958 to 1973

Year	Sex	Totl	Fibr	Fat C	Bil C	Card	A typ	A' typ	B typ	C NOS	B' typ
1958	M	118	0	0	1	0	1	0	24	44	0
	F	30	0	0	0	0	0	0	0	1	0
1959	M	126	3	0	1	0	0	0	27	29	1
	F	30	1	0	0	0	0	0	3	7	1
1960	M	149	1	0	0	0	3	0	29	61	0
	F	43	0	0	0	0	0	0	5	13	0
1961	M	176	1	0	0	1	6	0	56	54	1
	F	52	2	0	1	0	1	0	12	15	0
1962	M	194	2	0	1	0	5	0	42	89	2
	F	30	0	0	0	1	0	0	11	4	0
1963	M	221	0	0	1	1	13	0	57	72	2
	F	45	1	0	0	1	3	1	1	12	1
1964	M	261	0	0	2	0	21	0	64	87	0
	F	76	2	0	1	0	3	1	14	18	2
1965	M	288	6	0	2	1	14	0	53	110	1
	F	62	0	0	0	0	2	0	12	18	1
1966	M	346	6	0	0	0	18	3	48	117	5
	F	83	1	0	1	1	3	2	12	19	1
1967	M	386	3	0	1	1	20	6	101	132	11
	F	97	2	0	0	0	3	2	16	24	1
1968	M	545	8	1	2	1	23	13	164	173	9
	F	116	0	0	1	0	2	0	37	26	0
1969	M	510	6	0	1	1	25	0	137	201	1
	F	117	2	0	2	1	7	0	18	28	0
1970	M	543	1	1	3	0	37	1	168	167	0
	F	113	0	0	0	1	12	1	24	24	0
1971	M	584	6	1	1	1	37	16	228	142	9
	F	136	0	0	0	0	8	2	32	23	3
1972	M	645	12	0	3	0	55	23	285	102	8
	F	139	3	0	1	0	15	6	51	13	4
1973	M	568	9	1	2	1	45	19	226	70	15
	F	162	0	0	0	0	13	4	56	14	6
Total	M	5,660	64	4	21	8	323	81	1,745	1,650	65
	F	1,331	14	0	7	4	72	19	305	268	20

Fibr=fibrosis, Fat C=fatty cirrhosis, Bil C=biliary cirrhosis, Card=cardiac cirrhosis, A typ=A type cirrhosis, B typ=B type cirrhosis, C NOS=cirrhosis NOS

Based on the above-mentioned Nagayo-Miyake's classification of cirrhosis, various types of cirrhoses associated with hepatocellular carcinoma, cholangiocellular carcinoma and those not associated with these two malignancies found among registered autopsies during 16 years are shown in Tables 8, 9 and 10. Other cirrhotic changes of the liver, such as Wilson's disease, hemochromatosis, Budd-Chiari's disease,

membranous obliteration of inferior vena cava in the hepatic part and primary biliary cirrhosis are not listed as these lesions were very small in number and rarely associated with hepatocellular and cholangiocellular carcinoma.

Tables 11 and 12 show that 70.0 percent of hepatocellular carcinoma in male and 53.3 percent in female are associated with cirrhosis. As a control of hepatocellular carcinoma, the association

TABLE 9
*Fibrosis and cirrhosis associated with intrahepatic cholangiocarcinoma
among autopsies (1958 - 1973)*

Year	Sex	Totl	Fibr	Fat C	Bil C	Card	A typ	A' typ	B typ	C NOS	B' typ
1958	M	30	0	0	0	0	0	0	1	1	0
	F	18	0	0	0	0	0	0	0	0	0
1959	M	21	0	0	1	0	0	0	0	2	0
	F	15	0	0	0	0	0	0	0	0	0
1960	M	41	1	0	3	0	1	0	3	2	0
	F	13	0	0	0	0	0	0	0	0	0
1961	M	26	1	0	0	0	1	0	0	3	2
	F	24	0	0	5	0	1	0	0	1	0
1962	M	37	0	0	2	0	0	0	2	2	0
	F	20	0	0	0	0	0	0	1	2	0
1963	M	31	0	0	1	0	1	0	1	3	1
	F	25	0	0	2	0	1	0	0	0	0
1964	M	41	0	0	2	0	1	0	2	2	0
	F	21	0	0	1	0	1	0	1	1	0
1965	M	63	1	0	7	0	1	0	2	5	0
	F	24	0	0	1	0	1	0	1	1	0
1966	M	50	1	0	6	0	0	0	4	6	0
	F	33	1	0	0	1	0	0	0	2	0
1967	M	94	3	0	13	0	0	0	4	4	0
	F	43	2	0	4	0	0	0	1	1	0
1968	M	79	2	0	3	0	0	0	7	4	0
	F	54	6	0	1	0	1	0	0	0	0
1969	M	68	0	0	4	0	2	0	3	5	0
	F	54	1	0	1	0	0	0	0	0	0
1970	M	59	2	0	2	0	5	0	5	4	0
	F	43	2	0	0	0	0	0	0	0	0
1971	M	76	1	0	4	0	3	0	6	2	0
	F	62	1	0	3	0	0	0	1	1	0
1972	M	81	1	0	1	3	0	0	4	5	0
	F	61	0	0	3	0	0	1	1	2	0
1973	M	151	4	0	11	1	1	0	0	1	0
	F	109	2	0	5	0	0	0	0	1	0
Total	M	948	17	0	60	4	16	0	44	51	3
	F	619	15	0	26	1	5	1	6	12	0

TABLE 10

*Fibrosis and cirrhosis not associated with hepatocellular nor
cholangiocarcinoma among autopsies in Japan (1958 - 1973)*

Year	Sex	Totl	Fibr	Fat C	Bil C	Card	A typ	A' typ	B typ	C NOS	B' typ
1958	M	241	21	2	31	18	25	0	72	70	2
	F	140	11	1	32	11	15	0	30	39	7
1959	M	312	33	2	56	26	28	0	78	82	7
	F	152	19	2	24	12	19	0	36	37	3
1960	M	340	28	2	43	25	46	0	96	93	7
	F	143	20	0	25	11	23	0	26	35	3
1961	M	417	46	5	55	24	52	1	109	121	4
	F	194	25	0	43	12	23	0	38	51	2
1962	M	481	51	8	67	32	53	5	107	145	13
	F	221	34	0	36	18	28	2	44	53	6
1963	M	502	73	9	62	26	64	1	111	141	15
	F	203	28	0	33	18	29	0	33	57	5
1964	M	528	67	4	63	28	78	6	99	169	14
	F	266	36	3	59	13	42	2	42	66	3
1965	M	621	90	8	71	25	81	2	123	209	12
	F	258	30	5	51	15	38	0	49	68	2
1966	M	701	118	3	67	21	113	5	142	219	13
	F	299	63	3	42	16	38	5	43	82	7
1967	M	760	140	13	60	27	76	17	197	217	13
	F	331	66	7	57	22	35	6	62	74	2
1968	M	959	152	20	78	38	134	26	216	282	13
	F	453	72	6	58	23	63	13	74	136	8
1969	M	929	141	22	66	35	136	7	238	266	18
	F	495	88	8	66	25	57	8	106	134	3
1970	M	847	132	13	60	31	158	3	250	196	4
	F	428	76	3	51	20	70	2	107	99	0
1971	M	895	137	19	54	30	136	26	306	160	27
	F	415	87	8	50	27	65	8	91	70	9
1972	M	845	119	24	68	42	131	36	268	136	21
	F	403	66	3	53	13	67	13	121	55	12
1973	M	1,017	141	41	78	23	151	57	346	149	31
	F	340	58	6	26	18	49	13	118	45	7
Total	M	10,395	1,489	195	979	451	1,462	192	2,758	2,655	214
	F	4,741	779	55	706	274	661	72	1,020	1,101	73

TABLE 11

Cirrhotic changes associated and not associated with malignacies(%)

Male	Total	With cirr	Fibr	Fatt	Bili	Card	A	A'	B	Cirr NOS	B'
None	10,395		14.3	1.9	9.4	4.3	14.1	1.8	26.5	25.5	2.1
Hepa.	5,660	3,961	1.6	0.1	0.5	0.2	8.2	2.0	44.1	41.7	1.6
Chol.	948	196	8.7	0	30.6	2.0	8.2	0	22.4	26.0	2.0
Female											
None	4,741		16.4	1.2	14.9	5.8	13.9	1.5	21.5	23.2	1.5
Hepa.	1,331	709	2.0	0	1.0	0.6	10.2	2.7	43.0	37.8	2.8
Chol.	619	66	22.0	0	39.4	1.5	7.6	1.5	9.1	18.2	0

TABLE 12

Association of hepatocellular carcinoma with cirrhotic changes among 275,857 autopsies during 16 years from 1958 to 1973

	Male	Female	Total
Hepatocellular Ca with cirrhot. changes (%)	70.0	53.3	66.8
Cirrhot. changes with hepatocellular Ca (%)	27.2	12.9	23.3

of intrahepatic cholangiocarcinoma (cholangiocellular carcinoma) with cirrhotic changes is shown in Tables 11 and 13. It shows that 20.7 percent of cholangiocellular carcinoma in male and 10.7 percent in female are associated with cirrhotic changes of the liver.

The association of fibrosis of the liver with hepatocellular carcinoma in male and female was found as 1.6 percent and 2.0 percent respectively, as shown in Table 11, which did not show any statistically significant difference of sex. Cholangiocellular carcinoma is also associated with fibrosis of the liver in the ratio of 8.7 percent in male and 22.0 percent in female with statistically significant difference of sex ($P > 0.05$).

As shown in Table 8, there has been an increasing tendency of A and A' type cirrhosis associated with hepatocellular carcinoma from 1958 to 1973. Those cirrroses not associated with hepatocellular carcinoma have also increased in number during the same period of time as shown in Table 10. There was a close association of biliary cirrhosis with cholangiocellular carcinoma compared with hepatocellular carcinoma, due possibly to secondary biliary cirrhosis caused by obstruction of bile duct with neoplasm.

TABLE 13

Association of cholangiocellular carcinoma with cirrhotic changes among 275,857 autopsies during 16 years from 1958 to 1973

	Male	Female	Total
Cholangiocellular Ca with cirrhotic change (%)	20.7	10.7	16.7
Cirrhotic changes with cholangiocellular Ca (%)	1.7	1.4	1.7

Table 11 shows that the majority of cirrroses associated with hepatocellular carcinoma were B type cirrhosis and cirrhosis NOS (Not Otherwise Specified), which amounted to 85.8 per cent in male and 80.8 percent in female. Among cirrroses not associated with hepatocellular and cholangiocellular carcinoma, as shown in Table 10 and 11, B type cirrhosis and cirrhosis NOS were found in the ratio of 50.0 percent in male and 44.7 per cent in female, revealing that these lesions are frequent cirrroses irrespective of the fact that whether these were associated with hepatocellular carcinoma or not.

On the other hand, B type cirrhosis and cirrhosis NOS are closely associated with hepatocellular carcinoma in the ratio of 38.3 and 37.9 percent in male, and 22.9 and 19.4 percent in female respectively. As far as percentages are concerned, a close association of A' and B' type cirrhosis with hepatocellular carcinoma is also noted. The ratio is 29.7 and 23.2 percent in male and 20.7 and 21.5 percent in female. However, the number of these cirrhotic changes is much smaller compared with B type and NOS cirrhosis.

Cholangiocellular carcinoma, in contrast to hepatocellular carcinoma, showed a less association with cirrhosis as

shown in Table 13. It was also noted from Tables 2, 8, 9 and 10 that the frequency of B type cirrhosis among total autopsies is 2.77 percent in male and 1.21 percent in female, and that of cirrhosis NOS 2.65 percent in male and 1.21 per cent in female. From these figures, it is assumed that cholangio-cellular carcinoma has not much to do with any type of cirrhosis except biliary cirrhosis, and cirrhosis itself has almost nothing to do with cholangio-cellular carcinoma.

4. Age-specific incidence of hepatocellular carcinoma and cirrhotic changes

Fig. 2 to 4 illustrate age incidence of hepatocellular carcinoma, B type cirrhosis and cirrhosis NOS in male and female. The peaks of hepatocellular carcinoma in male and female are at

Fig. 2 Age distribution of autopsied patients with hepatocellular carcinoma (1958 - 1973).

Fig. 3 Age distribution of autopsied patients with B type cirrhosis (posthepatic) (1958 - 1973).

Fig. 4 Age distribution of autopsied patients with cirrhosis NOS (1958 - 1973).

the age of 55, and those of B type and NOS cirrhosis are at the age of 60. It was not postulated whether the cirrhotic changes are precursor of hepatocellular carcinoma or not, but slight abnormality of age incidence of B type cirrhosis was noted in male as well as in female. A small crest of cirrhosis NOS at the age group of 0-2 led to the belief that some of them could be attributed to congenital anomalies of the bile duct, as biliary cirrhosis reaches a peak at the age group of 0-2, which was caused mostly by congenital atresia or obstruction of intra- and extra-hepatic bile ducts.

As Fig. 2 shows that comparatively few cases are in the age group younger than 25 years, those cases are deducted in Table 14, which shows hepatocellular carcinoma of older than 25 years of age, to which 96.2 percent of cases (96.8 percent in male and 93.5 percent in female) belonged.

DISCUSSION

Increasing incidence of cirrhosis among autopsy cases has been noted by many authors (Caroli et al, 1970; Knopp, 1967; MacDonald, 1956; Manderson et al, 1965; Purtilo and Gottlieb, 1973; Schmitz, 1971). MacDonald (MacDonald, 1956) has observed an increase of hepatocellular carcinoma among autopsy cases with the increase of cirrhosis in number, and the same effect has been demonstrated by Péquignot (Péquignot et al, 1967), Epstein (Epstein, 1964), Manderson (Manderson et al, 1965), and Elkington (Elkington et al, 1963). However, the incidences of hepatocellular carcinoma in their autopsy cases have been much smaller than those of Japan, 3.26 percent in male and 1.13 percent in female as shown in Table 15. Most of these figures were

TABLE 14
Frequency of hepatocellular carcinoma among autopsies of over 25-years-old during 16 years from 1958 to 1973

Year	Total		Hepat. Ca.	
	M	F	M	F
1958	3,763	2,201	114	28
1959	3,749	2,451	115	30
1960	4,316	2,573	138	40
1961	4,834	3,166	164	46
1962	5,293	3,535	190	28
1963	6,209	3,904	210	43
1964	6,697	4,098	253	67
1965	7,662	4,602	283	56
1966	8,138	5,274	337	77
1967	9,589	6,163	373	94
1968	11,824	7,737	531	105
1969	11,165	7,362	492	108
1970	10,322	6,788	531	105
1971	10,319	6,627	573	128
1972	10,723	6,959	625	134
1973	11,118	7,253	551	156
Total	125,72	180,69	5,480	1,245

less than 1 percent except for those from Africa (G. Thomson), India (Srinivasa and Sharman, 1968) and China (Ying et al, 1963). On the other hand, the incidence of cirrhosis among autopsy cases in Japan, taking cirrhosis of unknown etiology (A, A', B, B' type and NOS), was 5.44 percent (6.87 percent in male and 3.32 in female) and 3.73 percent (4.43 percent in male and 2.67 percent in female) excluding those associated with hepatocellular and cholangiocellular carcinoma, as calculated from Tables 8, 9 and 10. These figures were not large compared with those of other countries, as shown in Table 16. Hence, it is noted that the incidence of hepatocellular carcinoma is considerably high among autopsy cases and in the Vital Statistics in

spite of the fact that the incidence of cirrhosis is not high compared with other countries. However, the cirrhosis in Japan, mostly B type and NOS, is

extraordinarily frequently associated with hepatocellular carcinoma, thus elevating the incidence of hepatocellular carcinoma to certain extent.

TABLE 15

Frequency of hepatocellular carcinoma and cholangiocarcinoma among autopsy cases in the world

Author(s)	Country	Number of autopsies	Number of H. C.	% of H. C.	Number of cholangiocarcinoma.
Edmondson and Steiner (1954)	U. S. A.	48,900	75	0.15	18
Köhn, K. (1955)	Germany	35,745	80	0.22	-
Roulet, F. C. (1977)	Switzerland	23,470	93	0.40	16
MacDonald, R. A. (1956)	U. S. A.	23,114	80	-	24
Berman, C. (1958)	South Africa	15,280	248	1.62	-
Gall, E. A. (1960)	U. S. A.	12,200 (over 21 y.)	76	0.62	20
Becker and Chatgidakis (1961)	South Africa	4,949 (white)	9	0.18	0
"	"	4,893 (native)	84	1.72	6
Wainwright, J. (1961)	South Africa	2,560	102	3.98	14
Shanmugaratnam, K. (1961)	Singapore	9,893	103	-	9
Glennert, J. (1961)	Denmark	14,881	50	0.34	36
Tiktiniski, O. L. (1961)	U. S. S. R.	6,163	17	0.28	-
Ying et al. (1963)	China	3,497	87	2.49	10
Elkington et al. (1963)	England	7,366	39	0.53	-
Sagebiel et al. (1963)	U. S. A.	23,275	100	0.43	-
Sundarsanam et al. (1963)	India	3,400	22	0.65	2
Miyai and Reubner (1963)	U. S. A.	25,000	64	0.26	8
Ervasti, J. (1964)	Finland	15,545	45	0.29	29
Patton and Horn (1964)	U. S. A.	12,980	47	0.36	13
Epstein, S. (1964)	U. S. A.	3,079	50	1.62	-
Saragoca et al. (1964)	Portugal	168	6	3.57	-
"	"	4,338	14	0.32	-
Ohlsson and Nordén (1965)	Sweden	8,837	120	1.36	1
San Jose et al. (1965)	U. S. A.	12,687	73	0.58	6
Manderson et al. (1965)	England	6,586	41	0.62	-
Ottolenghi, A. (1966)	Italy	6,241	94	1.51	-
"	"	4,000	124	3.10	-
Péquignot et al. (1967)	France	2,540	42	1.65	-
Voigt and Helbig (1968)	Germany	26,235	75	0.29	42
Srinivasa and Sharma (1938)	India	1,293	29	2.24	2
Wöckel and Altrock (1968)	Germany	15,568	40	0.26	-
Sievers, B.-U. (1973)	Germany	4,411	36	0.82	11
Purtilo and Gottlieb (1973)	U. S. A.	14,000	84	0.60	12
Elsner and Jauregui (1974)	Argentina	22,170	54	0.24	10

H. C., hepatocellular carcinoma.

With the progress of treatment of cirrhosis, cirrhotic patients can expect a longer survival than before, which has been attributed to an increasing incidence of hepatocellular carcinoma (Caroli et al., 1970; MacDonald, 1956; Péquignot et al., 1967). However, as

mentioned above, the incidence of cirrhosis among autopsy cases is not high compared with Western countries, yet cirrhotic changes in Japan has shown a close association with hepatocellular carcinoma. It is considered that the background of Japanese people might be

TABLE 16
Frequency of cirrhosis among autopsy cases in the world

Author(s)	Country	Number of autopsies	Number of cirrhosis ^a	% of cirrhosis
Hall and Sun (1951)	U. S. A.	12,000	490	4.08
Meyer, P. G. (1951)	Germany	20,295	575	2.83
Lunzenauer, K. (1955)	Germany	26,515	603	2.27
Parker, R. G. F. (1957)	England	17,732	184	1.04
Dible, J. H. (1957)	England	7,217	109	1.51
Gall, E. A. (1960)	U. S. A.	16,332	654	-
Riva and Weiner (1960)	Switzerland	5,482	331	6.04
Börner, F. (1961)	Germany	3,129	142	4.54
Thomson, G. (1961)	South Africa	1,473 (white)	77	5.23
		1,319 (colored)	22	1.67
		358 (aborigine)	22	6.15
Becker and Chatgidakis (1961)	South Africa	4,949 (white)	291	5.88
		4,893 (aborigine)	242	4.95
Wainwright, J. (1961)	South Africa	1,326 (white)	95	7.16
		2,560 (aborigine)	183	7.15
Shanmugaratnam, K. (1961)	Singapore	9,893	353	3.57
Knopp, J. (1961)	Germany	55,587	1,628	2.93
		5,175	555	10.72
MacDonald, R. A. (1956)	U. S. A.	23,114	1,824	7.89
Tung et al. (1964)	China	6,468	-	9.49
Elkington et al. (1963)	England	7,366	157	2.13
Miyai and Ruebner (1963)	U. S. A.	25,000	446	1.86
Borel, C. A. (1964)	Switzerland	10,000	787	7.87
Ervasti, J. (1964)	Finland	15,545	478	3.07
Ohlsson and Norden (1965)	Sweden	8,837	271	3.07
Ottolenghi, A. (1966)	Italy	6,241	649	10.40
Péquignot, H. et al. (1967)	France	2,540	373	14.69
Voigt and Helbig (1968)	Germany	26,235	1,166	4.44
Wöckel and Altrock (1968)	Germany	15,568	458	2.94
Lopez-Corella et al. (1968)	Mexico	6,558	880	13.42
Purtilo and Gottlieb (1973)	U. S. A.	14,000	-	11.5
Elsner and Jauregui (1974)	Argentina	22,170	805	3.63

^a Cirrheses of known etiology such as biliary and cardiac were excluded as much as possible.

different from Western people in respect to viral infection, nutritional status, environmental factors, ethnic and demographic characteristics.

Alcoholic beverages have been implicated in cirrhosis as a potential cause. Recently, Purtilo and Gottlieb (Purtilo and Gottlieb, 1973) have reported progressively increased frequency of cirrhosis and hepatocellular carcinoma, especially cirrhosis associated with chronic alcoholism in Boston City Hospital. They noted that alcoholic cirrhosis or fatty nutritional cirrhosis increased from 31 percent (1971-1926) to 61 percent (1955-1968). Sievers (Sievers, 1973) also reported that as an etiological cause of cirrhosis, chronic alcoholism was found to the extent of 46.8 percent. Leevy et al. (Leevy et al., 1964) demonstrated by multiple biopsies that alcoholic cirrhosis sometimes progressed to postnecrotic cirrhosis, hemochromatosis and hepatoma. Sakurai (Sakurai, 1969), who has studied the influence of alcohol in the development cirrhosis on 4,032 consecutive autopsies in Japan, reported that there was remarkable influence of Japanese rice wine on the production of cirrhosis, as there was marked difference between drinkers and nondrinker among patients with cirrhosis and hepatoma. However, he also added that Japanese rice wine is mildly toxic to the liver, and it was exceptionally rare to see typical histologic features of alcoholic liver disease in Japan.

From the peculiar geographical distribution of hepatocellular carcinoma in the world, nutritional deficiency has been considered as an important cause of the lesion (Berman, 1951). It is possible that undernutrition might make the liver liable to be injured by noxious agents (Kasliwa and Gupta, 1963), particularly in view of the fact that incidences of hepatocellular carcinoma of

colored and Asian people lowered sharply when they immigrated to the United States. Koizumi and others (Koizumi et al., 1971) studied dietary habits of 30 patients with hepatocellular carcinoma and found that there was a difference concerning calory, protein and vegetables compared with the controls when they were young, and had a tendency of less intake of protein all through their lives.

Viral hepatitis undoubtedly has close association with cirrhosis, and it has been demonstrated by epidemiological studies and by use of multiple biopsies that viral hepatitis transformed into cirrhosis and sometimes developed hepatocellular carcinoma in the long run (Kosaka, 1963; Nielsen, 1971; Prince, 1970; Purtilo and Gottlieb, 1973). Since the discovery of hepatitis B antigen (HBAg) by G. S. Blumberg in 1965, association of viral hepatitis with cirrhosis became more evident (Prince, 1970; Nishioka, 1972), and familial clustering of HBAg has been demonstrated (Ohbayashi et al., 1972; Ohbayashi and Mayumi, 1974). HBAg has been positive in 34.1 percent of cirrhosis and in 48.3 percent of hepatocellular carcinoma (Nishioka, 1972). However, very few patients suffering from viral hepatitis develop cirrhosis and hepatocellular carcinoma, and the reason for this exception remains to be studied.

Aflatoxin has been found as a potent carcinogen to the liver, and Alpert (Alpert et al., 1969) found 29.6 percent of 480 food samples collected in Uganda contained aflatoxin at detectable levels, and 3.7 percent of them contained more than 1 ng/kg. He also added that in the area of high incidence of hepatocellular carcinoma the frequency of aflatoxin contamination was particularly high. Japan is a country where many fermented products have been consumed, and fungus producing afla-

toxin was isolated (Kurata, 1968). Other mycotoxins have been also studied (Saito, 1972), but it was not established that they have any meaning to frequent hepatocellular carcinoma in Japan.

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