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Changing Incidence of Hepatocellular Carcinoma in Japan

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ABSTRACT

A trend in the incidence of hepatocellular carcinoma (HCC) in Japan was studied from the data of the Osaka Cancer Registry (population, 8,512,351 in 1981) for the period of 1963–1983, the Vital Statistics of Japan, Ministry of Health and Welfare, and the Japan Autopsy Registry which contained 594,132 individually filed cases in the 26-year period from 1958 to 1983. Both cancer registry data and autopsy records showed a more than 2-fold increase in HCC incidence, particularly in the last 10 years or so, among males and a less pronounced increase in females. The same trend was borne out by the cancer registries of Nagasaki City and Miyagi Prefecture and the Vital Statistics. When studied with the autopsy data, it was found that the numbers of autopsies for cirrhosis without HCC and autopsies for HCC (with and without cirrhosis) were about the same in 1958–1961 and that currently (1980–1983) the latter is about 2 times the former. As one of the possible causes of increase in HCC incidence other than prolonged survival of patients with cirrhosis, chronic non-A, non-B hepatitis is discussed.

INTRODUCTION

HCC[2] is one of the most malignant solid tumors and has a very poor prognosis. Despite the recent progress in early diagnosis and therapeutic measures the overall fatality rate has not changed appreciably (1). This cancer has a peculiar global distribution and it is now known to be closely related to hepatitis B viral infection (2). Southeast Asia is second to Mozambique in the incidence rate of HCC and Japan is among the intermediate incidence countries (3).

There is a recent unanimous opinion among gastroenterologists in Japan that they are seeing many more patients with HCC than before; pathologists also believe that there were more deaths due to cirrhosis alone in the past but that the majority of cirrhotic livers autopsied now have complicating HCC. However, there are no epidemiological data to validate these notions. This study, therefore, was undertaken to elucidate the recent trend in the incidence of HCC in relation to cirrhosis in Japan based on the Osaka Cancer Registry, the Vital Statistics of Japan produced by the Ministry of Health and Welfare of Japan, the Annual Autopsy Registry, and autopsy records at the University of Tokyo. The epidemiological data were taken from two other cancer registries of long establishment for comparison with those from the Osaka Cancer Registry.

MATERIALS AND METHODS

Osaka Prefecture Cancer Registry. The Osaka Prefectural Health Department began its cancer registry in collaboration with the Osaka Medical Association and the Center for Adult Diseases, Osaka, in 1962. This cancer registry is now regarded as one of the most reliable registries in the country, covering 8.5 million population in 1981. In the past 10 years, the rate of cancer cases registered from death certificates only was 22–26%, and that for liver cancer was 32% in 1981–1983. The reliability of this registry may be assessed from the data shown in Table 1 in which the rate of hospitalization among all registered patients was more than 90% after 1978 and the frequency of microscopically confirmed cases (tissue and cytology diagnosis) among them was 85.1% for all malignancies in 1981–1983. The rate of microscopic diagnosis for liver cancer was 51% in 1981–1983. One of the reasons for the lower rate of microscopic diagnosis for liver cancer is that the diagnosis of HCC is possible in most patients without biopsy in Japan due to improved imaging and α-fetoprotein measurements (4).

Hepatic secondaries are much less common at the clinical setting in Africa and Far East including Japan and misdiagnosis of metastatic for primary liver cancer is rather uncommon compared to western countries (3, 4). As shown in Table 2, the number of deaths due to metastatic liver cancer in mortality statistics has been very small compared with that due to all liver cancers. The liver cancers not specified as primary or secondary include some deaths due to metastatic liver cancer. However, even if this category consisted of only metastatic cancers (such assumption is totally unacceptable in Japan), still there were more deaths due to primary liver cancer than to metastatic liver cancer.

To confirm the trend of incidence data in Osaka, two other cancer registries of long establishment within the country were utilized, Nagasaki City Tumor Registry (data provided by Professor A. Ikeda) and Miyagi Prefectural Tumor Registry (Dr. A. Takano). In these three registries including the Osaka registry, cancer site has been classified by the 4-digit system of the ICD. In order to minimize the biases in classification of liver cancer caused by progress in diagnosis and knowledge, we defined liver cancer in this paper as "primary liver cancer plus liver cancer not specified as primary or secondary." Therefore, liver cancer in morbidity statistics includes ICD No. 155 + 156 in ICD-7, 155.0 + 197.8 in ICD-8, and 155.2 in ICD-9, although cases in Osaka classified by ICD-7 (before 1967) were reclassified by the ICD-8 system.

Vital Statistics of Japan Compiled by the Ministry of Health and Welfare. The Japanese Ministry of Health and Welfare files and publishes annually the "Vital Statistics" of the nation which contains all statistics related to health (5). The statistics for liver cancer has been prepared as a sum of primary liver cancer, liver cancer not specified as primary or secondary, and metastatic liver cancer. It is expressed in ICD code number as 155 + 156 in ICD-7, 155 + 197.8 + 197.7 in ICD-8, and 155 + 199.1C (metastatic liver cancer) in ICD-9. As shown in Table 2. the number of deaths due to metastatic cancer and cancer of the intrahepatic bile duct has been very low. Therefore, the definition of liver cancer in the vital (mortality) statistics is actually very similar to that in the morbidity statistics.

National Autopsy Registry of Japan. The Japan Society of Pathology began compiling all autopsies in 1958. All autopsies performed at major hospitals are filed every year with the Society as individual cases with the information on age, sex, residence, clinical diagnoses, principal disease diagnosed by histopathological examination, coexistent lesions and diseases, and treatments. The society prints all cases in a thick volume each year. The first year (1958) registered 9,297 cases, and the number of autopsies registered each year increased steadily to the recent figures of about 40,000 yearly. They constitute approximately 90% of all autopsies carried out in this country. Each volume carries analyses of malignancies with respect to the number of cases, sex, age distribution, and histological types. The total of listed autopsies in the past 26 years has been 594,132 of which 311,436 are malignant cases. Autopsy data on cirrhosis and liver cancer up to 1973 were computer analyzed by Miyaji (6) and his data have been utilized; the data after 1974 have been similarly analyzed by one of the authors (Y. U.).

Autopsy Records at the University of Tokyo. The University of Tokyo Faculty of Medicine has the longest history of human autopsy in Japan; therefore, the autopsy records at the Department of Pathology, Uni-

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[2] The abbreviations used are: HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; ICD, International Classification of Diseases.

Table 1 *Osaka Cancer Registry*

1980 Registry			
Primary site	No. of patients registered	% hospitalized (at least once)	% microscopically confirmed
All sites	12,006	91.3	83.3
Stomach	3,471	91.4	84.5
Liver	1,055	93.7	51.4
Pancreas	347	92.0	90.5
Colon	605	93.7	77.7

Trends in 15 years						
	% registered by death certificate only		% hospitalized (at least once)		% microscopically confirmed	
Period	All sites	Liver	All sites	Liver	All sites	Liver
1966–1968	27.8	44.2	70.5	64.6	49.4	24.6
1972–1975	25.7	39.9	80.7	80.2	64.0	40.8
1978–1980	25.3	36.6	90.4	92.4	82.1	56.8
1981–1983	21.7	32.2	93.3	94.7	85.1	50.5

Table 2 *Annual deaths due to primary liver cancer, liver cancer not specified as primary or secondary, and metastatic liver cancer in mortality statistics in Japan, 1979–1984, both sexes*

Cause of death (Code no. in ICD-9)	No. of deaths in each year					
	1979	1980	1981	1982	1983	1984
Primary liver cancer (155.0)	8,078	8,758	9,598	10,521	11,453	12,283
Liver cancer, not specified as primary or secondary (155.2)	5,252	5,106	5,146	5,223	5,284	5,401
Metastatic liver cancer (199.1C)	463	442	578	697	760	786
Total	13,793	14,306	15,322	16,441	17,497	18,470
Intrahepatic bile duct (155.1)	93	104	103	116	149	137

versity of Tokyo Faculty of Medicine, were analyzed for the time trend of primary liver cancer.

RESULTS

Time Trend in Incidence Rate of Liver Cancer in Osaka (Cancer Registry). In males (1981 population, 4,218,107), the age-adjusted incidence rate of all malignancies has been rather constant since 1966 except for a slight increase in the last 5 years or so. Whereas esophagus and stomach cancers showed a definite decline, primary liver cancer increased from 16.3 per 100,000/population adjusted to the world population in 1966–1968, to 35.6 in 1983, more than doubled (Table 3). Of the other cancers that increased, gallbladder and bile duct cancer and colon cancer showed the most marked increase. In females (population, 4,294,244), the incidence rate of all malignancies has been very constant for the past 20 years. Stomach cancer decreased, bile duct cancer showed the most striking increase, and lung and pancreas cancers were on a mild increase. Liver cancer started to increase after 1980, but the increment is small. In this registry, histological diagnosis was available in only about one-half of the liver cancer cases, because diagnosis is obvious from increased α-fetoprotein levels and coexistent cirrhosis, not requiring biopsy which often causes intraabdominal bleeding as HCC is highly arterialized. Table 4 gives the trend of age-adjusted incidence rates of liver cancer in the Nagasaki City and Miyagi Prefecture Registries. In both Nagasaki and Miyagi, there has been a similar trend although its magnitude was less and the obvious increase was noted more recently.

Intrahepatic bile duct carcinoma (cholangiocarcinoma) constitutes a certain proportion of primary liver cancers, but HCC is by far the commonest as shown in Table 5 which is based on the autopsy Registry.

Time Trend in Mortality Rate of Liver Cancer in the Vital Statistics of Japan, Ministry of Health and Welfare. From the Annual Vital Statistics of Japan, Ministry of Health and Welfare, the age-adjusted death rates of malignancies in some of the major organs are given in Table 6, which also clearly demonstrates a trend for increase of liver cancer among males, but not in females. The predominant cancer of the liver in Japan is HCC, and the increase of HCC among males is also supported by the vital statistics. The increase in cancer death rate is also apparent with the colon, gallbladder, and biliary tract and lung.

Relative Frequency of HCC among Autopsies. The numbers of all autopsies, autopsies for all malignancies, and those for HCC during the last 10 years show steady increases in relative frequency of HCC among malignancies in both sexes. In the past 26 years, the relative proportion of malignancies among all autopsies increased from 38.4% (3,577 of 9,297) in 1958 to 57.7% (22,833 out of 39,583) in 1983. This trend is perhaps due to the progress in diagnosis and changes in the interest on the part of physicians and surgeons in these years. The incidence of HCC in both sexes combined relative to all autopsies and autopsies for malignancies is given in Fig. 1. The relative frequency of HCC has been increasing at a sharp angle in the recent 12 years or so, whether among all autopsies or among all malignancies. There is no reason why liver cancer was more

Table 3 *Age-adjusted incidence rates of malignancies in the Osaka Cancer Registry (4,218,107 male and 4,294,244 female population, 1981)*
Rates have been adjusted to the world population (14).

Year	All sites	Esophagus	Stomach	Colon	Rectum	Liver	Gallbladder, bile duct	Pancreas	Lung	Urinary bladder	Leukemia and malignant lymphoma
Males											
1966–1968	207.0	9.7	98.2	4.8	6.1	16.3	1.5	5.5	20.1	5.3	8.1
1969–1971	202.3	9.1	89.2	5.6	6.8	15.8	2.4	5.5	22.5	5.4	8.6
1972–1974	202.7	9.0	83.0	6.2	7.4	17.4	2.6	5.5	26.1	5.9	9.2
1975–1977	212.8	8.3	78.0	8.6	8.5	21.2	3.2	6.0	31.5	5.8	10.8
1978–1980	225.6	7.5	74.1	10.2	9.4	26.7	4.2	7.2	34.1	6.8	11.1
1981–1982	244.4	7.8	75.1	12.5	10.4	34.2	5.2	7.8	36.0	7.6	12.7
1983	243.2	7.2	70.6	12.6	10.6	35.6	5.4	8.3	36.6	7.4	12.7
Females											
1966–1968	150.5	3.4	48.8	3.8	4.8	7.2	1.3	2.8	6.2	1.9	4.7
1969–1971	144.2	2.9	44.7	4.7	4.6	7.0	2.1	3.1	6.7	1.5	5.6
1972–1974	143.7	2.4	41.9	4.7	4.6	6.9	2.9	3.3	8.2	1.7	5.8
1975–1977	141.3	2.0	38.6	6.2	5.0	6.3	3.1	3.5	8.9	1.6	6.6
1978–1980	143.3	2.2	36.1	7.2	5.4	6.9	3.9	4.1	9.7	2.0	6.8
1981–1982	149.2	2.0	34.0	8.6	6.2	8.3	4.5	4.6	10.5	1.7	7.5
1983	147.3	1.9	31.7	8.5	5.9	8.9	4.9	5.1	10.5	2.0	7.7

Table 4 *Trends of age-adjusted incidence rates of liver cancer in the Miyagi and Nagasaki City Tumor Registries in Japan*

Rates have been adjusted to the world population (14). Sources of data: Fujimoto *et al.* (41); and Hanai *et al.* (42).

Nagasaki City			Miyagi Prefecture		
Year	Male	Female	Year	Male	Female
1963–1967	24.6	11.9	1962–1964	9.1	5.7
			1965–1967	9.6	5.5
1968–1972	24.9	8.9	1968–1970	9.5	4.9
			1971–1973	9.9	3.9
1974–1976	20.9	7.0	1974–1976	8.7	4.0
1977–1979	26.1	8.0	1977–1979	10.6	4.3
1980–1982	27.5	8.4	1980–1982	11.9	3.9

Table 5 *Ratio of hepatocellular carcinoma to cholangiocarcinoma among primary liver cancers (National Autopsy Registry)*

Year	No. of hepatocelluar carcinoma cases (H)	No. of cholangio-carcinoma cases (C)[a]	H:C ratio
1955–1966	779	143	5.45
1967–1969[b]	1,115	260	4.29
1970–1971	1,376	242	5.69
1972–1973	1,516	338	4.49
1974–1975	1,758	322	5.46
1976–1977	2,270	377	6.02
1978–1979	3,113	442	7.04
1980–1981	4,131	667	6.19
1982–1983	4,921	702	7.01

[a] Cholangiocarcinoma after 1974 includes poorly differentiated primary liver cancer.

[b] The year 1968 is not included because of an error in the statistics.

selectively admitted to large hospitals and autopsied than other malignancies.

Relative Frequency of HCC among Autopsies at the University of Tokyo. The autopsy records at the Department of Pathology, Tokyo University, showed that the relative frequency of HCC in males rose to 12.58% in 1970–1983 after a long period of a rather constant frequency (4.84–6.03%) in 1900–1969. No such trend was apparent among females (Table 7).

Changes in Age Distribution of HCC Patients. When age distribution of HCC autopsies was analyzed it was noted that the age distribution curve for HCC shifted slightly to older ages in males. In 1958–1961, the peak age was 50–54 years with a median age of 52.92 years, whereas in 1983 it was shifted to 55–59 years with a median age of 59.85 years, and the difference analyzed by the Mann-Whitney test was significant ($P < 0.001$). This shift might be due to the increased size of aged population. However, in the 1983 distribution, a second peak is apparent in 65–69 years beside the main peak in 55–59 years. It could indicate that there is another group of patients generally older than the main group. This same trend has been more apparent in females; the median age was 54.57 years in 1958–1961 and 66.65 years in 1983 ($P < 0.001$).

Time Trends in Mortality Rate of Cirrhosis (Vital Statistics) and Relative Frequencies of Cirrhosis Associated and Not Associated with HCC (Autopsy Registry). It is well established that the majority of HCCs arise on the background of liver cirrhosis (7, 8) and that more than 80% of HCCs have cirrhosis in Japan (9, 10). If cirrhosis itself increases, HCC will also increase proportionally. Regrettably, no statistics are available on incidence rate of liver cirrhosis in Japan. Therefore, mortality rate was studied. Table 8 gives the age-adjusted mortality rates of liver cirrhosis and chronic liver disease (ICD 571) and time trends based on the Vital Statistics of Ministry of Health and Welfare from 1955–1984. The mortality rate increased up to 1975 and then decreased among males in Japan. For females, the rates are gradually decreasing in Japan.

The autopsy registry data were analyzed with respect to the relative frequency of cirrhosis alone (excluding biliary cirrhosis and hepatic fibrosis) and of cirrhosis complicated by HCC comparing the periods of 1958–1961 and 1980–1983 as described in "Materials and Methods." To represent the northern part of Japan, University Hokkaido, University of Hirosaki, Tohoku University, Sapporo Medical College, and Iwate Medical College were selected and cases autopsied there were analyzed. To represent a central region or the Tokyo area, the University of Tokyo, Keio University, and Chiba University were chosen; and for the south, University of Kyushu, Kurume University, Nagasaki University, and Kumamoto University all on Kyushu Island were selected. The number of autopsies studied for the period of 1958–1961 was 11,317 cases and for the period of 1980–1983 it was 13,111 cases. As shown in Fig. 2, in 1958–1961 the number of cirrhosis cases alone (253 cases) and the number of HCC with or without cirrhosis (245 cases) were about equal, and there was no difference among the three regions. In 1980–1983, there were 305 cases of cirrhosis alone, 648 cases of cirrhosis with HCC, and 277 cases of HCC without cirrhosis. Thus, the number of HCCs far exceeded that of cirrhosis alone in recent years and more of the cirrhotic livers were associated with HCC at autopsy. Furthermore, this trend was much more apparent in the south compared to the north. Some of these cases with cirrhosis complicated by HCC could have been diagnosed as simple cirrhosis cases in death certificates without autopsy, and it is expected that the national statistics based on death certificates will register some of the cirrhosis + HCC cases as cirrhosis.

A similar analysis was made of 311,436 autopsy cases in the past 10 years. In this study, all types of cirrhosis and hepatic

Table 6 *Age-adjusted mortality rates of malignancies and time trends in the Vital Statistics of Japan, Ministry of Health and Welfare*

Rates have been adjusted to the 1935 population of Japan.

Year	All sites	Esophagus	Stomach	Colon	Rectum	Liver	Gallbladder, bile duct	Pancreas	Lung	Urinary bladder	Leukemia and malignant lymphoma
Males											
1965	96.5	4.5	46.3	2.1	3.2	8.2	1.6	2.9	8.6	1.3	9.7
1970	96.6	5.1	42.3	2.5	3.1	8.6	1.9	3.7	10.5	1.4	10.2
1975	94.4	4.6	36.5	3.2	3.7	8.5	2.3	3.9	12.6	1.3	10.9
1980	97.2	4.6	31.4	3.9	4.0	11.0	2.8	4.7	15.3	1.5	11.0
1982	96.6	4.4	28.7	4.2	3.9	12.0	2.9	4.9	16.5	1.4	10.9
1984	97.7	4.3	27.5	4.6	4.0	12.9	3.1	4.9	17.1	1.2	10.8
Females											
1965	78.0	1.7	28.5	2.5	2.9	5.7	1.7	2.2	3.8	0.7	7.0
1970	75.3	1.6	26.7	2.8	3.0	5.0	2.5	2.6	4.2	0.7	7.4
1975	71.2	1.3	22.7	3.4	3.2	4.4	3.0	2.9	5.6	0.7	7.9
1980	68.7	1.1	19.2	3.9	2.9	4.3	3.6	3.3	5.6	0.7	7.7
1982	66.5	1.0	17.3	4.2	2.8	4.3	3.8	3.4	5.9	0.6	7.7
1984	66.6	0.9	16.1	4.4	2.8	4.3	4.2	3.4	6.1	0.6	7.8

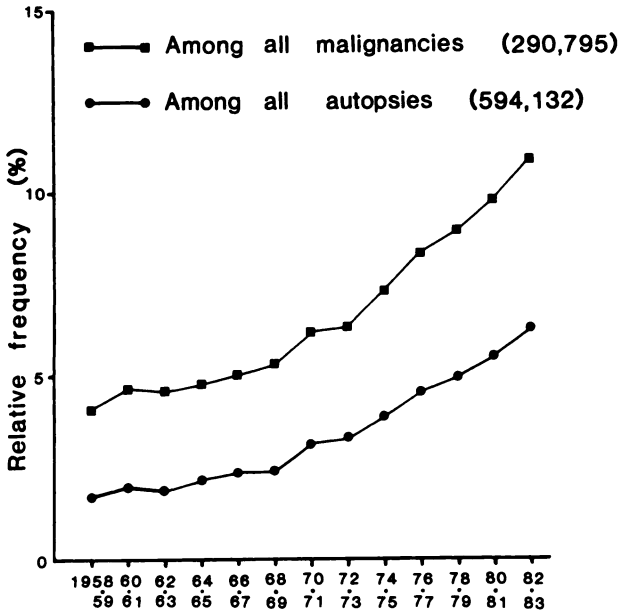

Fig. 1. Relative frequency of HCC among all autopsies (594,132) and all autopsies for malignant diseases (290,795 cases) in the Japan Autopsy Registry in 1958–1983. It was 1.90% of all autopsies in 1958–1959 and it steadily increased reaching 6.28% in 1982–1983. Similarly, the relative frequency of HCC among all autopsies for malignancies was 4.10% in 1958–1959 and it rose to 11.65% in 1982–1983.

Table 7 *Relative frequency of primary liver cancer among all malignant neoplasms autopsied at the University of Tokyo*

	Male		Female	
Year	All malignancies	Liver cancer (%)	All malignancies	Liver cancer (%)
1900–1919	863	52 (6.03)	405	11 (2.72)
1920–1939	806	39 (4.84)	331	8 (2.42)
1940–1959	1,448	84 (5.80)	781	26 (3.33)
1960–1969	1,437	81 (5.64)	806	16 (1.99)
1970–1983	1,932	243 (12.58)	926	25 (2.70)

Table 8 *Age-adjusted mortality rates of liver cirrhosis and chronic liver disease and time trends in Japan based on the Vital Statistics of Japan, Ministry of Health and Welfare*

Rates have been adjusted to the population of Japan in 1935.

	Mortality (per 100,000 population)	
Year	Male	Female
1955	9.5	6.5
1960	10.5	6.2
1965	10.8	6.6
1970	13.1	5.6
1975	14.0	4.9
1980	13.3	4.5
1982	12.4	4.3
1983	12.3	4.3
1984	11.9	4.2

fibrosis were included. As shown in Fig. 3, the frequency of cirrhosis alone has been constant whereas those of cirrhosis plus HCC and all HCC (including those with and without cirrhosis) have been steadily increasing and surpassing the former.

DISCUSSION

Cancer registration is usually far from perfect and in countries where a particular cancer is prevalent, death certificate figures may be preferred (11). However, the Osaka Cancer Registry is sufficiently reliable as discussed and the remarkable trend for increasing liver cancer in the past 15 years or so

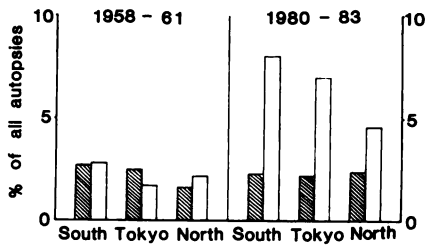

Fig. 2. Relative frequencies of cirrhosis alone ■ and of HCC □ (associated and not associate with cirrhosis) based on autopsy records comparing the past (1958–1961) and present (1980–1983) in three areas of Japan, each being represented by 3 to 5 major university hospitals. Note that in 1958–1961, cirrhosis alone and HCC were about the same in frequency among all autopsies, but the relative frequency has markedly changed and HCC is now much more frequently seen at the autopsy table. The relative frequency of cirrhosis alone has not changed in these years. In this study, biliary cirrhosis and hepatic fibrosis were not included in cirrhosis.

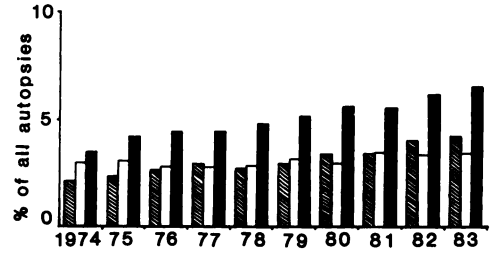

Fig. 3. Changes in relative incidence of cirrhosis with ■ and without (□) HCC and of HCC (■) among all autopsies in the past 10 years. The number of cirrhosis alone cases (without complicating HCC) was about equal to that of HCC before 1974. The relative frequency of HCC has been steadily increasing whereas that of cirrhosis has remained unchanged. Cirrhosis included biliary cirrhosis and hepatic fibrosis.

among males shown by this registry seems to be a real one, as the same but less marked trend was corroborated by the cancer registries of Nagasaki City and Miyagi Prefecture and the Vital Statistics of Japan, Ministry of Health and Welfare. It is established that liver cancer is less frequent in the northern part of Japan such as Miyagi Prefecture than the southwestern part (Nagasaki), and the data in Fig. 2 clearly show the difference. Although the liver cancer incidence rate is higher among Koreans living in the Osaka area, they constitute only 1.9% of the population studied in this cancer registry (12) and will not affect the overall trend appreciably. Autopsy records are accurate in terms of cancer origin and histological diagnosis but are biased in epidemiological information. The relative proportion of autopsied males and females depends largely on the socioeconomic status of the country, and certain diseases are more often autopsied than others. Autopsy constitutes only a small fraction of all deaths in that community. However, in large cities like Tokyo, autopsies represent as much as 20% of all deaths due to malignancies and an incidence among all autopsies provides the minimum incidence rate for that particular disease.

Although treatment of liver cancer has been improved in recent years, ultimate death from the disease is almost unavoidable (13) and the relative frequency of HCC among all autopsies for malignancies provides a reliable information on the trend. The discrepancy in the time trend in relative frequency of HCC in females between cancer registry and autopsy study is not well understood, but perhaps the former showing a mild increase only in the past several years is more reliable.

Saracci and Repetto (14) analyzed the three volumes of *Cancer Incidence in Five Continents* (15–17) for the years 1951 and 1972 and calculated that HCC significantly increased in 17 of 37 populations (45.9%) in males and in 10 (27.0%) in females whereas a significant decrease was demonstrated in only one

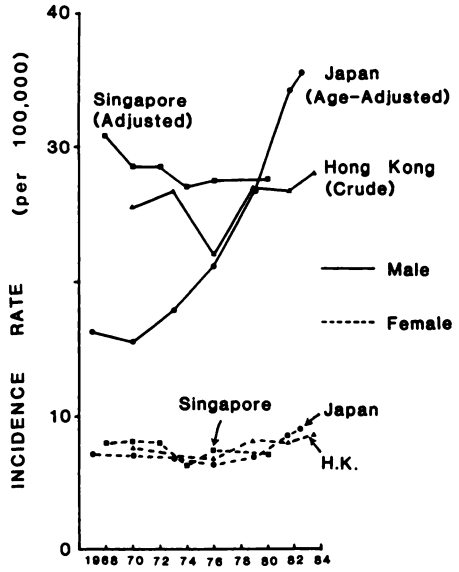

Fig. 4. Time trends in the incidence rate of primary liver cancer in Japan, Singapore, and Hong Kong. Whereas the age-adjusted or crude rate of primary liver cancer in males has been rather constant during the past 15 years or so in Singapore and Hong Kong (*H. K.*), it rose at a sharp angle in Japan. By contrast, the incidence among females has been much lower and the increase in Japan is not as prominent as that in males.

male population (El Paso, Latins in the United States). The most remarkable increase in males was seen in two Polish city registries followed by the Bombay registry. However, no such increase has been noted in Southeast Asia; the Singapore Cancer Registry (18)[3] showed rather a slight decrease during the period from 1968 to 1982, and a study in Hong Kong based on cancer registry and death certificates showed no increase (19).[4] Fig. 4 compares Osaka, Singapore, and Hong Kong in the time trends in incidence rate for primary liver cancer. The increase in Japan is pronounced with a sharp rise. In China, a steady increase was noted during the period of 1963–1975 in Shanghai and Quidong (20). Several reports have appeared based on autopsies that dealt with the time trend, all showing increases; one at the Boston City Hospital from 1917 to 1968 (21), at Wuppertal, Germany, from 1931 to 1980 (22), at Los Angeles from 1954 to 1973 (8), at Florence, Italy (23), etc.

The following was observed in this study: (*a*) male mortality rate of liver cirrhosis decreased in the period of 1975–1984; (*b*) male mortality rate and incidence rate of liver cancer increased in the same period; (*c*) the magnitude of increase of liver cancer was greater than that of decrease of liver cirrhosis; and (*d*) the age distribution of HCC cases was shifted to older ages. These may reflect the fact that male cirrhotics now live longer and some of them develop HCC or the presence of another type of cirrhosis that gives rise to HCC at older ages. It is established that cirrhosis itself (24), particularly the macronodular variety, whether posthepatitic or alcoholic, gives rise to HCC most frequently (25).

It is not likely, however, that prolonged survival of cirrhotic patients alone will account for the large increment of HCC cases in excess of the past incidence rate. One candidate as a cause of increased HCC is non-A non-B hepatitis (26, 27). In the past 10 years or so, Japanese physicians are experiencing increasing numbers of patients with cirrhosis and HCC who have no hepatitis B seromarkers and who had blood transfusions in the long past, 20 to 35 years earlier, for various medical reasons, often for operations for pulmonary tuberculosis during the postwar period. In a recent study on 108 cases of HCC in Tokyo, 40% had a history of past blood transfusion with an average time lapse of 20 years (28). There was a period when commercial blood banks collected blood from professional donors and as many as 80% of patients developed posttransfusion hepatitis after major surgical operations in this country. It is now well established that more than one-half of patients with acute non-A non-B hepatitis develop chronic hepatitis and many of them terminate in cirrhosis (29, 30). The positivity rate for HBsAg among HCC cases which had been about 50% (31, 32) [it is about 90% in Taiwan (33)] has steadily declined to less than 30% in a national study in Japan (34–36). In other words, hepatitis B virus unrelated HCC seems to be increasing in this country. Reports on patients with non-A non-B hepatitis who developed HCC are increasing (37) at the same time. It has been suggested that HBsAg negative HCC patients tend to be older at cancer detection compared with HBsAg positive cases (27). At the moment, no serological markers for non-A non-B hepatitis virus are available to corroborate the suspected involvement of this virus in the cause of cirrhosis and HCC.

Another possibility is an increase of hepatocarcinogens in our environment. Most known hepatocarcinogens are biotransformed by the liver cells to carcinogenic derivatives and are excreted into bile. It is interesting to postulate that increased levels of hepatocarcinogens will affect the biliary tract mucosa and cause more frequent biliary tract carcinomas. Although the rise in the incidence of biliary tract carcinomas in the autopsy records was not as acute as that shown by the Osaka Cancer Registry, a similarly acute, 3-fold increase (1983:1960) has been tabulated by the Japan Ministry of Welfare Vital Statistics. Ethanol is not a strong hepatocarcinogen in itself although it enhances the activity of the mixed function oxidase which converts some of the organic compounds to carcinogens; the slope of increasing consumption of this hepatotoxin does not parallel the acute rise in HCC incidence. The mortality due to cirrhosis rather showed a decrease (Table 7). Smoking is yet another possible factor (38, 39), but the smoking population is decreasing in Japan (40).

The reason for male preponderance in HCC is not well understood. Chronic liver diseases including chronic hepatitis and cirrhosis are much more common in males, and the greater increase in HCC among males may be explained by whatever mechanism predisposes males to chronic liver disease to a greater extent than females.

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