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TRENDS IN MORTALITY FROM PRIMARY LIVER CANCER, CIRRHOSIS OF THE LIVER, VIRUS HEPATITIS, AND OTHER LIVER DISEASES 1968–1984 IN JAPAN

ZHU-MIN HUANG, M.D., RYUICHIRO SASAKI, M.D., and KUNIO AOKI, M.D.

Department of Preventive Medicine, Nagoya University School of Medicine, Tsurumai-cho, Showa-ku, Nagoya 466, Japan

ABSTRACT

The trends in mortality from liver cancer and its allied liver diseases in Japan indicated substantial changes over time. The age-adjusted mortality rates from all liver diseases for men were stable during the 17 years 1968–1984, but those for women showed a slightly declining curve. A slightly declining curve in the mortality rates from liver cancer that paralleled that of those for liver cirrhosis was also observed in women. For other liver diseases that excluded cancer, cirrhosis, and infections hepatitis, a continuous declining trend was observed for both sexes. The decreasing trend, however, was more rapid in women than in men. The mortality curve for liver cancer in men rose after 1975, but the curve for liver cirrhosis in men was seen to decline. The intersection of these two trend curves in 1983 is a manifestation worthy of notice in the current study of liver diseases. The increasing trend of liver cancer was demonstrated by calculation of the consistency of clinical diagnosis with pathological findings by autopsy. Etiological factors yet to be determined may be attributable to the excessive consumption of alcohol in certain age groups and to the particular circumstances to which people born in 1920–34 were exposed.

Key Words: primary liver cancer, cirrhosis of the liver, age-adjusted mortality, birth cohort.

INTRODUCTION

In many Asian and African countries primary liver cancer has had the first or second highest common mortality rate among deaths from cancer of all sites. High incidence and mortality have also been found in Middle and South America, and Eastern Mediterranean countries. However, in Western Europe and Northern America, the mortality rates are lower.

Mortality from primary liver cancer ranked third among the deaths from cancer of all sites for males in Japan 1978–79.[1] The significant increase in the deaths from liver cancer especially among men aged 40 years and older has attracted attention in the last decade.[2] The proportion of hepatocellular carcinoma among all the autopsies in Japan during the 20-year period from 1959 to 1978 also showed an increasing trend,[3] although these autopsy cases were not randomly selected among all deaths in Japan.

The purpose of the present study was to observe trends in the mortality rate from primary liver cancer by sex and age in the period 1968–84 and to investigate the correlation between liver cancer and liver cirrhosis, infectious hepatitis, and other liver deseases.

黄志明，佐々木隆一郎，青木国雄

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MATERIALS AND METHODS

The data of mortality from all liver diseases used in this paper were based on Vital Statistics of Japan published by the Statistics and Information Department, Minister's Secretariat, Ministry of Health and Welfare.[4] According to the eighth and ninth revisions of the International Classification of Diseases (ICD), all liver diseases were classified as shown in Table 1.

Table 1. International classification of diseases

	The 8th Revision (1965)
155	Malignant neoplasm of the liver and intrahepatic bile ducts, specified as primary
	155.0 Liver
	155.1 Intrahepatic bile ducts
	197.8 Malignant neoplasm of the liver, unspecified
070	Infectious hepatitis
570	Acute and subacute necrosis of the liver
571	Cirrhosis of the liver
572	Pyogenic hepatitis and liver abscess
573	Other liver diseases
	The 9th Revision (1975)
155	Malignant neoplasm of the liver and intrahepatic bile ducts
	155.0 Liver, specified as primary
	155.0A Liver, specified as primary
	155.0B Only recorded liver cancer
	155.1 Intrahepatic bile ducts
	155.2 Malignant neoplasm of the liver, unspecified
070	Virus hepatitis
570	Acute and subacute necrosis of the liver
571	Chronic liver diseases and cirrhosis of the liver
572	Pyogenic hepatitis and liver abscess
573	Other liver diseases

To compare the data before 1978 with those after 1979, the cases of death from ICD-155 and ICD-197.8 in 1968–1978 were combined as the deaths from liver cancer. In addition, the diseases coded as ICD-570 and ICD-572 were added to ICD-573 as other liver diseases. The death rates from primary liver cancer before 1967 could not be compared with those form 1968 to 1984, because of the different ICD classification.

The age-adjusted mortality rates from the four kinds of liver diseases by sex were calculated using the Segi-Doll's world standard population.[5] Age-specific mortality rates were confined to the age-ranges from 35 years and over because deaths from primary liver cancer were rare under the age of 35. The rate for those aged 70 years and over was computed as one group.

Autopsy records published by the Japanese Pathological Society were reviewed to confirm the accuracy of clinical diagnosis during the study period.[6]

RESULTS

Time Trends

Trends in age-adjusted mortality rates from all liver diseases (ICD 155, 197.8, 070, 570, 571, 572, 573), and the four groups in 1968–1984, were shown in Figures 1 and 2.

The age-adjusted mortality rates from all liver diseases remained stable for men during the 17-year study period, but they showed a slightly declining curve for women. The age-adjusted mortality rates from liver cancer for men slightly but steadily increased after 1975, although the trend had been stable until 1974. The rates rose from 12.1 per 100,000 population in 1975 to 17.4 in 1984. If the period 1975–1984 were divided into two five-year parts, the average rates in increase were similar: 3.93% in the first five years and 3.29% in the latter five years. The trend in the mortality rate from liver cirrhosis had also been stable before 1975, but a gradual decrease in the rate could be seen after 1975. The rate declined from 19.2 per 100,000 population in 1975 to 16.1 in 1984. The average rates of decrease were 0.72% and 2.11% in each five-year period, respectively, showing a greater declining trend in the more recent five-year period. The two curves related to liver cancer and liver cirrhosis showed inverse trends and interested each other in 1983. In women, the age-adjusted death rates from liver cancer and liver cirrhosis showed similar declining trends and both curves seemed to run parallelly. The mortality rates from other liver diseases for both men and women continuously declined with time but the decreasing trend in women was more acute than that in men. For infectious hepatitis, the mortality trend curve before 1972 had sharply increased in both men and women, then leveled off and remained stationary.

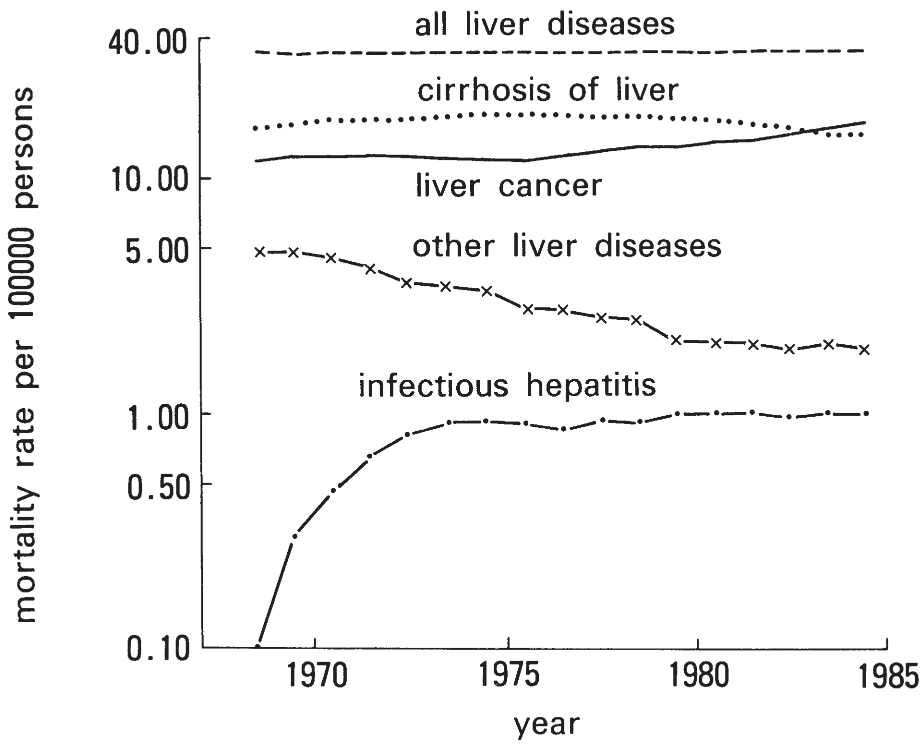

Fig. 1 Trends in age-adjusted mortality rate from liver diseases for men in Japan 1968–1984

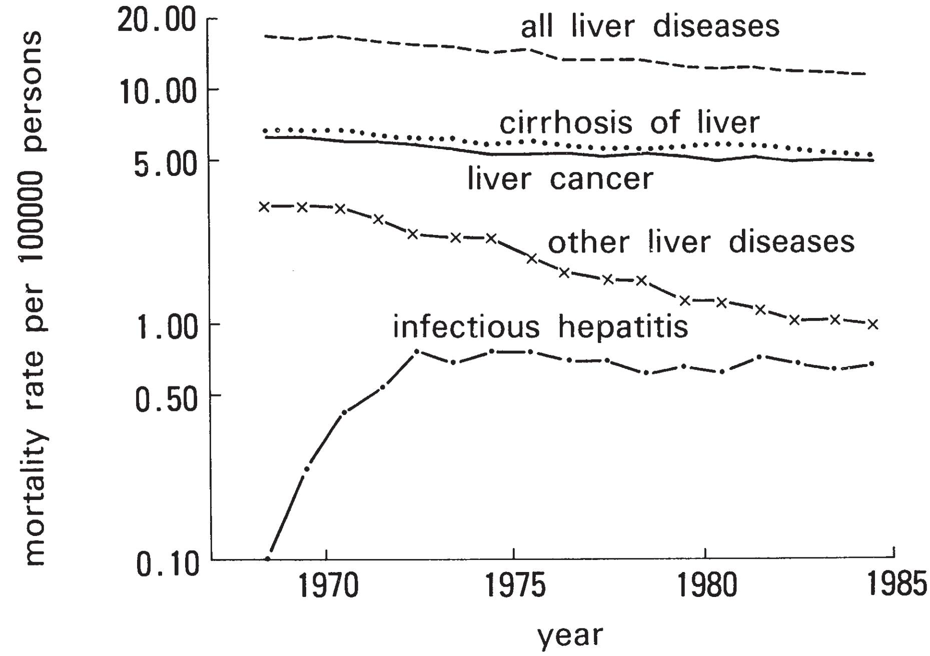

Fig. 2 Trends in age-adjusted mortality rate from liver diseases for women in Japan 1968–1984

Age Patterns

The mortality rate from primary liver cancer in the 45- to 64-year-old age groups for men had been stable before 1974, then increased gradually. However, the rate in the 40- to 44-year-old group showed a levelling off after 1980 (Fig. 3). The rise in the trend curve for the 50- to 54-year-old group was the steepest among those for the groups aged 45–64 years. The death rate in the group aged 50–54 years doubled from 22.9 per 100,000 population in 1975 to 47.9 in 1984. The average rate in increase per year was 10.9%, but in the groups aged 45–49, 55–59, and 60–64, the rate was not remarkable, ranging from 4.4% to 7.5% per year. The groups aged 44 years and less showed similar stable trends, but for those aged 65 years and older, the trends showed a very slight increase for the last decade. For liver cirrhosis (Fig. 4), the rising trends in the 45–49 and 50–54 age groups for men were remarkable. The death rates for the age group of 50–54 years increased steadily after 1978, increasing from 47.13 per 100,000 in 1978 to 59.00 in 1984. The mortality rates in the group aged 45–49 years showed a small peak in 1979, then levelled down slightly. In the groups aged older than 55 years, slightly, but continuously decreasing trends could be observed after 1975, and a remarkable decreasing trend in the 35–39-year-old group was seen as depicted in Fig. 4. The group aged 40–44 years showed an intermediate trend between those of the groups aged 35–39 years and 45–49 years.

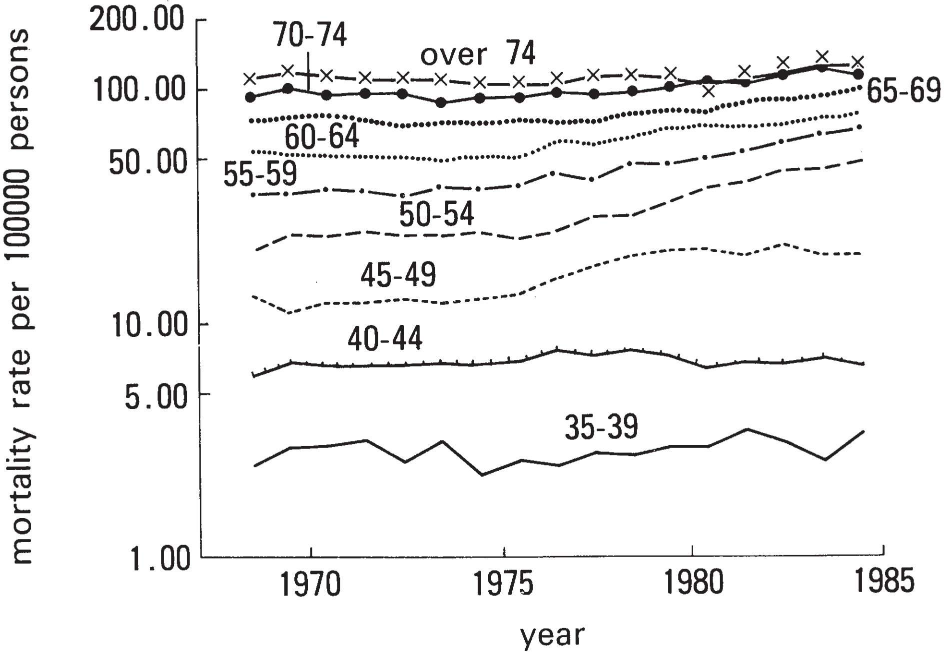

Fig. 3 Trends in age-specific mortality rate from liver cancer for men in Japan 1968–1984

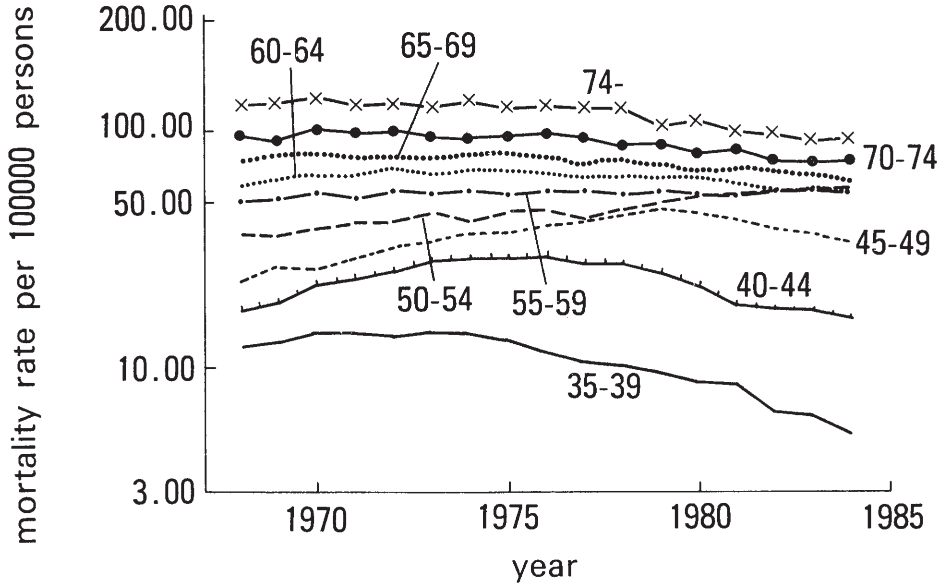

Fig. 4 Trends in age-specific mortality rate from liver cirrhosis for women in Japan 1968–1984

Average annual age-specific mortality rates from primary liver cancer for the two periods 1968–75 and 1976–84 were calculated to compare the changes in the rates (Table 2). The increase in mortality rates between the two time periods was 38.1% for men aged 40–49 years, and 49.08% for men aged 50–59 years, but little change was observed in the rates for men aged 30–39 years and those aged 70 years and older. Therefore, the increasing trend in mortality rates from primary liver cancer observed during the period 1976–1984 is mainly a reflection of the trend in the groups aged 40–59 years.

Table 2. Average annual age-specific mortality rates (per 100,000) from primary liver caner in men and percent change in rate 1968–1975 and 1976–1984

Age groups	Death years	Rates	% change
30–39	1968–1975	3.85	8.05
	1976–1984	4.16	
40–49	1968–1975	18.93	38.14
	1976–1984	26.15	
50–59	1968–1975	59.54	49.08
	1976–1984	88.76	
60–69	1968–1975	123.77	21.81
	1976–1984	150.77	
70 +	1968–1975	202.65	7.04
	1976–1984	216.91	

Age-specific death rates by birth cohort were shown in Fig. 5 for men aged 30 years and older born in the period 1900–34. Although the rates are somewhat unstable due to the short time period

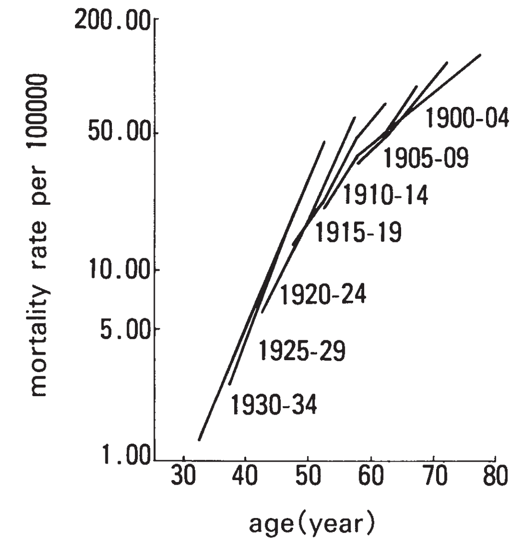

Fig. 5. Trends in mortality rate from liver cancer by birth cohorts for men in Japan 1968–1984

observed (only 17 years), the curves related to age-specific death rates showed a slight difference between each successive cohort, experiencing higher rates than those in the previous cohort. The slopes of the three most recent birth cohorts, 1920–24, 1925–29, and 1930–34, were progressively steeper than those of the previous cohorts, so that a substantially high rate in mortality among each age group is expected in the near future. However, the slopes and the rates of the curves for those born in 1925–29 and 1930–34 are very similar. This seems to suggest that the increasing trend in the mortality by birth cohort will be levelling off for the recent birth cohorts. The remarkable increase in the birth cohorts between 1920–24 and 1925–29 corresponds to the marked increase in age-specific mortality of the groups aged 45–64 years in the period 1975–1984 which were shown in Fig. 3.

Effect of Changes of Clinical Diagnostic Level on Trends in Mortality

Table 3 showed the consistency of clinical diagnosis with pathological findings by autopsy for liver cancer and liver cirrhosis, based on the data of the autopsy records published by the Japanese Pathological Society. The proportions of consistency for primary liver cancer were 69.68% in

Table 3. The consistency (%) of clinical diagnosis compared with autopsy diagnosis of primary liver cancer by age* and cirrhosis of liver, registered and published by the Japanese Pathological Society 1969–1984.

Time (Year)	Primary liver cancer (%)					Cirrhosis of liver (%)
	All ages	40–49	50–59	60–69	70 +	All ages
1969	69.68	–	–	–	–	86.25
1974	73.39	64.94	81.42	68.47	64.41	90.66
1979	79.83	–	–	–	–	92.50
1984	84.21	89.90	90.47	88.26	87.89	92.15

* only for men

1968, 73.39% in 1974, 79.83% in 1979, and 84.21% in 1984. Therefore, the approximately 10% increase during the first ten years of the study period might be due to the improvement of medical diagnosis. When the changes in the above consistency by age were observed in the groups aged 40–49, 60–69, and 70 years and older, the approximately 20–25% increase in mortality from liver cancer seemed to be due to improvement in diagnosis. However, the increse rate in mortality from liver cancer in the age groups of 40–49 and 50–59 were 38% and 49%, respectively, as shown in Table 2. Therefore, the increases in the mortality rates for the groups aged 40–49 and 50–59 years do not seem to be caused by improvement in clinical diagnosis alone. While the consistency rate for liver cirrhosis was higher than that for liver cancer, i.e., 86.25% in 1969, 90.66% in 1979, 92.50% in 1979, and 92.15% in 1984, the improvement of clinical diagnosis remained only about 6% for these 15 years.

DISCUSSION

The ICD has been revised every ten years to maintain efficiency in classifying causes of death, and the eighth and ninth revisions were issued in 1968 and in 1979, respectively. Malignant neoplasms of the liver unspecified as primary were not included in ICD-155 in the 8th Revision, but were classified as ICD-197.8. In the 9th Revision, however, they were included in ICD-155 considering their epidemiological findings. In Japan, it was generally supposed that a fairly large percentage of cases of primary liver cancer were classified as ICD-197.8, because of insufficient pathological data.[7] Considering this possibility and the data from previous reports,[8] the numbers of cases of ICD-197.8 during 1968-1978 were combined with those of ICD-155 as primary liver cancer in this paper. These combined mortality data were effective for the present analysis because they eliminated the discrepancy in the mortality rate between 1978 and 1979. These findings were used for epidemiological analyses in this paper.

In the present study, one of the special findings was the increase in the mortality rate from primary liver cancer after 1975 for men, while a decrease was observed in the rates from liver cancer for women and from liver cirrhosis for both sexes. The two trend curves of cancer and cirrhosis crossed at 1983 as seen in Fig. 1. Improvement in medical services over any given period is reflected in improved clinical diagnosis of disease, and also in the accurate statements of the cause of death on death certificates. The diagnosis of primary liver cancer was based mainly on symptomatology and physical examination until the advent of AFP test and other new, advanced techniques. That the survival period for patients with liver cancer in the recent decade was prolonged seems to be true, which may be partly due to easier detection of early stages of the tumors[9] and partly due to the increase in the survival rate. In Japan, the survival rate after resection of hepatocellular carcinoma rose from 28% for one year in 1977[10] to 50% for 19 months in 1983.[11]

The accuracy of diagnosis for liver diseases has probably become gradually better in recent decades. Considering this improvement of clinical diagnosis, we investigated whether or not the death rates from primary liver cancer have been truly increasing in Japan in recent years. As shown in Tables 2 and 3, the increase in the rate for the last decade was more than 38% in the groups aged 40–49 years and 50–59 years, and the contribution of the improved diagnosis was around 20% for these age groups, but it was less than 10% for the other groups aged 39 years and less. Therefore, it is clear that the mortality from liver cancer for the groups aged 40–59 years indicated a real increase. Other factors such as medical care systems certainly might play some role in the increase, but there seemed to be little influence on the mortality for the groups aged 39 and less. As for the older aged groups, other factors such as accessibility and utilization of improved modern medical facilities may be considered, even though these groups showed only a small increase in mortality. The increase in the consistency of clinical diagnosis with findings of autopsies for liver cirrhosis was less than that for liver cancer, being about 6% for this 17-year period. Therefore, the decreaseing trend in mortality from live cirrhosis seems to be true too. It is expected that the increase in mortality from primary liver cancer for men will continue but may level off in the near future, considering the increasing trend in age-specific death rates by birth cohorts as shown in Fig. 5. The trends in mortality from other liver diseases are estimated to be levelling down continuously.

If the increase in mortality from primary liver cancer for men since 1975 is true, the following foctors should be considered:

1. The close relationship of hepatocellular carcinoma to liver cirrhosis: In Japan, it has been reported that incidence of liver cirrhosis with hepatoccellular carcinoma was as high as 85.8%, and that the development rate of hepatocellular carcinoma among patients with liver cirrhosis was found to be 32% by autopsy.[12] The death rate from liver cancer continued to increase at a relatively high rate in the last decade, while the mortality from liver cirrhosis showed a mild declining trend, i.e., the average rate of increase in liver cancer in each five-year period after 1975 was 3.93% and 3.29%, respectively, but the decrease in liver cirrhosis was only 0.27% and 2.11%, respectively. The difference in these trends indicates that misdiagnosis cannot entirely explain the increasing trend of liver cancer.

Sunami, S. reported that in males the time difference showing a significant association between liver cancer and liver cirrhosis mortality is five to ten years.[13] This seems to suggest that if hepatocellular carcinoma indeed occur in the patients with liver cirrhosis, the development of liver cancer from liver cirrhosis requires at least more than five years. Because patients have received better treatment and the survival rate has increased, the prevalence of liver cirrhosis may be increasing. If an increase in the prevalence of liver cirrhosis is true, the influence on the mortality rate from liver cancer will continue in the near future, although liver cirrhosis is not a main risk factor in the development of hepatocellular carcinoma.

2. The mortality in birth cohorts: The increase in death trends for primary liver cancer in men between the years 1975 to 1984 seems to be mostly due to the rise in the death rates for the groups aged 40–59 years. People in these age groups were born in the period 1920–34. The higher rates of increase are from these birth cohorts, born in 1920–24, 1925–29, and 1930–34. The cohorts born in 1920–34 were from 5 to 25 years old during the second world war. The growth and development of the liver might have been affected by a lack of nutrients (such as, vitamin and protein) as well as by other socio-environmental factors including psychological stress. The birth cohort effects among people born after 1945–50 should be analysed in the future.

3. Increase in exposure to some risk factors in relation to development of the tumor: It has been reported that the development of liver cancer is related to the following risk factors: HBV,[14] aflatoxin,[15] non-A, non-B virus,[16,17] schistosomiasis,[18,19] fat,[20] alcohol,[18,21-23] sex hormones,[24] and so on. At a World Health Organization meeting the participants reported that up to 80% of worldwide primary liver cancer is attributable to HBV infection, and HBV is believed to be second only to tobacco among the known human carcinogens.[25] Although the fact of HBV infection resulting in liver cancer has been commonly accepted, other studies have shown that the contribution to all liver cancer is not large. There seems to be no significant increase in HBV infection in Japan based on the data from certain regions such as Gifu Prefecture, the city of Yokohama,[26] and Kyoto Prefecture.[27] Some studies showed that the increase in male liver cancer in Japan induced by HBV infection was probably slight after 1975 and that even in the future HBV infection's contribution will be small. Whether or not epidemic occurrence of HBV infection was experienced several decades ago in Japan could not be determined because of lack of a available information, but there appears to be no evidence of a high prevalence of HBV infection in those people aged 40–64 years despite high mortality rates from liver cancer in these age groups. The evidence of increase in level of aflatoxin in foodstuffs, in oral contraceptive steroids, and in schistosomiasis infection could scarcely be found in Japan in the last two decades. Even though the development of liver cancer might be associated with schistosmasis infection in a few prefectures, for example, Yamanashi Prefecture which has higher mortality rates for both primary liver cancer an liver cirrhosis, the influence on the total mortality rate for the whole country seems to be small.

Some studies have suggested that the rise in alcohol consumption was partly associated with the increase in the deaths from primary liver cancer.[18,21-23] There are higher rates in the development of primary liver cancer among liver cirrhotic patients with both HBsAg positivity and alcoholic history than among those with only HBsAg seropositivity.[28] The alcohol consumption in Japan gradually increased in the 1970s (Fig. 6).[29] According to the data of death from male liver cirrhosis sampled from Tokyo Metropolitan Komagome Hospital 1975–83, the highest numbers of deaths were observed in the 45–49 age group with alcohol abuse.[27] The number of daily drinkers was greatest in Japan among men aged 40–84 years, accounting for 40%–50% and showed an increasing trend with time. In women, the daily drinkers accounted for only about 7%. A large proportion of the increase in mortality rates from liver cancer after 1975 is attributable to the mortality rates for the groups aged 45–59 years. The excessive consumption of alcohol in the groups aged 40–59 may be associated with lower hygienic knowledge, unawareness of cancer signals, stress, and strenuous work. But to clarify the direct biological relation between alcohol drinking and liver cancer, further careful study will be needed.

In the consumption of nutrients, the intake of fats and oils has remarkably increased in the last

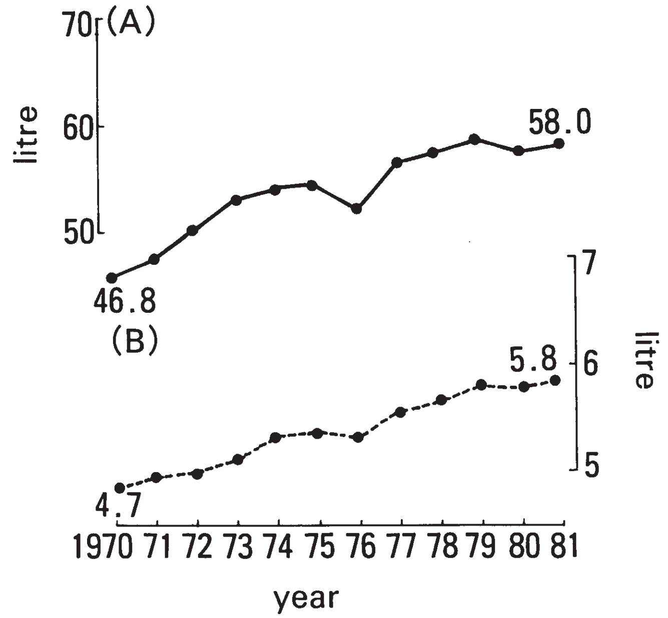

Fig. 6 The yearly average consumption of alcohol
(A)
(B) per one person in Japan 1970–1981

two decades in Japan (Fig. 7). Experiments on rats have shown that the excessive intake of these fats and oils can induce the development of tumors,[20] and that excessive intake of fats, especially, not only induced occurrence of liver cancer but also showed dose-response relation. There is, however, no epidemiological evidence yet of an association of primary liver cancer with the intake of fats.

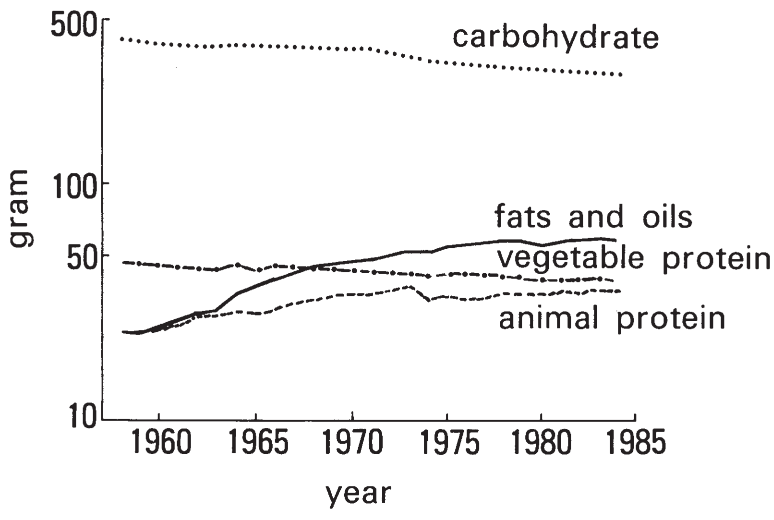

Fig. 7 The daily average intake of nutrient elements per one person in Japan 1958–1984

Recently, some researchers have attached a major role to non-A, non-B virus in the development of liver cancer, and have reported a higher rate of accompaniment of hepatocellular carcinoma among the patients with cryotogenic type liver cirrhosis that might belong to non-A, non-B infection.[16] Liver cancer induced by post-transfusion hepatitis has also been documented.[17] An increasing trend in post-transfusion hepatitis has been found in the past decade in Japan. Therefore, non-A, non-B virus may also be important factor in the prevention of liver cancer.

It should be noted that a very stable trend in age-adjusted death rates from all liver diseases for men was observed, despite considerable changes in mortality from the four kinds of liver diseases. Considering the slightly decreasing trend of all liver diseases for women, external etiological factors related to liver disease deaths may have been decreasing in recent years, except for male liver cancer and for liver cirrhosis in the age group of 50–54 years. The risk factors for developing liver cancer and the causes of liver cirrhosis are so consistent that the increase in mortality from liver cirrhosis in this group might be associated with their birth and growth during the second world war, and/or increased exposure to pathogenetic factors such as alcohol considered to be liable to increase the mortality from liver cancer as stated above.

Trends in liver cancer and liver cirrhosis should be analysed using the morbidity data in a given population, but these data were not available for large population for a period of several decades. Trends in the morbidity of liver cancer obtained from the Osaka and Miyagi cancer registries were very similar for the last decade, although the rates between morbidity and mortality were different. In the near future, similar analyses should be done in Japan using morbidity statistics.

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