

A large-scale cohort study on risk factors for primary liver cancer, with special reference to the role of cigarette smoking

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Summary. A large-scale cohort study in Japan (1966–1982) on life styles and primary liver cancer in men (123 out of 1709273 person-years) revealed a close association with cigarette smoking comparable to that for lung cancer, the relative risk (r.r.) for those smoking 1–29 and 30 or more cigarettes daily being 3.09 (1.78–5.35), 6.83 (3.56–13.10) for liver cancer, and 4.45 (3.77–5.25), 6.80 (5.51–8.41) for lung cancer, respectively. For liver cirrhosis, daily cigarette smoking was of less importance compared to daily alcohol drinking, r.r. = 1.17 (1.00–1.36) and 1.82 (1.63–2.04). However, for liver cancer, the risk from daily cigarette smoking was much higher than from daily alcohol drinking, r.r. = 3.14 (1.82–5.42) and 1.89 (1.40–2.55). The risk of liver cancer among the liver cirrhosis cases was therefore calculated as 2.67 (1.49–4.79) for daily cigarette smokers and 1.00 (0.72–1.38) for daily alcohol drinkers. These results must be of special importance in interpreting the reason for the increasing, unique mortality trend of liver cancer in men in recent years in Japan.

Introduction

Liver cancer mortality has been sharply increasing in recent years in Japan in men but not in women [3] (Fig. 1). In order to clarify the risk factors for primary liver cancer, the results of a large-scale cohort study in Japan were analyzed. As a result, the exceedingly important role of cigarette smoking was identified as raising liver cancer in combination with alcohol drinking. The risk of developing liver cancer from liver cirrhosis was found to be remarkably high in daily smokers.

Materials and methods

A large-scale cohort study was conducted from 1965 to 1982 in Japan (Table 1). The Mantel-Haenszel methods were used for the analysis.

Results

A large-scale cohort study was conducted in 29 Health Center Districts in six Prefectures in Japan for 17 years (1966–1982) (Table 1). The observed person-years for men

and women were 1709273 and 2140364, respectively. Out of the 788(M) and 463(F) cases of liver cancer occurring during the 17 follow-up years, 123(M) and 28(F) cases of primary liver cancer were detected. These cases were either diagnosed as such or developed in those with a clear-cut history of liver cirrhosis.

Out of the various risk factors associated with lifestyle a significant increase in risk of primary liver cancer was detected for cigarette smoking, alcohol drinking and daily meat consumption, while a significant risk reduction was found for the daily consumption of soybean paste soup (Fig. 2).

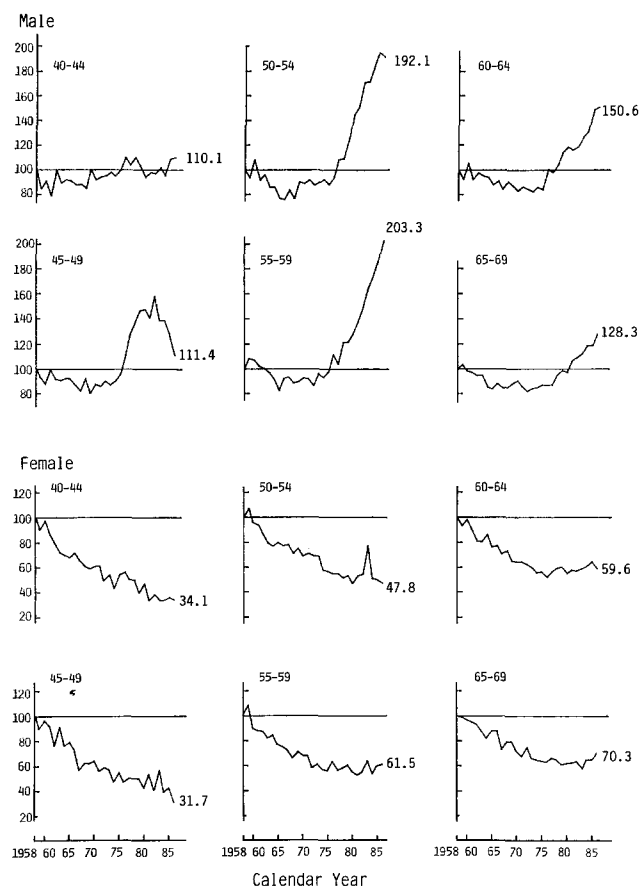


Fig. 1. Annual trend of age-specific death rate for cancer of the liver in Japan (1958–1986, 1958 = 100)

Table 1. Census-population-based prospective cohort study in Japan

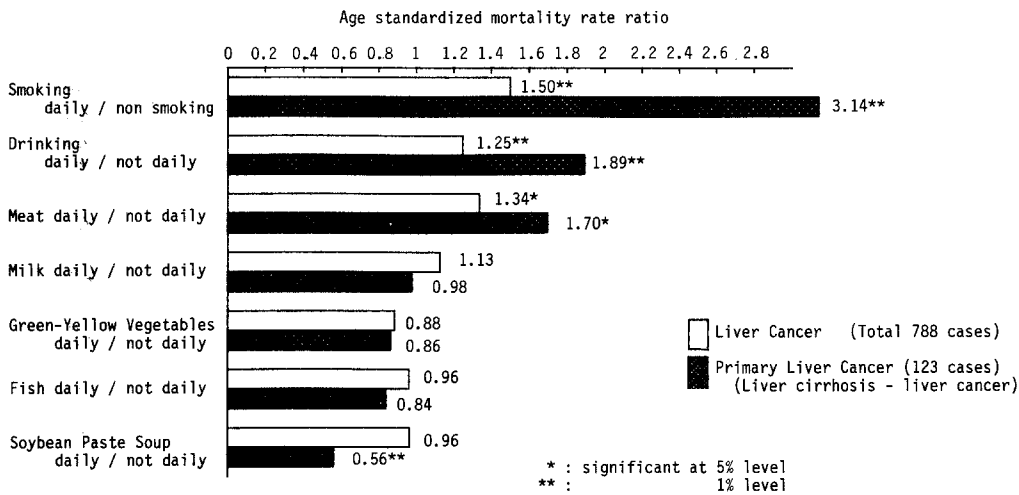
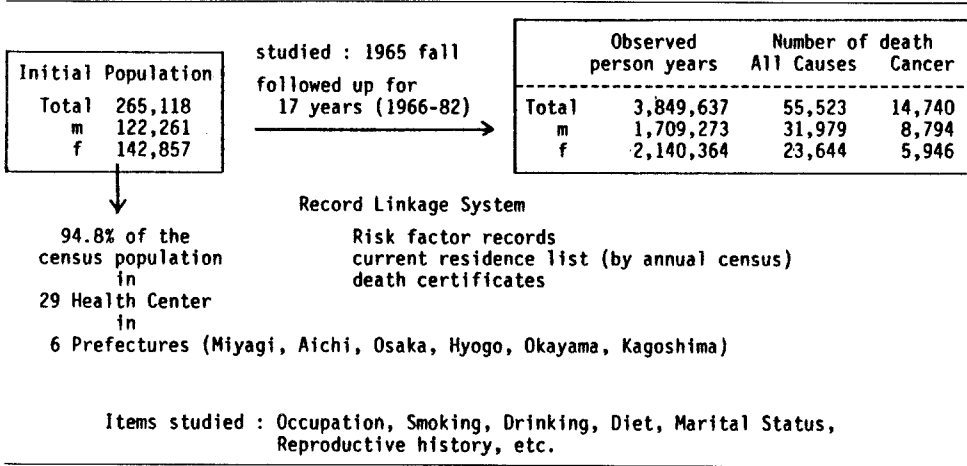


Fig. 2. Liver cancer and life styles: cohort study, 1966-1982, Japan (men)

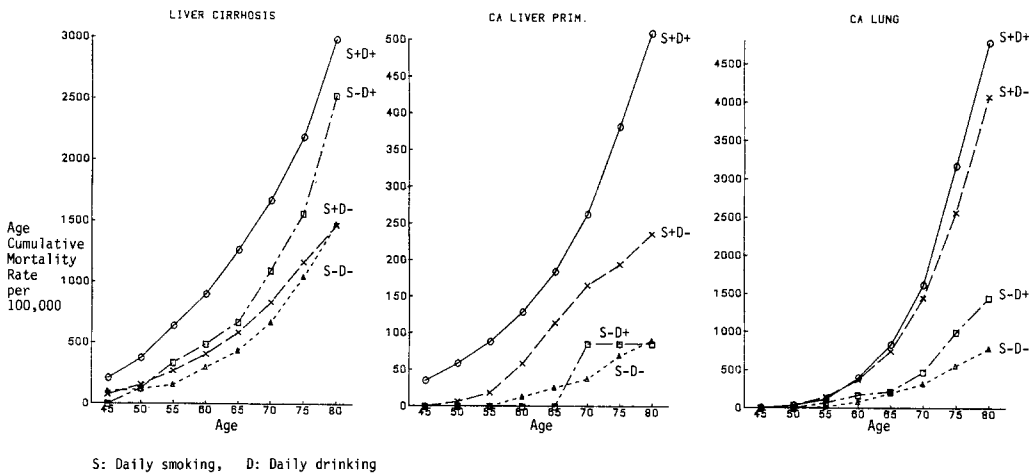


Fig. 3. Age cumulative mortality rate for liver cirrhosis, primary liver cancer and lung cancer by habit of smoking and drinking: cohort study, 1966-1982, Japan

A clear-cut, dose-response relationship was observed with cigarette smoking and the risk of primary liver cancer, which is almost comparable to that for lung cancer. The relative risk (r.r.) for those smoking 1-29 and 30 or more cigarettes daily was 3.09 (1.78-5.35),

6.83 (3.56-13.10) for primary liver cancer, and 4.45 (3.77-5.25), 6.80 (5.51-8.41) for lung cancer, respectively.

The daily habit of cigarette smoking (s) and the habit of alcohol drinking (d) were cross-tabulated. The cumulative age distributions of those with lung cancer, primary

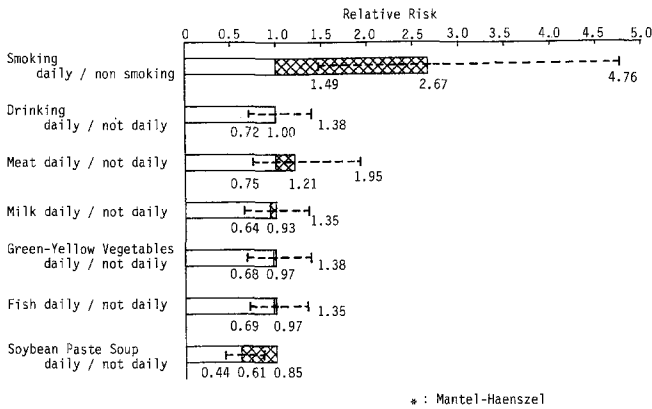


Fig. 4. Relative risk (Mantel-Haenszel analysis) and 90% confidence limits for primary liver cancer (control, liver cirrhosis): cohort study, 1966-1982, Japan (men)

liver cancer, and liver cirrhosis were mutually compared for each group, s(+)*d*(+), s(+)*d*(-), s(-)*d*(+), s(-)*d*(-) (Fig. 3). Those with both smoking and drinking habits showed the highest risk for all of these diseases. However, in the case of lung cancer, those with a smoking habit only also showed a similar high risk, while in the case of primary liver cancer, such a group showed a considerably lower risk. In the case of liver cirrhosis, the risk for such a group with a smoking habit only was quite low and almost similar to the risk for those with no such habit.

For liver cirrhosis, daily cigarette smoking was observed to be of lesser importance compared to daily alcohol drinking, r.r. being 1.17 (1.00-1.36) and 1.82 (1.63-2.04), respectively. For liver cancer, the risk from daily cigarette smoking was much higher than from daily alcohol drinking, r.r. being 3.14 (1.82-5.42) and 1.89 (1.40-2.55), respectively. The risk of developing liver cancer from liver cirrhosis was calculated as 2.67 (1.49-4.79) for daily cigarette smokers and 1.00 (0.72-1.38) for daily alcohol drinkers (Fig. 4).

Discussion

These results are of special importance in interpreting the unique mortality trend of liver cancer observed in recent years in Japan, a tendency only manifest in men. The possible reasons for such a liver cancer mortality increase in men are as follows.

1. Advances in liver cancer diagnosis

Owing to the rapid advances made in the diagnosis of liver cancer, e.g., the α -fetoprotein test, liver function test, biopsy, and methods of diagnostic imaging, there is no doubt that more cases of liver cancer have been detected in recent years. However, if this is the main reason for the mortality increase, such an increase should also appear in women.

2. Advances in liver cirrhosis treatment

Owing to the advances made in medical care and treatment, the survival period of liver cirrhosis patients has been prolonged. This must have made the chances of developing liver cancer from liver cirrhosis much higher. But such an effect, if it exists, should also appear in women as frequently as in men.

3. Hepatitis virus infection

Carriers of chronic hepatitis B virus have been identified as a high-risk group for liver cancer in Japan just as in other countries in Asia and Africa [2]. However, since the proportion of hepatitis B virus carriers in liver cancer patients has shown a downward trend in recent years in Japan, the chronic infection of non-A non-B hepatitis virus is more likely to be the reason for the recent increase in liver cancer mortality. However, evidence supporting such a hypothesis is still inadequate, and it is also necessary to clarify the reason why the increase is limited to men only.

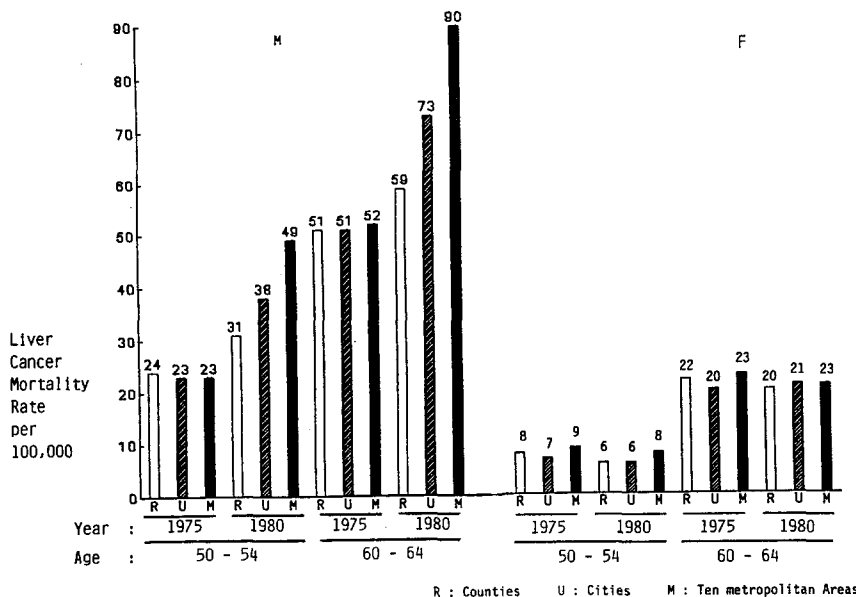


Fig. 5. Age-specific mortality rate for liver cancer in 1975 and in 1980 in counties, cities and ten metropolitan areas in Japan. R, counties; U, cities; M, 10 metropolitan areas

4. *Combined effect of smoking and drinking*

Since the increasing tendency is limited to men only, and since the possibility of increasing the risk is clear when cigarette smoking is combined with alcohol drinking, as shown in various epidemiological studies including the present one, the combined effect of smoking and drinking is the most likely reason for the increase in liver cancer mortality in men in recent years in Japan.

The ratio of increase is most striking in metropolitan areas, followed by other cities, and is lowest in the countryside in the case of male patients. No such tendency has been observed for women [1] (Fig. 5). These observations are compatible with the above-mentioned hypothesis, which considers the predominantly male habit of cigarette smoking, combined with the habit of alcohol drinking, as

the most likely reason for the recent increase in liver cancer in men in Japan.

References

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