Prospective study on the relation of cigarette smoking with cancer of the liver and stomach in an endemic region

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Background  
Smoking has not been confirmed as a risk factor for cancers of the liver and stomach. The authors examined prospectively the relationship between smoking and these cancers in an endemic region.

Methods  
The data used were a cohort study on the relationship between lifestyle and health in the region having the highest liver cancer mortality in Japan. Of the cohort members, 4050 males aged ≥40 years were included in the present analysis with a 9-year mean follow-up. Cox proportional hazards regression was used to estimate relative risks (RR) for cancer of the liver, stomach, smoking-related sites and others, while adjusting for age, residence, and alcohol intake.

Results  
By the end of the study period, 59 cases of liver cancer and 53 cases of stomach cancer were identified. Current smokers, compared to subjects who had never smoked, had a threefold risk of liver cancer (RR = 3.3; 95% CI: 1.2–9.5) and a twofold risk of stomach cancer (RR = 2.2; 95% CI: 0.8–5.7). Sub-cohort analysis showed that adjustment for history of chronic liver disease did not attenuate the risk of liver cancer. Light/medium smokers had almost the same risk of these cancers as heavy smokers, while they showed a relatively low risk of smoke-related cancers.

Conclusions  
The present results indicate that smoking is a risk factor of liver and stomach cancer in a population with a high background risk for these cancers. However, causal inferences should be made cautiously due to a lack of information on known risk factors.

Keywords  
Liver neoplasms, mortality, prospective studies, smoking, stomach neoplasms

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Method

Study population

Details of the present cohort study have been described previously. Briefly, the baseline survey was conducted from 1986 through 1989 among the general population of Fukuoka. This region has the highest liver cancer mortality in Japan: annual liver cancer mortality 1988 through 1992 was 52.5 per 100,000 males. All inhabitants, aged 30–79 in: A town, B village, and selected districts of C city and D town (15,417 in total), were invited to participate in a questionnaire survey that asked about health-related lifestyles, including smoking, alcohol drinking, diet, sporting activity, stress, history of disease, and so on. The response rate was 84.3% (n = 13,000). Of those inhabitants aged ≥80 who were living with the participants, 270 inhabitants completed the questionnaire and were also included in the cohort. Thus, a total of 13,270 inhabitants constituted the cohort.

A follow-up survey was conducted annually, with the collaboration of each municipal office, to verify the vital status of participants. The participant list was matched, using a computer, with resident records that included deaths and changes of address as well as information on current residents at the time of the follow-up. The computerized search method was not used for B village, where municipal personnel verified vital status information manually. For deceased subjects, the cause of death was determined from the death certificate at the regional health center, with the permission of the Management and Co-ordination Agency of the Japanese Government, and classified according to the International Classification of Diseases, 9th Revision (ICD-9). The present analysis uses follow-up data up to 31 March 1996 for C city and A town, that up to 31 July 1996, for D town, and that up to 31 October 1996, for B village.

Death classification

Cancer deaths were classified into four groups: primary liver cancer (ICD-9, 155), stomach cancer (ICD-9, 150), smoke-related cancers identified by the International Agency for Research on Cancer, (i.e. cancer of the mouth [except for the salivary glands], pharynx [except for the nasopharynx], larynx, lung, oesophagus, bladder, pancreas, and renal pelvis), and cancers of other sites.

Smoking and covariates

Respondents were categorized into four smoking categories: those who had never smoked (never smoker), those who had quit smoking (ex-smoker), current smokers consuming <25 cigarettes/day (light/medium smoker), and current smokers consuming ≥25 cigarettes/day (heavy smoker). Covariates used in the multivariate analysis were residential area, age category (40–54, 55–64, 65–74, and ≥75 years), and alcohol consumption. Based on their responses concerning frequency and amount per occasion of alcohol intake, subjects were classified into four drinking categories: those who never drank or who drank less than once a week, those who had drunk habitually but had quit drinking, those who drank at least once a week consuming at most two sake-equivalent servings at a time (one sake equivalent contains 27 ml of ethanol) and those who drank at least once a week consuming more than two sake-equivalent servings at a time. History of chronic hepatitis or liver cirrhosis was also included in an additional analysis for liver cancer using a sub-cohort.

Exclusions

Females were excluded from the analysis because of an insufficient number of cancer deaths in females for site-specific analysis, as well as a low proportion (8.5%) of female current smokers. Among the 5928 males, those excluded were: those aged <40 at the baseline survey (n = 1369), those who were lost to follow-up (n = 5), those who did not provide details of smoking status or alcohol intake (n = 462), and those with any history of cancer (n = 42). Thus, data for the remaining 4050 males were used in the present analysis. A further analysis for liver cancer was performed using data for 2477 males from study areas other than A town, for which history of liver disease was not investigated.

Statistical analysis

Age-adjusted mortality rates for the cancer groups were calculated for each smoking category using the direct method, in which mortality rates for each age group were multiplied by the corresponding weights of person-years in the total population analysed, and summed. Cox proportional hazards regression analysis was employed to estimate relative risk (RR) and its 95% CI. Indicator terms for residential area, age category, and alcohol intake, as well as smoking habits, were included in the model to calculate adjusted RR. Further analysis for liver cancer also included an indicator term for history of chronic hepatitis or liver cirrhosis. Differences in the proportions of subjects with histories of chronic hepatitis or cirrhosis among smoking categories were assessed by the χ² test. The calculations were performed by the Statistical Analysis System.

Results

The total person-years were 35,785 with an 8.8-year mean follow-up. By the end of the study period, 586 (14.5%) of the subjects had died, 244 (6.0%) had died from cancer, and 234 (5.8%) had moved to other areas.

In all, 80% of the male subjects had a history of smoking; 50% were current smokers and 30% had quit smoking (Table 1). Among current smokers, two-thirds (67.2%) were light/medium smokers consuming <25 cigarettes/day. Smoking rate decreased with age; in particular, the proportion of subjects who smoked ≥25 cigarettes/day markedly decreased as age increased.

The three major cancers (stomach, liver, and lung) accounted for two-thirds of all cancers: liver cancer was the most frequent (24.2%), followed by stomach cancer (21.7%) and lung cancer (17.2%) (Table 2). Among subjects aged 45–64 years, liver cancer accounted for 35.3% of all cancer deaths. The median ages at death were 66.6 (inter-quartile range 61.6–72.6), 70.2 (63.1–76.8), 72.2 (65.9–79.3), and 72.8 (65.9–79.7) for cancers of the liver, stomach, smoke-related sites, and lung, respectively.

The three major cancers showed almost the same mortality rates among never smokers, while liver cancer was the leading cause of cancer deaths, followed by stomach cancer and lung cancer, among current smokers (Table 3). In the case of current smokers, the lung cancer site was the lung in those who smoked ≥25 cigarettes/day, while this site was the liver in those who smoked <25 cigarettes/day. Ex-smokers showed almost
the same mortality rate for cancer of the liver and stomach as current smokers.

As shown in Table 4, current smokers had a twofold risk of all cancers (RR = 2.1; 95% CI: 1.4–3.3) and those who smoked ≥25 cigarettes/day had a threefold risk (RR = 2.8; 95% CI: 1.7–4.6), when both groups were compared to never smokers. Current smokers had a threelfold risk of liver cancer (RR = 3.3; 95% CI: 1.2–9.5), without showing a dose-response relation. Ex-smokers had almost the same risk of liver cancer as current smokers (RR = 2.9; 95% CI: 1.0–8.4). For stomach cancer, smokers had a twofold risk (RR = 2.2; 95% CI: 0.8–5.7), without a dose-response relation. An increased risk of stomach cancer was also observed among ex-smokers (RR = 2.2; 95% CI: 0.8–6.0). In contrast, an elevated risk with a clear dose-response relation, including a lower risk among ex-smokers than among current smokers, was found for the smoke-related cancers. Light/medium smokers had a relatively low risk for the cancers (RR = 1.8; 95% CI: 0.8–4.1).

The proportions of subjects with a history of chronic liver disease were 8.9%, 11.2%, and 9.6% for never smokers, ex-smokers, and current smokers, respectively (χ² = 2.2; d.f. 2; P = 0.33). Further analysis was conducted for liver cancer using a sub-cohort additionally adjusted for history of chronic liver disease. The RR values for current smokers, with and without adjustments for history of liver disease, were 3.5 (95% CI: 1.0–11.7) and 3.7 (95% CI: 1.1–12.6), respectively.

Discussion

This study is unique in that the cohort members were from the general population of a region with the highest liver cancer mortality rate in Japan. The leading site of fatal cancers in the present cohort was the liver, followed by the stomach and the lungs (Table 2). Using a population with such a high background risk, we found that cigarette smoking, irrespective of consumption rate, was strongly associated
with liver cancer and moderately associated with stomach cancer.

Hepatitis C virus (HCV) infection is an identified risk factor for hepatocellular carcinoma, and approximately 80% of hepatocellular carcinoma cases in Japan are anti-HCV positive. The present study area has a high prevalence of HCV infection, with an anti-HCV infection rate of more than 5% in those aged over 50. Thus, it would be reasonable to infer that the majority of liver cancer deaths in the present cohort were related to HCV infection.

The threefold risk of liver cancer among current smokers compared with never smokers found by our study is very similar to the results of a recent cohort study for other endemic regions of liver cancer in Japan. However, this risk is higher than those reported for other areas where HCV infection is not a major determinant for liver cancer. Most HCV-related liver cancers arose in people with cirrhotic livers, suggesting that few direct transitions to cancer from chronic hepatitis occur in the absence of cirrhosis. Furthermore, previous studies have shown that smoking promotes transitions to a higher risk state in hepato-carcinogenesis, as in the following examples: from chronic viral hepatitis to liver cirrhosis, an identified risk state for liver cancer, from liver cirrhosis to liver cancer, and from HCV-related chronic liver disease to liver cancer. These findings indicate that smoking affects several steps in HCV-related hepato-carcinogenesis, thus supporting the present strong association between smoking and liver cancer in a high risk area for HCV-related liver cancer.

Consistent with the present findings, a positive association between cigarette smoking and stomach cancer has been observed in previous studies, including cohort studies and case-control studies in the Japanese population and cohort studies in western populations. The magnitude of the association observed in our study, a twofold risk for current smokers compared to never smokers, is somewhat higher than the RR of 1.59 for males that was obtained by a meta-analysis that summarized relevant worldwide studies, but falls in the median range of RR from positive studies for the Japanese population.

The present finding of the lack of a dose-response relation between smoking and cancer of the liver and stomach is consistent with the results of many positive studies. This finding is in marked contrast to that for smoke-related cancers. The presence of a dose-response relation suggests the hypothesis that the relation is causal, but the absence of the relation does not always refute the hypothesis. Although we have no plausible explanation for the absence of a dose-response relation, we speculate as follows. First, the magnitude of the risk of smoking for these cancers is not large enough to show a dose-response relation when compared with that of risk factors such as hepatitis virus infection. Second, heavy smokers are at a higher risk of developing smoke-related cancers than lighter smokers, thus the dose-response relation in cancers weakly associated with smoking is likely to be concealed.

Finally, the limitations of this study should be mentioned. Serological measurements were not obtained for each of the cohorts, namely hepatitis virus infection for liver cancer and H. pylori infection for stomach cancer. The sub-cohort analysis performed in the present study revealed that smoking status did not correlate with history of chronic hepatitis or cirrhosis, a strong predictor of liver cancer, and that the adjustment for a history of such liver diseases had little effect on the estimates. For stomach cancer, the prevalence of H. pylori infection is as high as 90% among aged people in a high risk area in Japan. Moreover, the Japanese study did not detect an increased risk of stomach cancer among the aged subjects who were positive for H. pylori. These findings indicate that H. pylori infection does not predict a future risk of stomach cancer among the aged population in Japan. Accordingly, we infer that this infection did not function significantly as a confounding factor in the present population. Nevertheless, we cannot rule out the potential confounding effects of these infections and thus should consider the lack of information on these factors as a limitation of our study.

In summary, the results of the present cohort study indicated that cigarette smoking is a risk factor for cancer of the liver and stomach in regions where mortality from these cancers is high. However, the lack of information on infection for these sites limits our causal inference. Further studies are needed to clarify the role of cigarette smoking in the carcinogenesis of these cancers while controlling for major confounding factors.

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References


