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RISK FACTORS FOR HEPATOCELLULAR CARCINOMA AMONG PATIENTS WITH CHRONIC LIVER DISEASE

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Abstract *Background and Methods.* To detect potentially curable cases of hepatocellular carcinoma, outpatients with chronic hepatitis or compensated liver cirrhosis who were seen at the Center for Adult Diseases (Osaka, Japan) were examined periodically by means of ultrasonography and measurement of serum alpha-fetoprotein. Risk factors for hepatocellular carcinoma were identified with a Cox proportional-hazards model.

Results. A total of 917 patients, 40 to 69 years old, were registered from May 1987 to March 1991. By the end of September 1991, liver cancer had developed in 54. The three-year cumulative risk of liver cancer was 12.5 percent for 240 patients with liver cirrhosis at enrollment and 3.8 percent for 677 patients with chronic hepatitis. Cox regression analysis showed that the risk of liver cancer was increased almost sevenfold in patients with hepatitis B surface antigen (rate ratio, 6.92; 95 percent confidence interval, 2.92 to 16.39) and fourfold in patients with hepatitis C antibody (rate ratio, 4.09; 95 percent confidence interval, 1.30 to 12.85). A high alpha-fetoprotein value at enrollment was also a risk marker for liver cancer.

Conclusions. Patients with hepatitis C virus infection have a greatly increased risk of liver cancer. Further studies are required to clarify the roles of other risk factors, including drinking and smoking habits. (N Engl J Med 1993;328:1797-801.)

LIVER CANCER is the third leading cause of deaths due to cancer in Japan.[1] The age-adjusted incidence rate has increased 1.7-fold during the past 10 years in Osaka,[2] but the survival rate remains very low. To detect potentially curable cases of hepatocellular carcinoma, outpatients with chronic liver disease who have been seen at the Center for Adult Diseases, Osaka, have been registered since May 1987 and examined periodically with real-time ultrasonography and measurement of serum alpha-fetoprotein. We analyzed the data on these patients for risk factors for hepatocellular carcinoma.

METHODS

Enrollment and Follow-up

Outpatients meeting the following criteria were enrolled in the study: (1) a clinical diagnosis of chronic hepatitis or compensated cirrhosis (without ascites or jaundice, or a history of bleeding esophageal varices) during the period May 1987 through March 1991; (2) a serum total bilirubin level of 2.0 mg per deciliter or less

(34 μmol per liter) and a serum albumin level of 3.0 g per deciliter or more; (3) age of 40 to 69 years; (4) no history of liver cancer or evidence of this disease at enrollment (patients in whom liver cancer was detected at the initial examinations or diagnosed within three months after enrollment were excluded); (5) no serious diseases; and (6) consent from both the patient and physician.

Among the registered patients, those with chronic hepatitis and an elevated serum alpha-fetoprotein concentration ($\geq$20 ng per milliliter) and those with liver cirrhosis were scheduled to undergo both ultrasonography and alpha-fetoprotein measurement at three-month intervals. Patients with chronic hepatitis and normal alpha-fetoprotein concentrations at enrollment were scheduled to undergo both tests at six-month intervals; the interval between examinations was reduced to three months if their alpha-fetoprotein concentrations increased to 20 ng per milliliter or more or if the clinical stage of the disease progressed to cirrhosis.

Serologic Evaluation

Routine serum biochemical tests were carried out with automated techniques (SMAC, Technitron, Tokyo, Japan). Hepatitis B surface antigen (HBsAg) was detected by reversed passive hemagglutination (Meguro Institute, Osaka), and hepatitis B core antibody (anti-HBc) by enzyme immunoassay (Abbott Laboratories, Tokyo). If a serum sample was positive for anti-HBc, a 200-fold dilution of the sample was retested for the antibody. If the percentage of inhibition in the diluted sample was $\geq$90 percent, the titer for anti-HBc was considered high. These tests were performed in all patients at enrollment. Hepatitis C antibody (anti-HCV, C100-3 antibody) was detected by enzyme-linked immunosorbent assay (ELISA, Ortho Diagnostics, Tokyo). This test became available in April 1990; in a majority of the patients, testing for anti-HCV was performed during the follow-up period, and before the date of diagnosis of liver cancer, although not at enrollment. Alpha-fetoprotein

was periodically measured by latex photometric immunoassay (Daiayatoron, Tokyo) (normal, <20 ng per milliliter).

Lifestyle Habits and Medical History

Information about cigarette smoking, alcohol drinking, the medical history, and family history of liver cancer was obtained at the time of enrollment through interviews by experienced public health nurses using a structured questionnaire.

Diagnosis of Liver Cancer

Space-occupying lesions detected or suspected at the time of ultrasonography or alpha-fetoprotein measurement were further examined with computed tomography, hepatic arteriography, fine-needle aspiration biopsy,[3] and other clinical diagnostic techniques such as hepatic scintigraphy, unless the ultrasonographic findings confirmed that the lesions were unquestionably benign (e.g., hemangiomas or cysts). A final diagnosis of hepatocellular carcinoma was based on histologic findings in resected hepatic tumors or biopsy specimens or on the radiologic findings of hepatic arteriography.

In spite of great efforts to prevent patients from dropping out of the study, some withdrew because they were transferred to other hospitals, declined to undergo the periodic examinations, or moved from the Osaka area. Their vital status as of the end of May 1991 was determined from their medical records or their resident offices. Copies of death certificates were also obtained from local government offices (Local Justice Bureau).

Statistical Analysis

The method of Kaplan and Meier[4] was used to estimate the cumulative risk of liver cancer according to the clinical stage of liver disease at enrollment. Cox proportional-hazards regression analysis[5] was performed to estimate rate ratios for possible risk factors for liver cancer. The period of observation used in calculating the risk of liver cancer began at the date of enrollment and ended at the date of diagnosis of liver cancer, the date of death, or the end of September 1991, whichever came first.

Data analysis was performed with the SAS/PC statistical package (SAS Institute, Cary, N.C.). All reported P values are two-tailed.

RESULTS

Characteristics at Enrollment

Table 1 shows the basic characteristics of the patients at enrollment. A total of 917 patients met the study criteria and were registered: 240 had clinically diagnosed cirrhosis of the liver, and 677 had chronic hepatitis. Serum alpha-fetoprotein levels were elevated in 214 patients at initial examination (≥20 ng per milliliter). HBsAg was detected in 80 of the 917 patients (8.7 percent), and anti-HBc was present in high titers in 56 patients (6.1 percent). Anti-HCV was detected in 433 of the 731 patients (59.2 percent) tested for the antibody. The proportion of patients under the age of 50 years was much smaller among the women than the men (2.3 percent vs. 20.8 percent); otherwise, the distributions of age as well as the other factors listed in Table 1 were similar with respect to sex.

Table 2 shows distributions of patients according to their medical histories and lifestyle habits as recorded during interviews at enrollment. Two hundred eleven patients had a history of blood transfusions; 53 of these patients had a history of post-transfusion hepatitis. Fifty-six patients had a family history of liver cancer in parents, siblings, or children. The male patients differed from the female patients in their smoking and drinking habits: 48.2 percent of the men were current

Table 1. Characteristics of Patients with Chronic Liver Disease at Base Line, According to Sex.

CHARACTERISTIC	MEN (N = 548)	WOMEN (N = 369)	TOTAL (N = 917)
	no. of patients (% of group)		
Age (yr)			
40–49	115 (21.0)	8 (2.2)	123 (13.4)
50–59	268 (48.9)	208 (56.4)	476 (51.9)
60–69	165 (30.1)	153 (41.5)	318 (34.7)
Stage of disease			
Liver cirrhosis	134 (24.5)	106 (28.7)	240 (26.2)
Chronic hepatitis	414 (75.5)	263 (71.3)	677 (73.8)
Alpha-fetoprotein level*			
≥100 ng/ml	20 (3.6)	33 (8.9)	53 (5.8)
20–99 ng/ml	88 (16.1)	73 (19.8)	161 (17.6)
Normal (<20 ng/ml)	440 (80.3)	263 (71.3)	703 (76.7)
Hepatitis virus markers			
HBsAg			
Positive	53 (9.7)	27 (7.3)	80 (8.7)
Negative	495 (90.3)	342 (92.7)	837 (91.3)
Anti-HBc			
High titer	39 (7.1)	17 (4.6)	56 (6.1)
Low titer	257 (46.9)	149 (40.4)	406 (44.3)
Negative	252 (46.0)	203 (55.0)	455 (49.6)
Anti-HCV			
Positive	256 (46.7)	177 (48.0)	433 (47.2)
Negative	185 (33.8)	113 (30.6)	298 (32.5)
Unknown status	107 (19.5)	79 (21.4)	186 (20.3)

*To convert values to grams per liter, divide by 1000.

smokers and 39.0 percent were current daily drinkers, whereas 10.6 percent of the women were smokers and 6.2 percent were drinkers.

The base-line characteristics of the 917 patients, including their medical histories and lifestyle habits, were compared with those of 215 patients who dropped out of the study before the end of the follow-up period. No remarkable differences were observed between the groups except in the prevalence of a family history of liver cancer (2.3 percent vs. 6.1 percent).

Development of Liver Cancer

During the follow-up period (from enrollment to the end of September 1991, a mean [±SD] duration of 35.7±13.0 months; range, 5 to 52), liver cancer developed in 54 patients. Hepatocellular carcinoma was diagnosed during the study in 20 patients on the basis of findings at hepatic arteriography, with or without elevated serum alpha-fetoprotein levels, and in 29 patients on histologic examination. Liver cancer was diagnosed post mortem in 5 patients during a follow-up study of deaths among the 215 patients who had dropped out. Three of these five patients died of liver cancer with cirrhosis of the liver, and two died of liver cancer with chronic hepatitis, according to their death certificates.

Of the 54 patients with liver cancer, 28 were found to have liver cirrhosis at enrollment and the other 26 were found to have chronic hepatitis. Ten of the 26 patients with chronic hepatitis had elevated alpha-fetoprotein levels at enrollment.

Cumulative Risk of Liver Cancer

Figure 1 shows Kaplan–Meier estimates of the cumulative risk of liver cancer, according to the stage of liver disease and the serum alpha-fetoprotein level at

Table 2. Medical Histories and Lifestyle Habits of the Patients, According to Sex.

VARIABLE	MEN (N = 548)	WOMEN (N = 369)	TOTAL (N = 917)
	no. of patients (% of group)		
Medical history			
Blood transfusion	100 (18.2)	111 (30.1)	211 (23.0)
Post-transfusion hepatitis	24	29	53
Surgical procedure	297 (54.2)	242 (65.6)	539 (58.8)
Liver cancer in family			
Parents, siblings, or children	36 (6.6)	20 (5.4)	56 (6.1)
Spouse	1 (0.2)	14 (3.8)	15 (1.6)
Lifestyle habits			
Smoking			
Current smoker	264 (48.2)	39 (10.6)	303 (33.0)
Exsmoker	204 (37.2)	22 (6.0)	226 (24.7)
Nonsmoker	80 (14.6)	308 (83.5)	388 (42.3)
Drinking			
Current daily drinker			
≥80 g of ethanol/day	79 (14.4)	3 (0.8)	82 (8.9)
<80 g of ethanol/day	135 (24.6)	20 (5.4)	155 (16.9)
Former daily drinker			
≥80 g of ethanol/day	66 (12.0)	7 (1.9)	73 (8.0)
<80 g of ethanol/day	114 (20.8)	30 (8.1)	144 (15.7)
Occasional drinker	56 (10.2)	34 (9.2)	90 (9.8)
Nondrinker	98 (17.9)	275 (74.5)	373 (40.7)

enrollment. The three-year cumulative risk (±SE) of liver cancer was 12.5±2.5 percent among the 240 patients with liver cirrhosis diagnosed at enrollment, and 3.8±0.8 percent among the 677 with chronic hepatitis. A log-rank test of the two curves (Fig. 1) showed a significant difference between these groups (P<0.001). Among the patients with chronic hepatitis, those who had an elevated alpha-fetoprotein level at enrollment were at significantly higher risk for liver cancer than those who had a normal level (P<0.001 by log-rank test); the three-year cumulative risk was 10.2±2.7 percent in the former and 2.9±0.8 percent in the latter.

Hazard Rate Ratios for Liver Cancer

Table 3 shows the results of Cox proportional-hazards regression analyses in which age, sex, and other possible confounders (stage of disease, serum alpha-fetoprotein levels, hepatitis virus markers, and drinking and smoking habits) were adjusted for simultaneously to estimate hazard rate ratios for the development of liver cancer.

The risk of liver cancer in men was 1.33 times that in women, but the difference was not significant. A positive association was observed between the risk of liver cancer and age at enrollment. Patients in their 60s had significantly higher rate ratios (6.46) than patients in their 40s. The chi-square value for the linear trend between age at enrollment and the risk of liver cancer was significant (P = 0.004).

The stage of disease constituted an independent risk factor for liver cancer after adjustment for possible confounders. Patients with liver cirrhosis diagnosed at enrollment had significantly higher rate ratios for liver cancer (1.93) than patients with chronic hepatitis.

The serum alpha-fetoprotein level at enrollment was also confirmed as a significant marker for a high risk, regardless of the stage of disease (chronic hepatitis or liver cirrhosis).

Each of the serum markers for hepatitis virus — HBsAg, anti-HBc (in high titer), and anti-HCV — was significantly associated with the risk of liver cancer. The adjusted rate ratios for HBsAg, anti-HBc, and anti-HCV were estimated to be 6.92, 4.54, and 4.09, respectively. Patients whose status for anti-HCV was unknown appeared to have an elevated risk of liver cancer, but this finding was considered an artifact. Since 11 patients who had liver cancer before April 1990 left the study before the test for anti-HCV became available at our institutions, their status for anti-HCV necessarily remained unknown.

Smoking and drinking were also possible risk factors for liver cancer, since many case–control studies[6-10] and a few cohort studies[11,12] have indicated a relation between these lifestyle factors and the risk of liver cancer. The risks in current smokers and ex-smokers were, respectively, 2.30 and 1.68 times the risk in nonsmokers, although these differences were not significant. The chi-square value for the linear trend between smoking and the risk of liver cancer approached significance (P = 0.07). Associations between drinking and the risk of liver cancer were not so evident, as shown by the adjusted rate ratios for drinking categories (Table 3).

Relations between smoking and drinking habits and the risk of liver cancer were further analyzed according to the clinical stage of liver disease at enrollment. Among the patients with liver cirrhosis, the adjusted rate ratios for current smokers and ex-smokers increased to 7.96 and 3.44, respectively (chi-square for linear trend, 8.617; P = 0.003); the rate ratio was 1.32 for current heavy drinkers (P = 0.75) and 3.75 for former heavy drinkers (P = 0.04). Among the patients with chronic hepatitis, there were no
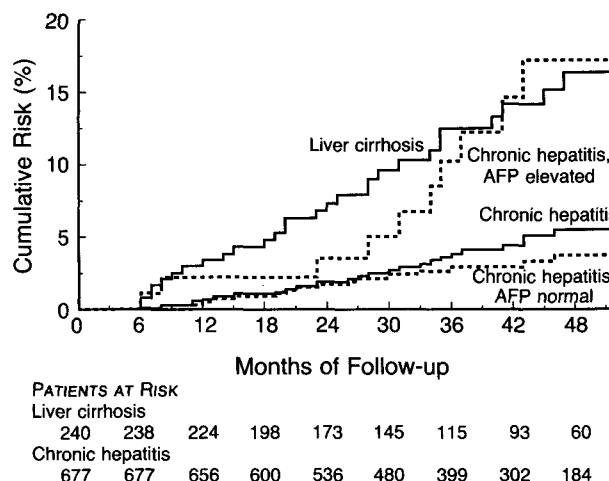
Figure 1. Cumulative Risk of Liver Cancer in 917 Patients with Chronic Liver Disease, According to the Clinical Stage of Disease at Enrollment.

AFP denotes the serum level of alpha-fetoprotein.

PATIENTS AT RISK								
Liver cirrhosis								
240	238	224	198	173	145	115	93	60
Chronic hepatitis								
677	677	656	600	536	480	399	302	184

Table 3. Results of Cox Proportional-Hazards Regression, Adjusted for Age, Sex, and Other Potential Confounders.

Variable	Adjusted Rate Ratio	95% CI*	Chi-Square
Sex			
Male	1.33	0.54–3.29	0.54
Female	1.00		
Age (yr)†			
60–69	6.46	1.68–24.93	0.007
50–59	2.88	0.77–10.80	0.12
40–49	1.00		
Stage of disease			
Liver cirrhosis	1.93	1.08–3.46	0.03
Chronic hepatitis	1.00		
Alpha-fetoprotein level‡			
≥100 ng/ml	3.27	1.22–8.77	0.02
20–99 ng/ml	3.21	1.73–5.96	0.0002
Normal (<20 ng/ml)	1.00		
HBsAg			
Positive	6.92	2.92–16.39	0.0001
Negative	1.00		
Anti-HBc			
High titer	4.54	1.66–12.42	0.003
Low titer	1.31	0.72–2.38	0.37
Negative	1.00		
Anti-HCV			
Positive	4.09	1.30–12.85	0.02
Unknown status	5.77	1.87–17.83	0.002
Negative	1.00		
Smoking§			
Current smoker	2.30	0.90–5.86	0.08
Exsmoker	1.68	0.63–4.47	0.30
Nonsmoker	1.00		
Drinking			
Current daily drinker			
≥80 g of ethanol/day	1.15	0.35–3.78	0.82
<80 g of ethanol/day	1.10	0.39–3.07	0.86
Former daily drinker			
≥80 g of ethanol/day	1.66	0.69–3.96	0.26
<80 g of ethanol/day	1.46	0.56–3.79	0.44
Occasional drinker	0.77	0.20–2.99	0.71
Nondrinker	1.00		

*CI denotes confidence interval.
†Chi-square for the linear trend was 12.715 (P = 0.004).
‡To convert values to grams per liter, divide by 1000.
§Chi-square for the linear trend was 3.194 (P = 0.07).

significant associations between these lifestyle factors and the risk of liver cancer.

A medical history of blood transfusions, post-transfusion hepatitis, or surgical procedures was not significantly associated with the risk of liver cancer (rate ratios after adjustment for age and sex, 1.24, 1.18, and 1.26, respectively). A history of liver cancer in a parent, sibling, or child or in a spouse showed a tendency toward an association with the risk of liver cancer (rate ratios after adjustment for age and sex, 1.93 and 2.66, respectively), but was not a significant risk factor.

DISCUSSION

Several case–control studies[13-16] have already reported that hepatitis C virus has an important role in the pathogenesis of liver cancer. In the only follow-up study of patients with hepatitis C virus and liver cancer, Colombo et al.[17] followed 447 Italian patients with well-compensated liver cirrhosis (including 201 positive for anti-HCV) for a mean period of 33 months and found a yearly incidence rate of 3 percent for

hepatocellular carcinoma. In their study, the cumulative hazard of hepatocellular carcinoma was higher among patients with elevated serum alpha-fetoprotein levels than among those with consistently normal levels, but the authors found no relation between the risk of liver cancer and specific causes of cirrhosis. By contrast, our study shows a close relation between the risk of liver cancer and hepatitis C virus. Our results also indicate that smoking may increase the risk of liver cancer among patients with chronic liver disease.

One limitation of our study was the use of a first-generation enzyme immunoassay for anti-HCV, since this test may be less sensitive and specific than second-generation assays.[18-21] The rate ratio for patients positive for anti-HCV in our study might be underestimated because of random misclassification of their status for the antibody.

Another limitation was that in a majority of the study patients, the anti-HCV status was determined during follow-up, not at enrollment. This limitation may have also led to the underestimation of the rate ratio for liver cancer, since some carriers of hepatitis C virus may lose their reactivity to anti-HCV during the follow-up period.[22,23] Besides, some of the patients who had liver cancer before April 1990, whose status for anti-HCV was necessarily unknown, may have been positive for the antibody.

The dropout rate in our study could be another problem: 215 patients dropped out before the end of the study period. If the patients with risk factors had dropped out at a higher or lower rate than those without risk factors, estimates of the rate ratios would have been biased. However, when we checked whether the observed risk factors for liver cancer would predict dropping out, by designating patients who dropped out as patients with liver cancer and designating patients who had hepatocellular carcinoma as "censored" patients in the proportional-hazards model, while still designating patients censored at the end of observation as "censored," the rate ratios for dropping out, which ranged from 0.71 to 1.31, were not significantly different from the referent value (1.00) for all variables listed in Table 3. Therefore, we do not consider the effect of dropping out to be sufficient to distort our results.

Although there were no significant associations between smoking and drinking habits and the risk of liver cancer among the patients with chronic hepatitis diagnosed at enrollment, among the patients with liver cirrhosis the risk was significantly increased in current smokers and former heavy drinkers but was small and insignificant in current heavy drinkers. On the basis of a large-scale cohort study in Japan, Hirayama[24] estimated the relative risk of liver cancer among the patients with cirrhosis to be 2.67 in daily cigarette smokers (as compared with nonsmokers) and 1.00 in daily alcohol drinkers (as compared with those who did not drink alcohol daily). Recently, Adami et al.[25] conducted a cohort study of Swedish patients with a diagnosis of alcoholism, liver cirrhosis, or both,

and found that alcoholism alone carried a moderately increased risk of liver cancer and that alcoholism with liver cirrhosis did not increase the risk more than cirrhosis alone. These results are supported by our findings and suggest that alcohol may be a liver carcinogen only because it is causally involved in the development of liver cirrhosis,[25] whereas cigarette smoking may be involved in the development of liver cancer from liver cirrhosis.[24] If so, intervention against drinking should be carried out as early as possible, before liver cirrhosis develops, and smoking-cessation programs should be offered even to patients who already have chronic liver disease, particularly those with liver cirrhosis.

Differences between Japan and the United States in types of hepatitis C virus have been reported.[26-29] Different types of the virus may have different clinical outcomes,[30] and these differences may also explain some of the differences between Italy[17] and Japan in the relation of anti-HCV to the risk of liver cancer. Comparative studies of the risks of liver cancer due to hepatitis C virus in other countries are needed.

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Quality.

Quantity.

A CASE-CONTROL STUDY OF HEPATOCELLULAR CARCINOMA IN OSAKA, JAPAN

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A case-control study was undertaken to evaluate the roles of hepatitis B virus (HBV), blood transfusion, alcohol drinking and cigarette smoking in the etiology of hepatocellular carcinoma (HCC) in Osaka, Japan. A total of 229 cases and 266 hospital controls were included in our study. The relative risks of HCC obtained after adjustment for age, sex and other important variables were 14.3 (95% confidence interval (CI): 5.7–36.3) for HBsAg positives, 4.3 (95% CI: 1.9–9.6) for blood recipients and 3.2 (95% CI: 2.0–5.1) for heavy drinkers. A statistically significant dose-response relationship was observed between the risk of HCC and total alcohol consumption. The overall risk for HCC was also significantly elevated among smokers; however, there was no consistent dose-response relationship between the risk and cigarette consumption. We conclude that HBV, blood transfusion and excessive alcohol drinking play important roles in the etiology of HCC in Osaka, Japan. Further investigation is needed to clarify the possible etiological role of smoking.

Liver cancer is the third leading cause of cancer mortality after stomach cancer and lung cancer in Japan. Osaka, in particular, is one of the prefectures with the highest liver-cancer risk in Japan. The age-adusted mortality rate of liver cancer among the male population in Japan has been increasing sharply since around 1975, while such an increase has not been observed among the female population (Japan Ministry of Health and Welfare, 1987; Kuroishi *et al.,* 1985). A similar time trend can be seen in the incidence of liver cancer (Hanai and Fujimoto, 1984) and the combined mortality of liver cirrhosis and chronic liver disease plus liver cancer (Hiyama, 1987). The reasons for such a sex difference cannot be solely explained by recent progress in diagnostic procedures and therapeutic measures nor by the changes in the classification of diseases.

Hepatitis B virus is a well-known major risk factor of hepatocellular carcinoma (HCC), which constitutes over 90% of primary liver cancers in Japan (Liver Cancer Study Group of Japan, 1988). However, the prevalence of HBsAg positives among HCC patients has been decreasing gradually in Japan. According to data from the Liver Cancer Study Group in Japan, it was about 40.7% (266/654) between 1968 to 1977 (Okuda and The Liver Cancer Study Group of Japan, 1980), and it decreased to 24.6% (476/1933) between 1984 to 1985 (Liver Cancer Study Group of Japan, 1988). In other words, HCC unrelated to hepatitis B virus seems to be increasing in Japan (Okuda *et al.,* 1987).

It is unlikely that alcohol *per se* is carcinogenic, but there is now good evidence to suggest that alcohol consumption sufficient to cause liver cirrhosis will also increase the incidence of HCC (WHO, 1988). Epidemiological studies have suggested a significant association between smoking and HCC (Trichopoulos *et al.,* 1980; Lam *et al.,* 1982). Both drinking and smoking are prevalent among males, and alcohol and cigarette consumption have been increasing since World War II in Japan (Health and Welfare Statistics Association, 1987; Fujimoto, 1986). Therefore, these 2 factors are the likeliest candidates for the etiology of increasing HCC among Japanese males. A hospital-based case-control study was conducted in order to eval-

uate the roles of HB virus, blood transfusion, alcohol drinking and cigarette smoking in the etiology of HCC in Osaka, Japan.

SUBJECTS AND METHODS

Cases

Eligible cases were patients aged 74 or below who were admitted to the Center for Adult Diseases, Osaka, and were newly diagnosed as HCC on the basis of both clinical and histological examination between November 1983 and June 1987. Of the 229 eligible HCC patients identified (192 males and 37 females), 221 (96.5%) were interviewed; 8 could not be interviewed because of extreme sickness or refusal by the patients or physicians.

Controls

We obtained as many controls as cases for males and twice as many controls for females. The controls were selected so that the sex-specific age distribution would be similar to that of the case group. The sources of the controls were the following: (1) patients admitted to the Department of Gastro-enterology; (2) persons admitted for multiphasic health checkups; (3) examinees in the Gastro-enterological Endoscopy Section. The following, however, were not included: (1) patients with liver disease, malignant neoplasms, and smoking- and alcohol-related diseases; (2) persons not tested for HBsAg.

As a result, a total of 266 valid controls was obtained between September 1984 and December 1987.

Data collection and analysis

All the cases and controls were interviewed at the time of admission and endoscopic examination by two specially trained interviewers using a standard questionnaire, which contained information on the following points: demographic characteristics, past medical history including blood transfusion, family history of liver disease and malignant neoplasms, history of alcohol drinking and cigarette smoking. Data of serum HBsAg were collected from their medical records. The test for HBsAg was conducted by the reversed passive hemagglutination method.

Blood recipients were defined as individuals who had received transfusion(s) more than 10 years before the interview; the others were counted as non-recipients.

Reported consumption of alcoholic beverages was converted into "sake" (Japanese wine) equivalents. One "go" (180 ml) of "sake" is equivalent to 60 ml of whiskey; 240 ml of wine; and 633 ml of beer, which contains about 27 ml of ethanol. Drinkers were defined as individuals who had been drinking at

least one "go" of "sake" per week 10 years prior to the interview. Heavy drinking was defined as drinking at least 3 "go"s of "sake" per day for more than 10 years. Smokers were defined as individuals who had been smoking at least 1 cigarette per day 10 years prior to the interview.

The age- and sex-adjusted odds ratios of HCC, together with their test-based 95% confidence intervals (CI), were first computed from data stratified for sex and age (35–44, 45–54, 55–64, 65–74) by means of the Mantel-Haenszel procedure. Secondly, to account simultaneously for the potential confounding effect of various risk factors, unconditional logistic regression analysis was employed, using the SAS statistical package (Breslow and Day, 1980; Harrell, 1986). The natural antilogarithm of regression coefficients of indicator variables was interpreted as the relative risk (RR) for HCC, and the 95% CI was similarly obtained from the regression coefficient and its standard error. All reported p values were 2-tailed.

RESULTS

Male study subjects comprised 192 cases and the same number of controls, and more than 70% of them ranged from 45 to 64 years of age. Females comprised 37 cases and 74 controls, and more than 80% of them ranged from 55 to 74 years. There was no significant difference in the distribution by 10-year age group between cases and controls. Eighty-seven cases were histologically confirmed, and 124 cases were diagnosed as HCC by angiography. The remaining 18 cases were diagnosed as HCC on the basis of other clinical examinations, such as computed tomography, ultrasonography, scintigraphy and alpha-fetoprotein. Of the 266 controls, 28% were diagnosed as almost normal, and the remainder were diagnosed as having a benign condition, such as gastritis or gastric polyps (24.8%), colorectal polyps (15.0%), diabetes mellitus (13.9%), scar from peptic ulcer (6.8%) and others.

Table I shows a comparison of the prevalence of HBsAg and the history of blood transfusion between cases and controls. Among the males, 17.7% of cases and 2.6% of controls were HBsAg positive; among the females, 24.3% of cases and 1.4% of controls were HBsAg positive. The age- and sex-adjusted odds ratio of HCC for HBsAg positives compared with HBsAg negatives was 9.5 with 95% CI 4.7 to 19.1.

Among the males, 13.0% of cases and 3.2% of controls were recipients of blood transfusions and the age-adjusted odds ratio of HCC for recipients compared with non-recipients was 4.5 with 95% CI 1.9 to 10.7. Among the females, 5.9% of cases and 5.4% of controls were recipients, but their difference was not significant.

As for drinking habits, 77.0% of cases and 76.0% of controls were drinkers among the males, and 17.6% of cases and 8.1% of controls were drinkers among the females. The age- and sex-adjusted odds ratios of HCC for drinkers who had consumed 0.1–2.9 and at least 3 "go"s of "sake" per day compared with never-drinkers were 1.1 and 1.3, respectively. These figures were slightly higher than unity, but not significant. Table II shows a comparison of the prevalence of a history of heavy drinking between cases and controls. Among the males, 44.4% of cases and 23.4% of controls had a history of heavy drinking, and among the females, only one of the 34 cases had a history of heavy drinking. The age- and sex-adjusted odds ratio of HCC associated with a history of heavy drinking was 2.6 with 95% CI 1.7 to 4.1.

Table III shows a comparison of smoking habits between cases and controls. Among the males, 85.6% of cases and 70.3% of controls were smokers, while 29.4% of cases and 13.5% of controls were smokers among the females. The age- and sex-adjusted odds ratio of HCC for smokers compared with never-smokers was 2.5 with 95% CI 1.4 to 4.5. Although the risk of HCC among smokers was significantly higher than among never-smokers, we did not see a positive dose-response relationship between the risk of HCC and the number of cigarettes smoked per day. The odds ratio of HCC associated with the smoking category of 1–19 cigarettes a day was higher than any other smoking category. Table IV indicates a comparison of cigarette index (number of cigarettes/day × number of years smoking) between cases and controls. A dose-response relationship between the risk of HCC and the cigarette index could not be seen in the same way as in Table III.

Table V shows a comparison of a family history of hepatitis or liver cirrhosis, liver cancer, and the other malignancies between cases and controls. The age- and sex-adjusted odds ratios of HCC associated with a family history of liver cancer and a history of hepatitis or liver cirrhosis were 1.6 and 1.2, respectively, which were slightly higher than unity, but not significant. As for a family history of the other malignancies, there was no difference between cases and controls.

Table VI indicates the multivariate risk estimates. In this analysis, 7 variables were selected; namely, age (35–44, 45–54, 55–64, 65–74), sex, HBsAg, history of blood transfusion, heavy drinking, cigarette index, and family history of liver cancer. The RR of HCC for HBsAg positives was 14.3 with 95% CI 5.7 to 36.3. The RR for blood recipient was 4.3 with 95% CI 1.9 to 9.6. The RR for heavy drinker was 3.2 with 95% CI 2.0 to 5.1. Using subjects with a cigarette index of less than 400 as a referent, we estimated the RRs of HCC as 1.9 for individuals with the indices of 400–799, 2.0 for subjects with the indices of 800–1199, and 1.0 for persons with the indices of 1200 or more. No specific trends were observed in the RRs for increased cigarette indices. The RR for HCC associated with a family history of liver cancer was small.

TABLE I – COMPARISON OF THE PREVALENCE OF HBsAg AND THE HISTORY OF BLOOD TRANSFUSIONS BETWEEN CASES AND CONTROLS

	Male			Female			Both sexes
	Cases (%)	Controls (%)	OR[1] (95% CI)	Cases (%)	Controls (%)	OR[1] (95% CI)	OR[2] (95% CI)
HBsAg							
Positive	34 (17.7)	5 (2.6)	8.0 (3.6–17.9)	9 (24.3)	1 (1.4)	19.7 (4.4–88.0)	9.5 (4.7–19.1)
Negative	158 (82.3)	187 (97.4)	1.0	28 (75.7)	73 (98.6)	1.0	1.0
Blood transfusion[3]							
Recipients	24 (13.0)	6 (3.2)	4.5 (1.9–10.7)	2 (5.9)	4 (5.4)	1.1 (0.2–6.5)	3.5 (1.6–7.4)
Non-recipients	161 (87.0)	184 (96.8)	1.0	32 (94.1)	70 (94.6)	1.0	1.0

[1]Age-adjusted odds ratio.–[2]Sex- and age-adjusted odds ratio.–[3]Blood recipients within 10 years before the interview were counted as non-recipients. Subjects who did not answer the relevant question were eliminated from the analysis.

TABLE II – COMPARISON OF THE PREVALENCE OF A HISTORY OF HEAVY DRINKING BETWEEN CASES AND CONTROLS

History of heavy drinking[1]	Male			Female			Both sexes
	Cases (%)	Controls (%)	OR[2] (95% CI)	Cases (%)	Controls (%)	OR	OR[3] (95% CI)
(+)	83 (44.4)	45 (23.4)	2.6 (1.7–4.0)	1 (2.9)	0 (0.0)	—	2.6 (1.7–4.1)
(−)	104 (55.6)	147 (76.6)	1.0	33 (97.1)	74 (100)	1.0	1.0

[1]Three "go"s of "sake" per day for more than 10 years.–[2]Age-adjusted odds ratio.–[3]Sex- and age-adjusted odds ratio.

TABLE III – COMPARISON OF SMOKING HABITS BETWEEN CASES AND CONTROLS

Smoking habits	No. of cigarettes smoked/day	Male			Female			Both sexes
		Cases (%)	Controls (%)	OR[1] (95% CI)	Cases (%)	Controls (%)	OR[1] (95% CI)	OR[2] (95% CI)
Smoker		160 (85.6)	135 (70.3)	2.3 (1.1–4.8)	10 (29.4)	10 (13.5)	2.9 (1.1–7.9)	2.5 (1.4–4.5)
	40–	20	37	1.0	1	2	[1.1]	1.1
	20–39	99	73	2.5	2	5		2.2
	1–19	41	25	3.4	7	3	[6.1]	4.2
Ex-smoker		15 (8.0)	34 (17.7)	0.8 (0.3–2.0)	0 (0.0)	1 (1.4)	—	0.7 (0.3–1.9)
Never		12 (6.4)	23 (12.0)	1.0	24 (70.6)	63 (85.1)	1.0	1.0

[1]Age-adjusted odds ratio.–[2]Sex- and age-adjusted odds ratio. [ ] = crude odds ratio.

Table VII shows the relationship between the risk of HCC and total alcohol consumption among males. This analysis was performed with unconditional logistic regression, including variables of age, HBsAg, history of blood transfusion, cigarette index, and family history of liver cancer. Although the risk of HCC associated with the category of 10,000–39,999 "go"s of "sake" was not higher than unity, chi-square for the linear trend was estimated at 4.87, statistically significant.

DISCUSSION

While Osaka is a high-incidence area of liver cancer in Japan, on a par with Shanghai and Hong Kong (Muir et al., 1987), prevalences of HBsAg among the general population and HCC patients in Osaka are far lower than those in Shanghai and in Hong Kong (Nishioka, 1975; Oshima et al., 1982; Ying et al., 1984). Furthermore, the age-adjusted incidence and mortality rate of liver cancer in Osaka have been markedly increasing for males (Oshima et al., 1982; Hanai and Fujimoto, 1984). Osaka appears to be an interesting region to clarify the risk factors for HCC besides HBV.

The strong association between HBsAg positivity and HCC has been demonstrated in case-control studies (Inaba et al.,

1984; Hiraga et al., 1986; Tanaka et al., 1988) and follow-up studies (Sakuma et al., 1982; Oshima et al., 1984; Fukao, 1985) also in Japan. The estimated RRs from these studies conducted in Japan range from 10 to 31. Our study further confirmed this association in Osaka.

Blood transfusion has been suspected as a risk factor for HCC from clinical follow-up studies and case-control studies. Ichikawa et al. (1984) conducted a long-term follow-up study of patients who had undergone gastrectomy in Japan, and showed that the incidence of liver cancer among those who had had blood transfusion at the time of the gastrectomy increased 4.7 times compared with the expected incidence among the general population more than 10 years after their blood transfusion. However, such an increase was not seen during the period of the first 10 years. This positive association between a history of blood transfusion and HCC was supported by case-control studies conducted in Japan (RR 4.7, Tanaka et al., 1988) and USA (RR 7.0, Yu et al., 1983). Our present study showed a significant positive association between a history of blood transfusion and HCC for males (RR 4.5) and for both sexes (RR 3.5), but failed to demonstrate it for females (RR 1.1). According to the data from the Liver Cancer Study Group in Japan (1988), 11.2% of male HCC patients (143/1281) and

TABLE IV – COMPARISON OF CIGARETTE INDEX BETWEEN CASES AND CONTROLS

Cigarette index	Male			Female			Both sexes
	Cases (%)	Controls (%)	OR[1] (95% CI)	Cases (%)	Controls (%)	OR	OR[2] (95% CI)
1200–	26 (13.9)	40 (20.8)	0.9 (0.5–1.7)	1 (2.9)	0 (0.0)	[1.6]	1.0 (0.5–1.8)
800–1199	58 (31.0)	40 (20.8)	1.9 (1.1–3.4)	1 (2.9)	3 (4.1)		1.8 (1.0–3.1)
400–799	61 (32.6)	54 (28.1)	1.6 (0.9–2.8)	4 (11.8)	4 (5.4)	[2.4]	1.7 (1.0–2.8)
0–399	42 (22.5)	58 (30.2)	1.0	28 (82.4)	67 (90.5)	1.0	1.0

[1]Age-adjusted odds ratio.–[2]Sex- and age-adjusted odds ratio. [ ] = crude odds ratio.

TAVLE V – COMPARISON OF FAMILY HISTORY OF LIVER CANCER, OTHER MALIGNANCIES, AND HEPATITIS OR LIVER CIRRHOSIS BETWEEN CASES AND CONTROLS

Family history[1]		Male			Female			Both sexes
		Cases (%)	Controls (%)	OR[2] (95% CI)	Cases (%)	Controls (%)	OR[2] (95% CI)	OR[3] (95% CI)
Liver cancer	(+)	12 (7.1)	8 (4.6)	1.6 (0.6–4.1)	2 (6.7)	2 (3.4)	1.8 (0.2–13.8)	1.6 (0.7–4.8)
	(−)	157 (92.9)	165 (95.4)	1.0	28 (93.3)	57 (96.6)	1.0	1.0
Other malignancies	(+)	55 (32.0)	67 (38.1)	0.8 (0.5–1.2)	12 (38.7)	26 (41.3)	0.9 (0.3–2.1)	0.8 (0.5–1.1)
	(−)	117 (68.0)	109 (61.9)	1.0	19 (61.3)	37 (58.7)	1.0	1.0
Hepatitis or cirrhosis	(+)	28 (16.5)	27 (15.8)	1.1 (0.6–1.9)	9 (29.0)	12 (19.7)	1.6 (0.6–4.3)	1.2 (0.7–1.9)
	(−)	142 (83.5)	144 (84.2)	1.0	22 (71.0)	49 (80.3)	1.0	1.0

[1]Prevalence of disease among parents and siblings. Subjects who did not answer the relevant question were eliminated from the analysis.–[2]Age-adjusted odds ratio.–[3]Sex- and age-adjusted odds ratio.

TABLE VI – ADJUSTED EFFECTS OF RISK FACTORS—UNCONDITIONAL LOGISTIC REGRESSION ANALYSIS

Variable	β^1	RR	95% CI	p
HBsAg (positive/negative)	2.662	14.3	5.7–36.2	<0.0001
Blood transfusion (recipient/non-recipient)	1.454	4.3	1.9–9.6	0.0004
History of heavy drinking[2] (heavy/not heavy)	1.155	3.2	2.0–5.1	<0.0001
Cigarette index (1200–/0–399)	−0.049	1.0	0.5–1.9	0.8879
Cigarette index (800–1199/0–399)	0.681	2.0	1.1–3.6	0.0245
Cigarette index (400–799/0–399)	0.638	1.9	1.1–3.3	0.0243
Family history of liver cancer (positive/other)	0.340	1.4	0.5–3.6	0.4827

[1]Logistic regression coefficients.–[2]Three "go"s of "sake" per day for more than 10 years.

18.5% of female patients (48/260) had a history of blood transfusion more than 10 years before the date of diagnosis. In light of these data, we suppose that the reason why a positive association was not noted between HCC and a history of blood transfusion for females might be an artifact resulting from a smaller sample of female HCC cases.

There is good evidence to suggest that alcohol consumption sufficient to cause liver cirrhosis will also increase the incidence of HCC, apart from the mechanism on liver carcinogenesis. Twelve case-control studies (Yu et al., 1983; Stemhagen et al., 1983; Oshima et al., 1984; Inaba et al., 1984; Hardell et al., 1984; Filippazzo et al., 1985; Austin et al., 1986; Hiraga et al., 1986; Choi et al., 1986; Yu et al., 1988; Tanaka et al., 1988; Pyong et al., 1988) except for one by Trichopoulos et al. (1980) and 3 cohort studies (Hirayama, 1981; Shibata et al., 1986; Kono et al., 1987) on liver cancer and alcohol drinking all showed a significant increased risk of liver cancer

for heavy drinkers and most of them also demonstrated a positive dose-response relationship between the risk of HCC and alcohol consumption. The estimated RRs of liver cancer for heavy drinkers from these studies range from 2 to 4 for the most part. Our present study also showed around 3 times higher risk of HCC among heavy drinkers, who had been drinking at least 3 "go"s of "sake" per day for more than 10 years.

The reasons why this study failed to demonstrate the excess risk among those who had consumed a total of 10,000–39,999 "go"s of "sake" appeared to be associated mainly with the following two points. One is the fact that the proportion of those who had drunk more than 10,000 "go"s of "sake" among controls who had not had a history of heavy drinking was larger than that among cases who had not had a history of heavy drinking (47.6% vs. 31.7% for males). Another is the possibility that the daily alcohol consumption might have

TABLE VII – RELATIONSHIP BETWEEN THE RISK OF HCC AND TOTAL ALCOHOL CONSUMPTION AMONG MALES—UNCONDITIONAL LOGISTIC REGRESSION ANALYSIS

Total alcohol consumption ("go"s of "sake")	Cases Number (%)	Controls Number (%)	β^1	RR (95% CI)	
40,000–	49 (26.2)	31 (16.1)	0.766	2.2 (1.2–4.0)	2
10,000–39,999	67 (35.8)	84 (43.8)	−0.025	1.0 (0.6–1.6)	
0–9,999	71 (38.0)	77 (40.1)	—	1.0	
Total	187 (100)	192 (100)			

[1]Logistic regression coefficients.–[2]χ^2 for linear trend = 4.87 (p = 0.0273).

decreased more significantly among cases than among controls, for example, due to the advent or deterioration of liver disease with age.

Apart from the above-mentioned risk factors of HCC, there is now considerable controversy about the possible etiological role of cigarette smoking for HCC. Trichopoulos et al. (1980) and Lam et al. (1982) reported a significant association between smoking and HCC patients who were negative for HBsAg. The Greek and the Hong Kong study reported that this association was stronger among those aged over 50 or 60. As for the association between cigarette smoking and HCC, 11 case-control studies (Yu et al., 1983; Stemhagen et al., 1983; Oshima et al., 1984; Hardell et al., 1984; Kew et al., 1985; Filippazzo et al., 1985; Austin et al., 1986; Choi et al., 1986; Yu et al., 1988; Tanaka et al., 1988; Pyong et al., 1988) and 3 cohort studies (Hirayama, 1981; Shibata et al., 1986; Kono et al., 1987) have been published, but with inconsistent results. Now, we can find no satisfactory explanation for the inconsistency in the results, but some of the disparity may be accounted for by differences in the etiology of HCC by geographic area and others may be caused by differences in controlling for confounding variables and selection of controls.

In our study, the risk of HCC among smokers was significantly higher than that among never-smokers. However, there was no consistent dose-response relationship between the risk of HCC and cigarette consumption. These findings were observed irrespective of sex, age and HBsAg (data not shown). The apparent absence of a positive dose-response relationship between the risk of HCC and cigarette consumption could be the result of bias. Indeed among the male controls, 12 and 26 patients were diagnosed as having scars from peptic ulcer and diabetes mellitus, respectively. Thirty-two percent of these patients were heavy smokers (cigarette index $\geqq 1200$), compared with 18% of the remaining controls. However, the exclusion of controls with the two diseases had very little effect on the RRs relating HCC and cigarette consumption. Lack of a dose-response relationship between the risk of HCC and cigarette smoking might also occur if HCC patients with a history of heavy smoking were selectively excluded from this study, for example, owing to death from lung cancer or myocardial infarction which were caused more specifically by smoking. We could not rule out this possibility.

Tanaka et al. (1988) have reported a case-control study of HCC conducted in Fukuoka, Japan, where HCC risk is one of the highest in this country. Their results were very similar to ours, except that they observed a positive dose-response relationship between the risk of HCC and cigarette consumption,

although the relationship at a young age was less clear. Their controls consisted of those who visited a health center to undergo a health examination. Thus, the possibility exists that they were more conscientious about health and might have included fewer smokers than the general population. The relationship between smoking and HCC in their case-control study might be overestimated. Further investigations are needed to clarify the possible etiological role of smoking for HCC.

We calculated the population attributable risk (PAR) of HCC for each risk factor (Breslow and Day, 1980), using the sex-specific RR derived from the logistic regression analysis and the proportion of controls with each risk factor which we assumed as the proportion of the general population in the exposed category. For males, the PAR of HBsAg, a history of blood transfusion and a history of heavy drinking were 21.4%, 12.8% and 32.9%, respectively. For females, the PAR of HBsAg was estimated as 27.1%. Of course these figures, especially the PAR of a history of heavy drinking, may be overestimated, since the hospital controls may not be representative of the general population with respect to factors such as drinking and smoking. If we estimate the proportion of the general population who are heavy drinkers as 15%, the PAR of heavy drinking accounts for 24% of male HCC patients. This figure may be more plausible.

The annual alcohol consumption per capita has increased about 3-fold from 1955 to 1984 in Japan (Health and Welfare Statistics Association, 1987). The increasing consumption of alcohol may be partly responsible for the upward trend of HCC among males in Osaka, Japan.

Non-A, non-B hepatitis (NANBH) has been suspected as a risk factor for HCC from clinical data. So far, however, no one has shown direct evidence of NANBH infection. Chiron Corporation (USA) has succeeded in cloning a NANBH virus genome (Choo et al., 1989) and has developed an immuno-assay to detect antibodies to NANBH virus (Kuo et al., 1989). It is an urgent task to clarify the role of NANBH in the etiology of HCC in Osaka, Japan.

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Incidence of Second Primary Cancers in Osaka Residents, Japan, with Special Reference to Cumulative and Relative Risks

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This study was conducted to examine the incidence rates and cumulative risks of second primary cancers in Osaka and to compare the observed number of second primary cancers with the expected number calculated using cancer incidence rates among Osaka residents. Study subjects were all reported cases aged 0–79 who were first diagnosed as having a first primary cancer between 1966–86. Incidence of second primary cancer among the study subjects was examined through to the end of 1989. The total number of study subjects was 217,307. During the follow-up period (mean duration: 3.7 years), second primary cancers developed in 5,071 patients (2.3%). Incidence of synchronous (interval <3 months) and metachronous (interval ≥3 months) second primary cancers increased in the later years. Incidence rates of second primary cancers were significantly associated with gender (male), age and calendar year at diagnosis of the first cancer. Based on the incidence rates, cumulative risk of developing metachronous second primary cancer was calculated. The ten-year cumulative risk was estimated as 10% for those who developed their first cancer during their sixties in 1978–83. The observed number of second primary cancers (including synchronous) was compared with the expected number. The ratios of observed-to-expected numbers were generally lower than 1.0 among those who developed their first cancer in 1966–77, while these ratios were higher than 1.0 among those who developed their first cancer in 1978–86. The ratios were much higher than 1.0 among those who developed their first cancer in their childhood and youth. Patients who had developed cancer of the colon, larynx, lung, bladder, or breast (female) showed significantly higher risk of developing second primary cancer during the period 1–4 years after diagnosis of the first cancer.

Key words: Second primary cancer — Time trend — Incidence rate — Cumulative risk — Ratio of observed-to-expected numbers

With increasing survival after treatment for many forms of cancer, and the use of chemotherapeutic agents and radiations in the treatment of malignant tumors, it is estimated that at present some 5% of all cancer patients develop a further independent primary cancer.[1-3] Although hospital-based studies have the advantage of diagnostic refinement, they are often limited by the relatively small number of patients with multiple primary cancer known to a single institution, which results in unstable risk estimates. These difficulties were overcome, for the most part, with the establishment of large population-based cancer registries.[4] Using a data file from the Osaka Cancer Registry, one of the oldest and largest population-based cancer registries in Japan,[5] we examined the incidence of second primary cancers developing in a relatively large and unselected population of cancer patients in Osaka.

MATERIALS AND METHODS

Outline of the Osaka Cancer Registry The Osaka Cancer Registry was founded in 1962 for the purpose of registering all malignant tumors and benign intracranial tumors arising in Osaka Prefecture (1990 Census popula-

tion; 8.7 millions).[5] The Registry assigns a unique registration number to each patient, and thus second or later multiple primary cancers can be easily identified. For each tumor, the site of origin, histologic findings, clinical stage, and primary treatment are identified. An additional code for multiple primary cancers is assigned which identifies each primary cancer. Follow-up information is also available, including the last date of contact and vital status.

Study subjects and definition of multiple primary cancers Study subjects were all reported cases aged 0–79 who were initially diagnosed as having a first primary cancer (invasive cancer and benign intracranial tumor) between 1966–86. The incidence of a second primary cancer among the study subjects was examined through to the end of 1989.

In this study, we have followed the rules suggested by the IARC as well as by the ICD-O second edition[6-8] to define the circumstances under which an individual is considered to have more than one cancer.

Analysis of metachronous second primary cancers Incidence rates of metachronous second primary cancers were calculated using a computer program developed by

Monson.[9] Metachronous second primary cancers were defined as all invasive tumors and intracranial tumors which were diagnosed at least 3 months after diagnosis of the first cancer. *In situ* carcinomas and any third or fourth (or more) primaries were excluded. The period of observation used in calculating the risks for second primary cancers began at the date of diagnosis of the first cancer and ended at either the date of diagnosis of the metachronous second primary cancer, the date of reaching 80 years old, the date of death, or December 31, 1989, whichever came first. Patients who were diagnosed as having a second primary cancer within 3 months (synchronous second primaries) or who did not survive for 3 months or more after diagnosis of the first cancer were all excluded from the analysis of metachronous second primary cancer risk.

Using the age-, sex-, and period-specific incidence rates calculated above, cumulative risks[10] of developing metachronous second primary cancers were estimated according to age and calendar year at diagnosis of the first cancer and number of elapsed years thereafter.

Poisson regression analysis was performed to estimate the incidence rate ratios of metachronous second primary cancers for each of the possible relating factors, together with their 95% confidence intervals, and to control possible confounding factors simultaneously. This analysis

was implemented with the statistical package for generalized linear interactive modelling, developed by the Working Party on Statistical Computing of the Royal Statistical Society.[11]

External comparison The observed number (O) of second primary cancers (including synchronous) for all sites was compared with the expected number (E), according to selected site of the first cancer and number of elapsed years thereafter. The IARC's definition[6-8] does not accept any tumors in the same site (ICD-9 3 digit level) as the first primary cancer as a second primary cancer, unless their major histologic types differ from the first primary cancer's. Therefore, the O/E ratios for all sites must be underestimated, particularly in the case of first cancers with large person-years, such as cancers of the stomach, colon, rectum, larynx, lung, bladder, thyroid, breast (female), and uterus. To avoid such underestimations in the case of those first cancers, we excluded both of the observed and the expected numbers of second primary cancers in the same site as the first cancer from the O/E for all sites.

Patients who were diagnosed as having a second primary cancer or who died within 3 months after diagnosis of the first cancer were included in this analysis.

A computer program developed by Monson[9] was used for these calculations. The significance of the O/E ratios
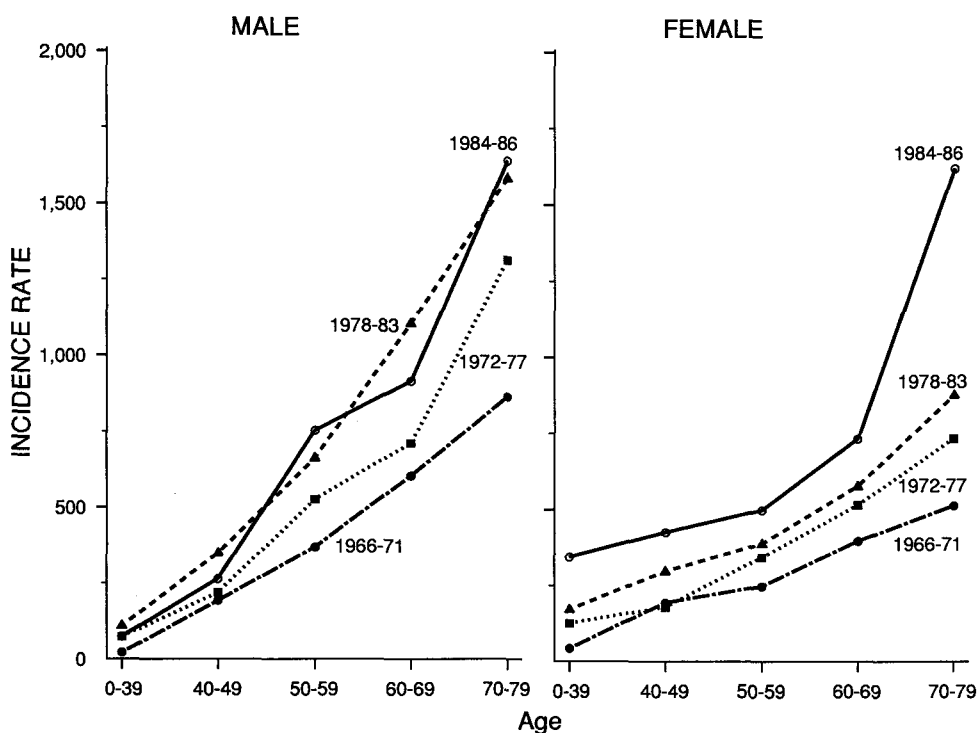

Fig. 1. Age-specific incidence rates of metachronous second primary cancers per 100,000 person-years, according to sex and calendar year at diagnosis of the first cancer, Osaka, 1966–86.

was tested by Poisson distribution analysis,[12] while their 95% confidence intervals were calculated using the CIA statistical package.[13]

Reported P-values were all two-tailed.

RESULTS

The total number of study patients was 217,307. During the follow-up period (mean follow-up duration: 3.7 years), second primary cancers developed in 5,071 patients (2.3%), of which 4,436 cases were metachronous second primary cancers.

Metachronous second primary cancers Fig. 1 shows age and sex-specific incidence rates of metachronous second primary cancers per 100,000 person-years, in which study subjects were classified into 4 groups according to calendar year at diagnosis of the first cancer. The incidence rates increased remarkably with an increase in age, and were higher among males than among females except for age groups of 0–39 and 40–49 years old. Age-specific incidence rates increased with calendar year at diagnosis of the first cancer, in particular, for females.

In order to elucidate risk factors relating to the development of primary second cancers, Poisson regression analysis was performed on the incidence data of meta-

chronous second primary cancers obtained during the first 0–4 years after diagnosis of the first cancer (Table I). Calendar year and age at diagnosis of the first cancer, as well as sex (male), were found to be independent significant risk factors for developing a second primary cancer.

Table II indicates cumulative risks of the metachronous second primary cancers, according to age and calen-

Table I. Risk Factors Relating to Development of Metachronous Second Primary Cancers: Poisson Regression Analysis

Factor		Adjusted rate ratio	95% CI
Year at diagnosis of first cancer	1966–71	1.00	
	1972–77	1.59	1.33–1.90
	1978–83	2.89	2.47–3.38
	1984–86	2.89	2.45–3.40
Age at diagnosis of first cancer	0–49	1.00	
	50–59	1.88	1.64–2.14
	60–69	2.94	2.60–3.32
	70–79	3.50	3.07–3.99
Sex	Male	1.00	
	Female	0.67	0.62–0.73

Table II. Cumulative Risk of Metachronous Second Primary Cancers, According to Age and Calendar Year at Diagnosis of the First Cancer: Both Sexes

Age	Duration (years)	Year at diagnosis of the first cancer 1966–71	1972–77	1978–83	1984–86	Total
0–14	5	0.7%	0.0%	0.2%	0.2%	0.2%
	10	0.7	0.6	0.4	–	0.6
	15	1.2	0.9	–	–	0.9
	20	1.2	–	–	–	0.9
15–29	5	0.0	0.9	1.1	0.7	0.7
	10	0.2	1.6	1.7	–	1.2
	15	0.6	2.1	–	–	1.6
	20	0.9	–	–	–	2.0
30–39	5	0.5	0.5	1.1	0.7	0.8
	10	1.3	1.2	2.0	–	1.5
	15	2.7	2.6	–	–	2.9
	20	4.3	–	–	–	4.4
40–49	5	1.0	1.1	1.9	1.7	1.5
	10	2.4	3.5	3.9	–	3.4
	15	4.6	5.6	–	–	5.6
	20	6.7	–	–	–	7.9
50–59	5	1.0	1.5	2.9	3.1	2.3
	10	3.3	5.2	6.1	–	5.3
	15	6.6	9.1	–	–	8.7
	20	10.8	–	–	–	13.0
60–69	5	1.5	2.7	4.7	4.5	3.6
	10	4.7	8.3	10.4	–	8.6
	15	9.0	13.1	–	–	13.1
	20	13.2	–	–	–	17.1

dar year at diagnosis of the first cancer. The 10-year cumu-
lative risk was estimated as around 10% for those who
developed their first cancer in their sixties in 1978–83.
**Observed and expected numbers of second primary
cancers** The observed number (O) of second primary
cancers (including synchronous) was compared with the
expected number (E).

Table III shows the O/E ratios according to sex,
calendar year at diagnosis of the first cancer, and number
of elapsed years thereafter. The ratios among those who
developed their first cancer during the earlier study
period (1966–77) were generally lower than 1.0, while
among those who developed their first cancer during the
later study period (1978–86) the ratios were higher than
1.0. During the period 1–4 years after diagnosis of the
first cancer, 8% and 20% excess risk of second primaries
was observed among males and females, respectively,
who developed their first cancer in 1978–86. The O/E
ratios during the 5–9 year period after diagnosis of the
first cancer among those who developed their first cancer

in 1978–86, which are parenthesized in Table III, should
be revised in the next several years, because of the high
proportion of censored data.

Table IV shows the O/E ratios according to age at
diagnosis of the first cancer and the number of elapsed
years. The ratios among those who developed their first
cancer in childhood (0–14 years old) and youth (15–29
years old) were 24.1 and 15.9 for the first year, 4.2 and
5.1 for the next 4 years, and 7.3 and 2.2 for the next
5–9 year period, respectively, after diagnosis of the first
cancer. These ratios were much higher than the ratios
among the total age groups. The observed numbers of
second primary cancers among those who developed
their first cancer in childhood and youth were so small
that we have only presented the O/E ratios for the entire
study period.

The O/E ratios among those who developed their first
cancer in 1978–86 were further examined according to
selected sites of the first cancer (Table V). Because of the
high proportion of censored data, the O/E ratios during

Table III. Observed and Expected Numbers of Second Primary Cancers, According to Years after Diagnosis of the First Cancer: Relation to Calendar Year at Diagnosis of the First Cancer and Sex

Sex	Year at diagnosis of the first cancer	Years after diagnosis of the first cancer					
		0		1–4		5–9	
		Obs	O/E (95% CI)	Obs	O/E (95% CI)	Obs	O/E (95% CI)
Male	1966–77	86	0.43[b] (0.35–0.54)	227	0.62[b] (0.55–0.71)	365	0.95 (0.86–1.05)
	1978–86	649	1.50[b] (1.39–1.62)	858	1.08[a] (1.00–1.15)	334	[1.02] (0.91–1.13)
Female	1966–77	74	0.67[b] (0.53–0.85)	230	0.88 (0.77–1.00)	304	1.03 (0.92–1.15)
	1978–86	358	2.01[b] (1.94–2.38)	496	1.20[b] (1.10–1.31)	219	[1.07] (0.93–1.21)

a) P<0.05. b) P<0.01. [ ]: see text.

Table IV. Observed and Expected Numbers of Second Primary Cancers, According to Years after Diagnosis of the First Cancer: Relation to Age at Diagnosis of the First Cancer, 1966–86, Both Sexes

Age at diagnosis of the first cancer	Years after diagnosis of the first cancer					
	0		1–4		5–9	
	Obs	O/E (95% CI)	Obs	O/E (95% CI)	Obs	O/E (95% CI)
0–14	10	24.1[b] (11.7–44.9)	4	4.2[a] (1.15–10.8)	4	7.3[b] (1.98–18.6)
15–29	11	15.9[b] (7.96–28.5)	13	5.1[b] (2.71–8.72)	8	2.2[b] (0.94–4.27)
0–79	1167	1.3[b] (1.20–1.34)	1811	1.0 (0.94–1.03)	669	1.0 (0.91–1.06)

a) P<0.05. b) P<0.01.

342

Table V. Observed and Expected Numbers of Second Primary Cancers, According to Years after Diagnosis of the First Cancer: Relation to Site of the First Cancer, 1978–86, Both Sexes

Site of the first cancer	Years after diagnosis of the first cancer					
	0		1-4		5-9	
	Obs	O/E (95% CI)	Obs	O/E (95% CI)	Obs	O/E (95% CI)
Stomach	237	1.48 [b] (1.30–1.68)	332	0.93 (0.84–1.04)	154	[0.88] (0.74–1.03)
Colon	62	1.46 [b] (1.12–1.87)	115	1.21 [a] (1.00–1.46)	49	[1.35] (1.00–1.79)
Rectum	58	1.57 [b] (1.19–2.02)	63	0.74 [a] (0.57–0.95)	34	[0.96] (0.67–1.34)
Larynx	40	2.65 [b] (1.89–3.60)	71	1.60 [b] (1.25–2.02)	29	[1.26] (0.84–1.80)
Lung	117	1.60 [b] (1.32–1.92)	90	1.27 [a] (1.02–1.57)	24	[1.22] (0.78–1.82)
Bladder	49	1.84 [b] (1.36–2.43)	97	1.36 [b] (1.10–1.66)	39	[1.22] (0.87–1.67)
Thyroid	11	1.85 (0.92–3.30)	27	1.34 (0.89–1.96)	15	[1.39] (0.78–2.30)
Breast (Female)	56	2.24 [b] (1.62–2.91)	117	1.35 [b] (1.12–1.62)	53	[1.12] (0.84–1.47)
Uterus	35	1.26 (0.88–1.76)	100	1.16 (0.94–1.41)	52	[0.95] (0.71–1.25)

a) $P<0.05$.   b) $P<0.01$.   [ ]: see text.

the 5–9 year period, which are parenthesized in Table V, should be revised in the next several years. Within the first year of diagnosis, the O/E ratios were significantly higher than 1.0 for almost all of these sites, due, in large part, to the possible detection bias.[4] During the next 4 years after diagnosis of the first cancer, the ratios were nearly equal to or under 1.0 for cancers of the stomach, rectum and uterus. Meanwhile significantly elevated risks were observed for cancers of the colon, larynx, lung, bladder and breast (female).

DISCUSSION

This study showed that the incidence rates of second primary cancers were significantly associated with gender (male), age and calendar year at diagnosis of the first cancer. The O/E ratios of second primary cancers during the period 1–4 years after diagnosis of the first cancer were generally lower than 1.0 among those who developed their first cancer in 1966–77, and higher than 1.0 among those who developed their first cancer in 1978–86.

Risk of second primary cancer can be modified ostensibly by improvement in medical scrutiny and notification of cancer patients.[4] Observed O/E ratios lower than 1.0 during the earlier study period might be indicative of underestimation of the risks for second primary cancers, since the reliability of such registration indices as 'the proportion of cases registered by death certificate only'

and 'the proportion of the cases verified histologically' were not so favorable in Osaka during the earlier period.[5] Recent increases in the risk of second primary cancer, therefore, seem partly attributable to improvements in medical scrutiny and notification of cancer patients, as well as to improvements in the survival length of cancer patients.

Another explanation for the increase in the risk of second primary cancer may be the increase in the risk factors of cancer in our environment, such as smoking and dietary habits, because time trends in the age-specific incidence rates of second primary cancers were in large part correlated with the incidence rates of cancer among Osaka residents (Fig. 1). Furthermore, we have to consider the etiological roles of chemotherapy and/or radiotherapy in the development of metachronous second primary cancers, because many reports suggest increased risk of second primary cancer among those patients treated with chemotherapeutic agents and/or radiation.[4]

The incidence rates or cumulative risks of second primary cancers were not so high among children and youths, but the O/E ratios were much higher than 1.0 (Table IV). Similar findings have also been reported by other researchers.[14, 15] Because of the limited number of cases, it was difficult to find any specific associations between the first and second primary cancers. Genetic predispositions, as well as treatment with chemotherapeutic agents and/or radiation, might play rather signifi-

Table VI. Specific Associations by Site of First and Second Primary Cancers, 1978–86

First cancer	Second primary		Male		Female	
	Site	(ICD-9)	Obs	O/E	Obs	O/E
Stomach	Colon	(153)	73	1.73[b]	18	1.22
	Rectum	(154)	59	1.87[b]	16	1.84[a]
	Breast	(174)	–	–	32	1.54[a]
Colon	Stomach	(151)	50	1.41[a]	18	1.36
	Rectum	(154)	14	2.62[b]	11	4.38[b]
	Ovary	(183)	–	–	9	5.95[b]
Rectum	Colon	(153)	13	1.88[a]	7	2.29
	Liver	(155)	10	0.53[a]	3	0.93
Larynx	Oral etc.	(140–149)	6	4.03[b]	1	16.33
	Esophagus	(150)	13	4.74[b]	0	–
	Liver	(155)	20	1.72[a]	0	–
	Lung	(162)	31	2.09[b]	5	9.30[b]
	Bladder	(188)	7	2.55[a]	0	–
	Thyroid	(193)	4	15.19[b]	2	25.50[b]
Lung	Colon	(153)	22	2.38[b]	1	0.45
	Prostate	(185)	11	2.23[a]	–	–
	Kidney etc.	(189.0–.1)	7	3.13[a]	2	6.33
	Thyroid	(193)	1	1.81	3	6.39[a]
Bladder	Uterus	(179–182)	–	–	6	3.57[a]
	Prostate	(185)	18	5.04[b]	–	–
Breast (Female)	Stomach	(151)	–	–	53	1.33[a]
	Colon	(153)	–	–	22	1.72[a]
	Lung	(162)	–	–	24	1.60[a]
	Thyroid	(193)	–	–	16	4.61[b]
Uterus	Lung	(162)	–	–	36	2.20[b]
	Hematopoietic	(200–208)	–	–	17	2.11[b]

a) $P < 0.05$. b) $P < 0.01$.

cant roles in the etiology of second primaries among children and youth.[16]

Our study has demonstrated that successfully treated cancer patients are still subject to increased risk of second primary cancers. Close surveillance is therefore recommended, in order to detect and treat second primary cancer as early as possible. In addition, health education should be conducted so that these patients have the chance to reduce their risk of developing second primary cancers.

Table VI shows some specific associations by site of first and second primary cancers, where the O/E ratios for males or females or both were found to be significantly greater or smaller than 1.0. Although we need to analyze these associations in more detail for a better understanding, some hypotheses can be put forward. For example, reciprocal associations may be explained by shared risk factors.[17] Such associations were demonstrated between colon and rectal cancer in the present study. Similar associations were also observed in part among smoking-related cancers for males, such as larynx, oral cavity, esophagus, lung and bladder.

When the association between two malignancies is not reciprocal, other possible explanations must be sought, such as a treatment effect or detection bias.[17] Increased risks of prostate cancer after bladder cancer, as well as thyroid cancer after laryngeal cancer,[18] and rectal cancer after stomach cancer,[19] were all supposed to be explained in large part by detection bias.

Further studies will be needed to clarify the relationships between first and second primary cancers more completely, and to assess the etiological roles of treatment with chemotherapeutic agents and/or radiation in the development of second primary cancers.

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