A Case-Control Study on Liver Cancer in the Chikuho Area, Fukuoka Prefecture

Hiroshi UNE*, Kenichi OSAJIMA**, Yoshito MOMOSE* and Hiroji ESAKI*

Abstract

We conducted an epidemiological study on liver cancer in the former coalmining area of Chikuho where mortality from liver cancer was high, using the data on liver cancer mortality in Iizuka Health Center in Fukuoka Prefecture.

Using the Japanese mortality from liver cancer as standard, we found that the ratios of observed to expected deaths from liver cancer in the Iizuka Health Center District between 1986 and 1988 were 213 for males and 198 for females.

Of those deceased from liver cancer, 17.4% were HBs antigen positive. A high positive rate of HBs antigen was particularly observed in the 30—39 age group (positive rate=100%) and the 40—49 age group (positive rate=42.9%) among the younger age groups.

To clarify the relationship of liver cancer to HBs antigen, blood transfusion, drinking habits and smoking habits, we also conducted a case-control study. We analyzed 133 cases who had died of liver cancer and 132 controls who were randomly selected from inpatients in the three large hospitals in the Iizuka Health Center District. The relative risks were 10.23 for HBs antigen positive ($p<0.001$) and 2.33 for blood transfusion ($p<0.01$), which were statistically significant, but 1.20 for drinking and 1.59 for smoking, which were not statistically significant. HBs antigen posi-

tive and blood transfusion were significantly associated with liver cancer.

Introduction

Liver cancer is the third leading cause of cancer mortality in Japan and recently mortality from it has increased sharply. Liver cancer mortality is high in western Japan and low in eastern Japan. In the 1985 age-adjusted mortalities in Japan, Fukuoka was one of the prefectures with the highest liver cancer mortality. The high mortality was particularly observed in the former coalmining area of Chikuho in Fukuoka Prefecture. Although it has been suggested that high mortality from liver cancer might be associated with high prevalence of HBs antigen positive and a lower socioeconomic level in Chikuho area (Masuda et al., 1982), one cannot adequately explain what factors contribute to these geographical differences in liver cancer mortality in Fukuoka Prefecture.

We studied the extent of liver cancer mortality and what factors are associated with liver cancer in the district covered by Iizuka Health Center (hereafter Iizuka Health Center District) in the Chikuho area.

Subjects and Methods**1. Ratios of Observed to Expected Deaths from Liver Cancer**

We obtained information on deaths from

* 福岡大学医学部衛生学教室

** 福岡県山門保健所

* *Department of Hygiene, School of Medicine, Fukuoka University*

** *Yamato Health Center, Fukuoka*

death certificates in Iizuka Health Center, listed up all the deaths from liver cancer (ICD 155 and 199.1 C) in 1986-1988, and calculated ratios of observed to expected deaths from liver cancer by age group, using the 1987 Japanese mortality rates for liver cancer as standard.

2. Case-Control Study

(1) Cases

There were 222 deceased from liver cancer in 1986-1988 in the Iizuka Health Center District. Of these, 190 were selected as cases because they had received treatment for liver

cancer in hospitals or clinics located in the Iizuka Health Center District.

(2) Controls

Because 66% of the cases had received treatment for liver cancer in the three large hospitals in the Iizuka Health Center District, we selected controls from these three hospitals at the rate of one control to one case, matched for sex and age (within 5 years). The controls had received treatment for diseases other than liver diseases. If cases received treatment for liver cancer in any of these three large hospitals, controls were selected

Table 1 Ratios of observed to expected deaths of liver cancer by age in Iizuka Health Center District, 1986-1988

Age	Male			Female			Both sexes		
	Observed	Expected	Obs./Exp. %	Observed	Expected	Obs./Exp. %	Observed	Expected	Obs./Exp. %
0~9	0	0.1	0	0	0.0	0	0	0.2	0
10~19	0	0.0	0	1	0.0	/	1	0.1	1,000
20~29	0	0.1	0	0	0.1	0	0	0.1	0
30~39	5	1.0	500**	0	0.2	0	5	1.2	417**
40~49	4	3.4	118	3	0.7	429*	7	4.4	159
50~59	49	21.1	232***	9	3.7	243*	58	26.3	221***
60~69	57	22.7	251***	20	8.7	230***	77	32.7	235***
70~79	31	19.4	160*	17	11.4	149	48	30.9	155**
80+	13	6.9	188*	13	7.0	186*	26	14.3	182**
Total	159	74.7	213***	63	31.8	198***	222	110.2	201***

Note: Expected deaths were calculated using mortality rates for all Japan in 1987 as standard.

*p<0.05 **p<0.01 ***p<0.001

Table 2 Positive rate of HBs antigen by age among the deceased from liver cancer in Iizuka Health Center District, 1986-1988

Age	Male	Female	Both sexes
	HBsAg positive	HBsAg positive	HBsAg positive
30~39	4/ 4 (100)	/	4/ 4 (100)
40~49	2/ 4 (50.0)	1/3 (33.3)	3/ 7 (42.9)
50~59	2/33 (6.1)	1/5 (20.0)	3/38 (7.9)
60~69	7/42 (16.7)	3/13(23.1)	10/55 (18.2)
70+	4/20 (20.0)	2/25(8.0)	6/45 (13.3)
Total	19/103(18.4)	7/46(15.2)	26/149(17.4)

Note: % in parentheses

from the same hospital; if not, controls were randomly selected from any of these three large hospitals.

We obtained information for the cases and the controls on HBs antigen, history of blood transfusion, drinking habits, and smoking habits from the medical records of hospitals and clinics.

Results

1. Ratios of Observed to Expected Deaths from Liver Cancer in Iizuka Health Center District

As shown in Table 1, the overall ratios were 213 for males and 198 for females, both of which were statistically significant. Statistical significance was observed in almost all age groups in both males and females.

2. Analysis of Cases

Information on HBs antigen was found in the medical records of 149 of the 190 cases. Table 2 shows positive rate of HBs antigen by age group among the cases. The overall positive rate of HBs antigen was 17.4% for both sexes, 18.4% for males, and 15.2% for females. In particular, high positive rates were observed among the younger age groups; 100% positive in the 30—39 age group and 42.9% positive in the 40—49 age group.

3. Case-Control Study

Information on all four factors (HBs antigen, history of blood transfusion, drinking habits, and smoking habits) was available for 133 of the 190 cases and 132 of the 190 controls. Therefore, these 133 cases and 132 controls were analyzed, using an unconditional multiple logistic regression model.

Table 3 shows adjusted relative risks (RRs) for liver cancer according to HBs antigen, history of blood transfusion, drinking habits,

Table 3 Adjusted relative risk for liver cancer according to HBs antigen, history of blood transfusion, drinking, and smoking

Factor	Male				Female				Both sexes			
	Cases	Controls	Adjusted RR ^s	95% CI	Cases	Controls	Adjusted RR ^s	95% CI	Cases	Controls	Adjusted RR ^s	95% CI
HBs antigen	-	80	1.00		32	40	1.00		112	129	1.00	
	+	16	7.63**	2.05—28.37	5	0	/		21	3	10.23***	2.89—36.22
History of blood transfusion	-	71	1.00		26	36	1.00		97	111	1.00	
	+	25	1.87	0.91—3.84	11	4	5.62*	1.38—22.84	36	21	2.33**	1.25—4.36
Drinking	-	39	1.00		32	36	1.00		71	78	1.00	
	+	57	1.08	0.57—2.05	5	4	2.87	0.57—14.40	62	54	1.20	0.66—2.18
Smoking	-	26	1.00		29	33	1.00		55	70	1.00	
	+	70	1.86	0.94—3.69	8	7	0.70	0.17—2.83	78	62	1.59	0.87—2.91

Note: ^sAdjusted for the effects of age and the other factors in this table.

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

RR = Relative risk CI = Confidence interval

and smoking habits.

Taking both sexes together, adjusted RRs were as follows: For HBs antigen positive, 10.23 with 95% confidence interval (CI) 2.89—36.22 ($p<0.001$). For history of blood transfusion, 2.33 with 95% CI 1.25—4.36 ($p<0.01$). No statistical significance was observed in adjusted RRs for drinkers (RR=1.20) and for smokers (RR=1.59).

Discussion

According to 1985 age-adjusted mortality data in Japan, Fukuoka was the prefecture with the second highest liver cancer mortality. In Fukuoka Prefecture, the former coal mining area of Chikuho had particularly high liver cancer mortality.

To clarify what factors are associated with high liver cancer mortality in the Chikuho area, we conducted an epidemiological study on liver cancer.

The prevalence of HBs antigen positives among hepatocellular carcinoma (hereafter HCC) patients has decreased year by year and had fallen to about 25% between 1984 and 1985 according to data from the Liver Cancer Study Group of Japan (hereafter LCSGJ) (1985). 17.4% of the cases in our study were HBs antigen positive. The prevalence of HBs antigen positive was slightly higher in the results of the LCSGJ than in our study. However, our study was conducted 2—3 years later than that of the LCSGJ, and the LCSGJ study comprised only HCC, whereas our study included liver cancer other than HCC. Because the LCSGJ is made up of doctors working in university hospitals or big educational hospitals, some bias might result from a higher proportion of HCC patients with HBs antigen positive visiting these hospitals.

Taking these things into account, it is likely that the prevalence of HBs antigen positive is little different between these two studies. Therefore, it seems likely that mortality from liver cancer with HB virus and mortality from liver cancer without HB virus were both almost twice as high in the Chikuho area as those in all Japan, because the ratios of observed to expected deaths from liver cancer was 201.

According to data on HBs antigen of blood donors in 1980, the prevalence of HBs antigen positive was 3.1% in the Kitakyushu and Chikuho areas, which was higher than the Japanese average rate (1.9%) (Taoka, et al., 1981). Therefore, the high prevalence of HBs antigen positive appears to be one of the factors which caused the high liver cancer mortality in Chikuho area.

Pyong *et al.* (1988) and Akagi *et al.* (1982) reported that the average age of HCC cases was lower in those with HB virus than in those without HB virus. In our study, the prevalence of HBs antigen positive was also much higher in the 30—49 age group (63.6%) than in those aged 50 or over (13.8%). Although liver cancer with HBs antigen positive has decreased year by year, HB virus still plays an important role in liver cancer in younger age groups.

The RR for HBs antigen positive was 10.23 in our study. Because the prevalence of HBs antigen positive in our controls (2.3%) was little different from that in blood donors (3.1%) in the same area (Taoka, *et al.*, 1981), it seems likely that our result had little bias.

Several papers have been published in Japan on the RRs of HCC for HBs antigen positive. Iijima *et al.* (1984) and Tokudome *et al.* (1988) reported that the observed to ex-

Table 4 Diseases among controls

Diseases	Number
Infectious diseases	4
All cancers	20
Gastric cancer	4
Colon cancer	5
Lung cancer	4
Benign tumors	4
Diabetes mellitus	7
Heart diseases	8
Cerebrovascular diseases	16
Respiratory diseases	13
Digestive diseases	21
Genitourinary diseases	5
Injuries	18
Bone fractures	14
Other causes	13
Health check-ups	3

pected ratios of liver cancer death among HBs antigen positive blood donors were 10.4 and 7.25 respectively in cohort studies. Inaba *et al.* (1981), Tsukuma *et al.* (1990) and Tanaka *et al.* (1991) reported that the RRs of HCC for HBs antigen positive were 10.0, 14.3 and 15.3 respectively in case control studies. The risks of liver cancer for HBs antigen positive reported in these studies were similar to our own results. HBs antigen positive was strongly associated with liver cancer.

It has been noted that blood transfusion is an important risk factor for liver cancer. Significant association was also observed between history of blood transfusion and liver cancer in our study. According to Tsukuma *et al.* (1990) and Tanaka *et al.* (1991), the RRs for blood transfusion were 4.3 and 3.8 respectively; both were slightly higher than that in our study. As shown in Table 4, most controls in our study were inpatients with diseases other than liver diseases, while the controls in the study of Tsukuma *et al.* (1990) included healthy persons admitted for multiphasic

health check-ups and in that of Tanaka *et al.* (1991) consisted of general healthy persons. This may be why the RR for blood transfusion was lower in our study than in these two studies.

Kono *et al.* (1979) found no association between SMR for liver cancer and consumption of alcohol in a geographical correlation study for 46 prefectures in Japan. However, many researchers have reported that alcohol drinking significantly increases the risk of liver cancer. The RRs of alcohol drinking were 3.2 among regular drinkers in the study of Inaba *et al.* (1981), and 3.2 and 2.2 among heavy drinkers in the studies of Tsukuma *et al.* (1990) and Tanaka *et al.* (1991) respectively.

Because the daily consumption of alcohol was not available in our study, we could not analyze the relationship between liver cancer and the daily consumption of alcohol and only compared the risk between regular drinkers and non regular drinkers. If we could have analyzed the data according to the daily consumption of alcohol, perhaps we would have observed a significant association between heavy drinking and liver cancer.

No significant association was observed between smoking and liver cancer in our study. Whether smoking significantly increases the risk of liver cancer is controversial. Significantly high RRs for liver cancer were found among smokers in some studies (Tsukuma *et al.*, 1990 and Tanaka *et al.*, 1988), but not in other studies (Shibata *et al.*, 1986 and Pyong *et al.*, 1988).

With respect to blood transfusion, drinking and smoking, bias may have arisen because we excluded from the analysis the 57 cases and 58 controls for whom this information

was not available on the medical records.

Blood tests for HCV antibody have recently become available. Colombo *et al.* (1989) reported that HCV antibody positive was detected in 86 of 132 patients with HCC. It has been noted that HCV is the most important risk factor for liver cancer. We unfortunately had no information on HCV antibody in this study because it started before the HCV antibody test was available. Further study, including data on HCV antibody, is needed in the Chikuhō area.

Acknowledgments: The authors are grateful to Dr. Hatada (Tagawa Health Center), Dr. Ishibushi (Iizuka Health Center), and the staffs of Iizuka Hospital, Chikuhō Rosai Hospital and Kaho Hospital for their cooperation.

References

- Akagi G., Furuya K., Otsuka H. (1982): Hepatitis B antigen in the liver in hepatocellular carcinoma in Shikoku, Japan, *Cancer*, 49, 678—682.
- Colombo M., Kuo G., Choo Q.L., Donato M.F., Del Ninno E., Tommasini M.A., Dioguardi N., Houghton M. (1989): Prevalence of antibodies to hepatitis C virus in Italian patients with hepatocellular carcinoma, *Lancet*, 2, 1006—1008.
- Iijima T., Saitoh N., Nobutomo K., Nambu M., Sakuma K. (1984): A prospective cohort study of hepatitis B surface antigen carriers in a working population, *Gann*, 75, 571—573.
- Inaba Y., Maruchi N., Matsuda M., Yoshihara N., Yamamoto S. (1981): A case control study on liver cancer and cirrhosis in Yamanashi Prefecture, *Jpn. J. Public Health*, 28, 362—369 (in Japanese)
- Kono S., Ikeda M. (1979): Correlation between cancer mortality and alcoholic beverage in Japan, *Br. J. Cancer*, 40, 449—455.
- Liver Cancer Study Group of Japan (1985): Survey and follow-up study of primary liver cancer in Japan, report 8, *Acta Hepatol. Jpn.*, 29, 1619—1626 (in Japanese)
- Masuda N., Mitoma M., Shigematsu T. (1982): Studies on geographical differences of selected causes of death in Fukuoka Prefecture, 1973—1977. VII. Geographical distributions of mortalities from cirrhosis of the liver, cancer of the liver, cancer of the gallbladder and bile duct, other liver diseases, *Med. Bull. Fukuoka Univ.*, 9, 377—392 (in Japanese)
- Pyong S.J., Lee H.U., Ubukata T., Hiyama T., Oshima A. (1988): A case-control study of liver cancer among Koreans in Japan, *Acta Hepatol. Jpn.*, 51, 1215—1221 (in Japanese)
- Shibata A., Hirohata T., Toshima H., Tashiro H. (1986): The role of drinking and cigarette smoking in the excess deaths from liver cancer, *Jpn. J. Cancer Res.*, 77, 287—295.
- Tanaka K., Hirohata T., Takeshita S. (1988): Blood transfusion, alcohol consumption, and cigarette smoking in causation of hepatocellular carcinoma: A case-control study in Fukuoka, Japan, *Jpn. J. Cancer Res.*, 79, 1075—1082.
- Tanaka K., Hirohata T., Koga S., Sugimachi K., Kanematsu T., Ohryohji F., Nawata H., Ishibashi H., Maeda Y., Kiyokawa H., Tokunaga K., Irita Y., Takeshita S., Arase Y., Nishino N. (1991): Hepatitis C and hepatitis B in the etiology of hepatocellular carcinoma in the Japanese population, *Cancer Res.*, 51, 2842—2847.
- Taoka Y., Ozeki T., Anan G., Morita Y., Miura Y. (1981): Epidemiology of liver cirrhosis and primary liver carcinoma in Fukuoka Prefecture, *J.U.O.E.H.*, 3, 441—457.
- Tokudome S., Ikeda M., Matsushita K., Maeda Y., Yoshinari M. (1988): Hepatocellular carcinoma among HBsAg positive blood donors in Fukuoka, Japan, *Eur. J. Cancer Oncol.*, 24, 235—239.
- Tsukuma H., Hiyama T., Oshima A., Sobue T., Fujimoto I., Kasugai H., Kojima J., Imaoka S., Horiuchi N., Okuda S. (1990): A case-control study of hepatocellular carcinoma in Osaka, Japan, *Int. J. Cancer*, 45, 231—236.

(Received on January 25, 1993)

〔原 著〕

旧産炭地・筑豊地域における肝がんに関する症例対照研究

畝 博* 嵯島 健一** 百瀬 義人* 江崎 廣次*

1985年の肝がんの訂正死亡率をみると、福岡県の肝がん死亡率は高く、都道府県別の順位では第2位であった。福岡県の中では、特に、旧産炭地・筑豊地域の肝がん死亡率が高い。

そこで、旧産炭地・筑豊地域に位置する飯塚保健所管内の1986～88年における肝がん死亡者を対象として、症例対照研究を行った。また、全国の肝がん死亡率を標準として期待死亡比を計算して検討した。

飯塚保健所管内における1986～88年の肝がんの期待死亡比は全体で201, 男で213, 女で198であり、肝がん死亡率は全国と比べて、約2倍高かった。

肝がん死亡者の17.4%がHBs抗原陽性であった。肝がん死亡者のHBs抗原陽性率を年齢階級別にみると、30～39歳群では100%, 40～49歳群では42.9%であり、若年層でHBs抗原陽性率が高かった。

症例対照研究の結果、HBs抗原陽性のRelative Riskは10.23($p<0.001$), 輸血歴のRelative Riskは2.33($p<0.01$)であり、両者は共に統計学的に有意であった。しかし、飲酒と喫煙のRelative Riskはそれぞれ1.20と1.59であり、両者とも統計学的に有意ではなかった。

Key words: Liver Cancer, Epidemiology, HBs Antigen, Case-Control Study, Chikuhō Area

肝がん, 疫学, HBs 抗原, 症例対照研究, 旧産炭地・筑豊地域