Risk of Death due to Hepatocellular Carcinoma among Smokers and Ex-smokers. Univariate Analysis of JACC Study Data

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Summary: Hazard ratios (HR) of death due to hepatocellular carcinoma (HCC) were analyzed by gender and age strata (40-59 and 60-79) among smokers and ex-smokers in 65,528 eligible subjects from a large cohort of males and females aged 40-79 years, based on information about several smoking-related characteristics. Both current smokers and ex-smokers among total older males had hazard ratios (HR) for dying from HCC that were 2 to 4 times higher than those who had never smoked at the baseline survey. When subjects were restricted to those without history of liver disease (LD), older male (60-79) ex-smokers presented a statistically significant HR of 5.0. Earlier age at start of smoking (15 to 19) showed a significantly increased HR of 4 to 8 for both current and ex-smokers. Moderate number of cigarettes smoked per day showed an increased HR, and later age at cessation of smoking had a higher HR compared to earlier cessation. Larger cumulative amount of smoking resulted in an elevated HR of 11 times than in those who had never smoked. Cigarette smoking was suggested to be an important risk factor for death from HCC regardless of whether the smoking habit was in the past or was continuing at present. To eliminate confounding effects and interaction with other risk factors of HCC and to clarify the net association between smoking habits and HCC, farther careful analysis using multivariate models is needed.

Key words JACC study, cigarette smoking, death from hepatocellular carcinoma, Japanese

INTRODUCTION

It has been reported that cigarette smoking may be a risk factor for death due to hepatocellular carcinoma (HCC) in some studies or may not in other studies

[1-14]. Many cohort studies reported a positive association between cigarette smoking and HCC, although half of the case-control studies reported no or an insignificant association between them.

Effects of several smoking characteristics on

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Abbreviations: HCC, hepatocellular carcinoma; HR, hazard ratio; LD, liver disease; C22.0, hepatocellular carcinoma; C22.9, malignant neoplasms of the liver, not otherwise specified.

death from HCC were analyzed in the large cohort data of The Japan Collaborative Cohort (JACC) Study as a part of a comprehensive evaluation of life style risk factors for HCC. In this analysis, surveyed items were analyzed separately as a preparation for a subsequent complex analysis using a hierarchically well formulated multivariate model.

MATERIALS AND METHODS

Subjects and identification of death from HCC

The JACC Study was established from 1988 to 1990 by enrolling subjects aged 40 to 79 at registration after obtaining informed consent for participation the study. The number of subjects to be followed is 110,792, consisting of 46,465 males and 64,327 females. Full details of the methodology for establishing the JACC Study cohort was described elsewhere [15].

Subjects were followed until the end of 1999. Residential and survival status were confirmed by searching official residential rosters for changes of address or death, and in cases of the death the death certificate was examined for cause and date of death, with permission from the Director-General of the Prime Minister's Office.

End point of this analysis was death due to HCC, code C22.0 in the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Subjects with past history of liver cancer were eliminated from follow-up. Additionally, subjects whose cause of death was coded C22.9 (malignant neoplasms of the liver, not otherwise specified) and subjects who died of HCC within 2 years after registration in the JACC Study were eliminated from

the analyzed dataset [16].

Questionnaire and data correction

Information was obtained by self administered questionnaire supplemented by direct or telephone interviews in some cases. Answers to the questionnaire in each survey field were transformed into the format of the JACC Study standard questionnaire. Transformed data sets were checked and corrected by a working group for cleaning up data. The data correction procedure was described in another report [17].

Smoking history

Baseline information obtained about cigarette smoking consisted of (1) smoking habits, either never, ex- or current smoker for all subjects, (2) number of cigarettes smoked per day and age at start of smoking for ex- and current smokers, and (3) age at cessation of smoking and years since cessation of smoking for ex-smokers.

Some variation in questionnaires used by collaborating institutes may result in systematic data gaps and cause large differences in the number of analyzed subjects for different questions. To minimize this difference in number of subjects, the analyzed subjects were restricted to persons from collaborating institutes with almost the same data format for drinking and smoking [16].

Statistical analysis

Only gender, age, past history of liver disease (LD) and collaborating institutes were considered as probable confounders because the major purpose of this analysis was to study the effect of each single characteristic in the questionnaire [16].

TABLE 1.
Age and sex distribution of subjects analyzed by past history of liver disease

Age at registration	Without history			With history			Total		
	Male	Female	Both	Male	Female	Both	Male	Female	Both
40-44	4,234	5,120	9,354	2	.	2	4,236	5,120	9,356
45-49	3,915	5,114	9,029	4	3	7	3,919	5,117	9,036
50-54	3,913	5,446	9,359	13	1	14	3,926	5,447	9,373
55-59	4,611	6,178	10,789	23	8	31	4,634	6,186	10,820
60-64	4,913	6,135	11,048	37	14	51	4,950	6,149	11,099
65-69	3,047	4,576	7,623	21	16	37	3,068	4,592	7,660
70-74	2,152	2,778	4,930	24	10	34	2,176	2,788	4,964
75-79	1,374	1,836	3,210	4	6	10	1,378	1,842	3,220
Total	28,159	37,183	65,342	128	58	186	28,287	37,241	65,528

TABLE 2.
Hazard ratio of death from HCC by several characteristics of smoking history among total subjects

Characteristics	Male						Female					
	40 – 59			60 – 79			40 – 59			60 – 79		
	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval
Smoking habits												
(Referent: never smoker)	3,830	1.00		2,237	1.00		20,419	1.00		14,432	1.00	
Ex-smoker	3,378	2.37	0.83 – 6.78	3,881	2.72	1.21 – 6.11	234	—		267	1.18	0.16 – 8.67
Currently smoker	9,507	1.96	0.75 – 5.14	5,454	2.62	1.18 – 5.84	1,217	2.82	0.61 – 13.09	672	1.49	0.46 – 4.87
Age at start of smoking (Current Smokers)												
(Referent: never smoker)	3,830	1.00		2,237	1.00		20,419	1.00		14,432	1.00	
Less than 20	1,869	1.92	0.55 – 6.71	645	3.66	1.27 – 10.52 *	56	—		—	—	
20 to less than 30	6,814	1.63	0.59 – 4.49	4,081	2.57	1.13 – 5.84 *	518	3.44	0.44 – 27.21	156	1.98	0.27 – 14.51
30 or more	459	1.59	0.19 – 13.63	513	1.41	0.29 – 6.81	566	—		425	0.77	0.11 – 5.66
Number of cigarettes smoked pre day (Current Smokers)												
(Referent: never smoker)	3,830	1.00		2,237	1.00		20,419	1.00		14,432	1.00	
— 10	1,176	4.42	1.40 – 13.97 *	1,288	1.93	0.67 – 5.50	593	2.92	0.37 – 23.11	413	0.81	0.11 – 5.95
11 – 20	5,047	1.83	0.64 – 5.19	3,287	3.21	1.41 – 7.31 *	478	—		207	3.07	0.73 – 12.84
21 – 40	2,917	0.96	0.26 – 3.59	801	1.59	0.46 – 5.45	91	—		28	—	
41 – 80	231	2.73	0.32 – 23.48	28	—		0	—		0	—	
81 –	1	—		0	—		0	—		0	—	
Inhalation of smoke (Current Smokers)												
(Referent: never smoker)	3,830	1.00		2,237	1.00		20,419	1.00		14,432	1.00	
Puff	1,395	1.11	0.22 – 5.78	1,360	2.43	0.90 – 6.56	408	4.14	0.52 – 32.79	333	0.94	0.13 – 6.92
Both	2,844	2.69	0.92 – 7.90	1,683	2.19	0.85 – 5.66	349	—		150	4.12	0.99 – 17.18 [^]
Inhale	4,846	1.47	0.50 – 4.32	2,146	3.14	1.32 – 7.44 *	392	—		139	—	
Quit smoking more than 3 month (Current Smokers)												
(Referent: never smoker)	3,807	1.00		2,227	1.00		20,350	1.00		14,400	1.00	
No	6,289	2.21	0.82 – 5.94	3,415	2.10	0.89 – 4.96	773	—		438	2.34	0.72 – 7.65
Yes	2,363	0.89	0.21 – 3.74	1,387	2.90	1.15 – 7.27 *	279	6.46	0.80 – 52.14	137	—	

¹⁾ Result from SAS PHREG procedure with STRATA statement on variable concerning with collaborating institute.

* p<0.05, ^ p<0.10

— HR is not available because of thin data.

TABLE 3.
Hazard ratio of death from HCC by characteristics of smoking history among restricted subjects without past history of liver disease

Characteristics	Male						Female					
	40 – 59			60 – 79			40 – 59			60 – 79		
	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval
Smoking habits												
(Referent: never smoker)	3,599	1.00		2,077	1.00		19,508	1.00		13,434	1.00	
Ex-smoker	3,078	—		3,405	4.23	0.96 – 18.72	210	—		233	—	
Currently smoker	8,817	—		4,985	4.44	1.04 – 19.06 *	1,136	8.18	1.48 – 45.03 *	607	2.41	0.54 – 10.77
Age at start of smoking (Current Smokers)												
(Referent: never smoker)	3,599	1.00		2,077	1.00		19,508	1.00		13,434	1.00	
Less than 20	1,719	—		579	7.07	1.27 – 39.44 *	50	—		21	—	
20 to less than 30	6,318	—		3,725	3.80	0.85 – 16.92	480	9.16	1.02 – 82.66 *	137	4.80	0.62 – 37.31
30 or more	435	—		477	4.37	0.61 – 31.11	534	—		385	1.91	0.25 – 14.74
Number of cigarettes smoked pre day (Current Smokers)												
(Referent: never smoker)	3,599	1.00		2,077	1.00		19,508	1.00		13,434	1.00	
– 10	1,104	—		1,182	1.91	0.27 – 13.56	550	8.75	0.96 – 79.68	365	2.06	0.27 – 15.83
11 – 20	4,673	—		2,995	6.14	1.41 – 26.68 *	452	—		194	3.40	0.44 – 26.58
21 – 40	2,699	—		737	1.34	0.12 – 14.88	81	—		25	—	
41 – 80	213	—		26	—		15	—		2	—	
81 –	0	—		—	—		0	—		0	—	
Inhalation of smoke (Current Smokers)												
(Referent: never smoker)	3,599	1.00		2,077	1.00		19,508	1.00		13,434	1.00	
Puff	1,308	—		1,256	6.17	1.27 – 29.88 *	384	12.63	1.37 – 116.82 *	301	2.14	0.27 – 16.73
Both	2,640	—		1,550	4.30	0.86 – 21.34	322	—		134	5.71	0.75 – 43.71
Inhale	4,476	—		1,938	3.38	0.68 – 16.85	367	—		125	—	
Quit smoking more than 3 month (Current Smokers)												
(Referent: never smoker)	3,579	1.00		2,067	1.00		19,441	1.00		13,404	1.00	
No	5,856	—		3,148	3.01	0.65 – 14.00	721	—		398	3.66	0.82 – 16.39
Yes	2,160	—		1,242	4.63	0.93 – 23.01	258	21.75	2.31 – 204.39 *	118	—	

¹⁾ Result from SAS PHREG procedure with STRATA statement on variable concerning with collaborating institute.

* $p < 0.05$, ^ $p < 0.10$

— HR is not available because of thin data.

TABLE 4.
Hazard ratio of death from HCC by characteristics in smoking history among total ex-smokers

Characteristics	Male						Female					
	40 – 59			60 – 79			40 – 59			60 – 79		
	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval
Age at start of smoking (Referent: never smoker)	3,830	1.00		2,237	1.00		20,419	1.00		14,432	1.00	
Less than 20	901	2.31	0.55 – 9.76	612	5.50	2.15 – 14.09 *	17	—		0	—	
20 to less than 30	2,226	2.80	0.93 – 8.45	2,794	2.17	0.92 – 5.11	112	—		89	3.57	0.49 – 26.20
30 or more	106	—		250	2.53	0.52 – 12.20	80	—		151	—	
Number of cigarettes smoked pre day (Referent: never smoker)	3,830	1.00		2,237	1.00		20,419	1.00		14,432	1.00	
– 10	532	1.37	0.16 – 11.77	767	3.85	1.48 – 10.01 *	130	—		146	2.49	0.34 – 18.29
11 – 20	1,559	4.02	1.33 – 12.12 *	1,803	1.69	0.65 – 4.37	61	—		75	—	
21 – 40	856	1.56	0.30 – 8.11	780	3.39	1.26 – 9.15 *	8	—		10	—	
41 – 80	151	—		139	3.98	0.82 – 19.31	3	—		3	—	
81 –	0	—		3	—			—			—	
Age at cessation of smoking (Referent: never smoker)	3,830	1.00		2,237	1.00		20,419	1.00		14,432	1.00	
less than 30	290	2.36	0.27 – 20.35	87	—		22	—		3	—	
30 to less than 45	1,738	1.20	0.29 – 5.07	543	1.85	0.54 – 6.36	95	—		21	—	
45 to less than 60	1,205	4.69	1.51 – 14.54 *	1,612	2.74	1.12 – 6.70 *	93	—		98	—	
60 or more	0	—		1,424	3.21	1.30 – 7.92 *	0	—		115	2.72	0.37 – 19.93
Years since cessation of smoking (Referent: never smoker)	3,769	1.00		2,200	1.00		20,023	1.00		14,163	1.00	
0 – 5	1,063	2.78	0.74 – 10.42	1,013	2.86	1.08 – 7.52 *	95	—		78	—	
6 – 10	936	4.28	1.29 – 14.17 *	861	1.98	0.66 – 5.92	50	—		62	4.97	0.68 – 36.60
11 – 15	570	—		577	4.49	1.66 – 12.13 *	29	—		38	—	
16 or more	565	2.37	0.45 – 12.37	1,019	2.53	0.95 – 6.69	31	—		48	—	

¹⁾ Result from SAS PHREG procedure with STRATA statement on variable concerning with collaborating institute.

* p<0.05, ^ p<0.10

— HR is not available because of thin data.

TABLE 5.
Hazard ratio of death from HCC by characteristics in smoking history among restricted ex-smokers without past history of liver disease

Characteristics	Male						Female					
	40 – 59			60 – 79			40 – 59			60 – 79		
	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval
Age at start of smoking (Referent: never smoker)	3,599	1.00		2,077	1.00		19,508	1.00		13,434	1.00	
Less than 20	824	—		509	8.48	1.54 – 46.58 *	15	—		4	—	
20 to less than 30	2,022	—		2,477	3.37	0.71 – 15.99	99	—		79	—	
30 or more	101	—		220	10.37	1.45 – 73.99 *	73	—		129	—	
Number of cigarettes smoked pre day (Referent: never smoker)	3,599	1.00		2,077	1.00		19,508	1.00		13,434	1.00	
– 10	486	—		670	4.66	0.77 – 28.08	121	—		129	—	
11 – 20	1,436	—		1,599	3.24	0.62 – 16.82	50	—		66	—	
21 – 40	773	—		678	4.92	0.81 – 29.80	8	—		7	—	
41 – 80	130	—		112	10.16	0.90 – 114.25	3	—		2	—	
81 –	1	—		2	—		0	—		0	—	
Age at cessation of smoking (Referent: never smoker)	3,599	1.00		2,077	1.00		19,508	1.00		13,434	1.00	
less than 30	266	—		74	—		18	—		2	—	
30 to less than 45	1,593	—		465	2.14	0.19 – 23.84	90	—		16	—	
45 to less than 60	1,088	—		1,409	4.30	0.86 – 21.42	79	—		89	—	
60 or more	0	—		1,265	6.44	1.32 – 31.31 *	0	—		99	—	
Years since cessation of smoking (Referent: never smoker)	3,548	1.00		2,045	1.00		19,126	1.00		13,178	1.00	
0 – 5	984	—		889	4.63	0.84 – 25.41	89	—		68	—	
6 – 10	848	—		756	2.80	0.39 – 19.95	40	—		55	—	
11 – 15	519	—		508	10.92	2.10 – 56.77 *	25	—		35	—	
16 or more	504	—		885	3.46	0.57 – 20.87	28	—		39	—	

¹⁾ Result from SAS PHREG procedure with STRATA statement on variable concerning with collaborating institute.

* p<0.05, ^ p<0.10

— HR is not available because of thin data.

TABLE 6.
Hazard ratio of death from HCC by cumulative amount of cigarette smoked among total current and ex-smokers

Characteristics	Male						Female					
	40 – 59			60 – 79			40 – 59			60 – 79		
	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval
Current smoker												
(Referent: never smoker)	3,830	1.00		2,237	1.00		20,419	1.00		14,432	1.00	
less than 500 ²⁾	3,267	2.10	0.70 – 6.28	1,110	1.48	0.47 – 4.66	930	1.77	0.22 – 14.05	465	0.72	0.10 – 5.29
500 to less than 1,000	4,708	1.69	0.59 – 4.90	3,008	3.32	1.45 – 7.61 *	172	—		120	2.51	0.34 – 18.47
1,000 to less than 1,500	969	0.68	0.08 – 5.88	860	1.92	0.61 – 6.06	0	—		23	—	
more than 1,500	165	3.88	0.45 – 33.49	256	1.47	0.18 – 12.02	0	—		0	—	
Ex-smoker												
(Referent: never smoker)	3,830	1.00		2,237	1.00		20,419	1.00		14,432	1.00	
less than 500	1,784	1.99	0.57 – 6.92	1,145	2.76	1.08 – 7.06 *	173	—		167	2.09	0.29 – 15.29
500 to less than 1,000	929	5.17	1.62 – 16.50 *	1,506	2.09	0.81 – 5.41	11	—		36	—	
1,000 to less than 1,500	227	—		440	3.18	1.00 – 10.08 *	—	—		7	—	
more than 1,500	57	—		255	4.73	1.37 – 16.31 *	—	—		4	—	

¹⁾ Result from SAS PHREG procedure with STRATA statement on variable concerning with collaborating institute.

²⁾ Brinkman index

* $p < 0.05$, ^ $p < 0.10$

— HR is not available because of thin data.

TABLE 7.
Hazard ratio of death from HCC by cumulative amount of cigarette smoked among restricted current and ex-smokers

Characteristics	Male						Female					
	40 – 59			60 – 79			40 – 59			60 – 79		
	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval	Number of subjects	Hazard Ratio ¹⁾	95% confidence interval
Current smoker												
(Referent: never smoker)	3,599	1.00		2,077	1.00		19,508	1.00		13,434	1.00	
less than 500 ²⁾	3,063	—		1,017	2.02	0.28 – 14.32	869	5.13	0.57 – 46.19	418	1.83	0.24 – 14.08
500 to less than 1,000	4,345	—		2,736	5.61	1.27 – 24.78 *	158	—		109	5.46	0.70 – 42.93
1,000 to less than 1,500	882	—		788	2.65	0.37 – 18.97	23	—		21	—	
more than 1,500	149	—		238	4.95	0.44 – 55.71	4	—		8	—	
Ex-smoker												
(Referent: never smoker)	3,599	1.00		2,077	1.00		19,508	1.00		13,434	1.00	
less than 500	1,645	—		997	3.09	0.51 – 18.63	157	—		145	—	
500 to less than 1,000	831	—		1,338	3.97	0.76 – 20.59	8	—		34	—	
1,000 to less than 1,500	211	—		382	5.71	0.79 – 41.08	3	—		5	—	
more than 1,500	46	—		212	11.42	1.58 – 82.55 *	1	—		2	—	

¹⁾ Result from SAS PHREG procedure with STRATA statement on variable concerning with collaborating institute.

²⁾ Brinkman index

* $p < 0.05$, ^ $p < 0.10$

— HR is not available because of thin data.

Hazard ratios of dying from HCC for each questioned item were calculated using the Cox conditional proportional hazards model based on stratification by institute (SAS PHREG procedure with STRATA statement [18]).

Analysis was done separately by gender, age (40-59: younger, 60-79: older) and LD. Subjects with unknown history of LD were omitted from the analysis.

This study was approved by the Ethics Committee of the Kurume University School of Medicine.

RESULT

Number of analyzed subjects

After elimination of subjects who were incident cases at the baseline and subjects who died with a diagnosis of C22.9 or who died in the first two years of follow-up, 110,688 subjects were left, including 401 subjects who had died with a diagnosis of C22.0 by the end of 1999.

After omitting 29,435 subjects from collaborating institutes whose data lacked some items concerned with smoking and drinking, a further 10,743 subjects with unknown LD and 4,982 subjects who did not respond to questions about smoking were also omitted. The final number of analyzed subjects was 65,528 (Male: 28,287, Female: 37,241) including 186 HCC cases (Table 1). Distribution of subjects by characteristics is presented in subsequent tables along with exposure strata (Table 2-7).

Hazard ratios by smoking characteristics

Results are presented for two types of datasets, i.e. one for total subjects that includes both those with LD and those without LD (total subjects), and another for restricted subjects without LD.

With regard to total subjects (Table 2), both current and ex-smokers among older males had elevated HRs of 2.7 and 2.6, respectively. Several other characteristics, i.e. earlier age at start of smoking, moderate amount of daily smoking, deep inhalation and experience of quitting smoking also presented elevated HRs among these older males in total subjects. Other age classes or gender groups also showed a few items associated with death from HCC (Table 2). After the subjects were restricted to those without LD, most of these elevated HRs remained high among older males and the HRs of these exposures increased in younger females (Table 3).

In ex-smokers, as with current smokers, earlier

age at start of smoking showed elevated HRs among older males. There was a fairly large increase in the HR in every stratum for cigarettes smoked per day among older males. Later age at cessation of smoking showed increased HRs among younger and older males, though the elevation of HRs was not correlated with the number of years since cessation of smoking (Table 4). After the subjects were restricted to those without LD, most of these findings remained among older males (Table 5).

Larger cumulative amount of cigarettes smoked seemed to be associated with increased HRs especially among total older males (Table 6). This increase of HRs for larger cumulative amount of cigarettes smoked was retained after the subjects were restricted to those without history of LD, especially for male ex-smokers (Table 7).

DISCUSSION

Information regarding exposure in this analysis was obtained through self-administered questionnaires mainly from participants in health checkup programs offered by local municipalities. This could have introduced a bias toward subjects that were healthier than the average in the areas they came from, and there could be large gaps in data in the analyzed data set. Nevertheless, the prevalence of smokers, 47% to 57% among males, was only a little less than the national average [19] and the subjects were assumed to be within a range representative of ordinary Japanese people as concerns smoking.

In 5 previous cohort studies, two reported that current smokers or heavy smokers suffered increased risk of HCC. [1,2] Another cohort study revealed that a cumulative smoking amount of 200 and more on the Brinkman Index resulted in elevated HR [3]. Two cohort studies reported no association [4] or one limited to females [5]. Many case-control studies reported no or very weak association between smoking and HCC [6,7-10], but some showed that any experience of smoking increased the risk [11-13]. Only one case-control study reported that current smokers but not ex-smokers had increased risk of HCC [14].

Although this study was based on a crude analysis without confounder control, its findings that any smoking experience increases HRs for death from HCC regardless of whether smoking had ceased or not support the major earlier findings. For more precise clarification, a multivariate analysis should be scheduled that will include evaluation of the interaction between smoking and other potential con-

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REFERENCES

1. Mizoue T, Tokui N, Nishisaka K, Nishisaka S, Ogimoto I et al. Prospective study on the relation of cigarette smoking with cancer of the liver and stomach in an endemic region. *Int J Epidemiol* 2000; 29:232-237.
2. Chiba T, Matsuzaki Y, Abei M, Shoda J, Tanaka N et al. The role of previous hepatitis B virus infection and heavy smoking in hepatitis C virus-related hepatocellular carcinoma. *Am J Gastroenterol* 1996; 91:1195-203.
3. Mukaiya M, Nishi M, Miyake H, and Hirata K. Chronic liver diseases for the risk of hepatocellular carcinoma: a case-control study in Japan. Etiologic association of alcohol consumption, cigarette smoking and the development of chronic liver diseases. *Hepatogastroenterology* 1998; 45:2328-2332.
4. Mori M, Hara M, Wada I, Hara T, Yamamoto K et al. Prospective study of hepatitis B and C viral infections, cigarette smoking, alcohol consumption, and other factors associated with hepatocellular carcinoma risk in Japan. *Am J Epidemiol* 2000; 151:131-139.
5. Evans AA, Chen G, Ross EA, Shen FM, Lin WY et al. Eight year follow up of the 90,000 person Haimen City cohort: I. Hepatocellular carcinoma mortality, risk factors, and gender differences. *Cancer Epidemiol Biomarkers Prev* 2002; 11:369-376.
6. Tanaka K, Hirohata T, and Takeshita S. Case-control studies of hepatocellular carcinoma and liver cirrhosis in relation to life style and other risk factors. *Gan No Rinsho* 1990; 36:305-312. (in Japanese)
7. Hiyama, T, Tsukuma, H, Oshima, A, and Fujimoto I. Liver cancer and life style drinking habits and smoking habits. *Gan No Rinsho* 1990; 36:249-256. (in Japanese)
8. Srivatanakul P, Parkin DM, Khlat M, Chenvidhya D, Chotiwan P et al. Liver cancer in Thailand. II. A case control study of hepatocellular carcinoma. *Int J Cancer* 1991; 48:329-332.
9. Mohamed AE, Kew MC, and Groeneveld HT. Alcohol consumption as a risk factor for hepatocellular carcinoma in urban southern African blacks. *Int J Cancer* 1992; 51:537-541.
10. Fernandez E, La Vecchia C, D'Avanzo B, Negri E, and Franceschi S. Family history and the risk of liver, gall-bladder, and pancreatic cancer. *Cancer Epidemiol*

- Biomarkers Prev 1994; 3:209-212.
11. Tanaka K, Hirohata T, Takeshita S, Hirohata I, Koga S et al. Hepatitis B virus, cigarette smoking and alcohol consumption in the development of hepatocellular carcinoma: a case-control study in Fukuoka, Japan. *Int J Cancer* 1992; 51:509-514.
 12. Yu MW, Chiu YH, Chiang YC, Chen CH, Lee TH et al. Plasma carotenoids, glutathione S transferase M1 and T1 genetic polymorphisms, and risk of hepatocellular carcinoma: independent and interactive effects. *Am J Epidemiol* 1999; 149:621-629.
 13. Kuper H, Tzonou A, Kaklamani E, Hsieh CC, Laggiou P et al. Tobacco smoking, alcohol consumption and their interaction in the causation of hepatocellular carcinoma. *Int J Cancer* 2000; 85:498-502.
 14. Tsukuma H, Hiyama T, Oshima A, Sobue T, Fujimoto I et al. A case-control study of hepatocellular carcinoma in Osaka, Japan. *Int J Cancer* 1990; 45:231-236.
 15. Ohno Y, Tamakoshi A, and the JACC Study group. Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho (JACC Study). *Journal of Epidemiology* 2001; 11:144-150.
 16. Ogimoto I, Shibata S, Kurozawa Y, Nose T, Yoshimura T et al. Risk of death due to hepatocellular carcinoma among drinkers and ex-drinkers. Univariate analysis of JACC Study data. *Kurume Medical Journal* 2004; 51:59-70.
 17. Shibata, A, Ogimoto I, Kurozawa Y, Nose T, Yoshimura T et al. Past medical history and risk of death due to hepatocellular carcinoma. Univariate analysis of JACC Study data. *Kurume Medical Journal* 2003; 50:109-119.
 18. SAS Institute. The PHREG Procedure. In: *SAS Procedures Guide, Version 8*, ed. Sawyer DM and Sall ME, SAS Institute Inc., Cary, NC, Vol 3, pp2569-2657, 1999.
 19. The Ministry of Health and Welfare, Health Service Bureau. Physical status. In: *National Nutrition Survey, 1989*. The Ministry of Health and Welfare, Health Service Bureau, Dai-ichi Shuppan, Tokyo, pp119-170, 1991. (in Japanese)