

HBV- and HCV- Infected Workers in the Japanese Workplace

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Abstract: HBV- and HCV- Infected Workers in the Japanese Workplace, Rie NARAI, et al. Department of Environmental Health, University of Occupational and Environmental Health—Around three million Japanese are persistently infected with HBV or HCV. Though most of them work in various industries, little is known about the actual conditions in their workplaces. To clarify the workplace conditions of workers with hepatitis, three kinds of questionnaire surveys, answered by occupational health physicians and workers with hepatitis, were carried out. The rates of workers recognized as workers with hepatitis B or C by occupational health physicians were 0.82% and 0.48% of 130,092 workers, respectively. About 30% of workers with hepatitis were engaged in “hazardous work”. The percentage of workers engaged in various types of hazardous work among workers with hepatitis was nearly the same as that among all Japanese workers. About 30% of occupational health physicians witnessed exacerbation of hepatitis in the workers at their workplaces, and 22% of workers with hepatitis experienced exacerbation of hepatitis. The rate of workers with hepatitis who had experienced exacerbation was not significantly different between workers with and without hazardous work. Workers with hepatitis have strong concerns about the relationship between work and exacerbation. As causes of exacerbation, occupational health physicians cited “unknown”, “drinking” and “quit treatment” while workers with hepatitis answered “work-related causes”, besides “unknown” and “drinking.”
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Key words: Occupational health, Hepatitis B, Hepatitis C, Hazardous work, Occupational health physician

Hepatitis B and C are endemic diseases in Japan as well as in southeast Asian countries. More than one million persons and two million persons are estimated to be infected with hepatitis B virus (HBV) and hepatitis C virus (HCV), respectively, in Japan^{1,2}. HBV and HCV cause a spectrum of clinical states ranging from the symptom-free carrier state through chronic hepatitis and cirrhosis to eventual hepatocellular carcinoma³. It is assumed that large numbers of persons who are persistently infected with HBV or HCV are employed in various industries in Japan. Many of them are thought to be engaged in jobs which are suspected to cause exacerbation of hepatitis because, for example, they involve extreme exhaustion due to overwork, lack of rest due to night work or shiftwork, or handling hepatotoxic chemicals. The Ministry of Health, Labour and Welfare is now laying emphasis on policy regarding the prevention of infection with hepatitis virus. In addition, coping with workers who are infected with HBV or HCV has become an emergent issue in occupational health. However, the workplace conditions of workers with hepatitis are not well known at present in Japan. In this study, we aimed to clarify the actual workplace conditions of workers with hepatitis and to identify possible work-related exacerbation factors.

Methods

Definition of terms concerning occupational health

Some words in this report are defined here because they are used with special meaning in the occupational health field in Japan.

Workers with hepatitis: Workers who are infected with

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Table 1. Subjects, purpose and contents of the three questionnaires

Questionnaire	Responding person	Study subject	Number of subjects	Aim	Content of questions
I	Occupational health physicians	Workplace	100 workplaces (81 occupational health physicians)	Workplace conditions of occupational health management for workers with hepatitis	Scale and characteristics of workplace Number of total workers and workers with hepatitis Occupational health management for workers with hepatitis Experience of exacerbation of workers with hepatitis
II	Occupational health physicians	Workers with hepatitis	408 workers	Information about individual workers with hepatitis through occupational health physicians	Characteristics of individual workers with hepatitis Clinical state of hepatitis Engagement in hazardous work Types of hazardous work State of occupational health management
III	Workers with hepatitis	Workers with hepatitis	116 workers	Direct answers from workers with hepatitis	Characteristics of individual workers with hepatitis Characteristics of their workplaces Engagement in hazardous work Types of hazardous work Worries about viral hepatitis Exacerbation of hepatitis and its suspected causes State of occupational health management

HBV or/and HCV, including carriers, and individuals with chronic hepatitis, cirrhosis, and liver cancer. *Workplaces*: Units of occupational health management. Usually, they are geographically independent factories, branches of companies, etc. *“Hazardous work”*: Types of work that are likely to cause health damage in workers. *“Hazardous work”* is defined in the Ordinance on Prevention of Organic Solvent Poisoning (The Ministry of Labour Ordinance No36, September 30,1972)^{5, 6)}, Ordinance of Prevention of Hazards Due to Specified Chemical Substances (The Ministry of Labour Ordinance No39, September 30,1972)⁷⁾, Ordinance on Prevention of Lead Poisoning (The Ministry of Labour Ordinance No37, September 30,1972)⁸⁾, Ordinance on Prevention of Hazards Due to Dust (The Ministry of Labour Ordinance No18, April 25,1979)⁹⁾ and Ordinance on Industrial Safety and Health, (The Ministry of Labour Ordinance No32, September 30,1972)¹⁰⁾ in Japan. The items related to “hazardous work” are as follows: a) organic solvents, b) specified chemical substances, c) lead, d) dust, e) ionizing radiation, f) hot places or cold places, g) extraordinary atmospheric pressures, h) vibrations, I) heavy objects, j) noise, and k) night work. *Clinical states*: A spectrum of clinical diagnoses of viral hepatitis, i.e., carrier, chronic hepatitis, cirrhosis and liver cancer. Clinical diagnoses were made by company employed physicians or their related medical organizations. *Treatment states*: Treatment states indicate the current status of treatment:

don’t need to follow, quit following, following, medication, and repetition of hospitalization and discharge.

Questionnaire

Three kinds of questionnaires (Table1) were used in this study. Questionnaire I and Questionnaire II were sent to 118 occupational health physicians, who were members of an occupational health physicians society. Eighty-one (68.6%) of these occupational health physicians answered the questionnaire. Questionnaire I was designed to investigate the present conditions of workers with hepatitis and the occupational health management in their workplaces. A total of 100 workplaces were surveyed in Questionnaire I because there were a few occupational health physicians who were in charge of multiple workplaces. Questionnaire II was designed to obtain information about each worker with hepatitis who was under the management of one of the occupational health physicians. In Questionnaire II, 408 cases were reported from 65 workplaces.

Questionnaire III was answered by workers with hepatitis and was designed to investigate their treatment states and their workplace conditions. From the viewpoint of the ethics of epidemiological surveys, Questionnaire III was sent to 40 occupational health physicians who had expressed their intention, in response to Questionnaire I, to participate in another survey in which workers with

hepatitis would answer the questionnaire directly. All workers with hepatitis who directly answered Questionnaire III gave informed consent after receiving an explanation from their occupational health physician. The total number of workers with hepatitis who answered was 116.

All three surveys (Questionnaire I, II and III) were carried out after gaining the permission of the ethics committee of the University of Occupational and Environmental Health, Japan.

Results

Present status of workers with hepatitis in the Japanese workplace

The sizes and types of the 100 workplaces where Questionnaire I was administered are shown in Table 2. The occupational health physicians at 96 out of the 100 workplaces had health information about the state of HBV or HCV infection in the workers at their workplace. At these 96 workplaces, where 130,092 workers underwent health examinations, 1,062 (0.82%) and 629 (0.48%) workers were recognized as being infected with HBV or HCV by occupational health physicians. In Questionnaire I, the occupational health physicians answered how many employees they had recognized as workers with hepatitis. Most cases were revealed to have been infected with HBV or HCV by testing for hepatitis B surface antigen (HbsAg) and antibody to HCV. Some of them were due to self-referral to occupational health physicians.

The workplace condition of each worker of hepatitis was surveyed through Questionnaire II. Fifty-six occupational health physicians out of the 81 who answered in Questionnaire I responded in Questionnaire II and reported the condition of 408 workers with hepatitis (male 362, female 42) in their workplaces. Seventeen workers with hepatitis (4.2%) were younger than 29 years old, 68 (16.7%) were 30–39 y.o., 135 (33.1%) were 40–49 y.o., 183 (44.8%) were 50–59 y.o., and 5 (1.2%) were older than 60. One hundred and eighty-five (45.9%) had HBV, 216 (53.6%) had HCV, and 2 (0.5%) had both HBV and HCV. Two hundred and seven (50.8%) workers were carriers, 183 (45.0%) had chronic hepatitis, and 17 (4.2%) had cirrhosis or hepatic cancer.

Among the 116 workers with hepatitis who answered Questionnaire III, 64 (55.2%) had HBV, 49 (39.7%) had HCV, and 1 (0.9%) had both. The 116 workers who answered Questionnaire III were not completely included in the 408 workers of Questionnaire II. However, Questionnaire III was sent to 40 occupational health physicians who had expressed their intention, in response to Questionnaire I, to participate in the survey. The treatment states of workers with hepatitis were queried as follows: not necessary to follow, quit following, following, medication, and repetition of hospitalization and discharge. These queries were used instead of queries

Table 2. The sizes and types of workplaces in Questionnaire I

	Number of workplaces
Type of industry	
Manufacturing	66
Office	18
Transport	6
Medical service	0
Other	10
Number of employees	
More than 1,000	33
100–999	48
50–99	18
Less than 49	1
Total number	100

about the clinical state (i.e., carrier, chronic hepatitis, cirrhosis and hepatic cancer) in Questionnaire III, because it was thought that workers with hepatitis would have difficulty answering questions about their diagnosis accurately. The results indicated that 27 (23.3%) workers with hepatitis didn't need to be followed or treated, 7 (6.0%) had quit being followed, 56 (48.3%) were being followed, 23 (19.8%) were under medication, and 2 (1.7%) had experienced repeated hospitalization and discharge.

Hazardous work

The engagement of workers with hepatitis in hazardous work was studied using two kinds of questionnaires answered by occupational health physicians (Questionnaire II) and by workers with hepatitis themselves (Questionnaire III). According to both questionnaires, 28.7% (117/408) of workers with hepatitis and 31.9% (37/116) were engaged in hazardous work. This percentage was similar to the estimated percentage of general workers in Japan (34.2%). The percentages of workers with hepatitis engaged in various types of hazardous work in Questionnaire II were compared with the percentages in all Japanese workers, estimated from the General Guidebook on Industrial Health 2003⁽¹⁾. The two distributions were almost the same (Fig. 1). Figure 2 compares the percentages of workers with hepatitis in various clinical states (a) and treatment states (b) between workers engaged and those not engaged in hazardous work. For clinical states, the percentages of workers with HBV and HCV who were engaged in hazardous work were 31.2% (68/218) and 27.4% (51/186), respectively. For treatment states the respective percentages were 29.2% (19/65) and 35.3% (18/51). There were no significant differences of the distribution of workers with

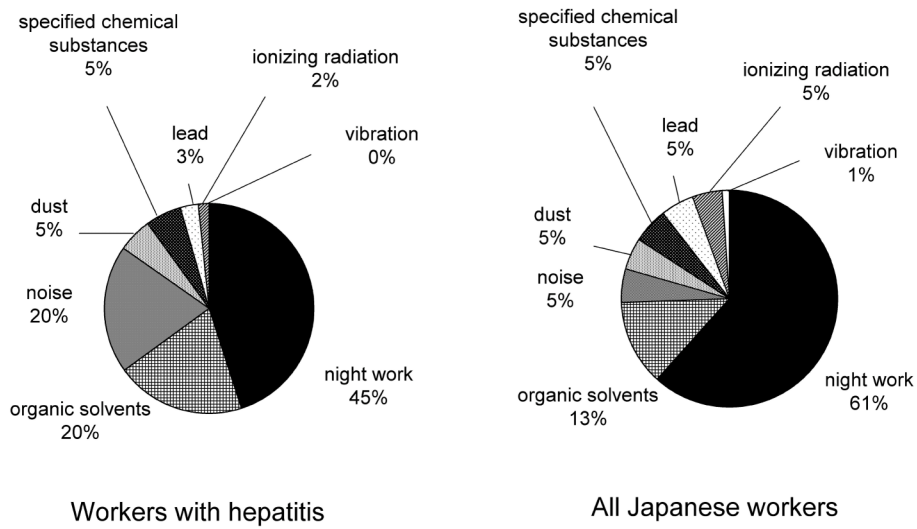


Fig. 1. Comparison of the percentages of workers engaged in various types of hazardous work between workers with hepatitis (Questionnaire II) and all Japanese workers (Estimation from the General Guidebook on Industrial Health 2003¹¹⁾).

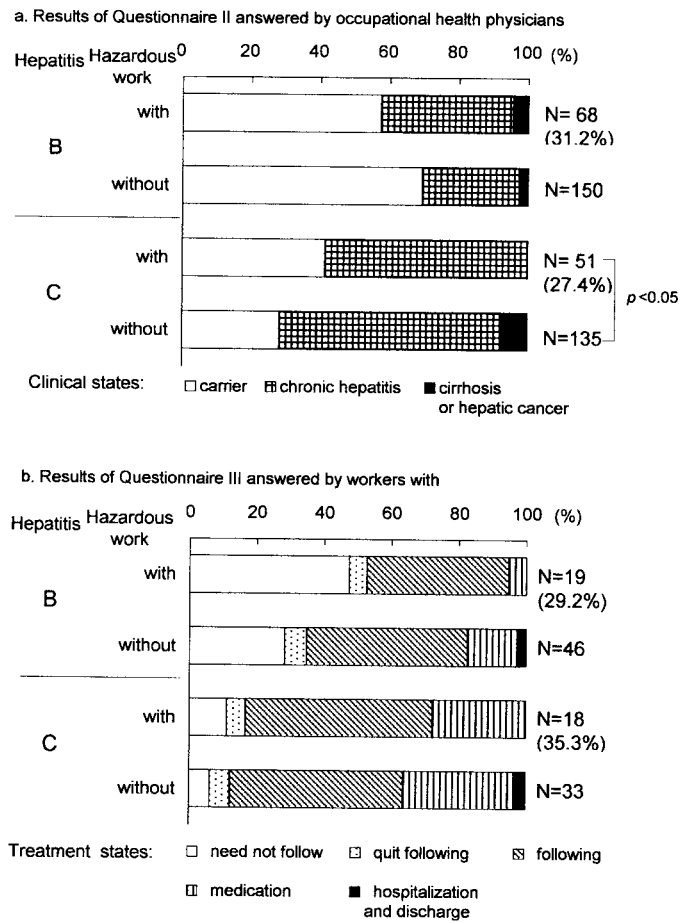
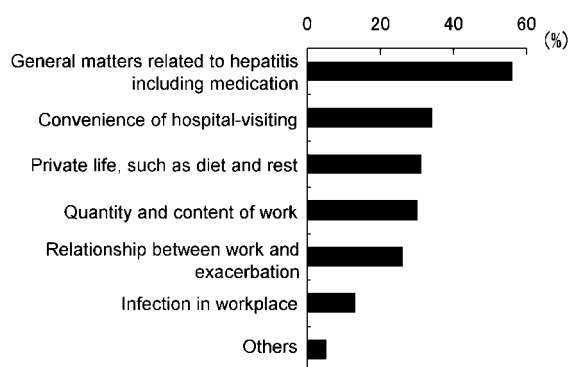


Fig. 2. Comparison of the percentages of workers with hepatitis in various clinical states (a) or treatment states (b) between those engaged and those not engaged in hazardous work. Figure 2a shows the results of Questionnaire II answered by occupational health physicians and Fig. 2b shows those of Questionnaire III answered by workers with hepatitis.

a. Occupational health physicians



b. Workers with hepatitis

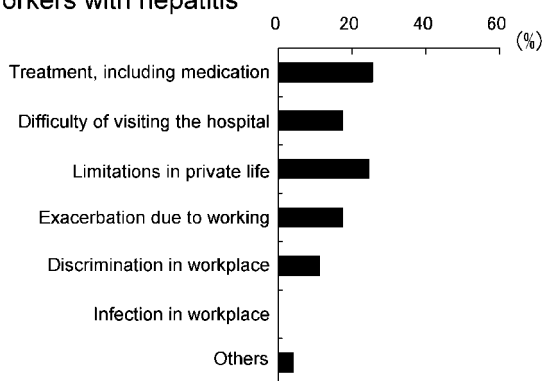


Fig. 3. Concerns of workers with hepatitis. Occupational health physicians answered questions about the details of consultations with workers with hepatitis in Questionnaire I (a). Workers with hepatitis answered questions about their concerns about their work and hepatitis in Questionnaire III (b).

hepatitis according to the various clinical states or treatment states between workers with and without hazardous work, except in the case of hepatitis C workers in Questionnaire II. No worker with hepatitis who had experienced repeated hospitalization and discharge was engaged in hazardous work in the case of either hepatitis B or hepatitis C.

Job-related concerns of workers with hepatitis

The concerns of workers with hepatitis were studied using two kinds of questionnaires answered by occupational health physicians (Questionnaire I and II) and one answered by workers with hepatitis (Questionnaire III). The consultations and questions by workers with hepatitis directed to occupational health physicians were most frequently related to matters concerning hepatitis in general, including treatments such as drug treatments. The exacerbation of hepatitis due to work was also one of the major consultation contents (Fig. 3a). Fifty-nine (52.0%) workers with hepatitis felt

some anxiety about hepatitis. Other than medication and limitations in their private lives, 17 workers with hepatitis (26%) worried about possible exacerbation of hepatitis due to their work (Fig. 3b).

Exacerbation of hepatitis

Thirty-one out of 100 (31%) occupational health physicians had experience of cases of exacerbation of hepatitis in workers under their management in the workplace according to Questionnaire I. Twenty-six out of 116 (22%) workers with hepatitis answered that they had experienced exacerbation of hepatitis according to Questionnaire III. Among the 26 workers, 7 were engaged in hazardous work: 3 in night work, 1 in work with noise, 1 with ionizing radiation, 1 with vibration and 1 with heavy objects. Among workers with hepatitis engaged in work with chemical substances, one worker handled chloroform, but had not experienced exacerbation. There were no workers who had experienced exacerbation due to work with organic solvents or specified chemical substances. The percentage of workers with hepatitis who had experienced exacerbation was not significantly different between workers with and without hazardous work (Table 3).

Possible causes of the exacerbation given by occupational health physicians and workers with hepatitis are shown in Fig. 4. About 20% of both occupational health physicians and workers with hepatitis answered “drinking” as a cause of the exacerbation. However, the most frequent reason which occupational health physicians answered was “unknown”. “Quit treatment” was the third-most frequent cause, following “drinking”. On the other hand, workers with hepatitis answered work-related causes, that is, “stress at work”, “overwork”, “overseas business trip” and “workplace transfer” besides “unknown” as causes. It is worth noting that a few occupational health physicians also answered work-related causes, that is, “overwork”, “stress at work”, “overseas business trip” and “domestic business trip”.

Discussion

As this study was not carried out by a random sampling method, the results obtained here are not representative of all Japanese workers. For example, 96% (around 6 million) of Japanese workers work in workplaces with fewer than 30 employees, whereas almost all workplaces in this study had more than 50 employees (33% of the workplaces in this study had more than 1,000 employees). It is very hard to collect information about workers with hepatitis from workplaces, especially from small workplaces. The reason for this is that most workers with hepatitis probably would not have disclosed their infection to their workplace in order to avoid prejudice and disadvantages in their work. Prejudice and disadvantages result from the fact that infection with HBV

Table 3. The numbers of workers who experienced exacerbation of hepatitis with and without hazardous work (From Questionnaire III)

	Exacerbation				Total (%)	
	Yes	(%)	No	(%)		
With hazardous work	7	(21.2)	26	(78.8)	33	(100.0)
Without hazardous work	19	(23.2)	63	(76.8)	82	(100.0)
Total	26		89		115	

(No answer 1)

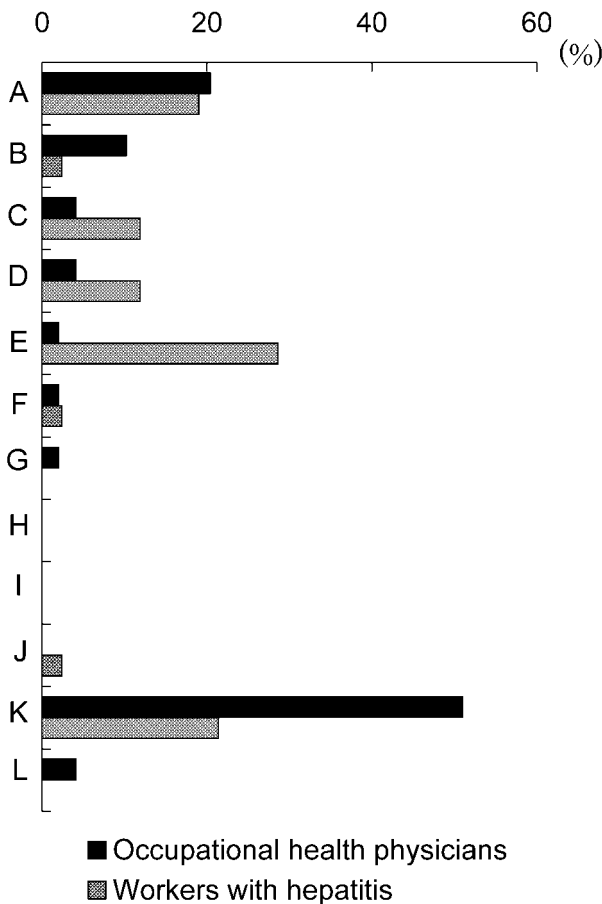


Fig. 4. Possible causes of acute exacerbation of hepatitis cited by occupational health physicians who responded to Questionnaire I and workers with hepatitis who responded to Questionnaire III. A: drinking, B quit treatment, C: overwork, D: stress or fatigue in private life, E: stress due to work, F: overseas business trip, G: domestic business trip, H: exposure to chemical substances, I: long-distance marriage, J: workplace transfer, K: unknown, and L: other.

or HCV is misunderstood to be similar to that with HIV (human immunodeficiency virus) by most Japanese people because of its historical background. The other reason is that interest in viral hepatitis is low, and examinations for HBV and HCV infection are rarely carried out in small workplaces. Accordingly, it is impossible to survey workers with hepatitis randomly and directly. The authors, therefore, constructed an original network, of which the nuclei were occupational health physicians, for collecting data about workers with hepatitis.

The real infection rate of hepatitis B and C virus in the Japanese workplace is still unknown. In this study, it was found that 0.82% and 0.42% of 130,092 workers in the 96 workplaces were recognized by their occupational health physicians as workers who were infected with HBV and HCV, respectively. The rates of prevalence of HBV and HCV carriers among healthy Japanese people aged 16–64 are estimated to be 0.63% and 0.49%, respectively, from the analyses of sera from first-time blood donors of the Japanese Red Cross Blood Center during 1995–2000¹²⁾. The two prevalence rates cannot simply be compared for the following reasons: 1) it is unclear whether the age distribution of the subject workers is in accord with that of the Japanese population, and the prevalence rates increased with age in workers; 2) the prevalence rates in the present study included patients with obvious clinical states, such as chronic hepatitis, cirrhosis and liver cancer, whereas the rates reported by the Japanese Red Cross Blood Center during 1995–2000¹²⁾ are applicable only for healthy blood donors; and 3) the rates in the present study did not include workers with hepatitis who had not been recognized by occupational health physicians. Although it is not possible to strictly compare the prevalence rates between the present study and the survey examining first-time blood donors¹²⁾, it can be said that the rates are not very different, assuming that the age distributions in the workplace and the Japanese population are similar.

It is suspected from the results of this study that limitations of job placement were not imposed on workers with hepatitis until they became seriously ill, because

the percentages of workers with hepatitis in various clinical states or treatment states did not differ between those engaged and those not engaged in hazardous work. Even workers with chronic hepatitis or cirrhosis were engaged in hazardous work. However, workers with repeated hospitalization and discharge were not engaged in hazardous work. The most important reason for this is that there is no reported evidence for exacerbating factors in work-related circumstances. Employers and/or occupational health physicians cannot limit the engagement of workers with hepatitis without any supporting evidence, because carriers, who constitute most of the workers with hepatitis, have no clinical symptoms.

Hepatitis B and C worsen over a long period. Acute or chronic exacerbation is the greatest concern of workers with hepatitis. Workers with hepatitis regulate their daily lives in order to prevent exacerbation, but it is hard to avoid exacerbating factors in the workplace. Some workers with hepatitis worried about exacerbation due to stress from work. On the other hand, workers with hepatitis want to be treated the same as healthy workers at their workplaces. They do not want to be recognized as patients because of the prejudice against people with hepatitis B and C.

Alcohol drinking is the most commonly reported risk factor for exacerbation¹³⁻¹⁷. Workers with hepatitis engage in many kinds of jobs, like other workers. There are some types of work that have an elevated chance of exacerbating viral hepatitis. Exposure to hepatotoxic substances is suspected to be an exacerbation factor. Luo *et al.*¹⁸ reported that HBV carrier status had synergistic effects with dimethylformamide in causing liver abnormalities. Wong *et al.*¹⁹ pointed out the interaction between occupational exposure to vinyl chloride and HBV infection for the development of liver cancer. Cordier *et al.*¹³ suggested that exposure to chemicals like pesticides may interact with HBV infection.

We nominated eleven kinds of jobs as hazardous work in the present study. Although some factors of hazardous work such as noise, dust and vibration, are not likely to cause exacerbation, we aimed to investigate all types of hazardous work in order not to eliminate any possibilities. As a result, the percentage of workers with hepatitis who had experienced exacerbation was not significantly different between workers with and without hazardous work. Especially, no worker handling organic solvents or specified chemical substances experienced exacerbation. There were no workers handling dimethylformamide or vinyl chloride which are suspected of inducing hepatotoxicity, but one worker was handling chloroform, a known hepatotoxin. Furthermore no occupational health physician or worker with hepatitis answered that exposure to chemical substances was a possible cause of exacerbation. The improvement of

workplaces and protection of workers from exposure by wearing glasses, gloves, masks, clothes etc., seems to be related to this result. On the other hand, the number of chemical substances handled in the workplace reaches about 60,000, and there is not enough information on the hepatotoxicity of them. Medical examination in the workplace is only required for workers handling 47 kinds of organic solvents by the Ordinance on Prevention of Organic Solvent Poisoning⁵, and 50 kinds of specified chemical substances by the Ordinance of Prevention of Hazards Due to Specified Chemical Substances⁷. There might be some workers with hepatitis who had handled hepatotoxic chemical substances among those who answered that they didn't engage in hazardous work.

Three workers who had experienced exacerbation were engaged in night work. Also, overwork, stress due to work, overseas business trip and domestic business trip were cited as causes of exacerbation in Questionnaire III by workers with hepatitis. There have been no reports which have investigated whether fatigue or overwork, for example, long working hours, night work, shiftwork and long business trips, exacerbate hepatitis or not. As infection with HCV causes feelings of fatigue^{21, 22}, the possibility that the feelings of overwork and stress due to work were the result of exacerbation cannot be ruled out. There were no workers who had answered night work as a factor of exacerbation, but some workers had answered overwork or stress of work as possible causes of exacerbation. Some hepatotoxic chemical substances and work with fatigue (e.g. night work, overwork, and stressful work) were possible work-related exacerbation factors of workers with hepatitis. There is a possibility that some work-related exacerbation factors are related. If workers with hepatitis had exacerbation, the possible work-related exacerbation factors should be investigated in more detail.

In conclusion, the prevalence of workers in Japan who are infected with HBV or HCV among all workers is estimated to be not so different from the prevalence in the general population. The percentage of workers engaged in the various types of hazardous work was nearly the same as that of Japanese workers in general. The exacerbation rates of hepatitis did not differ with engagement in hazardous work. Workers with hepatitis have strong concerns about the relationship between their work and exacerbation. About 30% of occupational health physicians had experience of exacerbation of hepatitis in workers under their care in the workplace. Twenty-two percent of workers with hepatitis had experienced exacerbation of their hepatitis. At present, there is no evidence for exacerbating factors in the workplace. It will be important to clarify the risks of various types of works or jobs for workers with viral hepatitis.

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References

- 1) Inoue O, Nakazawa Y and Mawatari H: Introduction of chronic hepatitis type B. *Nippon Rinsho* 62 (Suppl 8), 285–289 (2004) (in Japanese)
- 2) Higuchi M, Tanaka E and Kiyosawa K: Epidemiology and clinical aspects on hepatitis C. *Jpn J Infect Dis* 55, 69–77 (2002)
- 3) Iino S: Natural history of hepatitis B and C infections. *Oncology* 62 (Suppl 1), 18–23 (2002)
- 4) Haas GJ: “Yakugai” AIDS and the Yokohama Xth international AIDS conference. *Common Factor* 10, 1–22 (1995)
- 5) Ministry of Health, Labour and Welfare. Ordinance on Prevention of Organic Solvent Poisoning. Japan International Center for Occupational Safety and Health, 2001. (online), available from <<http://www.jicosh.gr.jp/english/law/OrganicSolvent/index.html>>, (accessed 2006-10-13).
- 6) Kawamoto T, Kodama Y and Kohno K: Interlaboratory quality control and status of n-hexane biological monitoring in Japan. *Arch Environ Contam Toxicol* 28, 529–536 (1995)
- 7) Ministry of Health, Labour and Welfare. Ordinance of Prevention of Hazardous Due to Specified Chemical Substances. Japan International Center for Occupational Safety and Health, 2001. (online), available from <<http://www.jicosh.gr.jp/english/law/Specified/index.html>>, (accessed 2006-10-13).
- 8) Ministry of Health, Labour and Welfare. Ordinance on Prevention of Lead Poisoning. Japan International Center for Occupational Safety and Health, 2001. (online), available from <<http://www.jicosh.gr.jp/english/law/LeadPoisoning/index.html>>, (accessed 2006-10-13).
- 9) Ministry of Health, Labour and Welfare. Ordinance on Prevention of Hazards Due to Dust. Japan International Center for Occupational Safety and Health, 2001. (online), available from <<http://www.jicosh.gr.jp/english/law/Dust/index.html>>, (accessed 2006-10-13).
- 10) Ministry of Health, Labour and Welfare. Ordinance on Industrial Safety and Health. Japan International Center for Occupational Safety and Health, 2001. (online), available from <http://www.jicosh.gr.jp/english/law/IndustrialSafetyHealth_Ordinance/index.html>, (accessed 2006-10-13).
- 11) Labour Standards Bureau, Ministry of Health, Labour and Welfare ed. Survey of executing health examination for workers exposed to specific occupational hazard in Japan. In: General guidebook on industrial health 2003. Tokyo: Japan Industrial Safety and Health Association, 2003: 312–314.
- 12) Tanaka J, Kumagai J, Katayama K, Komiya Y, Mizui M, Yamanaka R, Suzuki K, Miyakawa Y and Yoshizawa H: Sex- and age-specific carriers of hepatitis B and C viruses in Japan estimated by the prevalence in the 3,485,648 first-time blood donors during 1995–2000. *Intervirology* 47, 32–40 (2004)
- 13) Cordier S, Le TB, Verger P, Bard D, Le CD, Larouze B, Dazza MC, Hoang TQ and Abenheim L: Viral infections and chemical exposures as risk factors for hepatocellular carcinoma in Vietnam. *Int J Cancer* 55, 196–201 (1993)
- 14) Bhattacharya R and Shuhart MC: Hepatitis C and alcohol: interactions, outcomes, and implications. *J Clin Gastroenterol* 36, 242–252 (2003)
- 15) Rigamonti C, Mottaran E, Reale E, Rolla R, Cipriani V, Capelli F, Boldorini R, Vidali M, Sartori M and Albano E: Moderate alcohol consumption increases oxidative stress in patients with chronic hepatitis C. *Hepatology* 38, 42–49 (2003)
- 16) Donato F, Tagger A, Chiesa R, Ribero ML, Tomasoni V, Fasola M, Gelatti U, Portera G, Boffetta P and Nardi G: Hepatitis B and C virus infection, alcohol drinking, and hepato-cellular carcinoma: a case-control study in Italy. *Brescia HCC Study. Hepatology* 26, 579–584 (1997)
- 17) Hassan MM, Hwang L-Y, Hatten CJ, Swaim M, Li D, Abbruzzese JL, Beasley P and Patt YZ: Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. *Hepatology* 36, 1206–1213 (2002)
- 18) Luo JC, Kuo HW, Cheng TJ and Chang MJ: Abnormal liver function associated with occupational exposure to dimethylformamide and hepatitis B virus. *J Occup Environ Med* May 43, 474–482 (2001)
- 19) Wong RH, Chen PC, Wang JD, Du CL and Cheng TJ: Interaction of vinyl chloride monomer exposure and hepatitis B viral infection on liver cancer. *J Occup Environ Med* Apr 45, 379–383 (2003)
- 20) Astbury C and Wyke RJ. Gastrointestinal and liver disorders. In: Cox RAF, Edwards FC, Palmer K, eds. *Fitness for work: the medical aspects*. Oxford: Oxford University Press, 2000: 293–305.
- 21) Poynard T, Cacoub P, Ratzu V, Myers RP, Dezailles MH, Mercadier A, Ghillani P, Charlotte F, Piette JC and Moussalli J: Fatigue in patients with chronic hepatitis C. *J Viral Hepat* Jul 9, 295–303 (2002)
- 22) Hassoun Z, Willems B, Deslauriers J, Nguyen BN and Huet P-M: Assessment of fatigue in patients with chronic hepatitis C using the Fatigue Impact Scale. *Dig Dis Sci* Dec 47, 2674–2681 (2002)