TABLE II – RELATIONSHIONSHIP BETWEEN POLYMORPHISM IN MMP-1 PROMOTER AND EXPRESSION

Genotype	HCC-M (2G/2G)	HCC-T (2G/2G)	HLE (1G/2G)	PLC/PRF/5 (1G/2G)	Huh-7 (2G/2G)
MMP-1 expression by RT-PCR	–	–	+	–	–
Enzymatic activity of MMP-1 by zymography	–	–	+	–	–

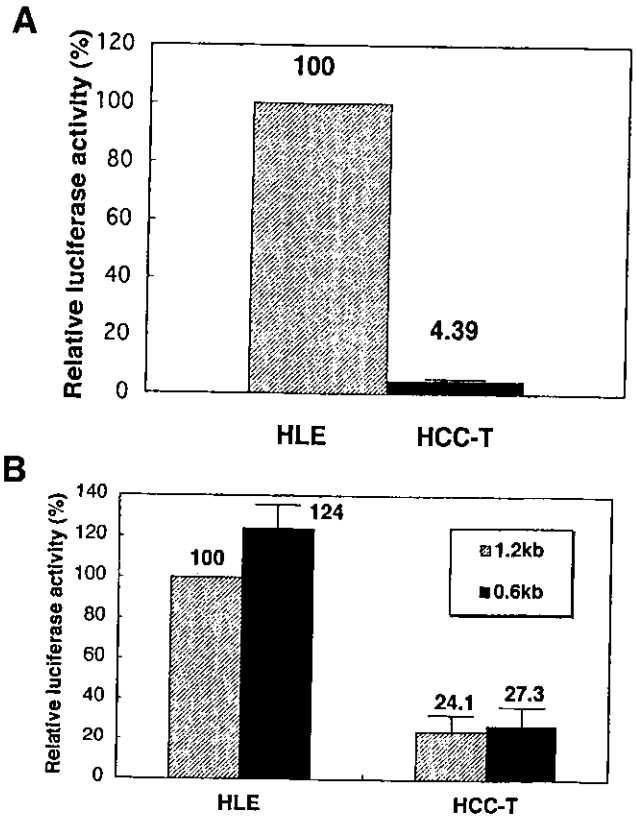

FIGURE 3 – Basal transcriptional activity of MMP-1 promoter in HLE and HCC-T cells. As described in text, HLE and HCC-T cell lines were transfected with human MMP-1 promoter/luciferase reporter gene construct (4.4 kb; *a*) and 2 5′ deletion constructs (1.2 or 0.6 kb; *b*) together with pRL-CMV. After transfection, cells were incubated for 48 hr. Relative luciferase activities (mean ± SD) were normalized for pRL-CMV activity and calculated as percent of the HLE promoter activity, which was transfected with 1.2 kb construct. Transfections and assays were performed independently 4 to 6 times, each run in duplicate.

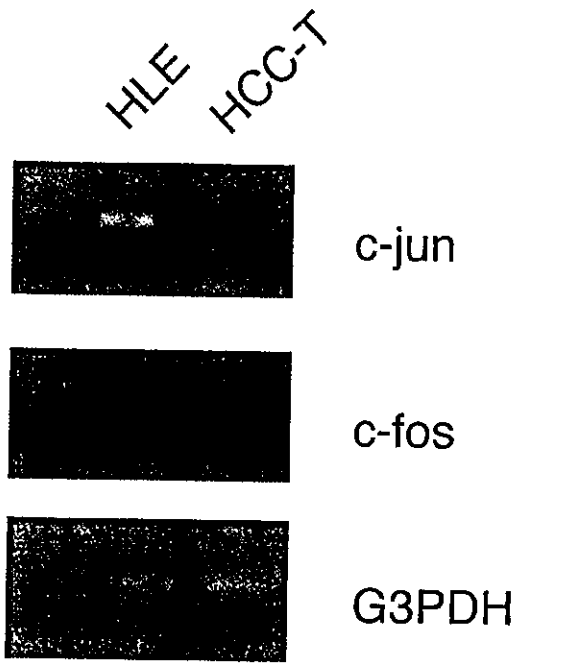

FIGURE 4 – c-jun and c-fos expression in HLE and HCC-T cells. c-jun and c-fos expression was detected with RT-PCR analysis. HLE cells, but not HCC-T cells, expressed c-jun mRNA without exogenous stimulation. c-fos mRNA was not observed in either HLE or HCC-T cells.

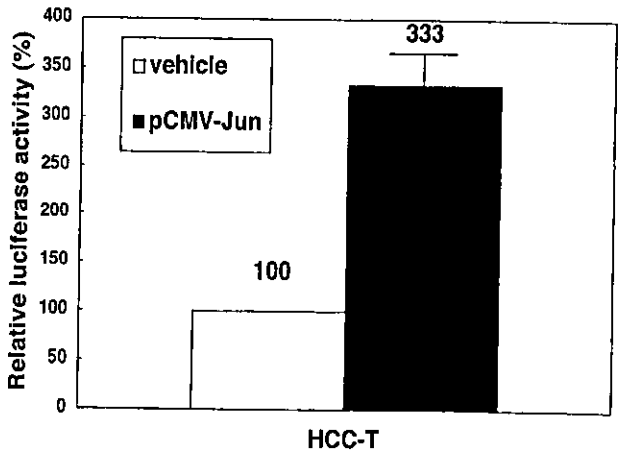

FIGURE 5 – Effect of c-Jun overexpression on HCC-T promoter activity. Human MMP-1 promoter/luciferase reporter gene construct (0.6 kb; 2.5 μg) was cotransfected with pCMV-jun vector (2.5 μg) in HCC-T cells and the effect of c-Jun on the activation of MMP-1 transcription was examined. Total amount of transfected DNA was adjusted with pCMV (vehicle) to 7.5 μg. After transfection, cells were incubated for 48 hr. Relative luciferase activities (mean ± SD) were shown after normalization for pRL-CMV activity. Transfections and assays were performed independently 4 times, each run in duplicate.

while HCC-M, HCC-T and HLE cells did not show these mRNAs (Fig. 1*c*). These results are coincident with the original characteristics of those cell lines, indicating PLC/PRF/5 and Huh-7 cells as well-differentiated HCC cells and HCC-M, HCC-T and HLE cells as less differentiated HCC cells.

Analysis of −1607 nucleotide polymorphism in MMP-1 promoter region

A single nucleotide polymorphism at −1607 nucleotide in the MMP-1 promoter region creates a PEA-3-binding site (5′-GGAA-3′) as shown in Figure 2 and affects the transcriptional level of MMP-1.[28] HCC-M, HCC-T and Huh-7 cells possessed 2G/2G genotype, while HLE cells showed 1G/2G genotype (Table II). There was no correlation between the genotypes and MMP-1 expression levels, indicating that another mechanism may regulate gene expression of MMP-1 in HCC cells.

Transcriptional activity of MMP-1 promoter in HLE and HCC-T cells

In order to clarify the contribution of transcriptional factors in HLE cells, 4.4 kb MMP-1 promoter construct, which covered the

entire promoter region, was transfected into HLE and HCC-T cells. The MMP-1 promoter activity of HLE cells was much higher than that of HCC-T cells (Fig. 3*a*). These data indicate that some transcriptional factors were involved in constitutive MMP-1 expression in HLE cells. Then, to determine the region responsible for the difference in the promoter activity between HLE and HCC-T cells, 2 5′ deletion constructs (1.2 or 0.6 kb) were prepared and transfected into HLE and HCC-T cells. The promoter activity in HLE cells was higher than that in HCC-T cells (about 4- or 5-fold) not only when transfected with the 1.2 kb construct but also with the minimal 0.6 kb construct (Fig. 3*b*). Since 3 AP-1 sites were present within the 0.6 kb promoter construct (Fig. 2), transcription factor AP-1 may be responsible for MMP-1 expression in HLE cells.

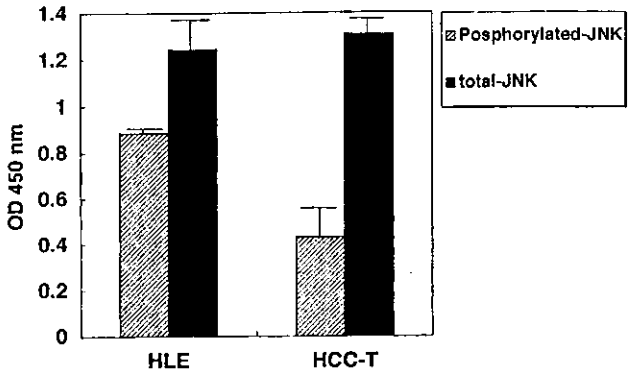

FIGURE 6 – Measurement of phosphorylated and total JNK. HLE and HCC-T cells were cultured in 96-well plates for 48 hr and the cells were fixed. Total and phospho-JNK were each assayed in triplicate using antiphosphorylated and anti-JNK antibodies from the FACE JNK Kit. Data were plotted (mean ± SD) after correction for cell number (performed through use of Crystal Violet). Note that the level of total JNK was almost the same with HLE and HCC-T cells.

Different c-jun and c-fos expression in HCC cells

Next we examined the gene expression of c-jun and c-fos in HLE and HCC-T cells to examine the contribution of AP-1 protein to MMP-1 expression in HLE cells. The definite band of c-jun was seen in HLE cells, while no band was detected in HCC-T cells (Fig. 4). c-fos gene expression was not noted in these cell lines. In order to determine the contributions of c-Jun to MMP-1 promoter activity, we transfected c-Jun expression vector (pCMV-jun vector) into HCC-T cells and measured the MMP-1 promoter activity. When c-Jun was overexpressed in HCC-T cells, 3.3-fold transcriptional activation of MMP-1 promoter was detected (Fig. 5).

JNK activity and c-Jun phosphorylation in HCC cells

To confirm the constitutive activation of JNK in HLE cells, phosphorylated and total JNK were measured with the FACE Kit. The amount of phosphorylated JNK protein in HLE cells was more than twice as much as that in HCC-T cells (Fig. 6), though the level of total JNK was almost the same in the 2 cell lines.

Then, phosphorylated c-Jun was analyzed by Western blot analysis. Phosphorylated c-Jun was detected with both phospho-c-Jun antibody (Ser63) and phospho-c-Jun antibody (Ser73) only in HLE

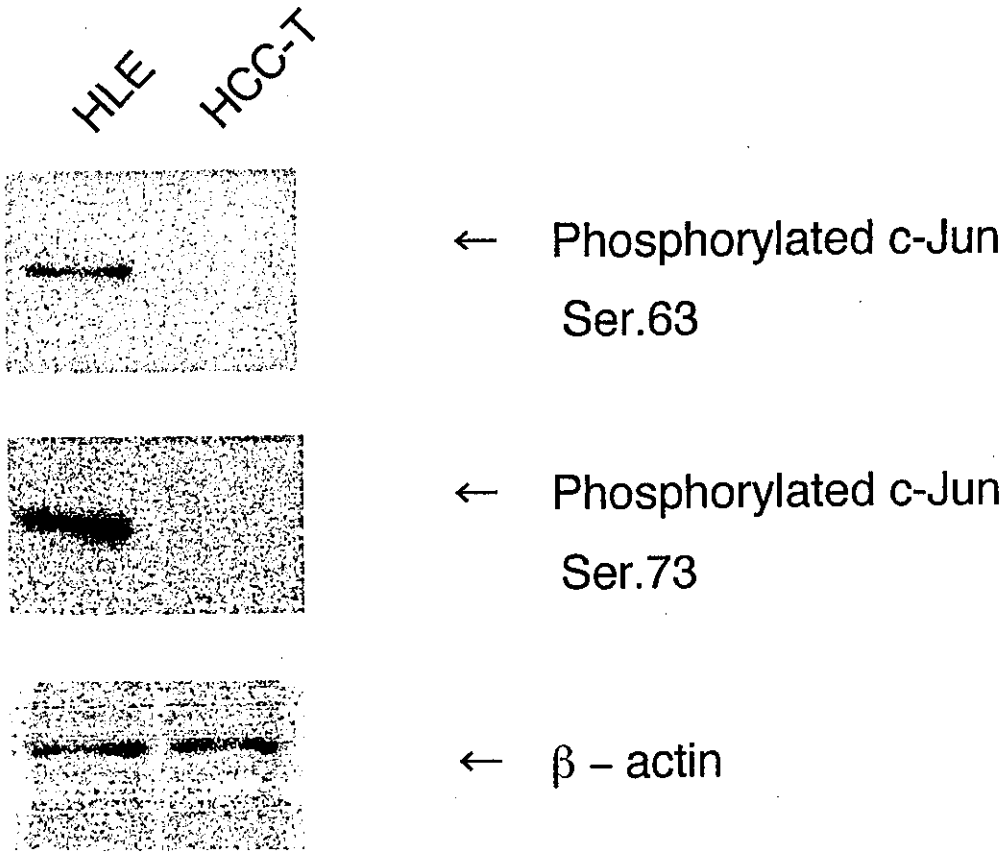

FIGURE 7 – Western blot analysis for phosphorylated c-Jun. Proteins were extracted from HLE and HCC-T cells and assessed by Western blot analysis using 2 antibodies to phosphorylated c-Jun (Ser63 and Ser73). In HLE cells, c-Jun was phosphorylated at Ser63 and Ser73. Blots were reprobed for β-actin to confirm the equal protein loading.

cells, but not in HCC-T cells (Fig. 7). These data suggested that the JNK pathway is constitutively activated in HLE cells, resulting in the high MMP-1 expression in the cells.

Effects of MAP kinase inhibitors on MMP-1 promoter activity

HLE cells had the ability to produce MMP-1 without exogenous stimuli and expressed c-jun (Fig. 4). As c-Jun activation is achieved by MAP kinase families, we used 3 MAP kinase inhibitors to determine the responsible enzyme of MAP kinase families for constitutive MMP-1 gene expression in HLE cell line. It was clearly noted that JNK inhibitor SP600125 (50 μM) reduced the promoter activity of 0.6 kb construct to approximately 40% (Fig. 8*a*), while either MEK/ERK inhibitor PD98059 (20 and 50 μM) or p38 inhibitor SB203580 (5 μM and 20 μM) did not reduce the promoter activity of MMP-1 (Fig. 8*b* and *c*), further indicating that c-Jun activation through JNK pathway may participate in constitutive MMP-1 expression in HLE cells.

Effect of JNK inhibitor on MMP-1 protein expression and gelatinolytic activity

To examine the inhibitory effect of SP600125 on MMP-1 expression directly, we performed Western blot analysis and zymography after treatment of HLE cells with SP600125. Both MMP-1 protein expression and gelatinolytic activity were actually reduced 48 hr after the addition of SP600125 (Fig. 9). In contract, the effect of SP600125 on MMP-2 expression was less effective. This result may reflect the number of AP-1-binding sites among the promoter regions of MMP-1 and MMP-2.

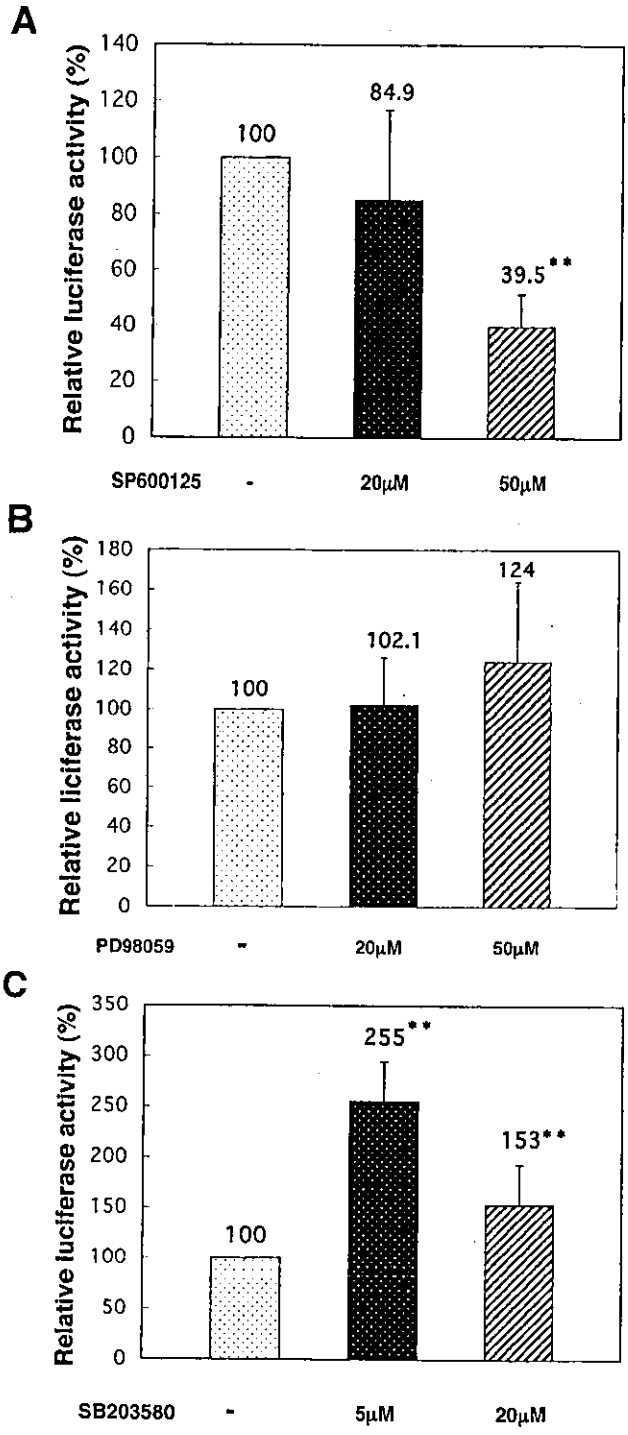

FIGURE 8 – Effect of MAP kinase inhibitors on MMP-1 promoter activity. Inhibition of MMP-1 promoter activities by 3 MAP kinase inhibitors was investigated in constitutively MMP-1-expressing HLE cells. Treatment of HLE cells with SP600125 (*a*) showed a significantly decreased activity in a dose-dependent fashion, but treatment with PD98059 (*b*) or SB203580 (*c*) did not reduce the MMP-1 promoter activity. Details were described in text. Before transfection, HLE cells were cultured for 24 hr in the presence of SP600125 (20 and 50 μM; JNK inhibitor), PD98059 (20 and 50 μM; MEK/ERK inhibitor), or SB203580 (5 and 20 μM; p38 inhibitor). After transfection with human MMP-1 promoter/luciferase reporter gene construct (0.6 kb) together with pRL-CMV, HLE cells were incubated for 48 hr in the presence of the same concentrations of each inhibitor. Transfections and assays were performed independently 4 to 6 times, each run in duplicate. Statistical significance was defined as $p < 0.01$ (double asterisk).

DISCUSSION

Clarification of the regulatory mechanism of MMP-1 gene expression in HCC cells is quite important because MMP-1 expression was observed only in an early stage of HCC[5] and this phenomenon is accountable to the histologic feature suggesting stromal invasion at the early stage of HCC. In advanced stage of HCC, tumor is encapsulated and does not express MMP-1. In general, HCC tumor cells show very slight atypia in the early stage and they are sometimes indistinguishable from normal hepatocytes. As the tumor grows, dedifferentiation occurs in HCC cells, where well-differentiated cancer cells are replaced by less differentiated cancer cells.[6,29] Since HCC usually arises from a rigid cirrhotic liver in which interstitial collagen is deposited predominantly,[8,10,30] tumor cells have to dissolve surrounding fibrous tissue for their expansion by producing MMP-1.

First we examined the expression of MMP-1 in cultured human HCC cell lines, which were derived from various stages of differentiation, and found that MMP-1 gene and protein expressions as well as enzymatic activity were observed only in HLE cells without any stimulation. It is true that HLE cells do not produce albumin or α-fetoprotein, but they may lie in a process of dedifferentiation of HCC cells and be considered as special cells to maintain early property of HCC cells. In any event, investigation of the mechanism of MMP-1 gene expression in HLE cells should provide precious clue to clarify the regulatory mechanism of MMP-1 expression in HCC. We thus used HLE cells and nonproducing HCC-T cells as a control for further analysis to explore the regulatory mechanisms of MMP-1 expression.

Transient transfection assay with the 0.6 kb construct (−522/+72) showed about 5-fold higher activity in HLE cells than that in HCC-T cells. Within this promoter region, there are 3 AP-1 sites at −436, −181 and −72 bp (Genbank accession number AF023338), 1 PEA-3 site (polyomavirus enhancer A-binding protein-3), 1 reversed PEA-3 site, CACCC box, TTCA motif and

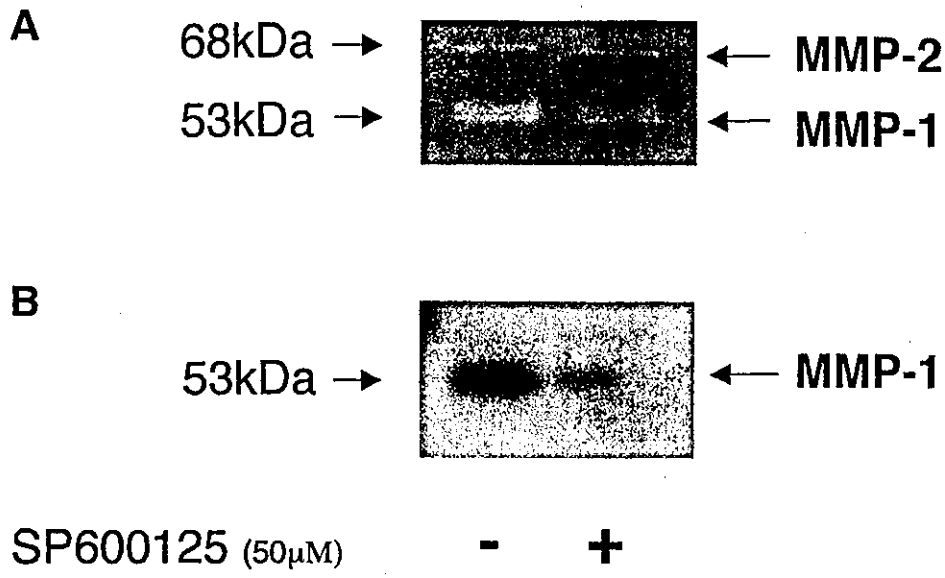

FIGURE 9 – Effect of JNK inhibitor on MMP-1 expression and gelatinolytic activity in HLE cells. HLE cells were cultured in serum-free media for 48 hr in the presence of 50 μM JNK inhibitor SP600125 and its effects on the expression of MMP-1 was analyzed by gelatin zymography (*a*) and Western blot analysis (*b*). Representative films are shown from 3 independent experiments. The enzymatic activity and protein level of MMP-1 were reduced to 62.7% ± 9.8% ($p < 0.05$) and 37.4% ± 5.8% ($p < 0.01$), respectively. The enzymatic activity of MMP-2 was slightly reduced to 92% ± 8.2%, but the statistical significance was not detected.

TATA box.[27] We could not detect any mutations in these transcription factor-binding elements in HCC cell line. Moreover, RT-PCR analysis showed that the expression of c-jun, but not c-fos, was detected without exogenous stimulation in HLE cells. Therefore, we hypothesized that in HLE cells, MMP-1 transcription was constitutively activated through the c-Jun-binding to the AP-1-binding sites. The AP-1 transcription factor itself can be formed by either the dimerization of Jun family members or the formation of Jun/Fos heterodimers.[31–33] Increased MMP-1 promoter activity observed in HCC-T cells tranfected with c-jun expression vector indicates that only c-Jun is enough for MMP-1 expression via AP-1-binding sites.

JNKs phosphorylate specific sites (ser63 and ser73) of c-Jun and enhance the transcriptional activity of AP-1, whose phosphorylation is induced after exposure to ultraviolet irradiation, growth factors, or cytokines.[34,35] To confirm activation of the JNK pathway in HLE cells, we next examined phosphorylation of JNK and c-Jun with Western blot analysis. Although we could not find any difference in the amount of total JNK between HLE and HCC-T cells, phosphorylated JNK in HLE cells was twice as much as that in HCC-T. Moreover, a strong band of phosphorylated c-Jun was detected in HLE cells, while no band or very faint band, if any, was found in HCC-T cells.

Transient transfection assays with 3 independent MAP kinase inhibitors[36,37] revealed that JNK- specific inhibitor SP600125 (50 μM) reduced the promoter activity of MMP-1 to approximately 40% in HLE cell line, while neither MEK/ERK-specific inhibitor PD98059 (20 and 50 μM) nor p38-specific inhibitor SB203580 (5 and 20 μM) reduced the promoter activity of MMP-1. SP600125 also reduced the gelatinolytic activity and MMP-1 protein expression in HLE cells. Taken together, JNK pathway is always activated in HLE cells, which results in constitutive expression of MMP-1.

Benbow *et al.*[38] reported that in melanoma cells, constitutive MMP-1 expression in the absence of the 2G single nucleotide polymorphism was mediated by p38 and ERK1/2 MAP kinases. Our data also support that, in the absence of 2G allele, HLE cells utilize the alternative activation mechanism to achieve high levels of MMP-1 expression.

Eferl *et al.*[14] have demonstrated that the requirement for c-Jun was restricted to the early stages of tumor (HCC) development by antagonizing p53 activity, resulting in suppression of apoptosis. JNK activation may be required for the early stages of HCC cells, because the activation leads the cells to be more invasive (through MMP-1 activation) and proliferative (via inactivation of p53). This activation seems to explain our previous findings showing that MMP-1 expression was restricted to the early stage of HCC. In addition, it is also reported that MMP-1 itself has an ability to induce hepatocyte proliferation.[13] Thus, these findings indicate the significance of not only c-Jun activation but also MMP-1 expression for the invasion and proliferation of HCC cells.

In summary, the present study indeed confirms the relationship between the JNK activation and MMP-1 expression in HCC cells and indicates the new aspect of c-Jun activation in the early stage of HCC development. Further investigations to clarify the difference in the regulatory mechanism of MMP-1 gene expression between regenerating hepatocyte and HCC cells will help us to reverse liver cirrhosis and to prevent HCC development by modifying MMP-1 expression.

ACKNOWLEDGEMENTS

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COMPARATIVE SOCIO-CULTURAL ANALYSIS OF SMOKING BEHAVIOR AND DIFFICULTY OF QUITTING SMOKING IN JAPAN AND THAILAND

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Objective Although education for smoking cessation is being conducted in Asian countries, the prevalence of smoking is still high. The present study was designed to clarify differences in the socio-cultural background in Japan and Thailand.

Methods Cross-sectional study. The Japan survey was conducted in Kanagawa and the Thailand survey in Suphanburi. Questionnaires written in English were translated into each language. The subjects were out-patients of community hospitals (331 males and 353 females in Japan and 293 males and 288 females in Thailand).

Results The prevalence of smoking was found to be higher in Thailand than in Japan for males but almost the same for females. A higher percentage of the subjects quit smoking in Japan than in Thailand. The motive for quitting smoking was "awareness of the harmful effects of smoking" in both countries, but "told by others to quit smoking" was also often encountered in Thailand. The method of quitting was most frequently "suppress the urge to smoke by will power" in both countries. Nicotine replacement therapy is not well known yet in either country.

Conclusion Smoking behavior was different although the difficulty of quitting smoking was common to both countries. The prevalence of smoking in younger males and females was established to be higher in Japan, and social and environmental regulations for quitting smoking were effective in Thailand. It suggests that such regulations should be made stricter in Japan. Enlightenment by providing knowledge may be particularly useful in Thailand.

Key words : smoking behavior, quitting smoking, international comparative study, socio-cultural analysis, education of smoking cessation, difficulty of quitting smoking

I. Introduction

Various types of large-scale clinical studies have shown effective prevention of lifestyle-related diseases and various types of cancer by smoking cessation[1~10]. WHO also proposed health education in smoking cessation as a first strategy[11]. Education of smoking cessation has diversified, and outpatient clinics for smoking cessation have been established in Asian countries[12~14] as well as in Western countries[14~18]. The prevalence of smoking among males in both Japan and Thailand, however, is approximately double that in Western countries[19]. In contrast, smoking among females in both Japan and Thailand is markedly less than in the West co, but has gradually been increasing in recent years[19].

It has been noted that the behavior and conduct of smoking and its cessation are influenced by social, ethical, cultural, religious, economic, educational, and other life-style factors[20~22]. In order to promote an effective education program for smoking cessation, relevant characteristic socio-cultural factors in Japan and Thailand must be clarified. For this purpose, we conducted the present comparative international socio-cultural study to examine the reason why it is difficult to quit smoking.

Five papers from international socio-cultural comparison studies for smoking have been published in the past five years. King et al.[23] researched differences in the smoking behavior of French and American women, while Bosanquet[24] investigated the

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smoking behavior of adolescents and young people in France and Spain. Cavelaars et al.[22] investigated international variations in smoking associated with educational levels in 12 European countries, and Baris et al.[25] surveyed priorities for tobacco control in developing countries through three meetings convened by Research for International Tobacco Control (RITC). Lastly, Steptoe et al.[26] reported an international comparison of tobacco smoking, beliefs and risk awareness in university students from 23 countries. However, none of these compared the socio-cultural factors in different countries using the same questionnaires for similar subjects on smoking habits and efforts made by individuals to quit smoking.

The present study is thus the first of its kind designed to clarify specific socio-cultural factors influencing the difficulties of smoking cessation conducted in both Japan and Thailand.

II. Methods

This international research project was designed by IO and SW in December 1999. The subjects and methods for both Japan and Thailand surveys were planned to be the same to make the comparison of results for the two countries epidemiologically valid.

Preparing the questionnaires

The questionnaires were prepared carefully and agreed upon by ethics committees at both universities. The original questionnaire was written in English and translated into Japanese and Thai. It consisted of 17 questions covering: sex, age group, smoking history group, efforts made in order to lead a healthy life, source of information on health, family members who smoke, age when started smoking, reasons for smoking and/or quitting smoking, number of cigarettes smoked per day, reason for still smoking, knowledge about terms "primary smoke" or "secondary smoke", number of trials for smoking cessation, method used to give up smoking, symptoms during smoking cessation, issues which make one feel stress, method to relieve stress.

The questionnaire was anonymous and self-administered. Sixteen of 17 questions were of the multiple choice type. The question about family members who smoke was the multiple-response type which means the respondent could choose more than one answer if necessary.

Study Participants

The Japan survey was conducted in the Kenou district of Kanagawa Prefecture, about 100 km from Tokyo, and the Thailand survey in Suphanburi province, about 100 km from Bangkok. These two areas were selected as being similar because middle class inhabitants live near metropolitan areas. Kenou district includes 5 cities and 3 large villages, with a total population of 848,937 (437,279 males and 411,658 females). There are two university hospitals, one government hospital, three Kanagawa Prefecture hospitals and nine community hospitals. The survey was conducted at Atsugi Prefecture Hospital and Ebina General Hospital, the largest representative community hospitals in the cities of Atsugi and Ebina.

Suphanburi province has a total population of 853,313 (417,093 males and 436,220 females) and comprises 10 districts. There are a total of 9 government-owned hospitals in the province, including one provincial hospital and 8 community hospitals. The survey was conducted in 7 community hospitals.

In both countries the survey was conducted as follows. Survey specialists interviewed out-patients in the hospitals. These out-patients were there to see physicians in a variety of departments in each hospital surveyed. The subjects were sampled according to eight groups by sex and age (i.e., in their 20s, 30s, 40s, and 50s). Interviews were continued till the number of subjects in each age-sex-group reached approximately 100.

The subjects numbered 684 (331 males and 353 females) in Japan and 581 (293 males and 288 females) in Thailand.

Informed consent

Interviewers explained the purpose of the study and the questionnaires to the subjects in such a way so the subjects understood that they would receive unbiased treatment even if they decided not to respond to the questionnaire, and gained informed consent.

Statistical analysis

Based on the questionnaires, the subjects were divided into four groups: the never-smoking group (Group 1), the ex-smoking group (Group 2), the failed-to-quit group (Group 3) and the smoking group (Group 4). Therefore, the subjects of Group 3 and Group 4 were defined as current smokers. The answers to the questionnaire were analyzed at the Department of Community Health, Tokai University School of Medicine and the Asian Institute for Health Development, Mahidol University, independently, and the data were then combined.

Statistical analysis, comparing both Japanese and Thai data, was mainly conducted by the χ^2 test using Stat View 5.0 J and SPSS ver. 11.0 J at both universities. If a multiple-response was allowed in the questionnaire, we applied the χ^2 test for each response. When the result of the χ^2 test was significant for a single-response question, we calculated the adjusted residual to make a cell-by-cell compari-

son of observed and expected frequencies. The residual was given by the formula

$$R=\frac{O-E}{\sqrt{E}}$$

where "O" is observed frequency and "E" is expected frequency of the cell. The adjusted residual was defined by the formula

$$\frac{R}{\sqrt{Var(R)}}$$

where "Var(R)" is the variance of residual R. With a value for the adjusted residual is higher than 3, the difference in frequency between the two groups was considered significant for each response[27].

III. Results

Comparison of the 4 groups in Japan and Thailand

In Japan, there were 292 subjects (62 males and 230 females) in Group 1, 121 (76 males and 45 females) in Group 2, 105 (68 males and 37 females) in Group 3, and 166 (125 males and 41 females) in Group 4 (Table 1). In Thailand there were 246 subjects (37 males and 209 females) in Group 1, 66 (49 males and 17 females) in Group 2, 98 (77 males and 21 females) in Group 3, and 171 (130 males and 41 females) in Group 4.

For males, the percentage for the whole age Group 1 was higher in Japan than in Thailand (18.7% vs. 12.6%; $P<0.05$) as shown in Table 1. The age group values for Group 1 subjects ranged from 11.5% to 25.8%, and the younger generation showed a higher percentage compared that for those in aged 40 and more in Japan. In Thailand this tendency was more remarkable, that is, the 26.1% for those in their 20s was the highest in Group 1.

The age group values for Group 2 subjects in Japanese males ranged from 12.3% to 38.1%, the highest being 38.1% in the people in their 50s. In Thailand the values ranged from 13.0% to 20.0%, and, and the percentage in their 50s (20.0%) was lower than in Japan.

Regarding values for Group 3 males, Thai were higher than Japanese in the 20s and particularly 30s (33.3% vs. 15.1%). The subjects of Group 4 in male Japanese ranged from 28.3% to 46.6%, the highest 46.6% were in their 20s. In contrast, the age groups of Group 4 in Thailand were 37.7% to 48.0%, and the lowest 37.7% in their 20s.

The prevalence of current smokers (Groups 3 and 4) in males overall was higher in Thailand than in Japan with statistical significance (70.3% vs. 58.3%, $P<0.05$). There was also the case for those in their 30s and 50s in Thailand (81.3%, 68.0%) as compared to Japan (60.3%, 50.4%) with statistical significance ($P<0.05$, $P<0.01$), respectively.

For females, Thailand showed a higher percentage in Group 1 compared with Japan with statistical significance overall as well as for those in their 20s (72.6% vs. 65.2%, 75.0% vs. 49.4%). The age group values for Group 2 female subjects ranged from 6.4% to 17.9% in Japan and from 2.8% to 9.9% in Thailand, being higher for younger generation in Japan. The age group values for Group 3 female subjects ranged from 7.6% to 14.5% in Japan and from 6.8% to 8.5% in Thailand. As to Group 4 females, those in their 40s in Japan showed the lowest percentage (4.5%), much lower than that for Thailand (23.0%).

Although the female prevalence of current smokers overall was almost the same in the two countries, the highest prevalence was seen in those in their 20s in Japan (35%) but in their 40s in Thailand (29.8%).

Socio-cultural analysis of smoking habit formation (Tables 2 and 3 for male, the tables for females not shown)

Of the subjects (Groups 2, 3, and 4) 41.2% for males and 42.3% for females in Japan and 69.1% for males and 58.2% for females in Thailand started smoking at the age of 10–19 years. For males, Group 2 and Group 4 in Thailand started smoking at the age of 10–19 years more frequently while those in Japan started at the age of 20–29 years more frequently. For female, there was no significant difference between the country.

Smokers started most frequently "out of curiosity" in both Japan and Thailand. In Thailand, "on someone's recommendation" was also often observed for both males and females. The reason they still smoked was most frequently "out of habit" in both countries. For males "need to have something in the mouth" was also a frequent reply in Group 4 while for females "relaxation" and "need to have something in the mouth" were also frequent replies in Group 4 in Thailand (Table 2).

The number of cigarettes smoked by current smokers per day was 12.5 ± 8.7 for males and 7.5 ± 4.2 for females in Thailand but 20.9 ± 10.0 for males and 15.2 ± 7.9 for females in Japan (Table 2).

In Groups 2, 3, and 4 overall, 55.0% of males and 58.5% of females had at least one family member who smoked in Japan and 40.3% of males and 54.9% of females in Thailand. Especially in Japan, Group 1 and Group 4 males and Group 3 females had a family member who smoked more frequently with statistical significance. The family member who smoked was most frequently the "father" in both countries (Table 3). For males, "brother" was also frequent, especially in Group 3 and Group 4 with statistical significance in Thailand. For females, "husband" was more frequent in Japan than in

Table 1. Numbers of subjects enrolled in the present study

		Male			Female		
		Japan	Thailand	Absolute value for adjusted residual	Japan	Thailand	Absolute value for adjusted residual
Whole age			*			**	
	Group 1 (Never-smoking)	62(18.7)	37(12.6)	2.1	230(65.2)	209(72.6)	2.0
	Group 2 (Ex-smoking)	76(23.0)	49(16.7)	1.9	45(12.7)	17(5.9)	2.9
	Group 3 (Failed-to-quit)	68(20.5)	77(26.3)	1.7	37(10.5)	21(7.3)	1.4
	Group 4 (Smoking)	125(37.8)	130(44.0)	1.7	41(11.6)	41(14.2)	1.0
	Total	331(100)	293(100)		353(100)	288(100)	
	Group 3+Group 4 (Current Smoker)		*			N.S.	
		193(58.3)	207(70.3)		78(22.1)	62(21.5)	
20–29 years			N.S.			**	
	Group 1 (Never-smoking)	16(21.9)	18(26.1)	—	41(49.4)	54(75.0)	3.3
	Group 2 (Ex-smoking)	9(12.3)	9(13.0)	—	13(15.7)	2(2.8)	2.7
	Group 3 (Failed-to-quit)	14(19.2)	16(23.2)	—	12(14.5)	5(6.9)	1.5
	Group 4 (Smoking)	34(46.6)	26(37.7)	—	17(20.5)	11(15.3)	0.8
	Sub-total	73(100)	69(100)		83(100)	72(100)	
	Group 3+Group 4 (Current Smoker)		N.S.			*	
		48(65.8)	42(60.9)		29(35.0)	16(22.2)	
30–39 years			***			N.S.	
	Group 1 (Never-smoking)	24(25.8)	3(4.0)	3.8	54(56.8)	50(70.4)	—
	Group 2 (Ex-smoking)	13(14.0)	11(14.7)	0.1	17(17.9)	5(7.0)	—
	Group 3 (Failed-to-quit)	14(15.1)	25(33.3)	2.8	10(10.5)	6(8.5)	—
	Group 4 (Smoking)	42(45.2)	36(48.0)	0.4	14(14.7)	10(14.1)	—
	Sub-total	93(100)	75(100)		95(100)	71(100)	
	Group 3+Group 4 (Current Smoker)		*			N.S.	
		56(60.3)	61(81.3)		24(25.2)	16(22.6)	
40–49 years			N.S.			**	
	Group 1 (Never-smoking)	9(17.3)	7(9.5)	—	50(75.8)	49(66.2)	1.2
	Group 2 (Ex-smoking)	11(21.2)	14(18.9)	—	8(12.1)	3(4.1)	1.8
	Group 3 (Failed-to-quit)	15(28.8)	18(24.3)	—	5(7.6)	5(6.8)	0.2
	Group 4 (Smoking)	17(32.7)	35(47.3)	—	3(4.5)	17(23.0)	3.1
	Sub-total	52(100)	74(100)		66(100)	74(100)	
	Group 3+Group 4 (Current Smoker)		N.S.			*	
		32(61.5)	53(71.6)		8(12.1)	22(29.8)	
50–59 years			*			N.S.	
	Group 1 (Never-smoking)	13(11.5)	9(12.0)	0.1	85(78.0)	56(78.9)	—
	Group 2 (Ex-smoking)	43(38.1)	15(20.0)	2.6	7(6.4)	7(9.9)	—
	Group 3 (Failed-to-quit)	25(22.1)	18(24.0)	0.3	10(9.2)	5(7.0)	—
	Group 4 (Smoking)	32(28.3)	33(44.0)	2.2	7(6.4)	3(4.2)	—
	Sub-total	113(100)	75(100)		109(100)	71(100)	
	Group 3+Group 4 (Current Smoker)		**			N.S.	
		57(50.4)	51(68.0)		17(15.6)	8(11.2)	

( ): Percentage data. *: $P<0.05$, **: $P<0.01$, ***: <0.001 significant by the chi-square test. N.S.: not significant.

Table 2. Socio-cultural analysis of the smoking habit (males in Groups 2, 3 and 4)

	Japan				Thailand			
	Group 2 (N=76) Ex-smoking	Group 3 (N=68) Failed-to-quit	Group 4 (N=125) Smoking	Total (N=269)	Group 2 (N=49) Ex-smoking	Group 3 (N=77) Failed-to-quit	Group 4 (N=130) Smoking	Total (N=256)
Age when started smoking (%)								
10–19 years	26.3(−5.4)	42.5	49.6(−2.8)	41.2	75.6(5.4)	68.8	66.9(2.8)	69.1
20–29 years	63.3(5.1)	54.5	46.4(2.6)	53.2	16.3(−5.1)	29.9	30.8(−2.6)	27.7
30–39 years	2.6(0.2)	1.5	2.4(1.0)	2.2	2.0(−0.2)	1.3	0.8(−1.0)	1.2
40–49 years	3.9(−0.6)	0.0	0(−1.4)	1.1	6.1(0.6)	0.0	1.5(1.4)	2.0
50– years	3.9(1.4)	1.5	1.6(2.0)	2.2	0.0(−1.4)	0.0	0.0(−2.0)	0.0
Reasons for starting smoking (%)								
Out of curiosity	38.3(−1.9)	36.8(−1.7)	46.4(−2.9)	41.7	55.1(1.9)	50.7(1.7)	63.7(2.9)	58.2
Those around you smoked	26.3(2.2)	14.7(−0.6)	20(0.8)	20.4	10.2(−2.2)	18.2(0.6)	16.1(−0.8)	15.6
No particular reason	28.9(2.8)	42.6(5.1)	29.6(3.7)	32.7	8.2(−2.8)	6.5(−5.1)	10.8(−3.7)	9.0
On someone's recommendation	3.9(−3.2)	1.5(−3.3)	0.8(−2.5)	1.9	22.4(3.2)	18.2(3.3)	6.9(2.5)	13.3
Other	2.6(−0.4)	4.4(0.5)	3.2(0.9)	3.3	4.1(0.4)	6.5(−0.5)	1.5(−0.9)	3.5
Number of cigarettes smoked on average per day								
Mean	20.5	20.0	21.5	20.9	14.4	8.4	14.2	12.5
Standard deviation	9.7	11.5	9.4	10.0	12.1	7.2	8.8	8.7
Proportion of smokers in each category (%)								
0–5 cigarettes	13.2(−2.6)	5.9(−5.0)	3.2(−2.4)	6.7	32.7(2.6)	41.6(5.0)	10.8(2.4)	24.1
6–10 cigarettes	21.1(0.4)	17.6(−3.5)	17.6(−4.3)	18.5	18.3(−0.4)	45.5(3.5)	42.3(4.3)	38.7
10–15 cigarettes	10.5(0.8)	22.1(4.0)	9.6(0.1)	13.0	6.1(−0.8)	1.3(−4.0)	9.2(−0.1)	6.3
16–20 cigarettes	28.9(−0.4)	35.3(3.8)	35.2(0.5)	33.5	32.7(0.4)	9.1(−3.8)	32.3(−0.5)	25.4
more than 20 cigarettes	26.3(2.2)	19.1(3.2)	34.4(5.8)	28.3	10.2(−2.2)	2.6(−3.2)	5.4(−5.8)	5.5
Reason why still smokes (%)				(N=193)				(N=207)
Relaxation	—	35.3	36.0	35.8	—	28.6	28.5	28.5
Out of habit	—	48.5	50.4	49.7	—	41.6	44.6	43.5
Need to have something in the mouth	—	14.7	12.0	13	—	18.2	24.6	22.2
Other	—	1.5	1.6	1.6	—	11.6	2.3	5.8
Terms "primary smoke" or "secondary smoke" (%)								
Have heard and understand both terms	39.5(1.5)	36.8	34.4(1.9)	36.4	26.5(−1.5)	33.8	23.8(−1.9)	27.3
Have heard both terms but don't know meaning	22.2(2.1)	22.1	12.8(2.1)	17.8	8.2(−2.1)	9.1	5.4(−2.1)	7.0
Have heard only one term	0.0(−3.1)	4.3	4.8(0.4)	3.3	12.2(3.1)	2.6	3.8(−0.4)	5.1
Have heard of neither term	38.3(−1.6)	36.8	48.0(−3.1)	42.4	53.1(1.6)	54.5	66.8(3.1)	60.6
Reason for thinking about smoking cessation			(N=93)	(N=237)			(N=91)	(N=217)
Awareness of the harmful effects of smoking	40.8	41.2	51.6(3.8)	39.8	49.0	32.5	24.2(−3.8)	32.7
Feeling ill	38.3	41.2	24.7(0.4)	29.7	24.5	36.3	22.0(−0.4)	27.6
Money was tight	3.9	7.3	3.2(−1.6)	4.1	0.0	6.5	8.8(1.6)	6.0
Being told by those around	7.8	3.0	10.8(−1.7)	6.7	12.2	13.0	19.8(1.7)	15.7
Those around gave up smoking	0.0	0.0	1.1(−0.6)	0.4	2.1	5.2	2.2(0.6)	3.2
Other reasons	9.2	7.3	8.6(−2.7)	7.4	12.2	6.5	23.0(2.7)	14.7

All data are percentages. ( ): adjusted residual.

Variables for each question were compared between the smoking groups in both countries by the chi-square test

*: $P<0.05$, **: $P<0.01$, ***: $P<0.001$ significant by the chi-square test.

†: subjects who have tried to quit smoking or who have considered it.

Table 3. Efforts to improve health and environmental conditions in the four groups (males)

	Japan					Thailand				
	Group 1 (N=62) Never-smoking	Group 2 (N=76) Ex-smoking	Group 3 (N=68) Failed-to-quit	Group 4 (N=125) Smoking	Total (N=331)	Group 1 (N=37) Never-smoking	Group 2 (N=49) Ex-smoking	Group 3 (N=77) Failed-to-quit	Group 4 (N=130) Smoking	Total (N=293)
Efforts made in order to lead a healthy life										
Living environment	9.7	9.2(1.6)	1.5	4.8(−2.1)	6.0	5.4	2.0(−1.6)	7.8	12.3(2.1)	9.6
Daily diet	24.2	26.4(−1.9)	19.2	26.4(−1.8)	24.5	16.2	43.0(1.9)	29.8	36.9(1.8)	33.4
No smoking	9.7	17.1(2.6)	2.9	3.2(2.1)	7.6	16.2	2.0(−2.6)	2.6	0.0(−2.1)	3.4
Avoiding alcoholic beverages	3.2	2.6(−0.4)	4.4	2.4(−1.2)	3.0	2.7	4.1(0.4)	6.5	5.4(1.2)	5.7
Exercise	24.2	18.4(0.9)	23.5	16.0(1.4)	19.6	29.8	12.2(−0.9)	13.0	10.0(−1.4)	15.3
Stress avoidance	9.7	9.2(0.6)	11.8	16.0(2.1)	12.4	5.4	6.1(−0.6)	3.9	7.7(−2.1)	6.9
Rest	9.7	5.3(−2.0)	8.8	11.2(0.1)	9.1	5.4	16.3(2.0)	15.6	10.8(−0.1)	13.8
Sleep	6.4	11.8(0.7)	23.5	16.0(2.5)	14.8	2.7	8.0(−0.7)	11.7	6.2(−2.5)	7.5
Other	0.0	0.0(−1.8)	0.0	0.0(−1.4)	0.0	8.1	4.1(1.8)	2.6	1.5(1.4)	3.1
None of the above	3.2	0.0(−1.3)	4.4	4.0(−1.7)	3.0	8.1	2.0(1.3)	6.5	9.2(1.7)	7.2
Source of information on health										
Media	80.6	80.3	76.5	83.2	80.7	91.9	71.5	76.6	82.3	80.2
Government administrative bodies	0.0	0.0	2.9	0.0	0.6	0.0	4.1	2.6	3.1	2.7
School/Workplace	12.9	2.6	5.9	5.6	6.3	2.7	2.0	0.0	3.1	2.0
Medical organizations	6.5	17.1	14.7	11.2	12.4	5.4	22.4	18.2	9.2	13.4
Other	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
None of the above	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.6	2.3	1.7
Family smoking										
No	24.2	57.9	48.5	45.6	45.0	59.5	73.5	51.9	59.2	59.7
Yes	75.8	42.1	51.5	54.4	55.0	40.5	26.5	48.1	40.8	40.3
Family member who smokes† (multiple-responses allowed)										
Father	31.9	37.5	45.7(−0.5)	42.6(0.9)	39.6	86.7	53.8	62.2(0.5)	62.3(−0.9)	64.4
Mother	6.4	9.4	11.4(1.1)	13.2(3.2)	10.4	6.7	7.7	5.4(−1.1)	1.9(−3.2)	4.2
Brother and sister	19.1	28.1	28.6(−2.2)	30.9(−4.0)	26.9	20.0	38.5	64.9(2.2)	45.3(4.0)	47.5
Grandfather	0.0	0.0	2.9(−0.8)	2.9(−0.8)	1.6	0.0	7.7	8.1(0.8)	9.4(0.8)	7.6
Grandmother	0.0	0.0	0.0(−0.9)	0.0(−1.2)	0.0	0.0	7.7	2.7(0.1)	3.8(1.2)	3.4
Husband/Wife	19.1	12.5	28.6(3.8)	11.8(2.1)	17.0	0.0	0.0	0.0(−3.8)	5.7(−2.1)	2.5
Children	14.9	9.4	2.9(1.1)	10.3(0.6)	9.9	6.7	15.4	0.0(−1.1)	13.2(−0.6)	8.5
Other	0.0	0.0	0.0(0.0)	0.0(−1.2)	0.0	0.0	0.0	0.0(0.0)	3.8(1.2)	1.7

All data are percentages. ( ): adjusted residual.

Variables for each question were compared between the smoking groups in both countries by the chi-square test

*: $P<0.05$, **: $P<0.01$, ***: $P<0.001$ significant by the chi-square test. †: N=182 in Japan, 118 in Thailand.

Table 4. Socio-cultural analysis of failure to quit smoking (males)

	Japan			Thailand		
	Group 2 (N=76) Ex-smoking	Group 3 (N=68) Failed-to-quit	Total (N=144)	Group 2 (N=49) Ex-smoking	Group 3 (N=77) Failed-to-quit	Total (N=126)
Number of attempts for smoking cessation		***				
1 time	22.4(−5.4)	30.9	26.4	71.5(5.4)	26.0	43.6
2 times	35.5(2.9)	25.0	30.6	12.2(−2.9)	31.2	23.8
3 times	18.4(0.9)	25.0	21.5	12.2(−0.9)	18.2	15.9
more than 3 times	23.7(2.9)	19.1	21.5	4.1(−2.9)	24.6	16.7
Method to give up smoking				**		
Sheer will power	65.9	29.4(−1.5)	48.6	63.2	41.5(1.5)	50.0
Chewing gum or sweets	19.7	41.2(1.3)	29.8	18.4	31.2(−1.3)	26.2
Exercise	2.6	1.5(−3.1)	2.1	4.1	16.9(3.1)	11.9
Drinking water	3.9	7.3(1.3)	5.6	8.2	2.6(−1.3)	4.8
Breathing deeply	1.3	1.5(0.1)	1.4	0.0	1.3(−0.1)	0.8
Other methods	6.6	9.1(2.3)	12.5	6.1	6.5(−2.3)	6.3
Symptoms during smoking cessation				**		
No particular symptoms	34.3	16.2(−0.5)	25.7	24.5	19.5(0.5)	21.4
Easily irritated	22.4	54.3(3.2)	37.4	38.8	28.5(−3.2)	32.6
Easily lose temper	7.9	4.4(−1.8)	6.3	18.4	13.0(1.8)	15.1
Loss of concentration	3.9	11.8(1.1)	7.6	4.1	6.5(−1.1)	5.6
Increased appetite	19.7	8.8(0.5)	14.6	6.1	6.5(−0.5)	6.3
Physically and mentally drained	2.6	1.5(0.1)	2.1	2.0	1.3(−0.1)	1.6
Increased anxiety	3.9	1.5(−2.4)	2.8	0.0	11.7(2.4)	7.1
Other symptoms	5.3	1.5(−2.6)	3.5	6.1	13.0(2.6)	10.3

All data are percentages. ( ): adjusted residual.
Variables for each question were compared between the smoking groups in both countries by the chi-square test
**: $P<0.01$, ***: $P<0.001$ significant by the chi-square test

Thailand.

Socio-cultural analysis of failure to quit smoking (Tables 2, 3 and 4 for males, tables for females not shown)

Among various efforts made in order to lead a healthy life, "daily diet" ranked first in all age groups for both genders in both countries, and more significantly in Thailand. In Japan, "sleep" was higher in Group 4 for males and in Group 1 for females, while "stress avoidance" and "sleep" were higher in Group 3 for females (Table 3).

In both countries, an overwhelming number of subjects obtained health information from the "media" (Table 3). More than 50% of the subjects in Japan knew or understood the terms "primary smoke" and "secondary smoke," but 60.6% of males and 70.9% of females in Thailand had never heard either term (Table 2). Especially males in Groups 1 and 4 had heard neither more frequently in Thailand than in Japan, with statistical significance.

The number of attempts at smoking cessation tended to be higher in Japan for both genders (Table 4), particularly in Group 2 for males and in Group 3 for females, with statistical significance.

The reason for thinking about quitting was often "awareness of the harmful effects of smoking" for males in both countries, especially in Group 4 in Japan with statistical significance ($P<0.001$) (Table 2). In contrast, "feeling ill" was often for females in both countries, especially in Group 4 in Japan. In Thailand, "being told by those around" was also often observed for both genders.

The method of quitting smoking was most frequently "sheer will power (suppress the urge to smoke)" in Group 2 for both genders in both countries (Table 4). In Group 3, "chewing gum or sweets" was selected frequently for both genders in Japan, and for female Thailand subjects who needed to have something in the mouth. Only few subjects used nicotine replacement therapy in both countries.

Concerning symptoms during smoking cessation, in Group 3, "easily irritated" was frequently noted for both genders in both countries. On the

Table 5. Participant's stress and means of stress relief in the four groups (males)

	Japan					Thailand				
	Group 1 (N=62) Never-smoking	Group 2 (N=76) Ex-smoking	Group 3 (N=68) Failed-to-quit	Group 4 (N=125) Smoking	Total (N=331)	Group 1 (N=37) Never-smoking	Group 2 (N=49) Ex-smoking	Group 3 (N=77) Failed-to-quit	Group 4 (N=130) Smoking	Total (N=293)
Issues which make one feel stress										
Social issues	72.5(2.9)	69.7(5.4)	70.6(5.2)	80.0(10.6)	74.3	43.2(−2.9)	20.4(−5.4)	27.3(−5.2)	13.8(−10.6)	22.2
Financial matters	9.7(−3.6)	7.9(−4.6)	7.4(−3.7)	8.0(−6.2)	8.2	40.5(3.6)	42.9(4.6)	32.4(3.7)	41.5(6.2)	39.3
Study	3.2(1.1)	1.3(0.8)	4.4(1.1)	0.8(0.0)	2.1	0.0(−1.1)	0.0(−0.8)	1.3(−1.1)	0.8(0.0)	0.7
Romantic issues	0.0(0.0)	3.9(1.4)	0.0(−0.9)	0.8(−1.0)	1.2	0.0(0.0)	0.0(−1.4)	1.3(0.9)	2.3(1.0)	1.4
Domestic issues	8.1(0.0)	13.2(−2.1)	17.6(−1.4)	9.6(−5.4)	11.8	8.1(0.0)	28.6(2.1)	27.3(1.4)	38.5(5.4)	30.0
Health problems	0.0(−1.8)	0.0(−1.3)	0.0(−0.9)	0.0(−1.0)	0.0	5.4(1.8)	2.0(1.3)	1.3(0.9)	0.8(1.0)	1.7
Other situations	6.5(1.6)	3.9(0.6)	0.0(0.0)	0.8(1.0)	2.4	0.0(−1.6)	2.0(−0.6)	0.0(0.0)	0.0(−2.3)	0.3
Never feel stress	0.0(−1.3)	0.0(−1.8)	0.0(−2.5)	0.0(−1.7)	0.0	2.7(1.3)	4.1(1.8)	9.1(2.5)	2.3(2.1)	4.4
Means of stress relief										
Work	4.8(−2.2)	3.9(−4.4)	8.8(−4.2)	1.6(−6.2)	4.0	18.9(2.2)	32.7(4.4)	39.0(4.4)	30.0(6.2)	31.3
Hobbies	46.8(2.8)	36.8(2.2)	39.7(3.1)	46.4(3.9)	42.9	18.9(−2.8)	18.3(−2.2)	16.8(−3.9)	23.0(−3.9)	20.2
Sports	27.4(0.0)	23.7(1.0)	20.6(2.5)	14.4(1.5)	20.3	27.0(0.0)	16.3(−1.0)	6.5(−1.5)	8.5(−1.5)	11.6
Alcohol	9.7(0.8)	11.8(1.5)	22.1(2.2)	20.8(0.8)	16.9	5.4(−0.8)	4.1(−1.5)	9.1(−0.8)	16.9(−0.8)	11.3
Smoking	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.8(−1.6)	0.3	0.0(0.0)	0.0(0.0)	0.0(1.6)	3.9(1.6)	1.7
Karaoke or listening to music	6.5(1.6)	3.9(0.0)	5.9(2.2)	8.8(2.3)	6.6	0.0(−1.6)	4.1(0.0)	0.0(−2.3)	2.3(−2.3)	1.7
Other methods	4.8(−3.4)	19.7(−0.6)	2.9(−4.1)	7.2(−2.1)	8.8	29.7(3.4)	24.5(0.6)	28.6(2.1)	15.4(2.1)	22.2

All data are percentages. ( ): adjusted residual.

Variables for each question were compared between the smoking groups in both countries by the chi-square test

**: $P<0.01$, ***: $P<0.001$ significant by the chi-square test.

other hand, the answer "no particular symptoms" was frequent in Group 2 for both genders in Japan and for females in Thailand (Table 4).

Regarding smoking and stress as well as the relation of success or failure of quitting smoking and stress, "social issues" caused stress significantly more often in Japan, and "financial matters" caused stress significantly more often for both genders, but especially for males, in Thailand (Table 5).

The means for relieving stress was most frequently "hobbies," followed in order by "sports," "alcohol" for both genders in Japan, while in Thailand "work," and "hobbies" were answered. In Thailand, "sports" and "alcohol" were also seen for males and "karaoke" for females. No special means of stress relief, however, were observed in relation to the success or failure of quitting smoking.

IV. Discussion

There are many barriers to be overcome in international comparative studies. The authors designed this project in detail to make a valid comparison possible. The first requirement is appropriate selection of the subjects of the survey in both countries. We could not confirm the validity of the comparison between two countries directly from this survey, but by using the same questionnaires and setting a similar situation for the subjects, most obvious criteria were met.

The present study showed that (1) current smokers were numerous overall, and in the population in their 30s and 50s in Thai male subjects, (2) the proportion of ex-smokers was higher overall and Japanese male subjects in their 50s, and (3) the proportion of unsuccessful subjects (Group 3) was higher overall, and in Thai males in their 30s and 50s as shown in Table 1. For females, the proportions of current smokers were almost the same between the two countries, and Group 1 was higher in whole age, 20s, and 40s of Thailand subjects.

Based on data reported by Japan Tobacco Inc. (JT), the prevalence of smoking in Japan in 2000 was 53.5% for males and 13.7% for females[19]. In Thailand, data in 1999 showed a prevalence of smoking of 38.9% for males and 2.4% for females (total, 20.5%)[28]. In the present study, the prevalence of smoking for both males and females in the present study was higher than the reported data described above in both countries and this may reflect the fact that the subjects were outpatients in hospitals.

In Thailand, the subjects often had a male family member who smoked, which is consistent with the higher prevalence of current smoker in the males and the low prevalence of current smoker in the females in this country. In Japan, evaluation according to the four smoking history groups showed a high percentage of subjects with a family member who smoked in Group 3. In Group 3, family members had smoked, providing an environment that readily allows smoking on the part of the subject. The number of cigarettes smoked per day based on the JT data is 8.9, which markedly different from the number observed in this study. This may also be due to the selection bias of the survey, having been conducted at hospitals.

Smoking starts often at a low age in Thailand. Supawomgse and Buasai[29] reported that 35.7% of 15-year-old males and 9.3% of 15-year-old females have smoking experience. As the motive for smoking or quitting in Thailand, "recommended by others around" was observed relatively often. The reason for the more marked influence of the actions and words by persons close to the subject on behavior in Thailand than in Japan is unclear, but it is possible that the effects of education on smoking cessation spread more easily in Thailand.

The present survey also showed that 87% of smokers considered quitting smoking. Many understood the harmful effects of smoking but did not attempt to quit smoking unless actual effects on health were observed. Concerning methods of quitting smoking, the subjects tended to only suppress the urge to smoke by will power without employing special measures. Kawakami et al.[30] surveyed the characteristics of ex-smokers and found these to include a low number of cigarettes smoked per day, short smoking years, low frequency of smoking, slight psychological withdrawal symptoms, knowledge of the adverse effects on fetuses, positive attitude to smoking restrictions in the workplace, history of many disorders, clerical work, presence of time to spare in private life, consumption of a lot of vegetables, and frequent exercise. In the present study, subjects of Group 2 generally could give up smoking with sheer will power. Group 3 who could not succeed to quit smoking not frequently tried with sheer will power or chewing gum or sweets. From these results, it is recommended that nicotine replace therapy be a candidate for the method of smoking cessation for Group 3.

The causes of stress and means for its relief were have found to differ between the two countries. The results suggested a harder life and an environment in which leisure time is difficult to obtain in Thailand. In Japan, the recent economic recession is not so serious as to make living hard, and many still have time to enjoy leisure.

These results should be re-confirmed in further studies, because the proportion of subjects was strati-

fied with gender and smoking history, but not with age-group in this study.

In Thailand, there are many health warnings on cigarette packages such as "tobacco may cause lung cancer," "tobacco may cause heart disease," "tobacco may cause weakening of sexual prowess," etc. Advertising of tobacco products in TV commercials is also banned and on TV programs and in movie theaters in Thailand, the images of people smoking are blurred over. Many restaurants separate smoking seats and no-smoking seats in Japan as well as in Thailand, but in Thailand there are more no-smoking seats than smoking seats. Japan requires more strategies to quit smoking in daily life, for example, eliminating TV commercials, providing stronger warnings of the harmful effects of tobacco on health on cigarette packages, and blurring images of smoking on TV programs because the smoking rate among the younger generation is on the rise and is more serious in Japan than in Thailand.

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解説

診療ガイドラインおよびMindsにおける医学文献の評価選定基準について

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Morizane T. (Department of Medicine, Kanagawa Dental College, 82 Inaokacho, Yokosuka, Kanagawa 238-8580, Japan) Evaluation criteria for selecting clinical studies for developing clinical practice guidelines and the Medical Information Network Distribution Service (Minds). *Igaku Toshokan* 2004;51(1):51-56

Clinical practice guidelines have been developed by official organizations to help healthcare workers with clinical decision-making. The use of these guidelines is expected to improve patients' outcomes. Critical appraisal of the clinical studies used to form a knowledge base is a crucial step in the process of developing guidelines. The quality of evidence depends on the study design, with randomized controlled trials providing the most reliable evidence. A meta-analysis of randomized controlled trials can reduce the chance of a statistical error and provides better evidence than a single trial. Only randomized controlled trials can provide a definite answer as to whether a specific intervention can improve the outcomes with clinical relevance. Evidence based on non-randomized clinical trials is weaker than that provided by randomized controlled trials. A hierarchical evaluation system according to study design, with meta-analyses at the top and experts' opinions at the bottom, has been used to determine the strength of recommendations. However, even randomized controlled trials are not immune to various biases. A more precise and detailed evaluation method for selecting clinical studies that are meaningful, valid, reliable, and relevant is needed. The Japan Council for Quality Health Care has developed the Medical Information Network Distribution Service (Minds) for Japanese. healthcare workers and the public. An evaluation system for this service is currently under development.

key words : Practice Guideline, Medical Information Network Distribution Service, Minds, Critical Appraisal, EBM, Evidence-based Medicine, Study Design

I. 診療ガイドラインとは

診療ガイドラインは通常学会・当局などの公的機関により組織された委員会によって作成される。目的は医師や他の医療ケア供給者の行う診療における意思決定や患者の意思決定を支援することである。たとえば英国の診療ガイドライン作成を行う中心的機関であるNICE (National Institute for Clinical Excellence)[1]では「診療ガイドラインは入手可能な最良のエビデンスを基盤として保健医療専門家による個々人のケアに関する推奨の記述である。診療ガイドラインは保健医療専門家の実践を援助はするがその知識や技術の代わりになるものではない。優れた診療ガイドラインは保健医療のプロセスを変えそのアウトカムを改善することができる」と述べている。

作成の過程は 1）臨床上の問題点（クリニカルクエスチョン）の特定と現在の診療の明確化 2）包括的な文献検索 3）論文の批判的吟味 4）エビデンスレベルの判定 5）クリニカルクエスチョンごとのまとめの作成 6）勧告（または推奨）作成とその強さの設定である[2][3]。このように診療ガイドラインはEvidence-based medicine (EBM)の手法に則ってこうすべきであるという勧告を作成し集めたものである。

診療ガイドラインの評価法としてShaneyfeltら[4]のチェックリストやAGREEの方法[5]が考案されている。なおAGREEは診療ガイドライン評価の国際的統一基準をめざして2001年にThe AGREE Collaboration[6]により作成された。AGREEのチェックリストの中には「ガイドライン作成グループは関連したすべての職業グループからの参加者を含んでいる」「患者の見方や嗜好が調査されている」といった項目が含まれている。わが国ではまだ実現していないがガイドライン作成委員会には患者・介護者の代表やコメディカルの代表，企業の代表も参加が求められることになる。英国の診療ガイドライン作成機関であるNICEのガイドライン開発プロセス[1]の中の診療ガイドラインの基本原則にも同様のこと

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表1. NICEの診療ガイドラインの基本原則

診療ガイドラインは：
• 臨床ケアの質の改善を目的とすべきである
• 治療法や管理法の臨床的有効性に取り組むべきである（すなわちそれらがどれだけ有効か）
• 治療法や管理法の費用対効果に取り組むべきである（すなわちそれらがコストに比してどれだけ有効か）
• 助言的であるべきである
• 当該ガイドラインの影響を受ける可能性のあるすべての人を考慮に入れたプロセスによって開発すべきである（通常は保健医療専門家，患者とその介護者，保健医療サービス管理者，より広範な一般市民，政府，保健医療産業をふくめる）
• 可能な限り最良のエビデンスおよび専門家のコンセンサスを基盤にすべきである
• 患者，National Health Service (NHS)，NHS stakeholdersが敬意を払うような方法によって開発すべきである
• 患者および保健医療専門家の参加の下に開発すべきである
• イングランドとウェールズのNHSにおいて合理的に予想しうる臨床ケアを提示すべきである

がうたわれている（表1）。

II. 研究デザインによる医学文献の評価

ガイドライン作成の過程ではそれぞれの論文の研究デザインに基づいてエビデンスレベルを決めエビデンスレベルに応じて勧告の強さを決める事が行われている。広く用いられているのが表2-Aに示すものあるいはこれに準じたものである。NICEで用いられている分類もこれと同じである。わが国で厚生労働省厚生科学研究費を用いて作成されたさまざまな診療ガイドラインでもほぼ同様の分類が用いられた（表2-B）。

臨床医学研究の評価はその研究結果が臨床の現場で用いられた場合に患者にベネフィットがもたらされるかどうかによって評価されるべきである。ベネフィットがあるということは患者にとって意味のあるアウトカムが改善することである。患者にとって意味のあるアウトカムとは 1）症状の改善 2）健康関連QOL（Quality of life生活の質）の改善 3）再発の抑制 4）生存の延長 5）発症の抑制 6）感染の防御などである。検査成績など臨床パラメータの改善はその改善がこれらアウトカムの改善と相関していることが証明される必要がある。

多くの場合症例対照研究あるいはコホート研究によって危険因子や病因が明らかにされる。そして病因や危険因子を制御することすなわち介入によって患者にとって意味のあるアウトカムが改善するかどうかが証明された時点で患者にベネフィットをもたらす方法が明らかにされる。これを確実に証明する研究デザインはランダム化比較試験である。言い換えると介入の効果を証明するゴールドスタンダードは正しく行なわれたランダム化比較試験である。したがってその結果が患者にベネフィットをもたらしうる医学研究の主なものはランダム化比較試験といっても差し支えない。さらにランダム化比較試験は介入を加える群とそうでない対照群はランダム割り付けによって作成されるので介入以外の点で差のない2群を比較することが出来る。したがってアウトカムに統計学的に有意な差が認められた場合にはその差が介入によってもたらされたものであることが確実に証明される。このように正しく行なわれたランダム化比較試験の結果は妥当性が高いということと患者へベネフィットをもたらす方法を確実に証明できるということが上記のエビデンスレベルの決め方の根底にある。しかしランダム化比較試験にともなう主要なバイアスとして 1）選択バイアス 2）実行バイアス 3）症例減少バイアス 4）検出バイアスが存在しランダム化比較試験でもさまざまな質

表2-B. 日本の診療ガイドラインで用いられてきたエビデンスレベルの分類

レベル	研究デザイン
I	システマティックレビュー/メタアナリシス
II	1つ以上のランダム化比較試験（RCT）
III	非ランダム化比較試験（CCT）
IV	分析疫学的研究（コホート研究や症例対照研究）
V	記述的研究（症例報告やケースシリーズ）
VI	患者データに基づかない専門委員会や専門家個人の意見

表2-A. 研究デザインによるエビデンスレベルの分類*

レベル	研究デザイン
Ia	複数のランダム化比較試験のメタアナリシスによる
Ib	少なくとも1つの，ランダム化比較試験による
IIa	少なくとも1つの，よくデザインされた非ランダム化比較試験による
IIb	少なくとも1つの，他のタイプのよくデザインされた準実験的研究による
III	比較研究や相関研究，症例対照研究など，よくデザインされた観察的研究による
IV	専門委員会の報告や意見，あるいは権威者の臨床経験

*Agency for Health Care Policy and Research (AHCPR)，現Agency for Health Quality and Research (AHQR)による分類。コホート研究はIIIに分類。

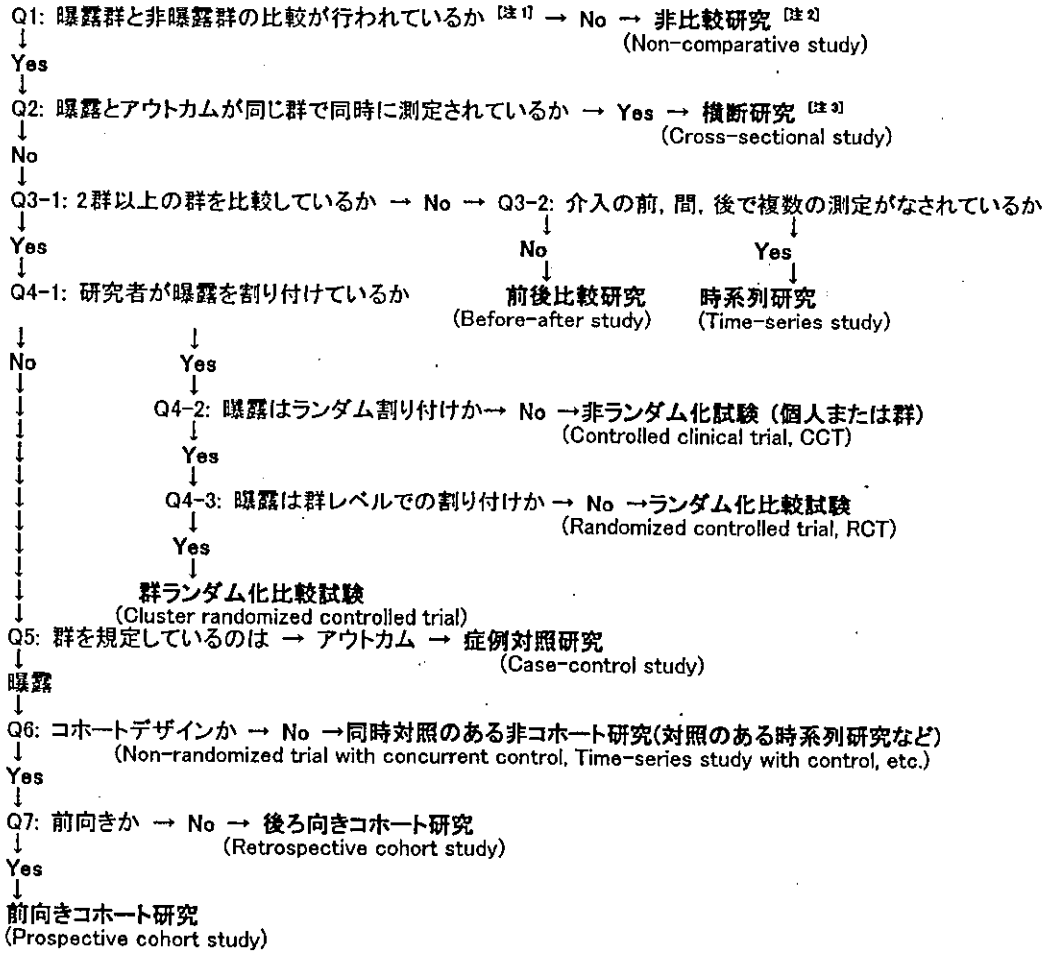
のものがあることに注意しなければならない。

さらに複数のランダム化比較試験をメタアナリシスによって統計学的に統合することによってより妥当性の高い結果を得ることが出来る。サンプルサイズが大きくなるため統計学的検出力が高くなりエフェクトサイズが改善さればらつきの小さい効果指標の値が得られる。

非ランダム化比較試験は対照の設定がランダム割付ではなく適当に割り当てられた同時対照であったり過去の症例を対照としたりするため観察された介入の効果が介入以外の因子によるものである可能性を完全に否定することが難しいことが多い。しかし倫理的にランダム化比較試験が困難なことも多く介入の効果を証明するための研究である点からランダム化比較試験の下ではあるがコホート研究や症例対照研究の上に位置づけられている。

症例対照研究は後ろ向き研究であり，ある疾患/病態といったアウトカムを持つ群とそれを持たない群で背景因子をマッチングさせ過去にさかのぼって危険因子への曝露の割合を比較する研究デザインである。コホート研

図1．Study Design Algorithm



[注1] 曝露とは危険因子への曝露と介入 Intervention との両方を意味している。また，1つの群で曝露前とその後でアウトカムを測定している場合には，曝露前を自己対照と考えることもできるので，Yes を選択する。

[注2] 非比較研究 Non-comparative study は記述的研究 Descriptive Study と同じ意味で用いられている。

[注3] この横断研究は危険因子とアウトカムの間の関連を分析して，因果関係などを明らかにすることを目的とする研究のことである。単に，陽性率などを記述するだけの研究は非比較研究に含める。

究は前向き研究であり危険因子に曝露した群と非曝露群（コホート）を経過観察し疾患/病態といったアウトカムの発生率を比較する研究デザインである。いずれも危険因子への曝露とアウトカムの間に相関が認められれば危険因子が同定されることになる。症例対照研究はすでに過去に起こったことを後で調査することになるので危険因子への曝露の観察が不完全になりやすいことと背景因子をマッチングさせた対照群の設定が難しくエビデンスレベルは前向き研究であるコホート研究よりは低いとされる。これら2つは介入が行なわれることは無いので観察研究とも呼ばれ主に危険因子の同定に用いられるが介入の効果を証明することに用いられることもある。

また診断に関する研究は横断研究として行なわれることが多くある時点でアウトカムと予知因子がほぼ同時に測定され疾患群でその因子の陽性率＝感度が高く対照群でその因子の陰性率＝特異度が高いことを証明する。この場合には疾患群の同定にはその時点での診断のゴールドスタンダードが用いられる。

このように医学文献の評価では研究デザインの同定が必ず必要であるがそのアルゴリズムを図1に示す[8]。ここで解説していないデザインについては文献を参照されたい[9]。

Ⅲ．より詳細な評価法

より詳細なエビデンスレベルの評価法[10]も可能である。臨床医学論文を評価するためのスコアシステムやチェックリストは現在まで少なくとも26個考案されている[11]。これらの評価法は互いに同じチェック項目を含んでいるがそれぞれ独自の項目も含んでおり評価の結果はかならずしも同じにはならない。それぞれの評価法を用いて質が高い論文と低い論文に分類しそれぞれでメタアナリシスを行った結果統合された効果指標の値と分類された論文の質の関係が同じではなく逆になるものも示されている[12]。すなわちこれらの評価法は同じ結果をもたらさない。Delphi法を用いたコンセンサスに基づき作成されたチェックリストとしてVerhagenら[13]のものがある。これは次のようなものでランダム化比較試験に適用されるが臨床疫学的見地の共通項とも言えるであろう。

1）治療割り付け
　1．ランダム化されているか
　2．コンシールメントが行なわれているか
2）最も重要な予後因子について群間に差が無いか
3）適格例の基準が決められているか
4）アウトカムの検査者は目隠しされているか

表3. 検索式の構成

項目		疾患/病態	予知因子（介入/曝露）	対照	アウトカム	研究デザイン
実際の語句		肝硬変において	βブロッカー投与	EVL	出血	ランダム化比較試験
文献検索	電子データベース	liver cirrhosis [mh]	adrenergic beta-antagonists [mh]	endoscopy, gastrointestinal [mh] AND(ligation [tw] OR ligate [tw] OR banding [tw] OR band [tw])	bleeding OR rupture	randomized controlled trial [pt]
	マニュアル検索	内科学消化器病学肝臓病学内視鏡に関する医学雑誌学会プロシーディングス書籍	内科学消化器病学肝臓病学内視鏡に関する医学雑誌学会プロシーディングス書籍			

*この例で実際にPubMedを検索する場合には次のような検索式を用いることができる。
liver cirrhosis [mh] AND adrenergic beta-antagonists [mh] AND endoscopy, gastrointestinal [mh] AND (ligation [tw] OR ligate [tw] OR banding [tw] OR band [tw]) AND (bleeding OR rupture) AND randomized controlled trial [pt]