generalized to other areas. The present study included no discussion of the relationships between alcohol consumption and depression and/or suicide. Further studies are required to evaluate the associations between how drinking alcohol facilitates conversation and outcomes of conversations in bar and *izakaya*-pub establishments, such as the effects on resolution of customers' problems and customers' health status. In addition, future assessments of the relations between alcoholism and frequenting bars and/or *izakaya*-pubs are necessary to determine the possible negative impacts of alcohol drink on customers' mental health status. The present study also did not directly target the customers of bar and *izakaya*-pub establishments. Therefore, it was not possible to discuss the detailed effects and outcomes on the customers after conversation with owners/managers, e.g., how many people avoided suicide, and the customers' intention to talk and consult with a professional regarding their personal/private problems. These points should also be investigated in future studies.

Despite these limitations, the study results indicated a potential for managers and owners of bars and *izakaya*-pubs, especially those with longer years of working experience, to play a role in assisting middle-aged and elderly men to seek professional mental care, by providing appropriate seminar and workshops on mental health, and building partnership with local governments and professional organizations.

Competing of interest

The authors declare that they have no competing interests.

Authors' contributions

MO was responsible for data analysis and for writing the manuscript. RN, RK and AN contributed to conceptualization of the study, data analysis, interpretations of the results and revisions of the draft manuscript. YH prepared the draft of the study proposal, and was responsible for data collection, and contributed to the writing of the manuscript. HN supervised conceptualization of the analytical framework, data analysis and writing of the manuscript. All authors read and approved the final manuscript.

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Impact of mental disorders on work performance in a community sample of workers in Japan: The World Mental Health Japan Survey 2002–2005

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ABSTRACT

Most studies that investigate the impact of mental disorders on work performance have been conducted in Western countries, but this study examines the impact of common mental disorders on sick leave and on-the-job work performance in a community sample of Japanese workers. Data from the World Mental Health Japan survey were analyzed. A subsample of 530 workers aged 20–60 years were interviewed using the WHO Composite International Diagnostic Interview 3.0. The WHO Health and Work Performance Questionnaire, was used to assess sick days and on-the-job work performance for the previous 30 days. Linear regression was used to estimate the impact of mental disorders on these indicators of work performance over 12 months. Mood disorders, including major depressive disorder, and alcohol abuse/dependence were significantly associated with decreased on-the-job performance. There were no significant associations between mental disorders and sick/absent days. Consistent with previous studies, major depression has a great impact on on-the-job work performance in Japan. The lost productivity was estimated at approximately 28–30 lost days per year. A similar decrease in on-the-job work performance was found for alcohol abuse/dependence, which is stronger than that in other countries, probably attributable to greater tolerance of problematic drinking at Japanese worksites.

1. Introduction

Mental disorders are known to be prevalent in the general population, and in the working population (Demyttenaere et al., 2004; Sanderson and Andrews, 2006), a factor that negatively affects life and role functions (Merikangas et al., 2007; Scott et al., 2009). Influences of mental disorders include loss of work productivity, which has been reported to create significant costs for the workplace (Greenberg et al., 2003; Stewart et al., 2003; Kessler et al., 2006). Estimating the impact of mental disorders on work productivity is important to set priorities and plan appropriate interventions for mental disorders in the workplace (Kessler et al., 2006; Loeppke et al., 2007). Work productivity losses consist of two components: absenteeism and presenteeism (Sanderson and Andrews, 2006). The former refers to the number of work days lost due to mental disorders; presenteeism refers to impaired work performance on the job, often described as extra effort days or work cutback days (i.e., work days with reduced work performance) or self-rated work performance (Kessler and Frank, 1997; Dewa and Lin, 2000; Lim et al., 2000; Kessler et al., 2006).

To date, five community-based epidemiologic studies have been conducted to measure the association between mental disorders and work productivity by using standardized diagnostic criteria, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) (Kessler and Frank, 1997; Dewa and Lin, 2000; Laitinen-Krispijn and Bijl, 2000; Lim et al., 2000; Kessler et al., 2006). Four of these studies were included in a systematic review by Sanderson and Andrews (2006). These studies demonstrated that major depression, bipolar disorders, and dysthymia were associated with increased absent days (Laitinen-Krispijn and Bijl, 2000; Lim et al., 2000; Kessler et al., 2006). One study reported an unexpected finding: any mood disorder was significantly associated with decreased absent days (Dewa and Lin, 2000). For anxiety disorders, only one study has reported that a simple phobia was associated with increased absent days among males (Laitinen-Krispijn and Bijl, 2000); otherwise, no statistically significant association has been found between anxiety disorders and absenteeism (Kessler and Frank, 1997; Dewa and Lin, 2000; Lim et al., 2000). Some studies have reported that alcohol dependence (Kessler et al., 2006) and substance or drug use disorder (Laitinen-Krispijn and Bijl, 2000; Kessler et al., 2006) were associated with increased absent days, but one study found no statistically significant association between alcohol or substance use disorders and absent days (Lim et al., 2000).

For presenteeism, three studies have confirmed that mood disorders (or affective disorders) were associated with increased cutback days or extra effort days (Kessler and Frank, 1997; Dewa and Lin, 2000; Lim et al., 2000), including major depression (Kessler and Frank, 1997; Lim et al., 2000; Kessler et al., 2006) and bipolar disorder (Kessler et al., 2006). Anxiety disorders were associated with increased cutback days or extra effort days in all studies that examined such an association (Kessler and Frank, 1997; Dewa and Lin, 2000; Lim et al., 2000). Generalized anxiety disorder (GAD) (Kessler and Frank, 1997; Lim et al., 2000), panic disorder, simple phobia, social phobia and agoraphobia (Kessler and Frank, 1997) were also associated with cutback days. Substance disorders (Kessler and Frank, 1997; Dewa and Lin, 2000), including alcohol and substance dependence (Kessler and Frank, 1997), also were associated with increased cutback days. The previous literature has indicated two important points: depressive disorder is more consistently associated with decreased work productivity (both for absenteeism and presenteeism); and the impact of mental disorders has been more consistently observed for presenteeism than absenteeism.

All previous research was conducted in Western countries. To our knowledge, there is no previous study on absenteeism or presenteeism due to a wide range of mental disorders using an internationally standardized set of diagnostic criteria and well-established diagnostic measures in a community sample of a non-Western country, such as Japan. Therefore, it is safe to say that the effects of mental disorders in diverse socio-cultural backgrounds have not been investigated. We should not simply transfer data regarding the costs of work disability from Western studies for two reasons. First, cross-national variation in prevalence and impairments of mental disorders has been shown (Demyttenaere et al., 2004), so we cannot demonstrate accurate losses in work productivity caused by mental disorders without investigating Japanese data. Second, although work disability is greater in high-income countries than in low- and middle-income countries (Ormel et al., 2008), other social and behavioral characteristics (i.e. worksite norms, culture or labor politics) may affect the association between mental disorders and decreased work productivity.

"Karo-jisatsu" (work-related suicide) has been claimed, at least in part, to be attributable to the fact that workers in Japan continue to work even when they feel sick (Nishiyama and Johnson, 1997; Hiyama and Yoshihara, 2008). In addition, although the average number of annual working hours per employed person was 1714 h in Japan in 2009, which is medium length among the Organisation for Economic Co-operation and Development (OECD) countries and has been decreasing during this decade (OECD, 2010); the proportion of workers working long hours, in 2001, was 28.1%, the highest in the developed societies (Lee, 2004). With these workaholic norms and workplace hierarchical social structure, Japanese workers who suffer from mental disorders may not take days off, but remain at the workplace, with deteriorating on-the-job work performance. Because Japan is known to have a permissive social climate for drinking problems (Milne, 2002; Hiro et al., 2007), such a workplace environment might allow workers with alcohol abuse/dependence to continue at the workplace, leading to decreased on-the-job work performance.

In addition, previous studies featured significant methodological variations in measuring absenteeism and presenteeism. Particularly for presenteeism, some studies used the number of cut-back days, while more recent studies used self-reported work performance using the WHO Health and Performance Questionnaire (HPQ), a standardized measure of absenteeism and presenteeism (Kessler et al., 2003; Kessler et al., 2004). Other methodological variations include the use of a broad diagnostic category (such as mood disorders) or specific diagnoses (such as major depression). It would be desirable to compare the impact of mental disorders on work performance while using a common measure of absenteeism and presenteeism by specific diagnosis.

The aim of the present study is to estimate the impact of mental disorders on work performance (absenteeism and presenteeism), as well as to ascertain the prevalence and demographic correlates in a community sample of workers in Japan who took part in the World Mental Health Japan (WMH-J) 2002–2005 surveys. This study provides the first findings regarding the association between mental disorders and work performance of community worker samples in a non-Western country. The study also assessed absenteeism and presenteeism using the WHO HPQ score associated with specific DSM-IV mental disorders.

2. Methods

2.1. Subjects

The data used in this study come from the World Mental Health Japan (WMH-J) 2002–2005 Survey (Kawakami et al., 2005). The WMH-J is an epidemiological survey of nine areas in Japan, including three larger cities and six rural municipalities. Carried out as part of the World Health Organization's World Mental Health (WMH) Survey Initiative (Demyttenaere et al., 2004), the survey was given to household residents aged 20 and older. The nine WMH-J sites were selected based on geographic variation, availability of site investigators, and local government cooperation. Interviews were carried out face-to-face with a total of 3417 respondents across the sites for a total response rate of 59.2%.

First, work-related measures were included in the part 2 sample ($n = 1305$). In the part 2 sample, 819 answered that they were employed; 684 fully answered and completed all questions used in this study; 530 met inclusion criteria (either employed or self-employed 20 h or more per week, aged 20–60 years). Therefore, this subsample of 530 respondents was used in the following analyses.

The data reported here were weighted to adjust for differential probabilities of selection and non-response. Details of the WMH-J design, field procedure and sample weights have been reported previously (Kawakami et al., 2005). The Human Subjects Committees of Okayama University, Japan National Center of Neurology and Psychiatry and Nagasaki University approved this study's recruitment, consent, and field procedures.

2.2. Diagnosis of mental disorders

Prevalences of mental disorders at 30 days and 12 months were assessed with Version 3.0 of the WHO Composite International Diagnostic Interview (CIDI) (Kessler and Ustun, 2004), a structured diagnostic interview designed to be administered by trained lay interviewers to generate diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994).

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2.3. Socio-demographic correlates

The sociodemographic variables included sex, age (20–29, 30–44, 45–60), education (less than high school, completed high school, some college, completed college), occupation ("Managers/professional", "Clerks (non-manual)", "Manual") and average expected work hours per week (20–39, 40 or more).

2.4. Work performance

Work performance was assessed using the WHO Health and Work Performance Questionnaire (HPQ; Kessler et al., 2003, 2004). The HPQ includes a self-reporting assessment of sickness/absence days in the month (30 days) before the survey along with a scale of on-the-job work performance in the same timeframe. The on-the-job work performance scale is a 0-to-10 self-anchoring scale in which 0 indicates the worst work performance that a person could have on their job and 10 represents performance of a top worker on their job. We used this 0-to-10 scale as an on-the-job work performance measure. Although there have been several methods created to assess work performance, no gold standard has been confirmed. It is argued that a 0–10 rating regarding work performance generates greater advantages than the assessments of perceived impairment used in previous studies (Kessler et al., 2003; Mattke et al., 2007). For example, Mattke et al. (2007) described the following three benefits: (1) benchmarking one's perceived performance provides a reference against which loss can be measured; (2) the values garnered from a 10-point performance scale or percentage scale can be more easily incorporated into a monetization formula; (3) attempts have been made to validate this 10-point scale by comparing it with supervisors' assessments or more objective archival performance measures of job performance (Kessler et al., 2003, 2004; Mattke et al., 2007). For these reasons, we adopted a 10-point scale work performance measure, a method that has been used in recent research regarding workplace costs of adult attention deficit hyperactivity disorder (Kessler et al., 2008).

2.5. Statistical analysis

All analyses were performed using survey procedures in SAS version 9.1.3 (SAS Institute Inc., Cary, NC, USA) or SAS-callable SUDAAN version 9.0 (Research Triangle Institute, Research Triangle Park, NC, USA) in order to account for the survey design of the WMH-J (for details, see Kawakami et al., 2005).

First, we estimated 12-month prevalence of each mental disorder within the subsample of 530 employed respondents to part 2 of the WMH-J 2002–2005 survey. Next, a subgroup comparison of prevalence estimates was used to study the sociodemographic correlates of mental disorders by calculating odds ratios adjusted for sex and age cohorts. Linear regression analysis was used to estimate associations of mental disorders with work performance over 30 days and 12 months. In order to conduct stable estimates of the mental disorders over 12 months, we included the mental disorders that had 15 or more unweighted cases in the analysis of sociodemographic correlates.

Mental disorders were coded as yes–no dummy predictor variables in linear regression analyses, whereas sociodemographic variables (sex, age, education, occupation, expected work time) were included as controls. The dependent variables in these linear regression equations were measures of the continuous outcomes of number of sickness absence days and on-the-job work performance.

3. Results

3.1. Prevalence and sociodemographic correlates

Estimates of 12 month prevalence (standard errors in parentheses) of DSM-IV mental disorders among employed WMH-J respondents are shown in Table 1. Major depressive disorder was the most frequent disorder in the employed sample, followed by specific phobia and alcohol abuse in last 12 months. Approximately 9% of working people had some mental disorder over the 12 months.

There were few sociodemographic correlates of mental disorders. Major depressive disorder was significantly lower among workers whose education included some college when compared with those who completed college (OR = 0.2, 95% Confidence Interval [CI] 0.04–0.97). It also was significantly lower among clerks than managers/professionals (OR = 0.4, 95%CI 0.1–0.9). As for anxiety disorders, less educated workers who did not complete high school had a greater 12-month prevalence of specific phobias than workers who completed college (OR = 5.6, 95%CI 1.2–27.3). Substance disorders were higher in men (OR = 22.3, 95%CI 2.1–236.0; OR = 24.0, 95%CI 2.3–254.0) than women. Substance use disorders were more common in 20–29-year-old workers than 45–60-year-old workers. There were no significant sociodemographic correlates among any other mental disorders.

Table 1
12-month prevalence of DSM-IV mental disorders among employed respondents in WMH-J.

Mental disorders	Weighted *n*	%	SE
Mood disorder			
Major depressive disorder	14.1	2.6	0.7
Dysthymia	1.3	0.3	0.2
Bipolar I and II	1.6	0.3	0.3
Any mood disorder	15.7	2.9	0.8
Anxiety disorder			
Specific phobia	12.5	2.3	0.4
Social phobia	5.7	1.1	0.7
Agoraphobia without panic disorder	0.4	0.1	0.1
Generalized anxiety disorder	5.3	1.0	0.3
Panic disorder	3.3	0.6	0.3
Posttraumatic stress disorder	2.6	0.5	0.3
Any anxiety disorder	27.2	5.1	0.9
Substance use disorder			
Alcohol abuse	8.7	1.6	0.6
Alcohol dependence	1.4	0.3	0.2
Any substance use disorder	9.2	1.7	0.6
Intermittent explosive disorder	3.7	0.7	0.3
Any mental disorder	48.7	9.1	1.1

n = 530; SE, standard error.

3.2. Associations of mental disorders with work performance

Only social phobia significantly predicted the expected duration of sickness/absence days (Table 2). Having this disorder was associated with an increase in absent days; however, it did not remain a significant predictor after adjusting for age, sex, education, occupation and expected number of hours of work per week. Major depressive disorder, mood disorders and alcohol abuse/dependence significantly predicted on-the-job performance (Table 3). Having these disorders was associated with a decrease in work performance. Major depressive disorder, mood disorders and alcohol abuse/dependence remained significant and any substance use disorder became a significant predictor after adjustment for age, sex, education, occupation and expected number of hours of work per week.

The 30-day prevalence of major depressive disorder (b = −1.9, 95%CI −3.6 to −0.3) and any mood disorder (b = −2.0, 95%CI −3.1 to −1.0) was significantly associated with a decrease in work performance, after adjusting for age, sex, education, occupation and expected number of working hours per week. On the other hand, generalized anxiety disorder (b = 0.8, 95%CI 0.3 to 1.3) and intermittent explosive disorder (IED) (b = 1.2, 95%CI 0.5 to 1.9) were associated with an increase in work performance.

4. Discussion

The present study indicates that major depressive disorder and alcohol abuse/dependence were positively associated with decreased on-the-job performance (presenteeism) in this sample of workers in Japan, while no mental disorders were associated with absence days (absenteeism). Additional analyses indicated that major depression was associated with decrease in on-the-job performance over 30 days

None of the mental disorders included in this study were significantly associated with absence days. This finding is inconsistent with previous community epidemiological studies which found that major depressive disorders were associated with an increase in OR = 1.87 for 1 year presence of sickness absence in men (Laitinen-Krispijn and Bijl, 2000), with an increase of 8.7 work loss days due to absenteeism for 1 year (Kessler et al., 2006) and 1.39 work loss days in the past month for depression (Lim et al., 2000) or even −0.3 additional disability day in past 30-days (Dewa and Lin, 2000). It also conflicts with a previous study indicating that bipolar disorder was associated with an increase of 27.7 work loss days due to absenteeism for 1 year (Kessler et al., 2006) and alcohol- and substance-use disorders were associated with 0.1 to 0.25 increased absence days in past 30 days (Kessler and Frank, 1997). However, it is consistent with above community epidemiological studies that found no association between mood disorders (Kessler and Frank, 1997; Dewa and Lin, 2000; Lim et al., 2000), anxiety and substance-related disorders (Dewa and Lin, 2000), anxiety disorders (Kessler and Frank, 1997; Lim et al., 2000) or substance disorders (Lim et al., 2000) with absent days. Having a common mental disorder might not be strongly associated with sickness absence in the Japanese working population, as observed in a few studies.

Any mood disorder and any substance use disorder, particularly major depression and alcohol abuse, were associated with a decrease in on-the-job performance in the present study. This finding is consistent with 2.77 to 4.17 cut-back days for major depression in past 30 days (Kessler and Frank, 1997; Lim et al., 2000), 18.2 work loss days due to absenteeism for major depressive disorder for 1 year (Kessler et al., 2006) and 0.17 cut-back days for alcohol abuse and 0.88 cut-back days for alcohol dependence in past 30 days (Kessler and Frank, 1997), as was found in the previous studies (Kessler and Frank, 1997; Dewa and Lin, 2000; Lim et al., 2000), among mental disorders, mood disorders had the largest impact on decreased on-the-job work performance.

The NCS-R study, which used the same measure of on-the-job work performance, reported that the work performance equivalent to 18.2 days per year was lost due to major depression (Kessler et al., 2006). Following a formula used in prior studies (Kessler et al., 2008), their estimate could be converted into a regression coefficient of −0.73 (−18.2 days divided by 250 annual work days and multiplied by 10), which was smaller than that observed in this WMH-J study. The impact of major depression on on-the-job work performance may be greater in the working population in Japan than it is in the US, possibly resulting from the workaholic norm in Japanese workplaces, which prevented those who were sick from leaving the workplace. However, because of the difference in measurement of on-the-job work performance, we could not compare the present estimate with previous studies reporting 2.8–4.2 cut-back days in the past 30 days as associated with major depressive disorder (Kessler and Frank, 1997; Lim et al., 2000).

Table 2
The relationships between mental disorders over 12 months and sick absent days among 530 employed respondents in part 2 of the World Mental Health Japan 200–2005.

Mental disorders	With each 12-month disorder		Without each 12-month disorder		Regression coefficients (12-month)			
					Model 1[a]		Model 2[b]	
	Mean	(S.E.)	Mean	(S.E.)	Estimate	(95% CI)	Estimate	(95% CI)
Mood disorders								
Major depressive disorder	0.6	0.4	0.6	0.1	0.0	−0.8 to 0.8	−0.0	−0.9 to 0.9
Any mood disorder	0.6	0.4	0.6	0.1	−0.1	−0.8 to 0.7	−0.0	−0.8 to 0.8
Anxiety disorders								
Specific phobia	1.8	1.1	0.6	0.1	1.1	−1.2 to 3.3	1.2	−1.1 to 3.4
Social phobia	0.6	0.5	0.6	0.1	0.9	0.1 to 1.8	−0.0	−1.3 to 1.2
GAD	1.7	0.9	0.6	0.1	1.0	−0.9 to 2.9	1.1	−0.8 to 3.0
Panic disorder	0.5	0.2	0.6	0.1	−0.2	−0.7 to 0.3	−0.1	−0.5 to 0.3
Any anxiety disorder	1.5	0.6	0.6	0.1	1.1	−0.1 to 2.3	1.0	−0.3 to 2.2
Substance use disorders								
Alcohol abuse or dependence	−0.2	0.5	0.6	0.1	−0.4	−0.8 to 0.0	−0.8	−2.0 to 0.3
Any substance use disorder	−0.2	0.5	0.6	0.1	−0.4	−0.8 to 0.0	−0.9	−2.0 to 0.3
Intermittent explosive disorder	1.4	0.6	0.6	0.1	0.8	−0.3 to 1.9	0.8	−0.5 to 2.1
Any disorder	1.0	0.3	0.6	0.1	0.5	−0.3 to 1.3	0.4	−0.4 to 1.2

n = 530; means were adjusted for covariate; S.E., standard error; 95% CI, 95% confidence interval.
[a] Based on ordinary least-squares regression analysis in which a dummy predictor variable that distinguished between workers with mental disorders (coded 1) and other workers (coded 0) was used to predict the continuous outcomes.
[b] Adjusted for sex, age-cohort, education, occupational category and work time on Model 1.

Table 3
The relationships between mental disorders over 12 months, and on-the-job work performance among 530 employed respondents in part 2 of the World Mental Health Japan 2002–2005.

Mental disorders	With each 12-month disorder		Without each 12-month disorder		Regression coefficients (12-month)			
					Model 1[a]		Model 2[b]	
	Mean	(S.E.)	Mean	(S.E.)	Estimate	(95% CI)	Estimate	(95% CI)
Mood disorders								
Major depressive disorder	5.9	0.3	7.0	0.1	−1.2	−2.0 to −0.4	−1.1	−1.8 to −0.3
Any mood disorder	5.8	0.3	7.0	0.1	−1.3	−2.0 to −0.6	−1.2	−1.8 to −0.5
Anxiety disorders								
Specific phobia	7.0	0.3	6.9	0.1	0.1	−0.7 to 0.8	0.3	−0.7 to 0.7
Social phobia	7.6	0.6	6.9	0.1	0.6	−0.4 to 1.5	0.7	−0.6 to 1.9
GAD	7.0	0.4	6.9	0.1	0.1	−0.5 to 0.7	0.1	−0.7 to 0.9
Panic disorder	6.6	0.7	6.9	0.1	0.2	−0.7 to 1.1	−0.3	−1.8 to 1.1
Any anxiety disorder	7.1	0.2	6.9	0.1	0.2	−0.2 to 0.7	0.2	−0.3 to 0.6
Substance use disorders								
Alcohol abuse or dependence	5.9	0.5	7.0	0.1	−1.1	−2.1 to −0.0	−1.1	−2.1 to −0.1
Any substance use disorder	6.0	0.5	7.0	0.1	−1.0	−2.0 to 0.0	−1.0	−2.0 to −0.0
Intermittent explosive disorder	6.4	0.8	6.9	0.1	−0.2	−1.7 to 1.3	−0.5	−2.1 to 1.1
Any disorder	6.5	0.2	7.0	0.1	−0.5	−1.1 to 0.1	−0.5	−1.0 to 0.0

n = 530; means were adjusted for covariate; S.E., standard error; 95% CI, 95% confidence interval.
[a] Based on ordinary least-squares regression analysis in which a dummy predictor variable that distinguished between workers with mental disorders (coded 1) and other workers (coded 0) was used to predict the continuous outcomes.
[b] Adjusted for sex, age-cohort, education, occupational category and work time on Model 1.

In this study, the association between alcohol abuse/dependence and work performance loss was significant, and also similar to that for major depressive disorder. Meanwhile, alcohol abuse/dependence was non-significantly associated with a slightly smaller number of sick leave days. This pattern may be unique to Japan because previous studies in western countries consistently showed greater decreases in work performance due to major depressive disorder than from alcohol abuse/dependence (Kessler and Frank, 1997; Dewa and Lin, 2000; Lim et al., 2000). In Japan, workers with alcohol abuse/dependence may be more likely to remain at their workplace, with deteriorated work performance instead of taking sick leave. This situation likely occurs because Japanese workplaces are more tolerant of problem drinking. For instance, heavily-drinking workers receive greater social support at work (Hiro et al., 2007). The present study indicated that the impact of mental disorders (particularly major depressive disorders and alcohol abuse/dependence) on work performance may vary from country to country, depending on characteristics of worksite culture and other labor-related factors. A future study should focus on the variability of the impact of mental disorders on decreases in work performance across countries, applying similar measures of work performance.

It was unexpected that the 30-day prevalence of GAD and IED was associated with increased on-the-job work performance. Previous studies have shown additional 3 to 4 work cut-back days among workers with GAD in the past 30 days (Kessler and Frank, 1997; Lim et al., 2000). No study reported the impact of IED on work performance. The impacts of GAD and IED may be less in Japan. Increased work performance for these disorders might be attributable to the self-rated measure of work performance. Those with anxiety or low impulse control may rate their work performance higher on such a scale. Detailed investigations with multiple measures of work performance loss due to GAD and IED are needed.

As we expected, we found low absenteeism but high presenteeism associated with major depression and alcohol abuse/dependence among workers in Japan. Employees tend to have fewer sick leave days on average in Japan than in Western countries (Muto et al., 1999; Kondo et al., 2006), taking a paid annual leave for only a few days when they are sick (Otsuka et al., 2007; Nakata et al., 2011). Only one fourth to one third of the total paid annual leave days given to employees were utilized in Japan (Ogura, 2004). Several anecdotal reports have described that workers in Japan continue to work even when they feel sick (Nishiyama and Johnson, 1997; Hiyama and Yoshihara, 2008), because of the workaholic norms, social pressure from supervisors and coworkers in their workplace. The social and cultural characteristics of companies in Japan may explain the finding. In addition, only one fourth of people who suffered from mental disorders sought professional help in Japan (Wang et al., 2007a), which was the lowest among developed countries. Thus most workers may not be aware of their having mental disorders. This may also be a reason for high presenteeism associated with mental disorders. Furthermore, specific to alcohol abuse/dependence, a permissive social climate for drinking problems in Japan (Milne, 2002; Hiro et al., 2007) might be an additional reason for high presenteeism associated with alcohol abuse/dependence.

According to the method used in Kessler et al. (2008), we calculate the day equivalent measure of performance decreases with those disorders that were significant predictors of work performance. The 0–10 work performance scale was used to represent proportional work performance (0–100%). Workers with major depression were estimated to have about 11–12% lower on-the-job performance than other workers. As for individual level, in a 250-day work year, this is equivalent to approximately 28–30 lost days of productive work or ¥453,394–¥494,611 yen lost annual salary associated with major depression (Ministry of Health, 2003). In the same manner, the lost days of productive work for alcohol abuse or dependence was 28 days. As for societal level, lost days of productive work which were multiplied by the number of workers with each mental disorder calculated from prevalences, were 31.4 million days for major depression and 20.5 million days for alcohol abuse or dependence. Next, above lost annual salary was multiplied by the number of workers with each mental disorder, this amounted to approximately ¥508 billion yen for major depression and ¥332 billion yen for alcohol abuse or dependence, respectively. It should be noted that many people might rate themselves as 10, a top worker in US, and might not rate themselves as a top worker in other countries (Iwata et al., 1995; Lee et al., 2002). We calculated the frequency of each 0–10 point and found that 4.0% of workers rated themselves 10 and 6% rated themselves 9, in Japan. These proportions seem not so extremely small. It would be needed, however, to describe a prevalence of a top worker in future international comparison.

Our prevalence estimates of mental disorders in an employed WMH-J subsample slightly varied from the whole community sample; they are almost consistent with the whole community sample (Kawakami et al., 2005). This difference might have occurred because of the younger age in the employed subsample. The prevalence was lower in Japan than in western countries (Demyttenaere et al., 2004; Kawakami et al., 2005). Consistent with previous studies of employed community samples, major depression, specific phobia and alcohol abuse were the most common mental disorders (Sanderson and Andrews, 2006). We can compare these findings directly with only two epidemiological surveys that investigated the prevalence of mental disorders over 12 months in employed samples (Laitinen-Krispijn and Bijl, 2000; Kessler et al., 2006).

There are a few implications from our results. A previous study indicates that sickness presenteeism may lead to a future long-term sick absence, while the finding was not specific to mental disorders (Bergstrom et al., 2009). Workers who suffer from mental disorders possibly need to take a day off to cope with work burden or to access medical care; otherwise, they might take a long-term sick absence in future. Changing workplace norms and supervisor attitude to allow workers to have more control over taking sick absence could be beneficial to workers with mental disorders and their employers in a country like Japan in which high presenteeism is associated with mental disorders. For alcohol abuse/dependence, appropriate interventions should be designed and implemented for early detection and treatment of the disorder, which is often masked by the workplace culture in Japan which is permissive to drinking.

5. Limitations

The present findings must be considered within the following limitations. First, the survey sites were selected from available areas in Japan, so it may not be completely representative of the national population because the data did not include a metropolitan city with a population of more than 1 million. The low response rate (59.2%) may also have limited the interpretation of the results, leading to underestimation or overestimation of prevalence. Second, although the HPQ is a validated scale, a psychometric comparison study should be conducted regarding the meaning of a 0–10 performance scale. Third, cases of mental disorders were so small that 95% CIs were wide and some important mental disorders (e.g. bipolar disorder) could not be estimated. Fourth, impact of mental disorders on work performance might be underestimated, because workers who suffer with severe symptoms of mental disorders possibly lose their job or attempt suicide (Dickerson et al., 2008).

Even within the context of these limitations, we found a substantive impact of mental disorders on work performance in Japan. To our knowledge, these results represent the first community-based epidemiological study to show mental disorder data in a non-western country. Future research should be conducted to replicate these findings in other East Asian countries as well as additional non-western countries in order to explore possible reasons for the observed cross-national differences.

Finally, we should view the consequence of workers' mental disorders from the perspective of return-on-investment; we found associations between some mental disorders and lost work productivity. From the employer's perspective, it is important to recognize lost work productivity as potential costs that might be reduced with best-practices, such as outreach and treatment of mental disorders (Wang et al., 2007b; Kessler et al., 2008).

Conflict of interest

None.

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Regular Article

Study of understanding the internalized stigma of schizophrenia in psychiatric nurses in Japan

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Aim: 'Internalized stigma' is a construct that reflects the degree to which a person accepts beliefs endorsed by society about mental illness. Among people with schizophrenia spectrum disorders, internalized stigma has been found to moderate the associations between insight and social function, hope, and self-esteem. Among families of patients with schizophrenia, internalized stigma may not only hinder help-seeking but also result in the families attempting to provide care themselves, without assistance from mental health services. Little is known about internalized stigma among service providers, especially psychiatric nurses in Japan. Therefore, we investigated the correlation between internalized stigma and 'beliefs about the most appropriate form of hospitalization' among psychiatric nurses.

Methods: The subjects were 215 psychiatric nurses employed in psychiatric hospitals who completed the personal stigma scale, perceived stigma scales, and Difficulty of Community Living Scale (DCLS) with respect to a chronic schizophrenia case vignette.

Results: Internalized stigma was positively correlated with greater 'beliefs about the most appropriate form of hospitalization' among psychiatric nurses. We also showed that stronger 'beliefs about the social disadvantages of schizophrenia patients in the community' was positively correlated with stronger 'beliefs about the most appropriate form of hospitalization'.

Conclusion: The present findings suggest that the psychiatric nurses employed at Japanese psychiatric hospitals have a pessimistic view of the community living of people with schizophrenia and their families. And these psychiatric nurses' beliefs were related to their understanding of the deeply dependent relationship between patients and families, and was related to the Confucian ideal.

Key words: hospitalization, Japan, nurses, schizophrenia, stereotyping.

THE DEFINITION OF stigma has been expanded from an individualistic focus to incorporate a set of social processes that link its components under one umbrella concept.[1] Stigma is thus defined as occurring when human differences are labeled, leading to stereotyping and cognitively separating 'us' from 'them'. It also causes loss of status and discrimination resulting in reduced life opportunities within the context of a power situation that allows these processes to unfold. The spectrum of emotional reactions that the stigmatizer (e.g. disgust) and the stigmatized (e.g. shame) experience has also been added as a key component to this process.[2]

Three main mechanisms of Chinese society's manifestations of stigma, which are shaped by cultural meaning embedded within Confucianism, have been investigated: direct individual discrimination, internalization of negative stereotypes, and structural discrimination.[3] Similar manifestations can be observed in Japan, especially in rural areas.

The public endorsement of stigma impacts many people, especially four groups: people with mental illness, their families, service providers, and the general public. Perhaps of greatest concern is the harm that public stigma causes people who are labeled mentally ill and their family members.[4,5]

In people with mental illness, 'internalized stigma',[6] a related construct reflecting the degree to which a person has internalized stigmatizing beliefs about mental illness endorsed by society (e.g. people with mental illness are violent and unable to function independently), takes on personal relevance and has been linked to depressed mood.[6] Internalized stigma among people with schizophrenia spectrum disorders moderates the associations between insight and social function, hope, and self-esteem,[5,7,8] leading to negative outcomes.[9,10]

Second, it has been extensively documented that caregivers of persons with serious and persistent mental disorders must successfully cope with many challenges to provide good care. In Japan, there are many advanced mental health inpatient facilities and a long-term hospitalization system. However, there might be little professional mental health care in the community, for example, screening for early intervention by general practitioners and assessment by psychiatric nurses in Japan. Furthermore, among families of patients with schizophrenia, internalized stigma may not only hinder help-seeking but it may also result in families attempting to provide care themselves, without assistance from mental health services. On the other hand, reluctance to seek help may be connected to fear of violent behavior by patients with schizophrenia, and the family's attitudes toward patients with schizophrenia might have a significant impact on patients' social adjustment.[11–13]

Third, public endorsement of stigma has an impact on service providers in Japan, especially inpatient psychiatric nurses. Further, compared to the situations of other medical workers in Japan, unpredictable patient behavior is easily construed as dangerous for psychiatric nurses.[14] This may be one of the reasons that psychiatric nurses have the greatest level of stigmatizing perceptions among medical workers. They tend to have close contact with inpatients on psychiatric wards, making them easy targets for patients' violent behavior. It may also be a reason why it is easy to predict that families will have difficulty taking care of a relative with mental illness.

Over the past few years, there has been a substantial increase in research on stigmatizing beliefs and attitudes among mental health professionals. It has been found that health professionals rate long-term outcomes more negatively than do the general public, and that the public is more optimistic about the long-term prognosis after treatment.[15,16] However, little is known about internalized stigma among service providers, especially psychiatric nurses working on psychiatric wards in Japan. Furthermore, little is known whether their internalized stigma correlate with their beliefs about care for inpatients with schizophrenia or not. Therefore, we investigated the correlation factors (e.g. internalized stigma) with psychiatric nurses' beliefs about the most appropriate form of hospitalization for schizophrenia patients.

METHODS

Procedure

The subjects were 215 psychiatric nurses employed at five psychiatric hospitals in Tochigi and Niigata prefectures in Japan who gave their informed consent to participate. Before conducting the survey, all subjects received a written explanation about the purpose of the study. The protocol for the present research project conforms to the provisions of the 1995 Declaration of Helsinki (revised in Edinburgh, 2000). The survey was conducted from November 2007 to January 2010.

Questionnaire

Participating psychiatric nurses completed a questionnaire composed of three parts, including sociodemographic features, questions about stigma and social distance, based on a vignette describing a case of chronic schizophrenia that meets diagnostic criteria, and the Difficulty of Community Living Scale (DCLS) with respect to the case vignette. Sociodemographic items were as follows: age, sex, registered nurse (RN) or licensed practical nurse (LPN), and total years of employment at a psychiatric hospital.

Stigma and Social Distance Scale

An interview questionnaire, which was developed for Australia and Japan, consisted of a common core of

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questions and some items that were country-specific.[17,18] Each subject was presented with a vignette of a male patient ('John') with chronic schizophrenia (see Appendix). The disorder depicted in the vignette satisfied ICD-10 diagnostic criteria for a schizophrenic episode.[19]

The subjects were asked a number of questions about the vignette to determine if they recognized the mental disorder it depicted. Stigma was measured using two scales with nine items.[18] The first scale assessed the respondent's personal attitudes toward the person described in the vignette (Personal Stigma). The second scale assessed the subject's beliefs about other peoples' attitudes towards the person described in the vignette (Perceived Stigma). Both scales contained essentially the same statements but differed in terms of whether they were aimed at personal attitudes or the perceived attitudes of others. An example of a statement from the Personal Stigma scale was: 'His problem is not a real medical illness'. The corresponding statement in the Perceived Stigma scale was: 'Most people believe that his problem is not a real medical illness'. Ratings for each item of each question were made on a 5-point Likert scale (1 = strongly agree, 2 = agree, 3 = neither agree nor disagree, 4 = disagree, 5 = strongly disagree), with a lower score indicating higher stigma. The internalized stigma score was calculated as the size of differences between personal stigma (personal attitudes) and perceived stigma (beliefs about others peoples' attitudes) toward the person described in the vignette, with a lower score indicating higher internalized stigma, which subjects perceived that 'I feel this way, and most people probably do'. This phenomenon may be indicated by 'characteristics of Japanese culture that facilitate individual decision-making while considering the maintenance of group harmony and unity'[20] and that may lead to the decision.

The Social Distance Scale assessed the self-reported willingness to make contact with the person described in the vignette using a 5-item scale.[21] In particular, subjects rated their willingness to: (i) move next door to the person in the vignette; (ii) spend an evening socializing with the person; (iii) make friends with the person; (iv) work closely on a job with the person; and (v) have the person marry into the family.[21] The Australian version of the test required the subject to rate each item on a 4-point scale (1 = definitely willing, 2 = probably willing, 3 = probably unwilling, 4 = definitely unwilling). The Japanese version of the scale incorporated an additional rating option for which the literal translation was '5 = strongly unwilling' on a 5-point Likert scale with a higher score indicating greater social distance.

Difficulty of Community Living Scale

The 12-item Difficulty of Community Living Scale (DCLS) for patients with schizophrenia[22] was used to rate psychiatric nurses' beliefs about the difficulty the person in the vignette would have living in the community. This self-administered scale consists of three subscales: 'beliefs about the most appropriate form of hospitalization', 'resources for living in the community', and 'social disadvantages in community living'. One of the subscale questions asked about 'beliefs about the most appropriate form of hospitalization'. Examples of statements from the scale were: 'People with a problem like John's cannot be cared for by family members who are not healthcare professionals', 'People with a problem like John's should be hospitalized and receive treatment', and 'Caring for someone with a problem such as John's is the role of psychiatric hospital workers'. Another subscale question asked about 'beliefs about social disadvantages in community living'. Examples of statements from the scale were: 'Family members caring for people with a problem like John's will sacrifice their lifestyles' and 'People with a problem like John's will suffer discrimination by living in the community'.

The DCLS uses a 5-point Likert scale (1 = strongly agree, 2 = agree, 3 = neither agree nor disagree, 4 = disagree, 5 = strongly disagree), with lower scores indicating greater difficulty living in the community for the person in the schizophrenia vignette.

Cronbach's alpha coefficient, which tests the content validity of the subscales, ranges from 0.69 to 0.75 in Japan for the following subscales: (i) 'beliefs about the most appropriate form of hospitalization', 0.75; (ii) 'resources for living in the community', 0.73; and (iii) 'social disadvantages in community living', 0.69.[21]

Participants

The mean age of the subjects was 41.4 years (SD = 10.3), and the age range was 22–66 years. There were 137 (63.7%) women. Overall, there were 129 (60.0%) registered nurses (RN) and 86 (40.0%) licensed practical nurses (LPN), with 165 (76.7%) staff nurses. The total number of years of employment in psychiatric hospitals was 0–3 years for 23 (10.7%), 3–10 years for 73 (34.0%), 10–20 years for 63 (29.3%), >20 years for 50 (23.3%), and no answer for six (2.8%) of the total 215 psychiatric nurses. In addition, 15 (7.0%) had experience in home visit nursing, 18 (8.4%) in outpatient nursing, and 21 (9.8%) in a daycare program.

Statistical analyses

The 12-item DCLS for patients with schizophrenia compared different sociodemographic characteristics using a *t*-test (for comparisons between two groups) and ANOVA (for comparisons among three or more groups). The correlations between 'beliefs about the most appropriate form of hospitalization' of the DCLS subscale and other factors were investigated using multiple regression analysis (stepwise). The item 'Beliefs about the most appropriate form of hospitalization' of the DCLS subscale was used as the dependent variable after deriving Spearman's rank-order correlation coefficients. SPSS 18.0 for Windows was used for all statistical analyses. The level of statistical significance was set at <5%.

RESULTS

Table 1 shows the results from the DCLS and the distribution of response scores for each item. For the DCLS, Cronbach's alpha was moderately high at 0.77. The mean total score for 'beliefs about the most appropriate form of hospitalization' of the DCLS subscale was 16.22 (SD = 3.36), the mean score for 'resources for living in the community' was 15.23 (SD = 2.47), and the mean score for 'social disadvantages in community living' was 8.33 (SD = 2.08).

Mean total score for 'beliefs about the most appropriate form of hospitalization' of the DCLS subscale was compared for each sociodemographic characteristic of the subject. The mean score had significant

Table 1. Mean and standard deviation for DCLS (12 items) ($n = 215$)

		Mean	SD
DCLS (12 items)[†]		39.78	5.57
1st factor : Beliefs about the most appropriate form of hospitalization		16.22	3.36
1	People with a problem like John's cannot be cared for by family members who have no experience as a healthcare professional.	3.52	0.87
2	People with a problem like John's can live with a greater peace of mind in the hospital rather than living alone in the community.	3.30	0.99
3	Caring for people with a problem like John's is the role of psychiatric hospital workers.	3.23	0.98
4	People with a problem like John's and who do not have a family member who can provide care cannot live in the community.	3.67	0.87
5	People with a problem like John's should be hospitalized and receive treatment.	2.49	0.98
2nd factor: Resources for living in the community[‡]		15.23	2.47
6	When people with a problem like John's live alone in the community, outpatient nurses can be depended on.	3.58	0.89
7	When people with a problem like John's live alone in the community, outpatient physicians can be depended on.	3.48	0.94
8	When people with a problem like John's live alone in the community, local public health nurses can be depended on.	3.61	1.11
9	When people with a problem like John's live alone in the community, hospital social workers can be depended on.	3.74	1.02
3rd factor: Social disadvantage in community living		8.33	2.08
10	People with a problem like John's will suffer discrimination by living in the community.	2.42	0.88
11	Family members caring for people with a problem like John's will sacrifice their lifestyles.	2.84	0.89
12	People with a problem like John's will suffer by living in the community.	3.07	0.89

[†]The DCLS uses a 5-point Likert scale (1 = strongly agree, 2 = agree, 3 = neither agree nor disagree, 4 = disagree, 5 = strongly disagree), with lower scores indicating greater difficulty living in the community for the person in the schizophrenia vignette.
[‡]The score for the 2nd factor (resources for living in the community) was reverse score, so that 1 = strongly disagree, 5 = strongly agree.
DCLS, Difficulty of Community Living Scale.

Table 2. Correlation factors with 'Beliefs about the most appropriate form of hospitalization' of the DCLS subscale ($n = 215$)

		Mean	SD	r	*P*
DCLS	Beliefs about the most appropriate form of hospitalization	16.22	3.36	–	–
	Resources for living in the community	15.23	2.47	0.136	0.047
	Social disadvantage in community living	8.33	2.08	0.521	<0.001
Stigma scale	Personal stigma	28.44	3.82	0.519	<0.001
	Perceived stigma	21.75	4.53	−0.058	0.399
	Internalized stigma	6.72	5.72	0.382	<0.001
Social distance		17.64	3.84	−0.365	<0.001

DCLS, Difficulty of Community Living Scale.

association with sex (the mean score for women [15.7, SD = 3.2] was lower than that for men [17.2, SD = 3.3] [$P < 0.01$]), nursing license (LPN [14.9, SD = 3.5] scored lower than RN [17.2, SD = 3.0]), and the total number of years of employment at a psychiatric hospital ($F = 3.0$, $P < 0.05$). Table 2 shows the results for the correlation factors with 'beliefs about the most appropriate form of hospitalization' of the DCLS subscale. Significant correlations were observed between 'beliefs about the most appropriate form of hospitalization' of the DCLS subscale and resources for living in the community ($r = 0.136$, $P < 0.05$), social disadvantages in community living ($r = 0.521$, $P < 0.001$), personal stigma ($r = 0.519$, $P < 0.001$), internalized stigma ($r = 0.382$, $P < 0.001$), and social distance scores ($r = -0.365$, $P < 0.001$).

Table 3 shows the results of the multiple regression analysis. Multiple regression analysis (stepwise) was performed using variables that were significantly associated with 'beliefs about the most appropriate form of hospitalization' of the DCLS subscale. Independent variables were sex, total years of employment at a psychiatric hospital, RN or LPN, personal stigma, internalized stigma, social distance, 'resources for living in the community', and 'social disadvantages in community living'. The DCLS subscale item 'beliefs about the most appropriate form of hospitalization' was the dependent variable. The item 'beliefs about the most appropriate form of hospitalization' was significantly associated with personal stigma ($\beta = 0.186$, $P < 0.05$), 'social disadvantage in community living' ($\beta = 0.370$, $P < 0.001$), RN or LPN ($\beta = -0.190$, $P < 0.01$), sex ($\beta = -0.132$, $P < 0.05$), internalized stigma ($\beta = 0.198$, $P < 0.01$), and total years of employment in a psychiatric hospital ($\beta = 0.150$, $P < 0.01$).

DISCUSSION

The present study shows two interesting findings (Table 3). One is that psychiatric nurses commonly

Table 3. Multiple regression for 'Beliefs about the most appropriate form of hospitalization' as a dependent variable ($n = 215$)

	β	t	*P*
Beliefs about the most appropriate form of hospitalization			
Personal stigma	0.186	2.546	0.012
Social disadvantage in community living	0.370	6.296	<0.001
Registered nurse or licensed practical nurse†	−0.190	−3.317	0.001
Nurses' sex‡	−0.132	−2.418	0.017
Internalized stigma	0.198	2.808	0.005
Total years of employment of psychiatric hospital§	0.150	2.635	0.009

Stepwise, adjusted R-square = 0.451.
†Registered nurse = 1 or licensed practical nurse = 2.
‡Nurses' sex: male = 1 or female = 2.
§Total years of employment of psychiatric hospital; rating from '1–3 years' = 1, to 'over 20 years' = 4.

believe that it is better for schizophrenia patients to be hospitalized in an appropriate manner than receiving treatment as outpatients because of the social disadvantages that these patients experience in the community. Also, in our prior research, Japanese psychiatric nurses were found to have pessimistic views concerning family caregivers of schizophrenia patients living in the community, as shown in the positive result for the following item, 'Family members caring for people with chronic schizophrenia will have to sacrifice their lifestyles'.[20] Furthermore, these nurses believe that if there is to be a risk of violence toward others by the person with chronic schizophrenia who appeared in the research, he should be hospitalized because he himself may become the subject of discrimination in the community.[20] From these studies, it is clear that the psychiatric nurses are concerned not only about the discrimination against patients in the community but also about the sacrifices that their families have to make in their lives.

Furthermore, in the present study, the psychiatric nurses' little reliability on the resources for living in the community, that is, social workers, psychiatrists, psychiatric nurses, and public health nurses for outpatient care, was correlated with their agreement on hospitalization as the appropriate form of treatment. Therefore, an educational program is needed in order to change psychiatric nurses' hospitalization-based awareness to a community-based one. Certainly in Japan there are not enough assertive community treatment teams in psychiatric rehabilitation facilities that provide effective support for discharge and maintaining living in the community. In addition, there are no options other than hospitalization no matter how high the risk of violence to others is during acute psychosis. This is unlike the situation in Western countries, where there are compulsory community treatment teams as possible options. The important tasks for the Japanese mental health system are deinstitutionalization and development of the community treatment system. Also, mental health professionals and policy-makers need to coordinate the system for new treatment programs as an alternative to hospitalization.

On the other hand, in our research on family caregivers of patients with schizophrenia, we demonstrated that factors such as current hospitalization of the family member with schizophrenia were a significant predictive factor of caregiver burden.[20] It might be considered that these results were caused by the responsibility and obligation of family members for nursing care imposed by Japanese civil law. Furthermore, the responsibility and obligation of making their family member with a mental disorder receive treatment is imposed by the Japanese Mental Health Act. Even if there is a dysfunctional family with a family member with schizophrenia, they should be responsible for making their family member with a mental disorder receive treatment. In addition, Japanese families are more likely than Korean families to think that a family member with schizophrenia should have care provided only by family members as much as possible, even though both cultures share the same cultural background of Confucian ideas and the tradition of providing care to family members.[21,22] Thus, they hope to take care of a family member with schizophrenia as long as possible, even if they have to make sacrifices in their daily life. It was suggested that families with higher degrees of care burden might despair of ever taking care of their loved one with schizophrenia solely within the family unit.

However, there is no compulsory community treatment for acute psychosis, so that family caregivers have to bring their family member with acute psychotic symptoms to a psychiatric clinic or hospital in Japan. The lack of compulsory community treatment in Japan might cause the primary family caregiver to consider the difficulty of home care for the family member with violent behavior based on positive symptoms. The psychiatric nurses' beliefs about hospitalization taking the lead in the Japanese Mental Health system might be correlated with worry about caregivers' burden.

The other important suggestion of our present study is that the psychiatric nurses' 'internalized stigma' was positively correlated with their beliefs about the most appropriate form of hospitalization for chronic schizophrenia patients. As confirmation, internalized stigma is the difference between personal stigma (personal attitudes) and perceived stigma (beliefs about others people's attitudes) toward the person described in the vignette, which subjects perceived that 'I feel this way, and most people probably do'. The study findings may be useful for identifying underlying factors related to internalized stigma or stereotype endorsement. Stereotype endorsement describes the degree to which subjects agree with common stereotypes about people with mental illness, which influence psychiatric nurses' beliefs about the most appropriate form of hospitalization. These phenomena have

been reported to be related to the characteristics of Japanese culture that facilitate individual decision-making.[23]

In conclusion, these psychiatric nurses' beliefs may be correct, since long-term hospitalization may be the only choice as a last resort to save family members from the caregiver burden associated with the risk of violence from patients with delusional features. However, the most important solution to the problem of reducing caregivers' burden is to provide care management of acute psychosis associated with relapse through psychiatric nurses' home visit treatment and intensive involuntary community treatment as an alternative to hospitalization.

Limitations of the present study and future research issues

This study had several limitations. First, one of the limitations, a methodological limitation, is how the psychiatric nurses of the five psychiatric hospitals were recruited. The target population is not representative of the general population, and the study is limited by its cross-sectional nature and the lack of a suitable comparison group. Second, it might be pointed out that insufficient resources for the nursing staff employed at a psychiatric hospital in the region, as well as insufficient education, affect the results. Further investigation is necessary to compare nurses' beliefs between communities with and without sufficient resources for persons with schizophrenia and their families. Third, it is necessary to compare the factors influencing the belief about hospitalization of persons with schizophrenia and internalized stigma among psychiatric nurses, family caregivers, and the general public in order to design more effective community support systems for persons with chronic schizophrenia.

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APPENDIX

Chronic schizophrenia vignette

John is 44 years old. He lives in a boarding house in an industrial area. He has not worked for years. He wears the same clothes regardless of the weather and has let his hair grow long and untidy. He is always on his own and is often seen sitting in the park talking to himself. At times, he stands and moves his hands as if to communicate to someone in nearby trees. He rarely drinks alcohol. He speaks carefully using uncommon and sometimes made-up words. He is polite, but avoids talking with other people. At times, he accuses shopkeepers of giving information about him to other people. He has asked his landlord to put extra locks on his door and to remove the television set from his room. He says spies are trying to keep him under observation because he has secret information about international computer systems that control people through television transmitters. His landlord complains that John will not let him clean his apartment, which is becoming increasingly dirty and is filled with glass objects. John says he is using these 'to receive messages from space'.

放射線の子どもへの健康影響

被ばくの精神ストレス

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はじめに

2011年3月11日に発生した東北地方太平洋沖地震とそれにともなって発生した津波，およびその後の余震により引き起こされた東日本大震災は，未曽有の大規模地震災害をもたらしました。この震災は，福島県に設けられた原子力発電所の事故をも引き起こし，今までの地震災害とはその性質が大きく異なっています。

これまでに海外や日本を含めて原子力発電所における事故が報告されています。なかでも1979年3月28日にアメリカ合衆国東北部ペンシルベニア州のスリーマイル島原子力発電所で発生したスリーマイル島原子力発電所事故と1986年4月26日にソビエト連邦（現：ウクライナ）のチェルノブイリ原子力発電所4号炉で起きたチェルノブイリ原子力発電所事故は，大規模な災害でした。残念ながら子どもの精神健康への影響については，十分に調査されていないのが現状です。しかし，多くは家族の被ばくととらえると，大変重大な問題と考えられます。このため，本稿ではチェルノブイリ原子力発電所事故に関連する海外の先行研究におけるメンタルヘルスについて概説し，そのケアについて考えていきたいと思います。

チェルノブイリ原子力発電所事故の子どもの精神健康への影響について

1986年のチェルノブイリ原子力発電所事故については，1990年代後期から現在までより多くの精神健康に関する疫学調査研究がなされています（表1）。チェルノブイリ原子力発電所事故の20回目の記念のチェルノブイリForumレポート[1]では，精神保健問題がチェルノブイリ原子力発電所事故によるもっとも重要な公衆衛生の課題であると結論づけられていることからも精神的健康の保持・増進が必要であると考えられます。

1）出生前胎内被ばくに関する研究

ここでは，事故が起きた際に原発に近い汚染された地域で生活し，幼かったあるいは，出生前であった子どもたちを対象とした研究報告を中心に概説します。

Nyaguら[2]は，汚染地域に住んでいた544人の出産前の被ばくの影響について，チェルノブイリ原発事故後6～8歳，9～10歳の影響を調査しています。この結果，6～8歳での被ばく群での低いIQ，問題行動（被ばく群：45%，対照群：29%），放射線被ばくとIQの有意な相関，9～10歳の被ばく群72%，対

著者プロフィール 1995年に九州大学大学院修了。2005年から長崎大学大学院医歯薬学総合研究科精神神経科学（准教授）。2009年より，同大学院医歯薬学総合研究科保健学専攻教授，2010年4月より同大学院医歯薬学総合研究科精神障害リハビリテーション学分野教授に就任し，現在に至る。専門分野は社会精神医学。関連著書は「ICD-10 精神および行動の障害 DCR研究用診断基準新訂版」（医学書院），「心のバリアフリーを目指して―日本人にとってのうつ病，統合失調症―」（勁草書房）等。

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表1 チェルノブイリ原子力発電所事故による児童小児を対象とした精神健康に関する疫学調査研究

出生前胎内被ばく影響	Nyaguら[2]（1998）	544人の出生前曝露群と759人のハリコフの対照群を6～8歳で評価，補完調査で50人ずつの曝露群と対照群を9～10歳で評価	IQ，行動症状調査（6～8歳），精神医学的評価，EEG（補完調査）	6～8歳での被ばく群での低いIQ，問題行動（被ばく群：45%，対照群：29%），放射線被ばくとIQの有意な相関，9～10歳の被ばく群72%，にICD-10による精神障害
	Kolominskyら[4]（1999）	138人の出生前曝露群と122人の対照群を6～7歳，10～12歳に評価	神経心理学的・精神医学的評価	6～7歳における被ばく群における低いIQ，10～11歳では認めない。被ばく群では，対照群に比べ情動の障害，言語における発達障害の有病率が高い
	Igumnovら[5]（2000）	250人の出生前曝露群と250人の対照群を6～7歳，10～12歳に評価	神経心理学的・精神医学的評価	6～7歳における被ばく群における低いIQ，10～11歳では認めない。被ばく群では，対照群に比べ情動の障害，言語における発達障害の有病率が高い。両親の高い個人の不安と子どもたちの情動障害間の中等度の相関関係を認めた
	Litcherら[6]（2000）	事故時に妊娠中あるいは生後15か月までの300人の避難者，300人の性別をマッチさせた11歳のクラスメート（対照群）	IQ，記憶，学習，学年，心理学的症状	出生前被ばくについて認知機能と心理学的指標に有意差なし
	Brometら[7]（2000）			
	Bar Josephら[11]（2004）	1629人のイスラエルへの移住者（汚染度高，低，非汚染地域）	認知機能	群間で有意差なし
	Loganovskyら[12]（2008）	100人の出生前曝露と50人の非曝露クラスメート	臨床精神医学的評価，IQ，行動評価，EEG	被ばく群では71%，対照群では34%に何らかの精神科疾患を認めた。被ばく群では低IQとEEG異常を認めた
	Huizinkら[13]（2007）	フィンランドの14歳の232人の出生前被ばくと572人の非被ばく双生児	DSM-Ⅲ-Rによる精神症状と精神障害	被ばく群では，思春期に2倍のうつ病とADHDのリスク増加が認められた
	Thormina ら[8]（2008）	19歳の265人の避難者，261人のクラスメート，327人のキエフ中心部対照群	IQ，記憶，学習，心理学的症状	認知機能，心理学的，精神医学的評価に有意差なし。避難者は，対照群に比較し，自身の健康満足していない。血液生化学臨床検査では有意差を認めない
	Bromet ら[9]（2009）		DSM-Ⅳによるうつ病，不安障害，自記式精神健康	
	Bromet ら[10]（2010）			
	Heiervang ら[14][15]（2010a，2010b）	84人の出生前被ばく群と94人のノルウェー対照群	神経心理学的評価，言語，ワーキングメモリー，実行機能，IQ	被ばく群では言語機能の低下を認め，IQを調整しても有意差を認めた。被ばく群の中で妊娠16週以前の被ばくに有意差を認めた
思春期被ばく	Korolら[16]	504人の避難者と，キエフ在住の200人の対照群	血液検査，甲状腺機能，腹部エコー，不安，性格検査	避難者で1987～1990年と1990～1995年に消化器系，心血管系に関する自律神経失調症状を有意に高い割合で認めた

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照群 28%に ICD-10[3]による精神障害（会話および言語の特異的発達障害，小児＜児童＞期に特異的に発症する情緒障害など）を指摘しています。妊娠期間中の被ばくにともなう精神障害のリスクについて示唆しています。

Kolominsky ら[4]と Igumnov と Dorzdovitch[5]は，曝露群と非曝露群について IQ や精神医学診断について調査しました。曝露群においては，非曝露群に比べて，6～7 歳において有意に低い IQ を示しました。10～12 歳では認めませんでした。また，甲状腺機能と IQ には用量依存関係はないこともあきらかとなりました。ただこの IQ と親の教育レベルや社会生活の困難さなどの社会心理的，社会文化的要因も関与すると述べています。さらに，ICD-10 により，子どもの発達障害（小児＜児童＞期に特異的に発症する情緒障害，運動機能の特異的発達障害）と診断されるケースもあり，これは両親の高い不安と中等度の関連を認めました。

Litcher[6]，Bromet[7]らは，事故時に原発より 30 km 圏内在住で妊娠中あるいは生後 15 か月までの 300 人の避難者と 300 人の性別をマッチさせた 11 歳のクラスメートを対照群として，IQ，記憶，心理学的症状・認知機能，血液検査について比較しました。その結果，出生前被ばくについて身体的検査，血液検査では異常は認めませんでした。認知機能と心理学的指標に有意差を認めませんでしたが，避難した住民の受ける多くのストレス経験が，子どもへの影響を及ぼすことを示唆しています。Taormina，Bromet ら[8)～10)]は，その後 2005～2006 年にフォローアップ調査を行いました。彼らは，19 歳になり被ばく群（265 人）と対照群（261 人）でした。調査の結果，認知機能，心理学的，精神医学的評価に有意差はなく，血液生化学臨床検査でもとくに異常も認めませんでした。しかし被ばく群は，対照群に比較し，自身の健康に満足していないことがわかりました。

Bar Joseph ら[11]は，事故後イスラエルへの移住者のコホート研究を曝露後 12 年の 1998～2001 年に実施しました。対象は，1,629 人の子どもたちで，それぞれ，汚染度高（41%），低（25%），非汚染地域（34%）に分けて，認知機能について比較しましたが，群間では有意差は認めませんでした。

Loganovsky ら[12]は，11～13 歳の 100 人の出生前曝露と 50 人の非曝露クラスメートとその母親を対象に調査をしています。子どもたちには，臨床精神医学的評価，IQ，行動評価，脳波について，母親には外傷後ストレス障害（PTSD）関連の質問票として IES（Impact of Event Scale）について調査しました。被ばく群では 71%，対照群では 34%に何らかの精神科疾患を認めました。また，被ばく群では低 IQ と脳波異常を認めました。母親のメンタルヘルス，ストレス，妊娠時被ばくの要因は，これらの結果に影響を与えているかもしれないことが示唆されました。

Huizink ら[13]は，フィンランドにおける 14 歳の 232 人の出生前曝露群と 572 人の非曝露群双生児を対象に，DSM-Ⅲ-R による精神症状と精神障害の診断を行いました。妊娠第 2 三半期の被ばくにより，抑うつ症状のリスクが 2.32 倍でした。また被ばく群では，思春期に大うつ病（OR＝2.48，95% CI：1.06－5.7）と ADHD（OR＝2.01，95% CI：1.14－3.52）のリスク増加が認められました。

Heiervang ら[14)15)]は，チェルノブイリ事故で放射性降下物放射を浴びたノルウェー在住の 84 人の出生前曝露群群と 94 人の対照群について 2005～2006 年にかけて調査しました。思春期被ばく群では言語機能の低下を認め，IQ を調整しても有意差を認めました。また被ばく群の中でも，妊娠 16 週以前の被ばくに有意差を認めたと報告しています。

2）児童・思春期被ばくに関する研究

被ばく時点ですでに，児童・思春期であった研究は限られています。Korol ら[16]は，事故当時 12～14 歳であった 504 人の避難者と，キエフ在住の 200 人の対照群について，血液検査，甲状腺機能などに加え，STAI（State-Trait Anxiety Inventory），

モーズレイ性格検査，文章完成法テストを実施しました。その結果，避難者は，対照群に比べ，不安，葛藤などが有意に高く，とくに母親との関係に葛藤状況であることが示されました。さらに避難者で 1987～1990 年と 1990～1995 年に消化器系，心血管系に関する自律神経失調症状を有意に高い割合で認めました。

以上の結果をまとめると，キエフ，ノルウェー，フィンランドで行われた出生前被ばくの子どもたちの研究では，放射線被ばくに関連した神経心理，心理学的障害を指摘しています。しかし，それ以外の研究では，有意な精神的不健康や認知機能に影響は認められませんでした。このように，一定の見解は得られていないのが現状です。わが国においては，残念ながら子どもおよび家族の精神健康への影響に関するエビデンスは十分とはいえません。今後の精神保健の立案のためにも，十分な倫理的配慮を行った調査・研究が望まれます。

ころのケア

災害時には，心的外傷や生活環境によるストレスにより，不安や抑うつ等の心の問題が発生します。多くの場合，それらは時間の経過とともに自然に治っていきます。しかし，中には PTSD，うつ病・他の不安障害，アルコール依存症，身体化障害，心身症などのさまざまな精神疾患に発展していくことがあります。被ばくによる直接的な精神健康への影響だけではなく，被ばく後も続くストレスによって，さまざまな精神健康問題が生じる可能性があります。子どもにおけるストレス関連問題については，①突然不安になったり，興奮する，②突然現実にないようなことを言い出す，③必要以上におびえたり，敏感すぎる，④落ち着きがなくなったり，集中力がなくなる，⑤表情の動きが少なく，ボーっとしている，⑥引きこもって周りの人とのかかわりがなくなる，⑦眠らない，⑧繰り返し怖い夢を見る，⑨著しい赤ちゃんがえりがある，⑩自分が悪いからこんなことになったとか，あれこれ心配しすぎる，⑪頭痛，腹痛，吐き気，めまい，頻尿，夜尿など体の症状や体の一部が動かなくなったり，ときには意識がなくなり倒れるなどの症状がある，などの状態が現れる場合には，専門家の治療を勧めます。

「こころのケア」は，こころのみを扱うものではありません。ケアを考えるうえでは，bio-psycho-social-ethical な多面的な視点について考える必要があると思います（表 2）。これらの問題に取り組むことによって，初めて十分なこころのケアが実践できると考えます。

表 2　こころのケアに必要な要因

bio
心身健康の回復
レジリエンス（回復力）
psycho
人間関係（家族・友人他）
安心・安全の確保
被爆に関連する心理的負担・生活ストレスの軽減
2 次的災害・トラウマからの保護
social
被ばくに関連する社会・経済的問題の軽減
災害弱者への支援
偏見・差別の克服
ethical
本人の意思に十分配慮した取材，調査・研究や援助活動

りに～回復のために～

若い子どもを持つ母親においては，彼らの家族の健康への悪影響が不安を長引かせるため，ハイリスクグループが持続していることも指摘されています。このことについては，避難生活や家族内の教育・社会環境を含めた心理・社会的要因のかかわりを無視することはできませ

ん。このため被災された子どもだけではなく，家族や支援者のケアも同時に考えていく必要があると思われます。いたずらに不安をあおることのないマスメディアの協力も必要でしょうし，健康不安解消のためのシステムの確立も求められると思います。「被ばく＝PTSD」といった単純な図式に基づく理解は，決して被災者のケアに役立つものではありません。記憶の鮮明さや被ばく体験がアイデンティティー形成に及ぼす影響や，体験後の被災者を取り巻く偏見・差別，レジリエンス（回復力）を阻害する要因も包含した長期的転帰に着目しながら，精神健康全般の保持増進が必要であると考えます。

最後に，チェルノブイリあるいは長崎や広島にて被爆された人たちにおいて，いまだ適切なケアが受けられず，精神的問題を抱えながら生活している現状が一部残っていることも示唆されています。この問題の改善とともに，今後福島の原発事故に関連する事象のなかでも同様のことが起こらぬよう切に願っています。

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特集 ——『被爆・被ばくを振り返って』

長崎の原子爆弾被爆による精神健康への影響

中根 秀之

抄録：

多くの災害による被災者においては，通常メンタル・ヘルスの回復に大きな影響をもたらさない。しかし，一部の被災者においてはその苦悩は続くことが考えられる。1945年8月に長崎に原子爆弾が投下され，1945年の末までに73,884人が死亡し，74,909人が負傷した。原爆投下以後60年を超えるが，被爆者のメンタルヘルスについては，身体的健康と同様に重大な問題となっている。日本においては，被爆者の身体的健康については多くの調査研究がある一方で，メンタルヘルスに関連する調査研究がいくつか存在しているものの多くはない。本稿では被爆者のメンタルヘルス研究について概説し，その適切なケアを考える。「被爆即ちPTSD」といった単純な図式に基づく理解は，決して被災者のケアに役立つものではない。記憶の鮮明さや被爆体験がアイデンティティー形成に及ぼす影響や，体験後の被災者を取り巻くスティグマ，レジリエンスを阻害する要因も包含した長期的転帰に着目した研究が必要であり，被爆者の精神健康全般の保持増進が重要であることを十分に理解するべきであろう。今後，被爆者に対する幅広い適切なサポート体制の充実が望まれる。

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索引用語：原子爆弾，被爆者，精神健康，疫学調査，社会精神医学
Atomic Bomb, Hibakusya, Mental Health, Epidemiology, Social Psychiatry

英文タイトル：Mental Health Status of A-Bomb Survivors in Nagasaki

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はじめに

1945年8月9日11時2分に，長崎に原子爆弾が投下され，長崎市の北部の松山町の上空約500mで炸裂した。この長崎型原子爆弾は，「ファット・マン」と呼ばれ，広島型原子爆弾のウラン爆弾とは異なり，プルトニウム爆弾で，広島より強力，TNT火薬21,000トン分の威力とされている。しかし，長崎は山で囲まれた地形であるため，熱線や爆風が山によって遮断され，広島よりも原爆の被害の拡大を防いだ。1945年12月末までの推定では，負傷者74,909人，死者73,884人であった。当時の長崎市の人口が約24万人であったことからも，その被害の大きさがわかる。これは，災害と一括りにできない人為的な深刻な事態であると考えられる。

わが国の原子爆弾の身体影響については，広島，長崎の日本はもとより，米国と共同して設立された放射線影響研究所により詳細な調査研究が継続的になされている。一方，精神健康については，通常の人為的災害を越えたトラウマティック・ストレスの影響を与えることが予想され，調査が続けられたが，被爆直後，急性期においては，残念ながら十分な検討が行われているとは言い難い。本稿では，長崎における原子爆弾被爆に関連する精神健康，社会的背景・影響，被爆者への支援について概説する。

1．原子爆弾被爆による精神的影響に関する研究

(1) 1945年-1980年代

当然ではあるが，当時の惨状から考えても原爆投下直後の研究は，皆無である。しかし，被爆後2，3週間から1945年11月初旬までの急性期に九州大学の奥村，疋田によって行われた貴重な研究[15]がある。大村病院（現：長崎医療センター）に収容されていた患者192人から無作為に50人を抽出し，3期に分けて（初期（8月末まで），中期（9月初旬から10月中旬），後期（10月中旬から11月初旬））調査した。当時は，被爆直後にさまざまな精神障害を認めたという伝聞があったが，彼らの調査により，一般的な神経症的な愁訴が確認されている。被爆後初期の2，3週間後に50例中情緒昏迷3例，歩行不能1例，中期には火傷や外傷が癒えない中神経衰弱様症候，それ以後の後期に神経症あるいは精神病に発展した症例を報告した。

長崎大学の築城ら[19]は，昭和26年に原爆被災者の中にはっきり精神疾患という診断は下せないものの種々の神経症的愁訴を有している一群を指摘している。

その後被爆後8～11年の再適応期には，同じく長崎大学の仁志川ら[14]によって1956年の被爆者総合検診受診者7,297人を対象とした調査が行われた。対象者の7.3%に神経症を認め，特に神経衰弱症候群を呈するものが多かった。またその頻度には被爆直後の「原爆症」症状の有無が関連していたことを報告している。急性の放射線症状を呈した神経症様患者30例における脳波検査では3例に異常を認め，放射線による器質的あるいは機能的障害に基づく一種のEncephaloseないしはSomatoseと考えるのが妥当としている。

このように，この時期の調査においては，いずれも神経症としての影響が記されている。

(2) 1990年代

原爆投下から長い時間が経過し，被爆者の高齢化も進む状況下で，彼らのメンタル・ヘルスに関して的確に評価され，必要なケアについて検討される必要がある。しかし，事例の適格性，加齢に関わる変化，身体的疾患，社会経済的背景などのさまざまなバイアスによって，その評価は非常に困難である。

長崎大学では，長崎市の協力を得て，原爆健康管理センター（長崎市）において被爆者定期健康診断受診者を対象に，1994年10月から1996年8月の期間に2段階抽出調査を行った[12]。その結果，のべ全受診者38,827人の中で，一次調査7,670人（男性：3,216人，女性：4,454人），二次調査226人（男性：105人，女性：121人）が調査に参加した。一次調査でGHQ-12の4点以上の高得点者については，9.3%であり，近距離被爆者が遠距離被爆者に比べGHQ高得点者の頻度が高く，被爆距離が全般的な心身健康レベルに影響を与えていることが示唆された。さらにCIDIによる二次面接では，226人中52人（23.0%）に（持続性身体表現性疼痛障害を除いた）何らかの精神疾患を有することが示唆された。WHOの主導する世界精神保健（World Mental Health, WMH）調査におけるこころの健康についての疫学調査（WMH日本調査，WMHJ）の結果[3]では，地域住民合計4,134人（平均回収率 55.1%）の中で，調査時点までの生涯に地域住民の4人に1人が，また過去12カ月間に10人に1人が，何らかの精神障害（DSM-IV診断による気分・不安・物質関連障害）を経験していた。このように一般住民を対象とした調査研究で得られたデータに近似している。この時期になり，被爆の精神影響は，神経症だけではなく感情障害も含んだCommon Mental Disorderの問題として扱われるようになってきている。

また，被爆者に加え被爆二世への精神影響調査も1,592人を対象に実施され，10代20代男性，10代女性にGHQ-12での4点以上の高得点者の割合が多いことが示され，今後の詳細な調査が必要であることが指摘された[9]。

(3) 2000年代

長崎大学では，2000年に被爆指定地域周辺の被爆体験住民における健康影響を調べるために，調査研究を太田らが「聞いてください！　私たちの心のいたで　原子爆弾被爆未指定地域証言調査報告書」[16]にまとめた。この中では，7,082人の原子爆弾未指定地域住民を対象に，被爆時の被災状況，現在の健康状態等について聞き取りの調査を行っている。さらにPTSD診断用構造化面接尺度であるClinician-Administered PTSD Scale for DSM-IV（CAPS）を用いて，PTSDの生涯有病率が，6.4%であり，不全型は18.3%という結果も得ている。これも当時の一般住民を対象にした地域調査はないが，Kesslerらによる米国の一般住民を対象としたPTSD生涯有病率が7.8%[5]，全湾岸戦争退役軍人における有病率10.1%[4]と比較しても近い値であることは否めず，また前述のWMH2000調査では，わが国における地域住民におけるPTSDの頻度が，生涯有病率で1%前後，12カ月有病率で0.4～0.6%程度みられたため，未指定地域における被爆体験住民におけるメンタル・ヘルス問題は無視できないと思われた。この調査は，原爆被爆者において被爆から長期経過後の初めての詳細な研究成果として注目され，災害精神医学[17]に端を発して，被爆者のPTSDに注目が集まることとなった。

また2002年の本田らの報告[2]では，被爆時の状況と現在の精神健康状況との関連を調査が行われ，GHQ-12で高得点者の割合が8.4%であり，原爆で知人・友人を亡くした人，爆心地から近い場所で被爆した人，被爆直後に身体的症状が出現した人，これまでに被爆の後遺症と考えられる症状がみられた人などに精神的問題を持つ可能性が高いという結果が得られた。

長崎以外の調査チームによる研究としては，2000年に設置された「原子爆弾未指定地域証言調査報告書に関する検討会」によって構成された厚生省科学研究特別事業「PTSD等に関連した健康影響評価に関する研究」班（主任研究者：吉川武彦）によるもの[20]がある。2001年3月から約1カ月間，原爆投下時に爆心から12km以内の原子爆弾未指定地域に住み，調査時点でもその地域に居住する人達の精神的・身体的状態に関する疫学調査を行った。この調査によって，放射線に被ばくしていなくても原爆投下と放射能被害に基づく精神的不安（トラウマ）が原因となって，原爆被害者は半世紀以上にわたり精神的後遺症を生じることが示された[6]。また爆心地の近くにいたことは精神的健康度の悪化と強く関連しており，放射線障害への誤った知識も中等度の関連があった。爆発そのものへの不安よりも放射線障害の可能性を知った不安が後の精神的不健康と関連していた[7]。

この後，長崎大学では2004年には，「被爆体験者委員会」による「被爆体験者（爆心地から半径12km以遠に居住する者）実態調査」が，国立精神

神経センターが行った調査方法を踏襲する形式で行われた。爆心地から12km以遠長崎県内に居住する被爆体験者（第2種健康診断受診者証所持者）のうち長崎県内に居住する1,071人（2003年9月30日現在）の中で，この調査の対象者である77歳以下の991人に対して事前アンケート調査したところ936人から回答を得た。その後，対面聞き取り調査のために，さらにこの936人から無作為抽出を行い，最終的に315人から回答を得た。この結果，GHQ-28では，6点以上のハイリスク群，14点以上の重度ハイリスク群はそれぞれ79.3%，26.9%を占め，前回調査の“被爆体験群”との間では有意差を認めなかった。また“対照（非被ばく）群”と比較すると有意に高かった。その結果，平均は21.8点で，日本語版のIES-Rにおいては，飛鳥井らにより24〜25点がcut off pointを参考にすると，本調査では25点以上は38.1%を占めていた。爆心地から12km以遠に居住する被爆体験住民についても，被爆体験に関連し，他の要因では説明困難な精神健康の悪化が認められた[1]。

さらに2006年にも，中川ら[11]により原爆ホーム等の施設入所者128人を対象にPTSD症状に関する調査研究が実施され，被爆後59年経った時点でも，被爆距離が短いことや被爆時の急性症状があることとPTSD症状に有意な関連を認めたことが示された。このように，長崎県においては継続して被爆者の精神健康について調査・研究が行われている。しかし，2000年以降では，主にトラウマティック・ストレスとしての被爆体験あるいは被爆者のPTSDという側面が特に知られるようになってきた。これは，大きな意味を持つ一方で，全般的なより広い意味での被爆者の精神健康を知る上では妨げとなるリスクも孕んでいる。

2. 被爆の与える社会的背景とその影響

被爆については，医学的問題以外にも多くの社会的背景についても理解しておく必要がある[13]。1954（昭和29）年3月に発生した第5福竜丸のビキニ環礁被ばく事件をきっかけに，広島・長崎の両県市による陳情の後，原子爆弾投下から11年半を経た1957（昭和32）年4月「原子爆弾被爆者の医療等に関する法律（原爆医療法）」が施行され，「原子爆弾が投下された際，当時の広島市もしくは長崎市の区域内または政令で定めるこれらに隣接する区域内にあった者」が被爆者とされることとなった。被爆当時の長崎市の行政区域とこれに隣接する町村の一部が被爆地域に指定されて，国庫負担による健康診断と治療が開始された。次いで，1960（昭和35）年に特別被爆者制度の創設と一般疾病医療費および医療手当の支給に関する原爆医療法の改正法が成立し，1968（昭和43）年には特別手当・健康管理手当等の各種手当の支給制度の創設を目的とした「原子爆弾被爆者に対する特別措置に関する法律（原爆特別措置法）」，その後も1994（平成6）年「原子爆弾被爆者に対する援護に関する法律（原爆被爆者援護法）」が成立した。

長崎における指定された被爆地域のいびつさは，指定地域周辺に居住する住民にとって多大な不平等感を生むものであり，長崎市・長崎県は被爆地域拡大是正の実現を長い間目指してきた。その結果，長崎では1974（昭和49）年10月健康診断特例区域が創設され，被爆地域外の周辺地域にいた者にも無料健康診断の実施を開始した。さらに1976（昭和51）年9月にも健康診断特例区域の拡大が行われ，長崎の爆心地から6km周辺町村の全域または一部を追加され，2003（平成14）年4月には，健康診断特例区域を，長崎の爆心地から12km以内の区域が第二種特例区域として追加されてきた。これにより，長崎においては，「被爆者援護法に準じた医療費の支給を行う」と「被爆体験者」という呼称のもとにおける援護措置が発表された。被爆者援護法附則第17条に基づく健康診断の実施，被爆体験による精神的要因に基づく疾病・疾患にかかる医療費の支給とカウンセリングの実施などの実施要綱が制定され，事業が開始されたのである。

以上のようなプロセスから，長崎には原爆被爆に関して行政上いくつかの被災者カテゴリが設定されている。いわゆる被爆者や健康特例区域の被爆者，そして被爆体験者の別であり，前二者は放射線の影響を身体的レベルで受けたと認定された人であり，後者は放射線による直接的影響はないが精神的健康上の不健康が目立つと見なされた人である。もちろん，被爆者であっても爆心地からの距離に比例して心身の不健康度を表すGHQ得点は高く，さらに精神科的臨床面接などで精神疾患への高い罹患性も確認され，こうした問題が原爆被爆という悲惨な人災に基づく影響の現れであることは否定できない。この道筋において，科学的根拠の必要性から，長崎あるいはそれ以外の研究者による調査研究の結果は大きな影響を与えているといえよう。これまでの調査研究と精神科医療の実践を通して医療者は被災者における具体的なさまざまな問題点を明確にするだけでなく，政策立案者などに積極的にアプローチして，行政的支援の在り方を提案していくことも必要かもしれない。

3. 原爆被害者支援を考える

(1) 在外被爆者の支援

在外被爆者については約4,300人といわれており，その内訳は，韓国：約2,930人，アメリカ：約970人，ブラジル：約160人，その他：約270人である。このため，長崎県・長崎市は，厚生労働省の委託による在外被爆者支援対策として，2002年6月より「在外被爆者支援事業」を開始した。長崎大学では，この事業に同行してソウル，テグ在住の在韓被爆者の精神健康について，大韓赤十字社，慶熙（キョンヒ）大学の協力を得て，2008年に心身健康の実態調査を行った。対象は，相談事業に参加した被爆者であり，被爆者群373人，非被爆者群429人に対して対面聞き取り調査を行い，その結果GHQ-12で4点以上の高得点者の割合が，非被爆者群に比べ被爆者群において高いことが示された[8]。被爆から65年経った現在まで，トラウマティック・ストレスによる精神的・心理的問題が生じており，在韓被爆者においても，国内被爆者と同様にメンタル・ヘルス・ケアの必要性が示唆された。

(2) 独居被爆者のケア

原爆投下から半世紀以上を経て，被爆者は平均年齢70歳を超え，原爆被害を心的外傷体験とした人々も，老化による身体的問題，子供の自立など家族構成の変化，退職等の社会的役割の変化，喪失体験も加わり，メンタル・ヘルス・ケアのニーズは高まっている。

このため，長崎県と協力し，県内に在住する65歳以上のひとり暮らし被爆者を対象に，心の悩み，生活上の困りごと，医療・福祉の問題などに関する総合的な心身のサポート事業が立案された[10]。2006年に3,291人に対し，訪問相談員の訪問を希望するか否かの確認のため郵送し，回答者のうち訪問を希望していた中から361人を対象に訪問活動が行われた。その結果，IES-R高得点群におけるGHQ平均点は3.17点，IES-R低得点群におけるGHQ平均点は1.42点となっており，IES-R高得点群のGHQ平均点は有意に高いことが明らかとなった。また，IES-R高得点群におけるWHO-QOL平均点は2.90点，IES-R低得点群におけるWHO-QOL平均点は3.13点で，IES-R高得点群のWHO-QOL平均点は有意に低かった。これらの結果から，被爆体験がトラウマとして強く残っている被爆者は，そうでない被爆者に比較すると，現在の精神的健康度が悪く，日常生活の質が低いことが確認された。

おわりに

被爆者を巡る調査・研究が継続的に長崎でも行われ，その成果が，社会的，政治的にも大きな影響を及ぼすことがある。特に，長崎においてはこれまで被爆地域の拡大や，居住要件の撤廃につながる一方で，「被爆体験者」という新たなカテゴリの設置に伴い，従来の「被爆者」とは別であるという問題が生じることになった。研究者の意図と異なる部分での社会的影響の大きさに不安を感じることもある。

一方で，これまでの研究報告を概観し，被爆者に与える精神影響は，長崎あるいは広島に限らず，被爆後65年を経た現在でもいまだ強く存在

し，長期にわたるケアの重要性が示唆された。それらは，被爆した者にとって，不安，抑うつ，不眠といった症状のみならず，生活の質（QOL）にも大きな影を落としている。直接的な被爆体験のみならず，被爆に関連する健康不安，偏見・差別体験といった事後的要因もこのメンタル・ヘルスの問題に関係している。このため，長崎においては高齢者化する被爆者のケアについても整備をはじめつつある。さらに現在，Posttraumatic Growth（PTG）[18]という視点もみられるようになり，新たな被爆者のケアに役立てる試みも検討されている。

「被爆即ちPTSD」といった単純な図式に基づく理解は，決して被災者のケアに役立つものではないと考える。記憶の鮮明さや被爆体験がアイデンティティー形成に及ぼす影響や，体験後の被災者を取り巻くスティグマ，レジリエンスを阻害する要因も包含した長期的転帰に着目した研究によって，被爆者の精神健康全般の保持・増進することを我々医療専門職は十分に理解し実践するべきであろう。今後，被爆者に対する幅広い適切なサポート体制の充実が望まれる。

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abstract

Mental Health Status of A-Bomb Survivors in Nagasaki

Hideyuki Nakane

The most survivors of disaster usually recover with few or no lasting effects on their mental health. However, in some portions of survivors, distress lasts long. The atomic bomb detonated to Nagasaki in August 1945 instantaneously destroyed almost all areas of the city, resulting in a total of ca. 73,884 deaths by the end of 1945 and about 74,909 injured people. Since the A-bomb survivors reached over 60 years of age, their mental health as well as physical health has become of great concern. Some studies on their mental health conditions have been carried out in Japan. I give an outline about a precedent study on mental health of the A-bomb survivors in this report. The mental health studies of the A-bomb survivors who paid attention to a being bombed experience, stigmatization, long-term outcome, recovery are necessary. The improvement of wide appropriate support system for the A-bomb survivors is expected in future.

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Selection and Accumulation of an HIV-1 Escape Mutant by Three Types of HIV-1-Specific Cytotoxic T Lymphocytes Recognizing Wild-Type and/or Escape Mutant Epitopes

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It is known that cytotoxic T lymphocytes (CTLs) recognizing HIV-1 escape mutants are elicited in HIV-1-infected individuals, but their role in the control of HIV-1 replication remains unclear. We investigated the antiviral ability of CTLs recognizing the HLA-A*24:02-restricted Gag28 -36 (KYKLKHIVW) epitope and/or its escape mutant (KYRLKHIVW) elicited in the early and chronic phases of the infection. Wild-type (WT)-epitope-specific CTLs, as well as cross-reactive CTLs recognizing both WT and K30R (3R) epitopes, which were predominantly elicited at early and/or chronic phases in HLA-A*24:02$^+$ individuals infected with the WT virus, suppressed the replication of the WT virus but failed to suppress that of the 3R virus, indicating that the 3R virus was selected by these 2 types of CTLs. On the other hand, cross-reactive and 3R-specific CTLs, which were elicited in those infected with the 3R virus, did not suppress the replication of either WT or 3R virus, indicating that these CTLs did not contribute to the control of 3R virus replication. High accumulation of the 3R mutation was found in a Japanese population recently recruited. The selection and accumulation of this 3R mutation resulted from the antiviral ability of these Gag28-specific CTLs and high prevalence of HLA-A*24:02 in a Japanese population. The present study highlighted the mechanisms for the roles of cross-reactive and mutant-epitope-specific CTLs, as well as high accumulation of escape mutants, in an HIV-1-infected population.

Human immunodeficiency virus type 1 (HIV-1)-specific cytotoxic T lymphocytes (CTLs) play an important role in the control of HIV-1 during the acute and chronic phases of an HIV-1 infection (22, 40). However, HIV-1-specific CTLs cannot completely eliminate HIV-1-infected cells, because HIV-1 escapes from CTL-mediated immune pressure by various mechanisms, such as selection of escape mutations, Nef-mediated HLA class I downregulation, and skewed maturation of memory HIV-specific CD8$^+$ T lymphocytes (5, 8, 9). The most documented escape mechanism is acquisition of amino acid mutations within the CTL epitope and/or its flanking regions. These mutations lead to reduced ability of peptide to bind to HLA class I molecules, impaired T cell receptor (TCR) recognition, and defective epitope generation (21, 31). These escape mechanisms are involved in impaired activities of HIV-1-specific CTLs to kill target cells infected with escape mutant virus and to suppress HIV-1 replication, contributing to the selection of escape mutant viruses (5, 10, 13, 20, 29, 35, 41).

There is growing evidence that escape mutations selected by HLA class I-restricted CTLs accumulate at the population level (7, 28, 36). The accumulation of escape mutants may affect the clinical outcomes for HIV-1-infected individuals (11, 37, 38). On the other hand, it is known that CTLs recognizing escape mutants are elicited after the emergence of the escape mutant selected by wild-type (WT) epitope-specific CTLs (2, 4, 12, 15, 33, 39). The escape mutant-specific CTLs were also elicited in new hosts carrying the same restricted HLA allele when they were infected with the mutant (15). Several studies showed that CTLs cross-recognizing the WT and its escape mutant epitopes are elicited before or after the emergence of the escape mutant in the same hosts (18, 25, 26, 33, 34). However, the antiviral abilities of these cross-reactive CTLs remain unknown, since the recognition of cross-reactive CTLs for synthesized epitope peptides was characterized by using the enzyme-linked immunosorbent spot assay (ELISPOT) or ^{51}Cr cytotoxic assay in those studies. We previously showed that HLA-A*24:02-restricted Nef 138-specific CTLs recognizing an escape mutant had weaker ability to suppress the replication of the mutant virus than that of the WT virus (15). However, it still remains unclear whether cross-reactive or escape mutant-specific CTLs contribute to the control of HIV-1, since the CTLs have not been analyzed in detail.

To clarify the abilities of cross-reactive and escape mutant-specific CTLs to recognize HIV-1-infected cells, we analyzed CTLs specific for HLA-A*24:02-restricted HIV-1 Gag28-36 (KYKLKH IVW; Gag28), which is the only immunodominant Gag epitope presented by this HLA class I allele (24). Since HLA-A*24:02 is found in approximately 70% of the Japanese population (42), the mutants of HLA-A*24:02-restricted epitopes may accumulate in HIV-1-infected Japanese individuals. We previously suggested that K30R (3R) in the Gag28 epitope is an escape mutation from HLA-A*24:02-restricted Gag28-specific CTLs (30) and that CTLs recognizing 3R are elicited in HIV-1-infected HLA-A*24:02$^+$ individuals (46). From these studies, we hypothesized that cross-reactive CTLs recognizing WT and 3R mutant epitopes and/or 3R-specific CTLs are elicited in HLA-A*24:02$^+$ HIV-1-infected individuals after the 3R mutant is selected and in new 3R virus-infected hosts carrying HLA-A*24:02. Here, we investigated the elicitation of Gag28-specific CTLs in 12 HLA-A*24:02$^+$ HIV-1-infected Japanese individuals who could be monitored from the early phase to the chronic phase of an HIV-1 infection, as well as the abilities of cross-reactive, 3R mutant-specific, and WT-specific CTLs to kill WT or 3R virus-infected cells and to suppress the replication of the WT or 3R virus. In addition, we investigated the accumulation of the 3R mutation in HIV-1-infected nonhemophiliac Japanese individuals, as well as in Japanese hemophiliacs who had been infected around 1983. The results clarified the role of CTLs recognizing the WT and/or 3R epitope in high accumulation of the 3R mutant in HIV-1-infected Japanese individuals.

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MATERIALS AND METHODS

Samples from HIV-1-infected individuals. This study was approved by the ethics committee of Kumamoto University and the National Center for Global Health and Medicine. Informed consent was obtained from all individuals according to the Declaration of Helsinki. For sequence analysis, blood specimens were collected in EDTA. Plasma and peripheral blood mononuclear cells (PBMCs) were separated from whole blood. HLA types were determined by standard sequence-based genotyping. Twelve HLA-A*24:02$^+$ individuals who could be monitored from the early to the chronic phase of an HIV-1 infection were recruited for CTL analysis. Early HIV-1 infection was confirmed by seroconversion within 6 months or by an increasing number and density of bands on Western blots. Four-hundred fifty-one chronically HIV-1-infected individuals were also recruited for sequence analysis.

Cells. C1R cells expressing HLA-A*24:02 (C1R-A2402) and 721.221 cells expressing CD4 and HLA-A*24:02 (721.221-CD4-A2402) were previously generated (27, 30). These cells were cultured in RPMI 1640 medium containing 5 to 10% fetal bovine serum (FBS) and 0.15 mg/ml hygromycin B. MAGIC-5 cells (CCR5-transfected HeLa-CD4/long terminal repeat–β-galactosidase [LTR–β-Gal] cells) were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% FBS as described previously (17).

Induction of Gag28-specific T cells. PBMCs from HIV-1-infected HLA-A*24:02$^+$ individuals were stimulated with WT or 3R peptide (1 μM) in culture medium (RPMI 1640 containing 10% FBS and 200 U/ml human recombinant interleukin-2 [rIL-2]). After 14 days, the cultured PBMCs were tested for gamma interferon (IFN-γ) production by performing an intracellular cytokine staining (ICC) assay.

ICC assay. C1R-A2402 cells were prepulsed or not with the WT or 3R peptide at concentrations from 0.1 to 1,000 nM at 37°C for 1 h and then were washed twice with RPMI 1640 containing 10% FBS. PBMCs cultured for 2 weeks after peptide stimulation were incubated with the C1R-A2402 cells in a 96-U plate (Nunc) at 37°C. Brefeldin A (10 μg/ml) was added after a 2-h incubation, and then the cells were incubated for an additional 4 h. Subsequently, the cells were stained with Pacific-blue-conjugated anti-CD8 monoclonal antibody (MAb) (BD Biosciences) and 7-amino-actinomycin D (7-AAD) (BD Biosciences) at 4°C for 30 min, after which the cells were fixed with 4% paraformaldehyde solution and rendered permeable with permeabilization buffer (0.1% saponin and 10% FBS in phosphate-buffered saline) at 4°C for 10 min. Thereafter the cells were stained with fluorescein isothiocyanate (FITC)-conjugated anti-IFN-γ MAb (BD Biosciences) at 4°C for 30 min and then washed twice with the permeabilization buffer. The percentage of CD8$^+$ cells producing IFN-γ was analyzed by flow cytometry (FACSCanto II).

Generation of Gag28-specific CTL clones. Gag28-specific CTL clones were generated from Gag28-specific bulk-cultured T cells by limiting dilution in 96-U plates, together with 200 μl of cloning mixture (1 × 10^6 irradiated allogeneic PBMCs from healthy donors and 1 × 10^5 irradiated C1R-A2402 cells prepulsed with the WT or 3R peptide at a concentration of 1 μM in RPMI 1640 containing 10% FBS, 200 U/ml rIL-2, and 2.5% phytohemagglutinin [PHA] soup). After 14 to 21 days in culture, the growing cells were tested for cytotoxic activity by performing the standard chromium release assay. Since TCRs on these CTL clones were not sequenced, it is still possible that they were oligonucleotide clones.

HIV-1 clones. An infectious provirus, HIV-1 pNL-432, was reported previously (1). NL-432gagSF2 and NL-432gagSF2-3R were previously generated (30).

Assay of cytotoxicity of CTL clones toward target cells prepulsed with the epitope peptide. The cytotoxic activities of Gag28-specific CTL clones were determined by use of the standard chromium release assay, as described previously (15). Briefly, 721.221-CD4-A2402 cells were incubated with 100 μCi of $Na_2{}^{51}CrO_4$ in saline for 1 h and then washed 3 times with RPMI 1640 containing 10% newborn calf serum. The labeled target cells (2 × 10^3/well) were prepulsed with the WT or 3R peptide at concentrations of 1 to 1,000 nM for 1 h and then cocultured at 37°C for 4 h with effector cells at an effector-to-target (E:T) ratio of 1:1 in 96-U plates (Nunc). The supernatants were collected and analyzed with a gamma counter. Spontaneous ^{51}Cr release was determined by measuring the counts per minute in supernatants from wells containing only target cells (cpm spn). Maximum ^{51}Cr release was determined by measuring the cpm in supernatants from wells containing target cells in the presence of 2.5% Triton X-100 (cpm max). Specific lysis was defined as (cpm exp − cpm spn)/(cpm max − cpm spn) × 100, where "cpm exp" is the counts per minute in the supernatant in the wells containing both target and effector cells.

Assay of cytotoxicity of CTL clones toward target cells infected with HIV-1. 721.221-CD4-A2402 cells were infected with WT or 3R virus, and then the infection rates were determined by detecting intracellular p24 antigen (Ag)-positive cells stained with FITC-conjugated anti-p24 Ag MAb (KC57-FITC; BD Biosciences). When approximately 50% of the total cells were p24 Ag-positive cells, they were used as target cells. The ^{51}Cr-labeled target cells (2 × 10^3/well) were cocultured with effector cells at E:T ratios of 0:1 to 2:1 in 96-U plates at 37°C for 6 h. The supernatants were collected and analyzed with a gamma counter.

Generation of HLA-peptide tetrameric complexes. HLA class I-peptide tetrameric complexes (tetramers) were synthesized as previously described (3). The WT or 3R peptide was added to the refolding solution containing the biotinylation sequence-tagged extracellular domain of the HLA-A*24:02 molecule and β2 microglobulin. The purified monomer complexes were mixed with phycoerythrin (PE)-labeled streptavidin (Molecular Probes) at a molar ratio of 4:1.

Tetramer binding assay. CTL clones were stained with PE-conjugated tetramer at concentrations of 1 to 100 nM at 37°C for 30 min. After 2 washes with RPMI 1640 containing 10% FBS (R10), the cells were stained with FITC-conjugated anti-CD8 MAb and 7-AAD at 4°C for 30 min. Thereafter, the cells were washed twice with R10 and then analyzed by flow cytometry (FACSCanto II). The mean fluorescence intensity (MFI) of tetramer-positive cells among CD8-positive cells was calculated.

Replication suppression assay. The ability of Gag28-specific CTLs to suppress HIV-1 replication was examined as previously described (43). CD4$^+$ T cells were isolated from PBMCs of healthy HLA-A*24:02$^+$ donors and incubated with a given HIV-1 clone at 37°C for 6 h. After 3 washes with R10, the cells (3 × 10^4/well) were cocultured with Gag28-specific CTL clones at E:T ratios of 0.1:1 to 1:1 in R10 containing 1% nonessential amino acid solution and, 1% 100 mM sodium pyruvate (complete medium) plus 200 U/ml rIL-2. From day 3 to day 7 postinfection, a 30-μl volume of culture supernatant was collected, and the volume removed was replaced with fresh medium. The concentration of p24 Ag was measured by using an enzyme-linked immunosorbent assay (ELISA) (HIV-1-p24-Ag ELISA kit; ZeptoMetrix).

Replication kinetics assay. The replication kinetics of the WT and 3R viruses were examined as previously described (17). After CD4$^+$ T cells (2 × 10^6) had been exposed to each infectious virus preparation (500 blue cell-forming units in MAGIC-5 cells) for 2 h and washed twice with R10, they were cultured in 1 ml of R10 containing 1% nonessential amino acid solution and 1% 100 mM sodium pyruvate (complete medium) plus 200 U/ml rIL-2. Then, 0.1 ml of the culture supernatant was collected from

day 2 to day 10 postinfection, and the volume removed was replaced with fresh medium. The concentration of p24 Ag in the supernatant was measured by using ELISA. Replication kinetics assays were performed in triplicate.

Sequence of autologous virus. Viral RNA was extracted from plasma samples from HIV-1-infected individuals by using a QIAamp MinElute virus spin kit (Qiagen). For clone sequencing, cDNA was synthesized from the RNA with SuperScript III and Random Primers (Invitrogen), and the Gag region was amplified by nested PCR with *Taq* DNA polymerase (Promega). Then, the PCR products were gel purified and cloned with a TOPO TA cloning kit (Invitrogen). For bulk sequencing, the Gag region was amplified from the RNA by using the SuperScript III One-Step RT-PCR System with Platinum *Taq* DNA Polymerase (Invitrogen) and Gag-specific primers, and then the second PCR was done. We prepared the Gag-specific primer sets shown below. For clone sequencing, 5′-TTTTT GACTAGCGGAGGCTAGAA-3′ and 5′-CACAATAGAGGGTTGCTAC TGT-3′ were used for the first PCR and 5′-GGGTGCGAGAGCGTCGG TATTAAGC-3′ and 5′-TAAGTTCTTCTGATCCTGTCTG-3′ for the second PCR. For bulk sequence, 5′-TCTCTCGACGCAGGACTC-3′ and 5′-AGGGTTCCTTTGGTCCTTGT-3′ were employed for the reverse transcription (RT)-PCR and 5′-TCTCTCGACGCAGGACTC-3′ and 5′-TCTCCTACTGGGATAGGTG-3′ for the second PCR. All DNA sequencing was performed by using a BigDye Terminator cycle-sequencing kit (Applied Biosystems) and an ABI Prism 310 or 3100 genetic analyzer.

RESULTS

Selection of the 3R mutation by WT epitope-specific CD8$^+$ T cells in individuals infected with WT virus. We investigated 12 HIV-1-infected HLA-A*24:02$^+$ individuals who could be monitored from the early to the chronic phases of their infections. We first analyzed the sequence of the Gag28 epitope at an early phase in the 12 HIV-1-infected HLA-A*24:02$^+$ individuals. The WT sequence of the Gag28 epitope was detected in 4 of these individuals, whereas 3R was found in the other 8, suggesting that the former and the latter individuals had been infected with WT and 3R viruses, respectively (Table 1). This is consistent with a previous finding that the 3R mutant is found in approximately 70% of HIV-1-infected HLA-A*24:02$^+$ individuals (30). We investigated the elicitation of Gag28-specific CD8$^+$ T cells in the individuals infected with WT virus. PBMCs from these individuals at early and chronic phases were stimulated with WT or 3R peptide and then cultured for 2 weeks. The frequency of Gag28-specific CD8$^+$ T cells among the cultured cells was measured by performing the ICC assay using WT and 3R peptides. Gag28-specific CD8$^+$ T cells were detected at the early phase in 3 of the 4 individuals when the PBMCs were stimulated with WT peptide (Table 2). In 2 individuals, i.e., KI-092 and KI-161, Gag28-specific CD8$^+$ T cells were much more WT specific than 3R mutant specific, whereas in KI-158 they recognized both peptides, but especially the WT peptide (Fig. 1). On the other hand, cross-reactive CD8$^+$ T cells were induced in KI-092 and KI-161 when their PBMCs had been stimulated with 3R peptide, although the frequency of cross-reactive CD8$^+$ T cells induced by stimulation with 3R peptide was lower than that of WT-specific cells induced by stimulation with WT peptide. The 3R peptide failed to induce Gag28-specific CD8$^+$ T cells in PBMCs from KI-158. Thus, WT-specific CD8$^+$ T cells were predominantly elicited at an early phase in the individuals infected with WT virus, although a small but significant number of cross-reactive T cells were also elicited in them.

To clarify the specificity of Gag28-specific CD8$^+$ T cells at the early phase in KI-092 and KI-161, we generated Gag28-specific CTL clones by stimulating early-phase PBMCs from KI-092 and KI-161 with the WT peptide. The CTL clones from KI-092 showed a much greater ability to kill cells prepulsed with WT peptide than to kill those prepulsed with the 3R peptide (Fig. 2A), suggesting that they were WT-specific CTLs. To further clarify the specificity of these T cell clones, we investigated the binding affinity of the clones for WT peptide-binding HLA-A*24:02 tetramer (WT tetramer) and 3R peptide-binding HLA-A*24:02 tetramer (3R tetramer). These clones exhibited much greater binding ability to the WT tetramer than to the 3R tetramer (Fig. 2B). These results together indicate that these were WT-specific CTL clones. We further analyzed the abilities of these clones to recognize HIV-1-infected cells. These CTL clones effectively killed WT-virus-infected cells, but not the 3R virus-infected cells (Fig. 2C), and showed the ability to suppress the replication of WT virus, but not to suppress that of the 3R virus (Fig. 2D). WT-specific CD8$^+$ T cell clones established from early-phase PBMCs of KI-161 also showed a similar ability to kill WT virus-infected and 3R virus-infected cells (Fig. 3). In these individuals, the 3R mutant virus became dominant 1 to 2 years after the early phase (Table 1). Taken together, these findings suggest that the 3R mutation was selected by WT-specific CTLs.

TABLE 1 Sequence at Gag30 in 12 HLA-A*24:02$^+$ individuals with an early-phase HIV-1 infection

Patient ID[a]	Sampling date (mo/day/yr)	Gag30 sequence	Method
KI-091	12/13/2000	3R	Cloning
	12/27/2000	3R	Direct
	1/7/2002	3R	Direct
	7/9/2003	3R	Cloning
	9/29/2004	3R	Cloning
	8/4/2005	3R	Cloning
KI-092	1/22/2001	WT	Cloning
	11/21/2001	WT	Cloning
	12/10/2002	WT/3R	Cloning
	8/14/2003	3R	Cloning
KI-102	5/11/2001	WT	Direct
	7/5/2004	WT	Direct
	3/28/2005	WT	Direct
KI-126	7/19/2001	3R	Direct
	1/18/2002	3R	Direct
	11/15/2004	3R	Direct
	9/12/2005	3R	Direct
KI-134	10/25/2001	3R	Direct
	6/30/2004	3R	Direct
KI-136	10/29/2001	3R	Direct
	7/10/2003	3R	Direct
KI-140	11/08/2001	3R	Direct
KI-151	5/2/2001	3R	Direct
	8/28/2003	3R	Direct
KI-154	4/12/2002	3R	Direct
KI-158	6/14/2002	WT	Direct
	10/11/2002	WT	Direct
	8/25/2003	WT	Direct
	11/14/2003	WT/3R	Direct
	2/23/2004	3R/WT	Direct
	11/1/2004	3R	Direct
	4/4/2005	3R	Direct
KI-161	2/15/2002	WT	Direct
	9/12/2002	WT	Direct
	3/4/2003	WT	Direct
	9/30/2003	WT/3R	Direct
	5/6/2004	3R	Direct
	1/27/2005	3R	Direct
	6/16/2005	3R	Cloning
KI-163	8/30/2002	3R	Direct
	9/27/2004	3R	Direct

[a] ID, identifier.

TABLE 2 Responses of CD8$^+$ T cells from individuals infected with WT virus to WT or 3R peptide

Patient ID	Virus sequence [mo/day/yr (type)]		PBMC sampling date (mo/day/yr)	PBMCs cultured with:	% IFN-γ-producing cells specific for each peptide among CD8$^+$ T cells[a]		
	Early phase	Chronic phase			Without	WT	3R
KI-092	1/22/2001 (WT)	8/14/2003 (3R)	5/24/2001	WT	0.2	**34.4**	**13.7**
				3R	0.1	**12.1**	**16.8**
			2/3/2003	WT	0.2	**5.8**	**4.2**
				3R	0.6	0.3	0.3
KI-102	5/11/2001 (WT)	3/28/2005 (WT)	7/11/2001	WT	1.0	0.6	1.1
				3R	1.1	1.5	2.0
			7/5/2004	WT	0.2	**28.7**	**9.3**
				3R	0.6	0.7	0.6
KI-158	6/14/2002 (WT)	4/4/2005 (3R)	10/11/2002	WT	1.4	**19.3**	**24.6**
				3R	0.1	0.5	0.4
			4/4/2005	WT	0.3	**23.3**	**23.8**
				3R	0.4	**18.8**	**20.9**
KI-161	2/15/2002 (WT)	6/16/2005 (3R)	7/26/2002	WT	0.0	**74.5**	**8.0**
				3R	0.2	**55.1**	**41.8**
			5/6/2004	WT	0.1	**21.4**	**4.9**
				3R	0.2	**42.5**	**43.9**

[a] Without, without peptide. Boldface, positive IFN-γ-producing response.

The 3R virus was not detected by approximately 4 years postinfection in KI-102, who had been infected with the WT virus (Table 1). This individual did not have Gag28-specific CD8$^+$ T cells at an early phase of the HIV-1 infection (Fig. 1). Interestingly, only WT-specific CD8$^+$ T cells were induced from PBMCs of this patient 2.5 year later. Thus, WT-specific CD8$^+$ T cells did not select 3R within about 2 years after the WT-specific CD8$^+$ T cells had been elicited in the patient.

Cross-reactive CD8$^+$ T cells in individuals who had been infected with WT virus and had selected 3R virus. We investigated whether the 3R-specific or cross-reactive CD8$^+$ T cells were elicited after the 3R mutant had been selected in individuals who had been infected with the WT virus. In KI-158, no Gag28-specific CD8$^+$ T cells were induced from early-phase PBMCs stimulated with the 3R peptide, whereas cross-reactive CD8$^+$ T cells were induced from chronic-phase PBMCs stimulated with WT peptide or 3R peptide (Fig. 1). In KI-161, Gag28-specific CD8$^+$ T cells recognizing WT peptide more than the 3R peptide were induced from early-phase PBMCs stimulated with WT peptide or the 3R peptide, whereas cross-reactive CD8$^+$ T cells were predominantly induced from chronic-phase PBMCs stimulated with the 3R peptide (Fig. 1). These results indicate that cross-reactive CD8$^+$ T cells became dominant in the Gag28-specific CD8$^+$ T cell population after the emergence of the 3R virus in these 2 individuals.

To investigate the function of these cross-reactive CD8$^+$ T cells, we generated Gag28-specific CTL clones from PBMCs at a chronic phase in KI-161 by stimulating them with the 3R peptide. The CTL clones evenly recognized both WT and the 3R peptides (Fig. 3A) and showed the same binding affinity to the 2 tetramers (Fig. 3B). These results suggest that the two peptides had the same binding affinity for HLA-A*24:02. They effectively killed WT-virus-infected cells and weakly killed the 3R virus-infected cells (Fig. 3C), whereas they suppressed the replication of the WT virus but not that of the 3R virus (Fig. 3D). These results indicate that these cross-reactive CTLs contributed to the selection of the 3R virus. In addition, the results strongly suggest weak presentation of the 3R peptide in the cells infected with 3R virus, because the cross-reactive CTL clones had TCR with the same binding affinity for both HLA-A*24:02-WT peptide and HLA-A*24:02-3R peptide complexes and because WT and 3R peptides had the same binding affinity for HLA-A*24:02. This reduced presentation may have affected the control of 3R virus by the cross-reactive CTLs.

Gag28-specific T cell repertoire in an individual infected with WT virus. The results in Fig. 1 suggest that both WT-specific and cross-reactive CD8$^+$ T cells were elicited at an early phase of HIV-1 infection in 3 individuals infected with WT virus (KI-092, KI-158, and KI-161). To characterize Gag28-specific CTLs elicited at that time, we established Gag28-specific CTL clones from PBMCs at an early phase in KI-161 by stimulating them with the WT peptide. We found 3 types of CTL clones among the 8 clones analyzed. As shown in Fig. 3A, 3 clones effectively recognized the WT peptide but not the 3R peptide (WT specific), 3 clones recognized the WT peptide more than the 3R peptide (WT dominant), and 2 clones evenly recognized both peptides (cross-reactive). We next investigated the binding affinity of TCRs on these clones to WT tetramer and 3R tetramer. The results confirmed the specificity of these 3 types of CTL clones (Fig. 3B). These results together indicate that KI-161 had a multiple T cell repertoire for the Gag28 epitope before the 3R virus had been selected.

Next, we analyzed the abilities of these T cell clones to kill HIV-1-infected cells. The WT-specific and WT-dominant CTL clones effectively killed the target cells infected with WT virus but failed to kill those infected with the 3R virus (Fig. 3C, left and right graphs under early phase). On the other hand, cross-reactive CTL clones weakly killed the target cells infected with the 3R virus and effectively killed those infected with the WT virus (Fig. 3C, middle

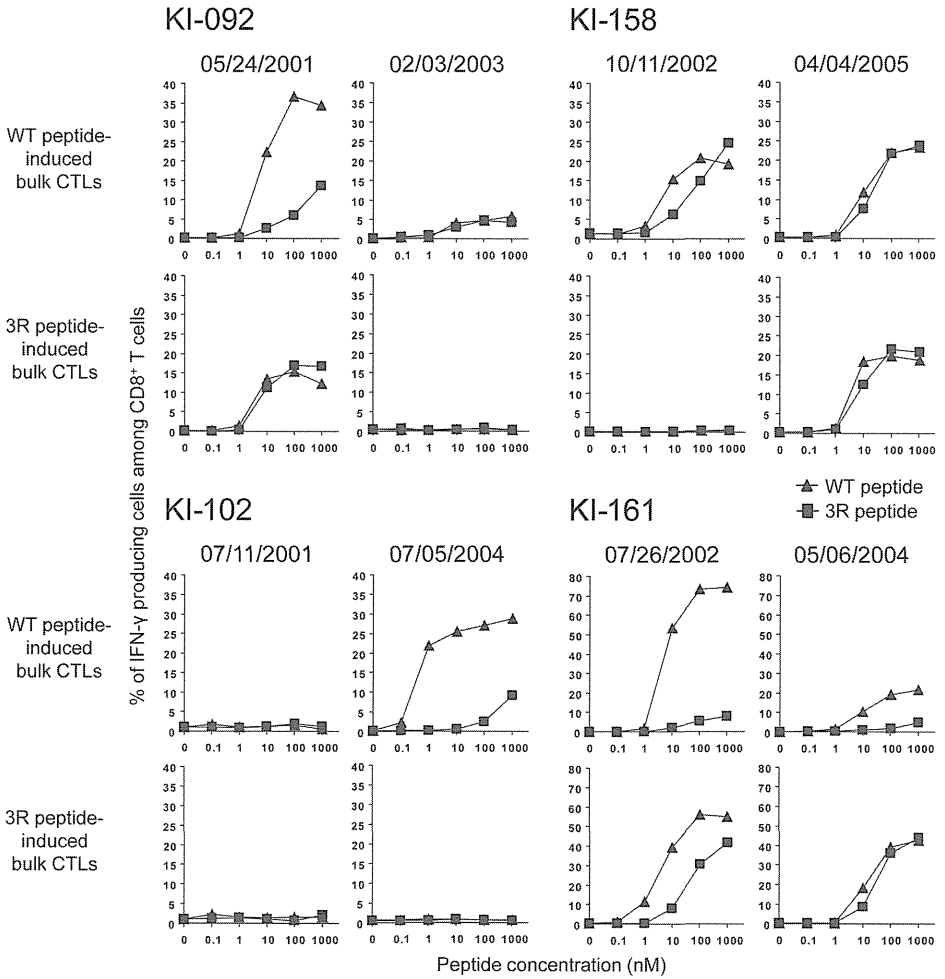

FIG 1 Gag28-specific CD8$^+$ T cells from individuals infected with WT virus at early and chronic phases. Gag28-specific CD8$^+$ T cells were induced by stimulating PBMCs from early and chronic phases in 4 WT-virus-infected HLA-A*24:02$^+$ individuals with WT or 3R peptide. The responses of these bulk-cultured cells to C1R-A2402 cells prepulsed with WT or 3R peptide at concentrations of 0.1 to 1,000 nM were analyzed by using the ICC assay.

graphs under early phase). Then, we analyzed the abilities of these CTL clones to suppress HIV-1 replication. Both WT-specific and cross-reactive CTL clones effectively suppressed the replication of the WT virus, whereas WT-specific and cross-reactive CTL clones exhibited no and weak ability, respectively, to suppress that of the 3R virus (Fig. 3D). These results indicate that WT-specific and cross-reactive CTLs could suppress the replication of the WT virus but that the former CTLs could not suppress the 3R virus *in vivo*. The latter CTLs may weakly suppress 3R virus *in vivo*. Interestingly, the WT-dominant CTL clones exhibited much weaker ability to suppress the replication of WT virus than did the WT-specific and cross-reactive CTLs (Fig. 3D), although no difference in killing activity against WT-virus-infected cells was found among these 3 CTL clones. Overall, KI-161 had a multiple Gag28-specific CTL repertoire at an early phase of HIV-1 infection, but only 2 types of Gag28-specific CTLs, which were the majority among the Gag28-specific CTLs, contributed to the suppression of WT virus replication.

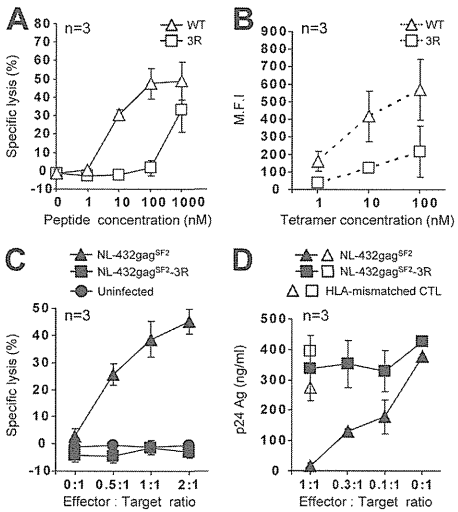

FIG 2 Antiviral activity of Gag28-specific CTL clones generated from early-phase PBMCs from patient KI-092, infected with WT virus. Gag28-specific CTL clones were generated from early-phase PBMCs from KI-092 by stimulating them with WT peptide. The activities of 3 CTL clones ($n = 3$) were analyzed. (A) Cytotoxic activity toward 721.221-CD4-A2402 cells prepulsed with the WT or 3R peptide at concentrations of 1 to 1,000 nM. The cytotoxic activity was measured at an E:T ratio of 1:1. (B) Binding affinity to WT and 3R tetramers at concentrations of 1 to 100 nM. The MFI values of the T cell clones are shown. (C) Cytotoxic activity against 721.221-CD4-A2402 cells infected with NL-432gag^{SF2} (WT virus) or NL-432gag^{SF2}-3R (3R virus). WT-virus-infected (49.1% of total cells were p24 Ag$^+$) and 3R virus-infected (48.6% of total cells were p24 Ag$^+$) cells were used as target cells. The cytotoxic activity was measured at E:T ratios of 0.5:1, 1:1, and 2:1. (D) Abilities of the clones to suppress the replication of WT or 3R viruses. The ability was tested at different E:T ratios. The error bars indicate standard deviations.

Cross-reactive CD8$^+$ T cells and 3R-specific CD8$^+$ T cells in individuals who were infected with 3R virus. Next, we analyzed the elicitation of Gag28-specific CD8$^+$ T cells in 5 individuals infected with the 3R virus. Gag28-specific CD8$^+$ T cells were detected at both early and chronic phases in 3 individuals, whereas they were found at only the chronic phase in the other 2 (Table 3). Cross-reactive CD8$^+$ T cells were induced by stimulating KI-091 PBMCs from both early and chronic phases, not only with 3R peptide, but also with WT peptide. To characterize Gag28-specific CD8$^+$ T cells in KI-091, we generated Gag28-specific CTL clones from PBMCs at a chronic phase in KI-091 by stimulating them with 3R peptide. We investigated the recognition of 3 CTL clones for WT and 3R peptides. These CTL clones evenly recognized both peptides (Fig. 4A) and revealed the same binding affinity for the 2 tetramers (Fig. 4B), indicating that they were cross-reactive CTLs. They moderately killed target cells infected with either WT or 3R virus (Fig. 4C) but did not suppress the replication of the WT and 3R viruses (Fig. 4D). Thus, Gag28-specific CD8$^+$ T cells elicited in KI-091 had no ability to suppress the replication of WT and 3R viruses. Further analysis of 13 other clones revealed similar characteristics (data not shown), supporting the data indicating that cross-reactive CTLs were predominantly elicited in KI-091.

In the chronic phase, KI-091 had cross-reactive CD8$^+$ T cells, whereas 3R-specific CD8$^+$ T cells were found in 4 other individuals (Table 3). To characterize these 3R-specific CD8$^+$ T cells, we generated 3R-specific CTL clones from KI-163 PBMCs at the chronic phase by stimulating them with 3R peptide. All 3 clones recognized the 3R peptide much more effectively than the WT peptide (Fig. 4A). These CTL clones bound to 3R tetramer, but not to WT tetramer (Fig. 4B), indicating that these CTL clones carried a 3R-specific TCR. In addition, we analyzed the abilities of these CTL clones to recognize virus-infected cells and found that they effectively killed target cells infected with 3R virus, but not those infected with WT virus (Fig. 4C). However, they failed to suppress the replication of either 3R or WT virus (Fig. 4D). These results indicate that Gag28-specific CD8$^+$ T cells elicited in all individuals infected with 3R virus had no ability to suppress the replication of WT or 3R virus. Thus, Gag28-specific CD8$^+$ T cells seem to have failed to control the 3R virus, although they were elicited in individuals infected with the 3R virus.

High accumulation of the 3R variant in the Japanese population. The results described above strongly suggest that WT-specific and cross-reactive CD8$^+$ T cells selected the 3R mutation in the individuals infected with the WT virus and that 3R-specific and cross-reactive CD8$^+$ T cells failed to control the 3R virus in the individuals infected with it. Therefore, we assume that this 3R mutation has accumulated in the HLA-A*24:02$^+$ individuals. In addition, since HLA-A*24:02 is found in approximately 70% of Japanese, we speculate that the mutation has accumulated to high levels in the Japanese population.

A previous study analyzed the frequency of 3R in only 32 HLA-A*24:02$^+$ and 26 HLA-A*24:02$^-$ individuals chronically infected with HIV-1 and showed that the frequency of 3R was significantly higher in HLA-A*24:02$^+$ individuals than in the HLA-A*24:02$^-$ individuals (30). To confirm the association of this mutation with HLA-A*24:02, we analyzed a large number of chronically HIV-1-infected nonhemophiliac individuals (220 HLA-A*24:02$^+$ and 154 HLA-A*24:02$^-$ individuals) recruited from April 2008 to March 2011 (2008 to 2011 cohort). The results confirmed that the frequency of 3R was significantly higher in HLA-A*24:02$^+$ individuals than in the HLA-A*24:02$^-$ individuals ($P < 0.0005$) (Fig. 5). Since 3R was found in 74.7% of the HLA-A*24:02$^-$ individuals in this cohort, we speculate that the mutation has been accumulating in the Japanese population. Therefore, we analyzed HIV-1-infected nonhemophiliac Japanese individuals who had been recruited from 1996 to 2002 (1996 to 2002 cohort), as well as Japanese hemophiliacs who had been infected around 1983 (hemophiliac cohort), and then compared them to the 2008 to 2011 cohort (Fig. 5). The association of this mutation with HLA-A*24:02 was also found in both the 1996 to 2002 cohort and the hemophiliac cohort ($P < 0.01$ and $P = 7.4 \times 10^{-7}$, respectively). The frequency of this mutation in HLA-A*24:02$^-$ individuals significantly increased from 0% in the hemophiliac cohort to 50.0% in the 1996 to 2002 cohort ($P = 0.0084$) and to 74.7% in the 2008 to 2011 cohort ($P = 2.6 \times 10^{-7}$). These results indicate that the 3R mutation was strongly selected by Gag28-specific CTLs and has

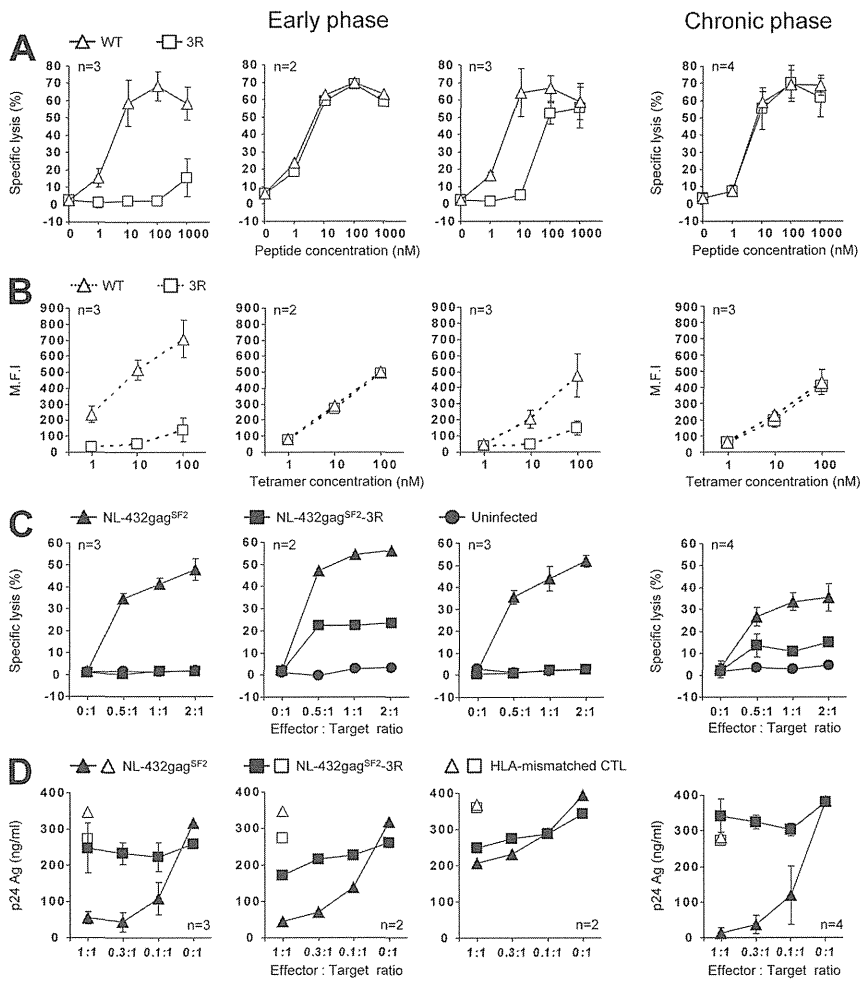

FIG 3 Antiviral activities of Gag28-specific CTL clones generated from PBMCs of patient KI-161, infected with WT virus. Gag28-specific CTL clones were generated from early-phase and chronic-phase PBMCs isolated from KI-161 after stimulating them with the WT and 3R peptides, respectively. Three types of Gag28-36-specific CTL clones, i.e., WT specific (left), cross-reactive (middle), and WT dominant (right), were generated from the early-phase PBMCs. (A) Cytotoxic activity against 721.221-CD4-A2402 cells prepulsed with the WT or 3R peptide at concentrations of 1 to 1,000 nM. The cytotoxic activity was measured at an E:T ratio of 1:1. (B) Binding affinity toward WT and 3R tetramers at concentrations of 1 to 100 nM. The MFIs of the T cell clones are shown. (C) Cytotoxic activity against 721.221-CD4-A2402 cells infected with WT virus or 3R virus. WT-virus-infected (49.0% of total cells were p24 Ag$^+$) and 3R-virus-infected (50.0% of total cells were p24 Ag$^+$) cells were used as target cells. The cytotoxic activity was measured at E:T ratios of 0.5:1, 1:1, and 2:1. (D) Abilities of the clones to suppress the replication of WT or 3R virus. The ability was tested at different E:T ratios. n, number of clones tested. The error bars indicate standard deviations.

been accumulating during the past 30 years in the Japanese population.

It is well known that some escape mutations affect replication capacity and that HIV-1 containing such mutations reverts to WT in individuals not carrying HLA class I restriction alleles (23, 32). We previously showed that the 3R mutation does not affect replication capacity when 2 T cell lines are used in an assay measuring it (46). Since a different effect of mutations on replication capacity between cell lines and CD4$^+$ T cells from a healthy individual is known (23), we measured the replication capacity of the 3R virus by using CD4$^+$ T cells from a healthy individual. The results confirm that this mutation did not affect the replication capacity (Fig. 6), suggesting that the 3R mutant could not revert in HLA-A*24:02$^-$ individuals.

TABLE 3 Responses of CD8$^+$ T cells from individuals infected with 3R virus to WT or 3R peptide

Patient ID	Virus sequence [mo/day/yr (type)]		PBMC sampling date (mo/day/yr)	PBMCs cultured with:	% IFN-γ-producing cells specific for each peptide among CD8$^+$ T cells[a]		
	Early phase	Chronic phase			Without	WT	3R
KI-091	12/13/2000 (3R)	8/4/2005 (3R)	12/13/2000	WT	0.2	**74.6**	**71.2**
				3R	0.3	**55.4**	**71.9**
			9/29/2004	WT	0.2	**77.7**	**65.5**
				3R	0.2	**61.1**	**69.3**
KI-134	10/25/2001 (3R)	6/30/2004 (3R)	10/25/2001	WT	0.4	0.6	0.8
				3R	1.0	1.1	**5.7**
			1/21/2004	WT	0.8	1.0	0.7
				3R	0.7	0.6	**2.0**
KI-136	10/29/2001 (3R)	7/10/2003 (3R)	10/29/2001	WT	0.1	0.4	0.2
				3R	0.1	0.2	0.2
			5/15/2003	WT	0.4	0.8	0.4
				3R	0.1	0.2	**24.8**
KI-151	2/15/2002 (3R)	6/16/2005 (3R)	11/21/2001	WT	0.3	0.7	0.8
				3R	0.7	0.6	**10.8**
			7/28/2004	WT	0.4	0.7	1.3
				3R	0.1	0.1	**44.5**
KI-163	8/30/2002 (3R)	9/27/2004 (3R)	8/30/2002	WT	0.2	0.3	0.2
				3R	0.2	0.4	0.2
			8/29/2005	WT	0.3	0.5	0.2
				3R	0.4	0.6	**6.9**

[a] Without, without peptide. Boldface, positive IFN-γ-producing response.

DISCUSSION

It is known that CTLs recognizing escape mutants are elicited after the escape mutant had been selected by WT epitope-specific CTLs (2, 4, 12, 15, 33, 39) or in new escape mutant virus-infected hosts having the same restricted HLA allele (15). However, since the CTLs recognizing escape mutants have been not well analyzed, the role of these CTLs in the control of HIV-1 infections remains unclear. In the present study, we investigated 2 groups, HLA-A*24:02$^+$ individuals infected with WT virus and those infected with 3R escape mutant virus. We found that both WT-specific and cross-reactive CD8$^+$ T cells were elicited in individuals infected with WT virus. Interestingly, cross-reactive T cells had been elicited before the emergence of the 3R escape mutant virus, though a similar finding was made in previous studies that analyzed other epitope-specific CTLs (18, 25, 26, 34). The present study shows that WT-specific CD8$^+$ T cells were predominantly elicited in an early phase of the infection and that the number of cross-reactive CD8$^+$ T cells increased in the chronic phase. The CTL clones from early and chronic phases in KI-161 showed similar abilities to kill WT virus-infected or 3R virus-infected cells and activities to suppress both viruses, suggesting that cross-reactive CD8$^+$ T cells elicited at the early phase were expanded via antigen presentation by 3R virus-infected cells at the chronic phase.

WT-specific and cross-reactive CTL clones from KI-092 and KI-161 at an early phase of the infection effectively killed WT-virus-infected cells and suppressed the replication of the WT virus, whereas they exhibited no and weak ability, respectively, to suppress that of the 3R virus. Cross-reactive CTL clones had the same ability to suppress the replication of WT virus as did the WT-specific CTL clones. These results strongly suggest that both CTLs selected the 3R virus in these individuals infected with the WT virus. The 3R virus was not selected within at least 1 year after Gag28-specific CTLs had been detected in the individuals infected with the WT virus. This finding indicates that the 3R mutation was more slowly selected by these CTLs than escape mutants selected at an acute phase of the infection (16, 19, 34, 44, 45). On the other hand, a previous study suggested that acute accumulation of mutations in this epitope occurs after an HIV-1 infection (6). However, the data shown in that study concerned mutations contained at position 1 of the epitope. In addition, those data may have included cases in which the individuals had been infected with the 3R mutant virus, because it may be assumed that 3R virus had accumulated in the cohorts analyzed. Cross-reactive CTL clones established from PBMCs at both early and chronic phases of KI-161 killed 3R virus-infected cells, though the killing activity against the 3R virus-infected cells was weaker than that against the WT virus-infected cells. These CTL clones weakly suppressed the replication of the 3R virus (Fig. 3C). This weak ability to suppress it might have delayed the emergence of the 3R mutation in these patients.

WT-specific CTLs were not induced by stimulation of early- or chronic-phase PBMCs from the 5 individuals in which the 3R mutation had been detected at the early phase with WT peptides. This finding supports the possibility that these individuals had been infected with the 3R virus. Only KI-091 had cross-reactive T cells at early and chronic phases of the infection. All CTL clones established from this patient had cross-reactivity, implying that the patient had been infected with WT virus and that 3R had been selected at an early phase. However, WT-specific CTL clones were not established from this patient. In addition, the cross-reactive

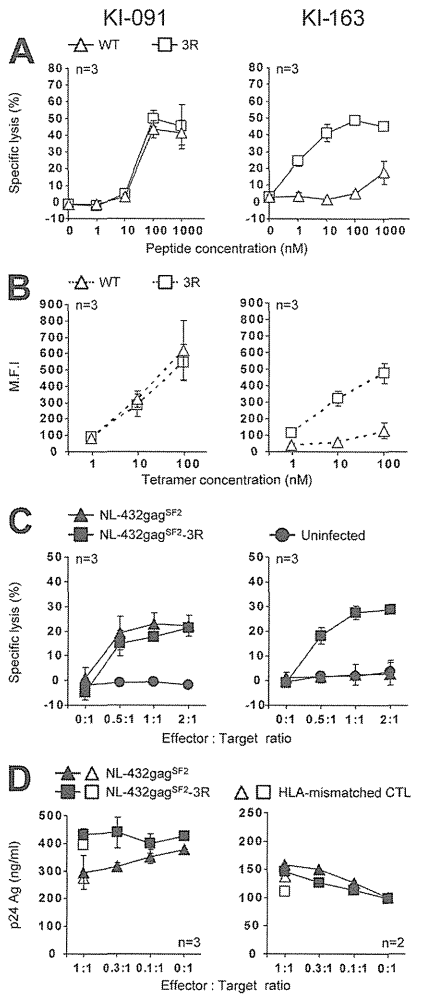

FIG 4 Antiviral activities of cross-reactive and 3R-specific CTL clones generated from patients KI-091 and KI-163 infected with 3R virus. Gag28-specific CTL clones were generated from chronic-phase PBMCs isolated from patients KI-091 and KI-163 after their stimulation with 3R peptide. The following activities of these CTL clones were analyzed. (A) Cytotoxic activity against 721.221-CD4-A2402 cells prepulsed with the WT or 3R peptide at concentrations of 1 to 1,000 nM. The cytotoxic activity was measured at an E:T ratio of 1:1. (B) Binding affinity toward WT and 3R tetramers at concentrations of 1 to 100 nM. The MFIs of the T cell clones are shown. (C) Cytotoxic activity against 721.221-CD4-A2402 cells infected with WT virus or 3R virus. WT-virus-infected and 3R virus-infected cells were used as target cells. The frequency of p24 Ag^+ cells among the HIV-1-infected cells was as follows: WT-virus-infected cells, 49.1% and 43.1% for CTL clones from KI-091 and KI-163, respectively, and 3R-virus-infected cells, 48.6% and 45.6% for CTL clones from KI-091 and KI-163, respectively. The cytotoxic activity was measured at E:T ratios of 0.5:1, 1:1, and 2:1. (D) Abilities of the clones to suppress the replication of WT or 3R virus. The abilities were tested at different E:T ratios. n, number of clones tested. The error bars indicate standard deviations.

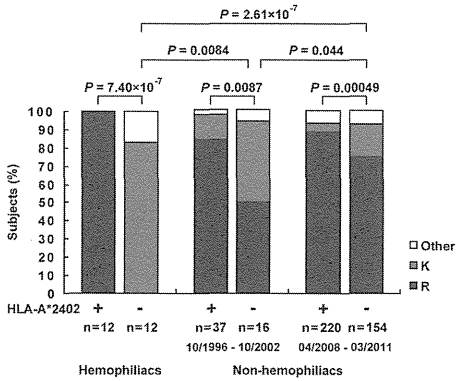

FIG 5 Frequencies of the 3R mutation in a Japanese hemophiliac cohort and nonhemophiliac cohorts recruited from 1996 to 2002 and from 2008 to 2011. The frequencies of mutations at position 3 of the Gag28 epitope in chronically HIV-1-infected HLA-A*24:02$^+$ or HLA-A*24:02$^-$ hemophiliac individuals and nonhemophiliac individuals recruited from 1996 to 2002 or from 2008 to 2011 are shown. The consensus sequence of this epitope in HIV-1 subtype B is KYKLKHIVW. The frequency of the 3R mutation between HLA-A*24:02$^+$ and HLA-A*24:02$^-$ subjects in each cohort or that in HLA-A*24:02$^+$ or HLA-A*24:02$^-$ subjects among the 3 cohorts was statistically analyzed by using Fisher's exact test.

CTL clones established from KI-091 did not have the ability to suppress the replication of the WT virus, although the CTL clones from individuals who had been infected with the WT virus had strong ability to suppress it. These findings suggest that this patient had been infected with the 3R virus rather than with the WT virus. However, it remains unknown why 3R-specific CTLs were elicited in the other 4 individuals but not in this patient. Thus, the abilities of CTLs to respond to WT peptide and to suppress the replication of WT virus together supported the idea that the individuals who had 3R virus in the early phase had been infected with 3R virus, although the possibility that they had been infected with WT virus cannot be completely excluded.

The 3R mutant epitope peptide would have been processed and presented to 3R-specific CTLs in 3R virus-infected cells, since 3R-specific and cross-reactive CTL clones effectively killed 3R virus-infected cells. However, these CTL clones failed to suppress the replication of the 3R virus. 721.221-CD4-A2402 cell lines were used as target cells for the killing assay, whereas $CD4^+$ T cells from healthy individuals were used for the replication suppression assay. The former cells express HLA-A*24:02 to a much higher degree than the latter cells. This difference between the 2 cell lines may account for the discrepancy of the results between the 2 assays. 3R-specific CTL clones failed to suppress the replication of the 3R virus, whereas cross-reactive CTLs from the individuals

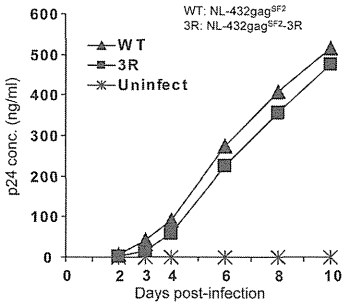

FIG 6 Replication kinetics of WT and 3R viruses in $CD4^+$ T cells. $CD4^+$ T cells (2×10^5) isolated from PBMCs from a healthy donor were infected with WT or 3R virus in triplicate at a blue-cell-forming unit of 500 (in MAGIC-5 cells) in a total volume of 0.2 ml and then incubated at 37°C for 2 h. The infected cells were washed twice with R10 and then cultured in 1 ml of complete medium plus rIL-2 at 37°C. A 0.1-ml volume of the culture supernatants was collected at days 2 to 10 postinfection. The concentration of p24 Ag was measured by using ELISA.

infected with WT virus effectively suppressed the replication of the WT virus but failed to suppress that of the 3R virus. These findings suggest that 3R virus-infected $CD4^+$ T cells could not effectively present the 3R mutant epitope. This finding also suggests that 3R virus-infected $CD4^+$ T cells were not the main source of antigen-presenting cells in 3R virus-infected individuals. A previous study showed that HIV-1-infected macrophages effectively present HIV-1 epitopes more than HIV-1-infected $CD4^+$ T cells (14), implying that 3R virus-infected macrophages are the main antigen-presenting cells and contribute to the elicitation of 3R-specific and cross-reactive CTLs in 3R virus-infected individuals. A further study should clarify the role of macrophages in the elicitation of 3R-specific and cross-reactive CTLs in 3R virus-infected individuals.

Cross-reactive CTLs were found in individuals infected with the WT virus or with the 3R virus. The CTL clones established from individuals infected with the WT virus had a strong ability to kill WT-virus-infected cells and to suppress the replication of the WT virus, whereas those established from an individual infected with the 3R virus showed moderate ability to kill WT-virus-infected cells and no ability to suppress the replication of WT virus. These findings indicate that cross-reactive CTLs from an individual infected with the 3R virus may have had less ability to recognize the WT epitope than those from an individual infected with the WT virus. Indeed, the former CTL clones exhibited lower sensitivity to reaction with WT peptide-pulsed cells than the latter CTLs, indicating that cross-reactive CTLs elicited in individuals infected with the WT virus had higher-affinity TCRs for WT peptide than those in an individual infected with the 3R virus. In addition, the latter CTL clones weakly killed 3R virus-infected cells, whereas the former clones showed the same killing activity against 3R virus-infected cells as against WT-virus-infected cells. Thus, cross-reactive CTLs in individuals infected with 3R virus have different characteristics than those in individuals infected with the WT virus. This finding suggests that cross-reactive CTLs elicited in individuals infected with the WT virus had TCRs with higher affinity for WT and 3R peptides than those in individuals infected with the 3R virus.

Japanese hemophiliacs were infected with HIV-1 via blood products from the United States around 1983, and HLA-A*24:02 is a rare allele in North America. Therefore, it may be speculated that HIV-1 in the blood product had not yet accumulated escape mutations. Indeed, the 3R mutation was not found in the 12 HLA-A*24:02$^-$ hemophiliacs tested, though other amino acid variants at position 3 were detected in 2 of these hemophiliacs. This mutation was found in 50.0% of HLA-A*24:02$^-$ individuals in the 1996 to 2002 cohort and in 74.7% of those in the 2008 to 2011 cohort, indicating that the mutation had accumulated in the Japanese population. The frequency of this mutation in HLA-A*24:02$^-$ individuals thus increased about 1.5-fold during the approximately 10-year period between these 2 nonhemophiliac cohorts. Thus, the mutation greatly accumulated over the last 10 years. Since HLA-A*24:02 is found in approximately 70% of Japanese, the high prevalence of the allele is the cause of the high accumulation of the 3R mutation in the Japanese population. In addition, this high accumulation resulted not only from a strong selection of the 3R mutation by WT-specific and cross-reactive CTLs elicited in the donors infected with WT virus, but also from a lack of reversion of the mutation in the HLA-A*24:02$^-$ individuals.

Our previous study concerning HLA-A*24:02-restricted Nef138-specific CTLs demonstrated that only WT epitope-dominant CTLs, which suppress the replication of WT virus but fail to suppress that of mutant virus, are elicited at an early phase in HLA-A*24:02$^+$ individuals infected with the WT virus and that mutant-epitope-dominant CTLs but not cross-reactive CTLs are elicited after the emergence of the mutant virus in them (15). In addition, only mutant-epitope-dominant CTLs are elicited in those individuals infected with the mutant virus. The mutant-epitope-dominant CTLs suppress the replication of WT virus but weakly suppress that of mutant virus (15). Thus, Nef138-specific CTLs elicited in individuals infected with WT or mutant viruses had different characteristics in terms of the recognition of WT and mutant epitopes than the Gag28-specific CTLs analyzed in the present study. The difference between Nef138-specific and Gag28-specific CTLs might be explained by a different CTL repertoire elicited at an early phase. These 2 studies suggest the elicitation of various HIV-1-specific CTLs in regard to recognition of escape mutations.

In the present study, we demonstrated that WT-specific and cross-reactive CTLs were elicited at an early phase in individuals infected with the WT virus and that cross-reactive CTLs were dominant in Gag28-specific CTLs after the emergence of the 3R virus. On the other hand, 3R-specific and cross-reactive CTLs were elicited in individuals infected with the 3R virus, though the former CTLs were predominantly elicited in these individuals. The CTLs elicited in the individuals infected with the WT virus, which had a strong ability to suppress the replication of WT virus, played a central role in the accumulation of the 3R mutation. In contrast, the CTLs elicited in those infected with 3R virus, which failed to suppress the replication of WT and 3R viruses, did not contribute to the control of the 3R virus infection. In addition, the high prevalence of HLA-A*24:02 and lack of effect of the 3R mutation on viral fitness may have strongly contributed to the high accumulation of the mutation in HIV-1-infeceted Japanese individuals.

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