

Increasing Prevalence of Japanese Cedar Pollinosis: A Meta-Regression Analysis

Yoshihiro Kaneko^a Yutaka Motohashi^a Hiroyuki Nakamura^b
Tomohiko Endo^c Akira Eboshida^d

^aDepartment of Public Health, Akita University School of Medicine, Akita, ^bDepartment of Environmental Medicine, Kochi University School of Medicine, Kochi, ^cDepartment of Otorhinolaryngology, Jikei University School of Medicine, Tokyo, and ^dDivision of Medical Intelligence and Informatics, Hiroshima University Graduate School of Biomedical Sciences, Hiroshima, Japan

Key Words

Japanese cedar · Meta-regression analysis · Cedar pollinosis prevalence · Urbanization

Abstract

Background: Japanese cedar pollinosis, caused by the pollen of the Japanese cedar tree (*Cryptomeria japonica*), is the commonest seasonal allergic disease in Japan. A number of epidemiological surveys have been reported on Japanese cedar pollinosis, but it has never been assessed systematically or quantitatively. To confirm the increasing prevalence of Japanese cedar pollinosis and related factors, we conducted a meta-regression analysis on population-based surveys in Japan. **Methods:** We searched for data from population-based surveys in which serological methods were used to test all participants. Weighted regression of logit-transformed prevalence and sensitization rates were used to evaluate the effects of the year of survey, age, and degree of urbanization. We also analyzed the relationship between prevalence and sensitization rate. **Results:** Thirty-eight reports with 27 subgroups for prevalence and 134 subgroups for sensitization rate were selected from the literature published in the years between 1986 and 2000.

The Japanese cedar pollen sensitization rate was found to be significantly correlated with the year of survey, age, and degree of urbanization (adjusted $R^2 = 0.55$). The coefficient for the correlation between the prevalence and the sensitization rate revealed a statistically significant correlation (Pearson's $r = 0.70$, $p < 0.001$). **Conclusions:** The prevalence of Japanese cedar pollinosis among adolescents was predicted to be 28.7% in metropolitan areas and 24.5% in the general population in urban areas in the year 2004, derived from the estimated sensitization rate and the relationship between sensitization rate and prevalence. The prevalence of Japanese cedar pollinosis increased 2.6-fold between 1980 and 2000, and the prevalence differed considerably according to age and degree of urbanization.

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Introduction

Japanese cedar pollinosis, caused by the pollen of the Japanese cedar (*Cryptomeria japonica*), is the commonest seasonal allergic disease in Japan. Every spring many people take medication for Japanese cedar pollinosis and wear facemasks or eyeglasses to protect themselves against

cedar pollen. Thus, the epidemic is a problem of great public interest and has become a major public health concern.

A rising prevalence of allergic diseases has been noted in most industrialized countries over the past 20–30 years [1], and the increasing prevalence of cedar pollinosis has been discussed in relation to the rising prevalence of other allergic diseases in Japan. After the first report of a case of pollinosis caused by Japanese cedar pollen in 1964 [2], a number of surveys have been conducted on cedar pollinosis in Japan. The results of epidemiological surveys of Japanese cedar pollinosis have revealed a prevalence of 10–20% in adults, and that the prevalence is rising, with the peak incidence occurring in young adults and a higher prevalence in urban areas [3–5]. However, these features have never been assessed systematically or quantitatively.

In the present study we conducted a meta-regression analysis based on epidemiological surveys of Japanese cedar pollinosis in Japan.

Material and Methods

Data Collection

We searched for surveys on the prevalence of Japanese cedar pollinosis and the sensitization rate as manifested by the detection of specific IgE antibodies to Japanese cedar pollen through the MEDLINE and the Igaku Chuo Zasshi (*Japan Centra Revno Medicina*, in Japanese) database and in the references of the surveys we found.

Selection criteria were defined in relation to the method, setting, and description. We targeted surveys conducted in Japan between 1964 and 2000. The year 1964 was selected because that was the year when the first report on Japanese cedar pollinosis was published [2]. We limited the surveys selected to those in which serological testing was performed in all participants. Serological methods of the specific IgE antibodies to Japanese cedar pollen included the radioallergosorbent test (RAST), enzyme-linked immunosorbent assay (ELISA) and skin scratch test. We also included the studies reporting only the IgE sensitization which was judged to be based on these methods. Only population-based surveys were eligible, and those that involved outpatients were excluded. We restricted the survey to those that reported the exact number of participants. The term 'prevalence' in this study means the percentage of the population who were sensitized and had one or more seasonal rhinoconjunctival symptoms.

Each survey contained one or more subgroups and they were divided by the year of the survey, the age of the participants, and the degree of urbanization of the survey area. Participants were classified into five groups according to age: 'children' (less than 13 years old), 'adolescents' (13–19 years old), 'young adults' (20–39 years old), 'adult' (40 years old and above), and 'general population' (all age groups). The survey areas were classified into four groups according to their degree of urbanization: 'metropolitan', 'urban',

'rural', and 'unknown', based on the residences of the participants. 'Metropolitan' included the Tokyo, Nagoya, Osaka, and Fukuoka area. 'Rural' was defined as areas with a low population density. 'Urban' refers to the remaining areas. If the population was studied nationwide or the participants did not identify their residence, the areas were classified as 'unknown' and excluded from the statistical analysis.

Statistical Analysis

Weighted regression of logit-transformed prevalence and sensitization rate was performed to evaluate the effect of the year of survey, age, and urbanization. Meta-regression analysis means a statistical synthesis of the comparable studies including regression analysis, leading to a quantitative summary. Our dependent variables, the sensitization rate and the prevalence, were proportion data. The logit transformation was needed to deal with the proportion data by a linear regression model which covers an unlimited range. The logit transformation is a commonly used transformation that transforms the proportion from the range 0 to 1 to $-\infty$ to ∞ . The logit of proportion p is defined as $\text{logit}(p) = \ln [p/(1 - p)]$. Year of survey was treated as a continuous variable. Age and urbanization were treated as categorical variables. Weights were set on the number of participants.

Only 18 prevalence subgroups were included in the regression analysis, and the analysis was mainly of the sensitization rate. Nine prevalence subgroups were excluded, because their participants were university freshmen and they were classified as of 'unknown' urbanization [15, 17]. The sensitivity analyses were conducted by a subgroup analysis of age.

We also performed a correlation analysis and regression analysis between sensitization rate and prevalence by using prevalence subgroups.

Results

We selected 38 papers with 27 subgroups for prevalence (14,865 participants) from the literature published between 1986 and 2000, and 134 subgroups for sensitization rate (46,357 participants) (table 1). The results of the regression analysis for prevalence did not show significant relationships with the year of survey, age, or degree of urbanization (results not shown).

For the sensitization rate, the years of the surveys were distributed between 1973 and 1999 (the 1973 subgroup was tested in 1986 by using conserved serum [21]). The settings of the survey ranged from schools to universities, workplaces, and the local community. According to age, there were 15 children subgroups (4,840 participants), 39 adolescent subgroups (12,192 participants), 30 young adult subgroups (8,676 participants), 31 adult subgroups (5,593 participants), and 19 'general population' subgroups (14,832 participants). According to the degree of urbanization, there were 21 metropolitan subgroups (9,233 participants), 66 urban subgroups (21,719 partici-

Table 1. Characteristics of included surveys

Authors, publication year and Ref. No.	Year(s) of survey	Sub-groups	Setting (age ^a)	Survey area(s) (degree of urbanization ^b)	Participants	Prevalence %	Instrument ^c
<i>Prevalence of Japanese cedar pollinosis</i>							
Hori and Ohyama (1986) [6]	1984	1	Junior high school (3rd trimester) (A)	Nagano (R)	195	11.8	RAST
Kushima et al. (1987) [7]	1986	4	Community (G)	Tochigi (U)	2,669	14.7	ELISA
Koizumi (1988) [8]	1981	1	Primary school (C)	Tochigi (U)	822	9.4	Scratch
Nakamura (1990) [9]	1986	1	Workplace (D)	Oita (U)	202	6.4	RAST
Inoue (1990) [10]	1987	1	Community (E)	Tokyo (M)	276	15.6	ELISA
Koizumi (1992) [11]	1990	2	Primary and junior high school (C, A)	Tochigi (U)	333	19.5	Scratch
Ozasa et al. (1995) [12]	1994	1	Primary school (C)	Kyoto (M)	397	8.1	RAST
Mori (1995) [13]	1992	1	Community (A)	Tochigi (U)	1,905	15.0	RAST
Kishikawa et al. (1995) [14]	1994	1	Community (G)	Fukuoka (M)	158	10.8	RAST
Nakamura (1996) [15]	1988–1994	7	University (A)	Oita (N)	5,979	15.4	RAST
Konno et al. (1998) [16]	1995	2	Primary and junior high school, community (A, G)	Chiba (U, R)	894	15.0	RAST
Suzuki et al. (2000) [17]	1995	2	University (A)	Shizuoka (N)	429	23.3	Unknown
Enomoto et al. (2000) [18]	1999	1	Community (G)	Wakayama (R)	160	33.8	RAST
Hashimoto et al. (2000) [19]	1998	1	Volunteer (E)	Tokyo (M)	121	5.8	RAST
Takahashi et al. (2000) [20]	1999–2000	1	Workplace (G)	Yamagata (R)	325	4.6	ELISA
Total		27			14,865		
<i>Japanese cedar pollen sensitization rate</i>							
Inoue et al. (1986) [21]	1973, 1984–1985	4	Community (E)	Gunma (U), Kanagawa (M)	1,088	29.0	ELISA
Inoue et al. (1986) [22]	1983–1984	2	Community (G)	Tochigi (3 districts) (U), Tokyo (M)	1,149	20.3	ELISA
Hori and Ohyama (1986) [6]	1984	1	Junior high school (15 years old) (A)	Nagano (R)	195	15.4	RAST
Enomoto et al. (1986) [23]	1985	6	Community (A, E, D)	Wakayama (R)	1,491	14.2	RAST
Kushima et al. (1987) [7]	1986	4	Community (G)	Tochigi (2 districts) (R)	2,669	22.9	ELISA
Inoue et al. (1988) [24]	1983–1987	9	Community (E)	Akita (U), Toyama (U), Aichi (M), Hyogo (M), Tokushima (U), Ehime (U), Oita (U), Kumamoto (U), Kagoshima (U)	3,435	19.4	ELISA
Sasajima et al. (1989) [25]	1988	1	Community (G)	Akita (R)	2,579	12.1	ELISA
Ogawa et al. (1989) [26]	1988	6	Community (A, E, D)	Aichi (M)	1,347	29.5	ELISA
Nakamura (1990) [9]	1986	1	Workplace (D)	Oita (U)	202	7.9	RAST
Inoue (1990) [10]	1987	1	Community (E)	Tokyo (M)	276	33.7	ELISA
Suzuki et al. (1990) [27]	1987	1	Workplace (E)	Tokyo (M)	433	32.8	ELISA
Sasajima et al. (1990) [28]	1989	16	Community (A, E, D)	Akita (R)	2,981	8.1	Unknown
Sasajima et al. (1991) [29]	1990	4	Primary and junior high school (C, A)	Akita (2 districts) (R)	2,133	10.9	RAST
Enomoto et al. (1991) [30]	1990	6	Community (A, E, D)	Wakayama (U)	1,317	18.8	RAST
Koizumi (1992) [11]	1981, 1990	3	Primary and junior high school (C, A)	Tochigi (U)	1,155	28.6	Scratch
Enomoto (1992) [31]	1985	9	Primary and junior high school (C, A)	Wakayama (U)	1,333	8.1	RAST
Nishikawa et al. (1992) [32]	1991	1	Community (G)	Yamaguchi (R)	200	33.5	RAST
Ogawa and Imai (1992) [33]	1991	2	Community (G)	Aichi (M, U)	2,818	34.7	ELISA
Ogawa et al. (1993) [34]	1989–1990	2	Community (G)	Aichi (M)	2,525	26.3	ELISA
Yamazaki et al. (1994) [35]	1991–1992	4	Community (E, D, G)	Aichi (U)	289	20.8	Unknown
Ozasa et al. (1995) [12]	1994	1	Primary school (C)	Kyoto (M)	397	25.2	RAST
Mori (1995) [13]	1992	1	Primary, junior high and high school (A)	Tochigi (U)	1,905	45.8	RAST
Kishikawa et al. (1995) [14]	1994	1	Community (G)	Fukuoka (M)	158	13.9	RAST
Nakamura (1996) [15]	1988–1994	14	University (A)	Oita (U, N)	5,979	32.8	RAST
Kato et al. (1996) [36]	1992–1994	6	Junior high school (A)	Aichi (3 districts) (M, U, R)	720	40.4	RAST
Saito et al. (1996) [37]	1994	1	University (A)	Gunma (N)	118	44.1	ELISA
Ukai et al. (1996) [38]	1995	4	Community (elderly) and primary school (A, C, D)	Mie (2 districts) (R)	264	25.0	Unknown
Yokoyama et al. (1996) [39]	1995	2	Workplace and community (D, N)	Aichi (R, N)	148	42.6	Unknown
Masubuchi (1998) [40]	1992	1	Primary and junior high school (A)	Tochigi (U)	335	21.8	RAST
Konno et al. (1998) [16]	1995	3	Community (A, N)	Chiba (2 districts) (U, R)	2,436	28.5	RAST
Takahashi et al. (1999) [41]	1988	1	Community (G)	Yamagata (U)	463	24.2	ELISA
Moro et al. (1999) [42]	1998	2	Community (D, N)	Kagoshima (R)	257	23.7	Unknown
Enomoto et al. (1999) [43]	1995	6	Community (A, E, D)	Wakayama (U)	1,321	30.8	ELISA
Kitahara et al. (1999) [44]	1998	1	Primary school (C)	Osaka (M)	405	48.9	RAST
Nitta and Nakai (1999) [45]	1998	2	Primary school (C)	Ibaraki (R), Tokyo (M)	802	33.4	RAST
Suzuki et al. (2000) [17]	1995	2	University (A)	Shizuoka (N)	429	61.5	Unknown
Enomoto et al. (2000) [18]	1999	1	Community (D)	Wakayama (U)	160	55.3	RAST
Hashimoto et al. (2000) [19]	1998	1	Volunteer (E)	Tokyo (M)	121	36.4	RAST
Takahashi et al. (2000) [20]	1999–2000	1	Workplace (G)	Yamagata (R)	325	8.6	ELISA
Total		134			46,357		

^a Age classified into children (C), adolescents (A), young adults (E), adults (D), and general population (G).

^b Degree of urbanization classified into metropolitan (M), urban (U), rural (R) and 'unknown' (N). Details are described in the Methods section in the text.

^c Instrument used to measure specific IgE antibodies. Scratch = Skin scratch test; unknown = instrument not described.

Fig. 1. Japanese cedar pollen sensitization rate by the year of survey. The size of the circle represents the number of the participants in the subgroup. High, middle, and low prediction curves correspond to the regression formula for adolescents in metropolitan areas, the general population in urban areas, and adults in urban areas.

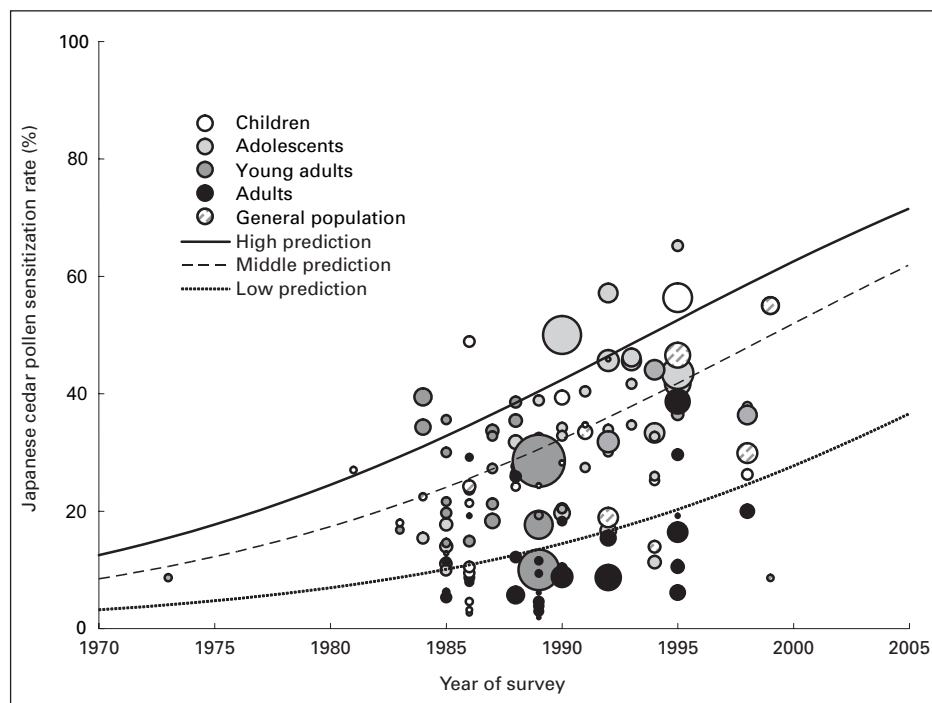


Table 2. Results of the meta-regression analysis of the Japanese cedar pollen sensitization rate ($n = 120$, adjusted $R^2 = 0.54$)

Variables of variation	d.f.	Sum of square	F	< p
Year	1	2,674.7	25.0	<0.001
Age group	4	676.3	6.3	<0.001
Degree of urbanization	2	1,535.3	14.3	<0.001
Age group $\times$ degree of urbanization	8	72.6	0.68	0.71

Table 3. Estimates of the Japanese cedar pollen sensitization rate by covariance of the year of survey of 1989

	Sensitization rate (95% CI), %
Age group	
Children	19.6 (15.3–24.9)
Adolescents	28.8 (21.9–26.9)
Young adults	26.4 (20.1–33.8)
Adults	11.4 (8.3–15.5)
General population	22.2 (19.4–25.2)
Degree of urbanization	
Metropolitan	29.7 (23.7–26.4)
Urban	22.5 (19.7–25.4)
Rural	13.2 (10.5–16.4)

pants), 10 rural subgroups (3,452 participants) and 37 ‘unknown’ subgroups (11,729 participants). Figure 1 shows a scatterplot of the year of the survey versus sensitization rates.

The Japanese cedar pollen sensitization rate was significantly correlated with the year of survey, age, and degree of urbanization (table 2; adjusted $R^2 = 0.55$). A total of 120 subgroups were included to the analysis. Fourteen subgroups were excluded: 10 groups were classified as of ‘unknown’ urbanization [15, 17, 37], 3 groups had too small a number of participants [28] and one was a subgroup of the year 1973 which was an outlier of this year of survey [21]. In the regression model, an estimated parameter of the year of survey was 0.08 (95% confidence interval; 0.05–0.11). Table 3 shows the adjusted estimates by categories. According to age, adolescents had the highest sensitization rate, and the lowest rate was in adults. The ratio between the estimated sensitization rate among adolescents and among adults was 2.5 to 1. The general population had a rate intermediate between the rate of young adults and adults. Age showed a reverse U-shaped relationship with the sensitization rate. According to the degree of urbanization, the metropolitan group had the highest sensitization rate. The ratio between the estimated sensitization rate of metropolitan residents to that of rural residents was 2.3 to 1, and the rate for urban resi-

Table 4. Results of subgroup analysis of meta-regression for the sensitization rate by age

Age group	Subgroups	Adjusted R ² (p)	Parameter of year of survey (p) ^a	Ratio of metropolitan areas/rural areas (p) ^b
Children	15	-0.01 (0.46)	0.01 (0.89)	2.2 (0.36)
Adolescents	29	0.41 (0.001)	0.14 (0.001)	1.8 (0.07)
Young adults	29	0.33 (0.004)	0.06 (0.02)	1.9 (0.01)
Adults	28	0.48 (<0.001)	0.13 (0.002)	3.8 (0.001)
General population	19	0.48 (0.004)	0.07 (0.02)	2.0 (0.02)

^a Estimated parameter of year of survey.

^b Ratio of estimated sensitization rate of metropolitan areas/rural areas by covariance of year of survey.

dents was intermediate between them. Three regression curves are superimposed in figure 1. The high prediction curve represents adolescents in metropolitan areas; the middle curve represents the general population in urban areas, and the low curve represents adults in urban areas. As an example, the regression formula for the high prediction curve is:

$$\text{logit (sensitization rate)} = 0.08 \times \text{year} - 159.67$$

The sensitivity analysis showed consistency through age (table 4). The effects of the year of survey and urbanization were statistically significant in regard to the age groups of adolescents, young adults, adults, and general population. The sensitization rate increased as time passed in every age group except the children group.

Prevalence correlated well with the sensitization rate ($n = 27$; Pearson's $r = 0.70$; $p < 0.001$). The regression coefficient without intercept was 0.44 (95% CI; 0.38–0.49). There were no significant differences according to the year of survey.

Discussion

Japanese cedar pollen sensitization rates were affected by the year of survey, age, and the degree of urbanization. The sensitization rate rose 2.6-fold between 1980 and 2000. The sensitization rate of adolescents was 2.5 times higher than in adults. The sensitization rate of metropolitan residents was 2.3-fold that of rural residents. The year of survey, age, and degree of urbanization explained more than half of the variance of the sensitization rate. Our results showed consistency in terms of the effect of age and the degree of urbanization. The results of the sensitivity analysis showed that the reliability of this study was sufficiently high.

The regression model of the prevalence of Japanese cedar pollinosis could not be formulated because of a small number of prevalence data. Therefore, we predicted the prevalence of Japanese cedar pollinosis derived from the estimated sensitization rate and the relationship between sensitization rate and prevalence. The prevalence of Japanese cedar pollinosis in this study was estimated by multiplying 0.44 times the Japanese cedar pollen sensitization rate. The prevalence observed in individual surveys may be affected by annual variations in pollen production and exposure. The sensitization rate appeared to be a potential predictor of the prevalence. The sensitization rate and prevalence among adolescents in metropolitan areas in the year of 2004 were predicted to be 65.2 and 28.7%, respectively, and 55.6 and 24.5%, respectively, in the general population in urban areas.

A limitation of the meta-analysis, including the meta-regression analysis, is that the result depends on the reliability of the pooled studies. Tanihara et al. [46] discussed several problems in regard to Japanese cedar pollinosis studies, such as the existence of differing diagnostic criteria and the absence of nationwide surveys. It is difficult to conduct nationwide surveys based on an accurate diagnosis by serological methods. The prevalence we estimated was higher than in a recent nationwide postal survey [4], but the prevalence in Tokyo, which is one of the areas with the highest prevalence of Japanese cedar pollinosis, was approximately the same as in our study. Since the surveys included in our study were restricted to surveys in which an accurate diagnosis had been made on the basis of specific IgE measurements, mainly by RAST or ELISA, and had been conducted in 24 of the 47 prefectures nationwide in Japan, we consider our results to be reliable and to represent the epidemiological status of cedar pollinosis in Japan.

The increasing prevalence of Japanese cedar pollinosis may be related to the marked increase in cedar pollen production in Japan. Cedar forests account for 18% of the total forest cover and 12% of the total area of Japan. Since the 1980s, the cedar forests planted after World War II began to produce large amounts of pollen [47], and with regard to urbanization it has been pointed out that pollen allergy is positively correlated with air pollution, especially diesel exhaust particulates from motor vehicles [48, 49]. In addition, a recent report on the relationship between the Japanese cedar pollinosis and urbanization in Japan suggested that westernized living condition such as wood floors related to an increase in the Japanese cedar pollinosis [50].

Our results may have been affected by the lack of data on the exposure dose. A nationwide cedar pollen survey reported diverse variations in areas and years [51]. The areas covered by cedar forest also differ widely according to the prefecture [47]. There is no clear relationship between pollen counts and the area covered by the cedar forest [47]. Many surveys included in our study did not report the exposure dose to Japanese cedar pollen. Thus,

we cannot report on the relationship between the increasing prevalence of Japanese cedar pollinosis and the increase in cedar pollen production in Japan.

The number of surveys on prevalence or sensitization rate have decreased since the mid 1990s. Our findings suggested that the prevalence of Japanese cedar pollinosis may continue to increase without reaching a plateau, and thus it will be necessary to monitor the prevalence of Japanese cedar pollinosis continuously and systematically.

In conclusion, we estimated a 2.6 times increase of the prevalence of Japanese cedar pollinosis in the past two decades and the increases differed greatly according to age and degree of urbanization. Meta-analysis of data from population-based epidemiological surveys provided evidence that will be useful for developing effective measures to control Japanese cedar pollinosis in Japan.

Acknowledgment

This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Culture and Sports of Japan.

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