Epidemiol. Infect. (2017), **145**, 1270–1275. © Cambridge University Press 2017
doi:10.1017/S0950268816003174

Association of cigarette smoking with a past history and incidence of herpes zoster in the general Japanese population: the SHEZ Study

J. BAN[1], Y. TAKAO[1,2], Y. OKUNO[2], Y. MORI[3], H. ASADA[4], K. YAMANISHI[2] AND H. ISO[1]*

[1] *Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, Osaka Japan*
[2] *The Research Foundation for Microbial Diseases of Osaka University, Kagawa, Japan*
[3] *Division of Clinical Virology, Kobe University Graduate School of Medicine, Kobe, Japan*
[4] *Nara Medical University School of Medicine, Nara Japan*

Received 2 October 2016; Accepted 6 December 2016;
first published online 16 January 2017

SUMMARY

Few studies have examined the impact of cigarette smoking on the risk for herpes zoster. The Shozu Herpes Zoster (SHEZ) Study is a community-based prospective cohort study over 3 years in Japan aiming to clarify the incidence and predictive and immunological factors for herpes zoster. We investigated the associations of smoking status with past history and incidence of herpes zoster. A total of 12 351 participants provided valid information on smoking status and past history of herpes zoster at baseline survey. Smoking status was classified into three categories (current, former, never smoker), and if currently smoking, the number of cigarettes consumed per day was recorded. The participants were under the active surveillance for first-ever incident herpes zoster for 3 years. We used a logistic regression model for the cross-sectional study on the association between smoking status and past history of herpes zoster, and a Cox proportional hazards regression model for the cohort study on the association with risk of incidence. The multivariable adjusted odd ratios (95% CI) of past history of herpes zoster for current *vs.* never smokers were 0·67 (0·54–0·80) for total subjects, 0·72 (0·56–0·93) for men and 0·65 (0·44–0·96) for women. The multivariable adjusted hazard ratios (95% CI) of incident herpes zoster for current *vs.* never smokers were 0·52 (0·33–0·81) for total subjects, 0·49 (0·29–0·83) for men and 0·52 (0·19–1·39) for women. Smoking status was inversely associated with the prevalence and incidence of herpes zoster in the general population of men and women aged $\geqslant$50 years.

Key words: Herpes zoster, Japanese adults, prospective cohort study, smoking status.

INTRODUCTION

Herpes zoster is a painful vesicular rash caused by reactivation of latent varicella zoster virus (VZV) dominant in dorsal root ganglia after its primary infection [1, 2]. Reactivation occurs when cellular immunity against the virus falls below the levels that would have maintained the latent status [3]. Elderly people, in particular, are likely to develop herpes zoster through reduced levels of the immune system along with ageing [4], immunosuppressive disorders like HIV [5] and cancer [6]. By contrast, people who had contact with varicella cases, e.g. physicians and primary school teachers, were less likely to develop herpes zoster because of boosted VZV-specific

* Author for correspondence: H. Iso, MD, Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita-city, Osaka 565-0871, Japan
(Email: iso@pbhel.med.osaka-u.ac.jp)

cell-mediated immunity [7, 8]. Furthermore, psychological stress [9, 10], mechanical trauma [11] and diets [12], such as low fruit intake, have been proposed as factors for developing herpes zoster probably through a reduced immune system [3].

Several previous studies [3, 9] noted an inverse association between smoking and risk of herpes zoster. However, those studies investigated smoking as a confounding variable, but not as a prediction for herpes zoster in a systematic way.

In this paper, we investigated the association of smoking status with a past history and incidence of herpes zoster in the Shozu Herpes Zoster (SHEZ) Study.

METHODS

The SHEZ Study is a 3-year community-based prospective cohort study in Shozu County, Kagawa Prefecture, which aimed to clarify the incidence and predictive and immunological factors for herpes zoster. The detailed methods of this study have been described elsewhere [13].

Subjects

The target population was Japanese residents aged $\geqslant 50$ years in Shozu County (Shodoshima and Teshima Islands in Kagawa prefecture). Of 19 058 residents (8424 men, 10 634 women) aged $\geqslant 50$ years on 1 October 2008, a total of 12 522 persons (5587 men, 6935 women) participated in the SHEZ study (overall participation rate 65·7%).

Baseline information collection at enrolment

The baseline survey was carried out between December 2008 and November 2009. The past history of herpes zoster was obtained at the registration interview by research physicians. The subject was asked whether and when he/she had received a diagnosis of herpes zoster from a physician. Information regarding family history of herpes zoster, underlying diseases (high blood pressure, hyperlipidaemia, diabetes mellitus, connective tissue disease, cancer, leukemia or other diseases), lifestyle behaviours, social and psychological factors were elicited by trained interviewers using a structured questionnaire. Smoking status was classified into three categories; current, former or never smoker. For current smokers, the number of cigarettes consumed per day was recorded and was categorized into 1–9, 10–19, 20–29 and $\geqslant 30$ cigarettes per day. A former smoker was defined as a person who had stopped smoking at baseline. Lifestyle behaviours included walking, exercise, sleep and diet (consumption of fruit, vegetables, fish, meat, eggs, miso soup, soybeans, milk and alcohol) were also enquired. Social and psychological factors included talking with others, opportunities for laughing, self-rated health, sleep satisfaction, perceived mental stress, a sense of purpose in life and social support. We excluded 163 subjects (78 men, 85 women) who did not provide information on smoking status and past history of herpes zoster from the analyses.

Surveys after enrolment

To confirm the development of herpes zoster, a telephone survey was conducted with each subject once every 4 weeks. Subjects who presented with symptoms suggestive of herpes zoster and did not consult a doctor at the time were invited to the medical institutions and were examined by physicians for diagnosis.

Statistical analysis

In the cross-sectional analysis, logistic regression analysis was used to estimate the odds ratios (ORs) and their 95% confidence intervals (95% CIs) for the association between smoking status and past history of herpes zoster after adjustment for selected confounding variables, i.e. age, sex, family history of herpes zoster and present history of underlying diseases.

In the cohort analysis, incidence of herpes zoster was expressed per 1000 person-years, and a Cox proportional hazards regression model was used to estimate hazard ratios (HRs) and their 95% CIs for the association between smoking status and incident herpes zoster. We adjusted for selected confounding variables, i.e. age, sex, family history of herpes zoster, present history of underlying diseases and psychological factors such as perceived mental stress and well-being. The data were analysed with SAS software for Windows v. 9.1 (SAS Institute Japan Ltd, Japan). All statistical tests were two-tailed and $P < 0{\cdot}05$ was regarded as significant.

Standard protocol approvals, registrations, and patient consent

The SHEZ Study was conducted in accordance with the Ethical Guidelines for Epidemiological Research and the Ethical Guideline for Clinical studies after

https://doi.org/10.1017/S0950268816003174 Published online by Cambridge University Press

Table 1. *Characteristics of participants at baseline, the SHES Study*

	Men	Women	*P* for difference
No. of total subjects for the cross-sectional analysis	5509	6850	
Age, years, mean ± s.d.	67·2 ± 10·1	68·9 ± 10·8	<0·001
Age, years, *n* (%)			
50–59	1488 (27·0)	1671 (24·4)	<0·001
60–69	1820 (33·0)	1962 (28·7)	
70–79	1440 (26·1)	1929 (28·2)	
⩾80	761 (13·8)	1282 (18·7)	
Smoking status, *n* (%)			
Never	1039 (18·9)	6406 (93·5)	<0·001
Former	2564 (46·5)	198 (2·9)	
Current	1906 (34·6)	246 (3·6)	
1–9 cigarettes per day	237 (4·3)	94 (1·4)	
10–19	651 (11·8)	94 (1·4)	
20–29	642 (11·7)	42 (0·6)	
⩾30	376 (6·8)	16 (0·2)	
Past history of herpes zoster, *n* (%)	660 (12·0)	1310 (19·1)	<0·001
No. of subjects without past history of herpes zoster for the cohort analysis	4849	5540	
Age, years, mean ± s.d.	66·8 ± 10·1	68·5 ± 10·9	
Age, years, *n* (%)			
50–59	1363 (28·1)	1456 (26·3)	<0·001
60–69	1621 (33·4)	1560 (28·2)	
70–79	1232 (25·4)	1511 (27·3)	
⩾80	633 (13·1)	1013 (18·3)	
Incidence of herpes zoster, *n* (%)	119 (2·5)	216 (3·9)	<0·001
Smoking status, *n* (%)			
Never	916 (18·9)	5158 (93·1)	<0·001
Former	2178 (44·9)	166 (3·0)	
Current	1755 (36·2)	216 (3·9)	
1–9 cigarettes per day	217 (4·5)	80 (1·4)	
10–19	605 (12·5)	81 (1·5)	
20–29	591 (12·2)	40 (0·7)	
⩾30	342 (7·1)	15 (0·3)	

obtaining informed consent from subjects [13] and was approved by the Ethics Committee of the Research Foundation for Biomedical Diseases of Osaka University, the National Institute of Biomedical Innovation and Nara Medical University.

RESULTS

Table 1 shows the characteristics of the participants at baseline. Men were slightly younger than women. Smoking status differed substantially between the sexes; 36·2% of men and 3·9% of women were current smokers, while 18·9% of men and 93·1% of women were never smokers. The prevalence of past history of herpes zoster was 12·0% in men and 19·1% in women. Similar trends were observed when participants with past history of herpes zoster were excluded for the cohort analysis.

Table 2 presents age- and sex-adjusted and multivariable adjusted ORs (95% CIs) of prevalent herpes zoster according to smoking status in total subjects, men and women. Compared to never smokers as the reference group, the age- and sex-adjusted ORs for current *vs.* never smokers were 0·64 (0·52–0·78) for total subjects, 0·71 (0·55–0·92) for men, and 0·63 (0·42–0·92) for women. The corresponding multivariable adjusted ORs (95% CIs) were 0·67 (0·54–0·80), 0·72 (0·56–0·93) and 0·65 (0·44–0·96), respectively. The age- and sex-adjusted ORs for former *vs.* never smokers were 1·15 (0·96–1·36) for total subjects, 1·30 (1·05–1·62) for men and 0·80 (0·54–1·17) for women. The corresponding multivariable adjusted ORs (95% CIs) were 1·13 (0·95–1·34), 1·26 (1·01–1·57) and 0·81 (0·55–1·19), respectively. There was no dose-response relationship between the number of cigarettes consumed per day and prevalence herpes zoster.

https://doi.org/10.1017/S0950268816003174 Published online by Cambridge University Press

Table 2. *Odds ratios (95% CIs) of past history of herpes zoster according to smoking status: the cross-sectional analysis*

	No. of participants	No. of prevalent cases (%)	Odds ratio (95% CI)		
			Age- and sex-adjusted	Multivariable adjusted*	*P* value
Total subjects					
Never smoker	7445	1371 (18·4)	1·00	1·00	
Former smoker	2762	418 (15·1)	1·15 (0·96–1·36)	1·13 (0·95–1·34)	0·182
Current smoker	2152	181 (8·4)	0·64 (0·52–0·78)	0·67 (0·54–0·80)	<0·001
No. of cigarettes smoked per day among current smokers					
1–9	331	34 (10·3)	0·67 (0·46–0·97)	0·67 (0·46–0·97)	0·033
10–19	745	59 (7·9)	0·59 (0·44–0·79)	0·61 (0·45–0·82)	0·001
20–29	684	53 (7·8)	0·62 (0·45–0·85)	0·65 (0·47–0·89)	0·007
⩾30	392	35 (8·9)	0·75 (0·52–1·10)	0·77 (0·53–1·13)	0·186
Men					
Never smoker	1039	123 (11·8)	1·00	1·00	
Former smoker	2564	386 (15·1)	1·30 (1·05–1·62)	1·26 (1·01–1·57)	0·039
Current smoker	1906	151 (7·9)	0·71 (0·55–0·92)	0·72 (0·56–0·93)	0·012
No. of cigarettes smoked per day among current smokers					
1–9	237	20 (8·4)	0·68 (0·41–1·11)	0·66 (0·40–1·09)	0·103
10–19	651	46 (7·1)	0·62 (0·43–0·88)	0·63 (0·44–0·90)	0·011
20–29	642	51 (7·9)	0·74 (0·52–1·05)	0·75 (0·53–1·07)	0·109
⩾30	376	34 (9·0)	0·88 (0·59–1·32)	0·89 (0·59–1·34)	0·585
Women					
Never smoker	6406	1248 (19·5)	1·00	1·00	
Former smoker	198	32 (16·2)	0·80 (0·54–1·17)	0·81 (0·55–1·19)	0·283
Current smoker	246	30 (12·2)	0·63 (0·42–0·92)	0·65 (0·44–0·96)	0·029
No. of cigarettes smoked per day among current smokers					
1–19	188	27 (14·4)	0·74 (0·49–1·12)	0·76 (0·50–1·15)	0·199
⩾20	58	3 (5·2)	0·26 (0·08–0·83)	0·28 (0·09–0·89)	0·031

* Adjusted for age, sex, family history and underlying diseases.

Table 3 shows age- and sex-adjusted and multivariable adjusted HRs for incident herpes zoster according to smoking status in persons without past history of herpes zoster. Compared to never smokers as the reference group, the age- and sex-adjusted HRs (95% CIs) for current *vs.* never smokers were 0·51 (0·32–0·79) for total subjects, 0·49 (0·29–0·83) for men and 0·51 (0·19–1·36) for women. The corresponding multivariable adjusted HRs (95% CIs) were 0·52 (0·33–0·81), 0·49 (0·29–0·83) and 0·52 (0·19–1·39), respectively.

DISCUSSION

In our epidemiological study of the general population, current smoking was associated with lower risk of prevalent and incident herpes zoster, compared to never smoking for total subjects, men and women, separately. There was, however, no dose-response relationship of the number of cigarettes smoked per day with risk of prevalent and incident herpes. For men, former smoking was associated with higher prevalence of herpes zoster, but was not associated with risk of incident herpes zoster.

A prospective cohort study of 4162 American men and women aged ⩾65 years (46% for whites, 54% for blacks) reported the HRs of incident herpes zoster according to smoking status [14]. The participants were interviewed at baseline and the in-person interviews were repeated at 3-year intervals for 6 years. The HR (95% CI) of incident herpes zoster for current smoker *vs.* current nonsmoker was 0·47 (0·25–0·89) after adjustment for age, race, sex, marital status, education, presence of a confidant, perceived adequacy of social support, the Social Network Scale, the Social Interaction Scale, chronic diseases, basic activities of daily living (ADLs), instrumental ADLs, depression, self-rated health and hospitalization. Our corresponding HR (95% CI) was 0·58 (0·35–0·97), which implies a similar result.

https://doi.org/10.1017/S0950268816003174 Published online by Cambridge University Press

Table 3. *Hazard ratios (95% CIs) of incident herpes zoster according to smoking status: the cohort analysis*

	Person-years	No. of incident cases	Incidence rate per 1000 person-years	Hazard ratio (95% CI)		*P* value
				Age- and sex-adjusted	Multivariable-adjusted*	
Total subjects without past history of herpes zoster						
Never smoker	17 971	236	13·1	1·00	1·00	
Former smoker	6854	68	9·92	0·88 (0·60–1·28)	0·87 (0·59–1·27)	0·456
Current smoker	5886	31	5·27	0·51 (0·32–0·79)	0·52 (0·33–0·81)	0·004
1–19	2930	15	5·12	0·47 (0·27–0·83)	0·48 (0·27–0·85)	0·012
⩾20	2956	16	5·41	0·55 (0·31–0·98)	0·56 (0·31–1·00)	0·051
Men						
Never smoker	2696	31	11·5	1·00	1·00	
Former smoker	6376	61	9·57	0·82 (0·53–1·26)	0·82 (0·53–1·26)	0·360
Current smoker	5247	27	5·15	0·49 (0·29–0·83)	0·49 (0·29–0·83)	0·008
1–19	2451	12	4·90	0·45 (0·23–0·87)	0·45 (0·23–0·87)	0·018
⩾20	2795	15	5·37	0·53 (0·28–1·00)	0·54 (0·29–1·01)	0·053
Women						
Never smoker	15 276	205	13·4	1·00	1·00	
Former smoker	479	7	14·6	1·10 (0·52–2·34)	1·12 (0·53–2·38)	0·766
Current smoker	640	4	6·25	0·51 (0·19–1·36)	0·52 (0·19–1·39)	0·192
1–19	479	3	6·26	0·50 (0·16–1·56)	0·51 (0·16–1·60)	0·250
⩾20	161	1	6·21	0·52 (0·07–3·75)	0·53 (0·07–3·80)	0·528

* Adjusted for age, sex, family history of herpes zoster and underlying diseases.

Regarding mechanisms, the reactivation of VZV has been suggested to have a relationship with the immune system of patients. The ratio of CD4+ to CD8+ lymphocytes (CD4+/CD8+ ratio), a surrogate marker for cellular immunity, was 40% lower in acute-phase herpes zoster patients compared to healthy persons [15], as a result of a 10% higher total of CD4+ lymphocytes and a 70% higher total of CD8+ lymphocytes in particular. The CD4+/CD8+ ratio was 5–10% higher in smokers than in non-smokers [16, 17]. Furthermore, the CD4+/CD8+ ratio was 10% higher in light to moderate smokers (10–49 pack-years) but 20% lower in heavy smokers (50–120 pack-years) compared to that of non-smokers [18]. These findings suggest that cellular immunity may be enhanced in light to moderate smokers but reduced in heavy smokers. The lower incidence of herpes zoster associated with current smoking can be explained in part by enhanced cellular immunity. No further risk reduction of incident herpes zoster associated with increased number of cigarettes smoked may be explained by a potential deleterious effect on cellular immunity by heavy smoking.

CONCLUSION

Smoking was inversely associated with incidence, as well as past history of herpes zoster. The inverse association between smoking and risk of herpes zoster does not imply the encouragement of smoking because of its strong health hazard. Our study result, however, helps to elucidate a part of the mechanisms for the development of herpes zoster.

ACKNOWLEDGEMENTS

We express our gratitude to the following medical organizations for their cooperation: Shozu County Medical Society, Shodoshima Federation of Self-Government Bodies, Tonosho Town Autonomous Liaison Council, Shodoshima Town Government and Tonosho Town Government.

This work was part of the SHEZ Study supported by Grants-in-Aid for Scientific research from the Japanese Ministry of Health, Labour, and Welfare for Research on Publicly essential drugs and Medical devices (fiscal years 2008–2010) (KHC1102) and for Public-private Sector Joint research on Publicly Essential drugs (fiscal year 2011–2012) (KHC1102), as well as research funds from the research Foundation for Microbial diseases of Osaka University.

DECLARATION OF INTEREST

None.

REFERENCES

1. **Brisson M, *et al.*** Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. *Epidemiology & Infection* 2001; **127**: 305–314.
2. **Gershon A, *et al.*** Advances in the understanding of the pathogenesis and epidemiology of herpes zoster. *Journal of Clinical Virology* 2010; **48**: S2–S7.
3. **Thomas SL, *et al.*** What does epidemiology tell us about risk factors for herpes zoster? *Lancet Infectious Diseases* 2004; **4**: 26–33.
4. **Arvin A.** Aging, immunity, and the varicella-zoster virus. *New England Journal of Medicine* 2005; **352**: 2266–2267.
5. **Morgan A, *et al.*** Herpes zoster and HIV-1 infection in a rural Ugandan cohort. *AIDS* 2001; **15**: 223–229.
6. **Hata A, *et al.*** Risk of Herpes zoster in patients with underlying disease: a retrospective hospital-based cohort study. *Infection* 2011; **39**: 537–544.
7. **Thomas SL, *et al.*** Contacts with varicella or with children and protection against herpes zoster in adults: a case-control study. *Lancet* 2002; **360**: 678–682.
8. **Salleras M, *et al.*** Contacts with children and young people and adult risk of suffering herpes zoster. *Vaccine* 2011; **29**: 7602–7605.
9. **Schmader K, *et al.*** Racial and psychosocial risk factors for herpes zoster in the elderly. *Journal of Infectious Disease* 1998; **178**: S67–S70.
10. **Irwin M, *et al.*** Cellular immunity to varicella-zoster virus in patients with major depression. *Journal of Infectious Disease* 1998; **178**: S104–S108.
11. **Thomas SL, *et al.*** Case-control study of the effect of mechanical trauma on the risk of herpes zoster. *British Medical Journal* 2004; **328**: 439–440.
12. **Thomas SL, *et al.*** Micronutrient intake and the risk of herpes zoster: a case-control study. *International Journal of Epidemiology* 2006; **35**: 307–314.
13. **Takao Y, *et al.*** Prospective cohort study of herpes zoster in Shozu county: The Shozu Herpes Zoster (SHEZ) Study. *Journal of Epidemiology* 2012; **22**: 167–174.
14. **Schmader K, *et al.*** Race and stress in the incidence of herpes zoster in older adults. *Journal of the American Geriatrics Society* 1998; **46**: 973–977.
15. **Higa K, *et al.*** T-lymphocyte subsets in otherwise healthy patients with herpes zoster and relationships to the duration of acute herpetic pain. *Pain* 1992; **51**: 111–118.
16. **Tollerud D, *et al.*** The effect of cigarette smoking on T cell subsets. *American Review of Respiratory Disease* 1989; **139**: 1446–1451.
17. **Mili F, *et al.*** The associations of race, cigarette smoking, and smoking cessation to measures of the immune system in middle-aged men. *Clinical Immunology and Immunopathology* 1991; **59**: 187–200.
18. **Miller LG, *et al.*** Reversible alterations in immunoregulatory T cells in smoking: Analysis by monoclonal antibodies and flow cytometry. *Chest* 1982; **82**: 526–529.