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

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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 ≥ 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
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 ≥50 years in Shozu County (Shodoshima and Teshima Islands in Kagawa prefecture). Of 19 058 residents (8424 men, 10 634 women) aged ≥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 ≥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 $P < 0.05$ 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...
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.
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 non-smoker 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.
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.

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**DECLARATION OF INTEREST**

None.

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

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

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


