Cigarette Smoking and Risk of Type 2 Diabetes Mellitus among Middle-aged and Elderly Japanese Men and Women

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For examination of sex- and age-specific relations between smoking and risk of type 2 diabetes mellitus, 39,528 nondiabetic men and 88,613 nondiabetic women aged 40–79 years who underwent health checkups in Ibaraki-ken, Japan, in 1993 were followed through 2002. Risk ratios for diabetes according to smoking habits were calculated using a Cox proportional hazards model. Compared with never smokers, the risk ratio for diabetes among current smokers, after adjustment for age, systolic blood pressure, antihypertensive medication use, alcohol intake, parental history of diabetes, body mass index, fasting status, blood glucose concentration, total and high density lipoprotein cholesterol levels, and log-transformed triglyceride level, was 1.27 (95% confidence interval (CI): 1.16, 1.38) in men and 1.39 (95% CI: 1.20, 1.61) in women. The excess risk was more pronounced among men with a parental history of diabetes than among men without one. The excess risk among current smokers was observed in both age subgroups (40–59 and 60–79 years). Respective multivariate risk ratios for the age subgroups were 1.37 (95% CI: 1.18, 1.60) and 1.20 (95% CI: 1.08, 1.34) in men and 1.45 (95% CI: 1.18, 1.79) and 1.34 (95% CI: 1.09, 1.66) in women. Smoking was independently associated with increased risk of type 2 diabetes among both middle-aged and elderly men and women.

diabetes mellitus; follow-up studies; risk factors; smoking

Abbreviation: CI, confidence interval.

Type 2 diabetes mellitus is one of the major public health problems in Japan. The estimated number of diabetic patients is approximately 6.9 million—8.2 percent of the national census population aged 20 years or more (1).

A positive association between smoking habits and the risk of type 2 diabetes among middle-aged men has emerged from many prospective studies carried out in Europe and Japan (2–9). However, findings among middle-aged women and elderly men and women have been limited and inconsistent (8–11). Thus, we examined sex- and age-specific relations between cigarette smoking and the risk of type 2 diabetes in a large cohort study.

MATERIALS AND METHODS

Study population

We enrolled in the study 192,125 Japanese subjects (63,379 men and 128,746 women) aged 40–79 years who underwent health checkups conducted by the Ibaraki Health Service Association in Ibaraki-ken in 1993. We excluded 3,614 men and 3,645 women with a fasting plasma glucose level of ≥7.0 mmol/liter or a nonfasting plasma glucose level of ≥11.1 mmol/liter and 1,333 men and 1,646 women with a history of diabetes mellitus at baseline. Moreover, we excluded 18,904 men and 34,842 women who did not participate in the 1994 survey so that the subjects were followed...
up for at least 1 year. The distribution of follow-up was as follows: 21.3 percent were followed up for 1 year, 14.5 percent for 2 years, 9.9 percent for 3 years, 7.9 percent for 4 years, 5.7 percent for 5 years, 4.6 percent for 6 years, 3.8 percent for 7 years, 3.9 percent for 8 years, and 28.2 percent for 9 years. The age-adjusted prevalence of current smoking was lower in persons followed than in those not followed (48 percent vs. 52 percent for men and 4 percent vs. 7 percent for women, respectively). However, the difference in the prevalence of nonfasting subjects was small between persons followed and persons not followed (83 percent vs. 79 percent for men and 82 percent vs. 80 percent for women, respectively). Mean plasma glucose levels were almost identical between persons followed and persons not followed (6.1 mmol/liter vs. 6.1 mmol/liter for men and 5.8 mmol/liter vs. 5.8 mmol/liter for women, respectively). Thus, the potential follow-up bias may have been small.

After the exclusions, the study subjects consisted of 39,528 men and 88,613 women. These subjects were followed annually until diagnosis of diabetes mellitus or the end of 2002. In annual follow-up examinations, measurement of plasma glucose levels was performed and an interview requesting information on use of diabetes medications was conducted. Persons who did not undergo checkups during the follow-up periods were censored at the date of their latest checkup. The average duration of follow-up was 4.5 years for men and 4.9 years for women.

**Baseline examinations**

At baseline, blood was drawn from seated participants into two polyethylene terephthalate tubes with an accelerator or with sodium fluoride and ethylenediaminetetraacetic acid. Fasting was not required. Plasma glucose level was measured by means of a glucose oxidase electrode method using a GA1140 device (Kyoto Daichi Kagaku, Kyoto, Japan) in the laboratory of the Ibaraki Health Service Association. Serum total cholesterol and serum triglyceride levels were measured by means of an enzyme method using an RX-30 device (Nihon Denshi, Tokyo, Japan). High density lipoprotein cholesterol was measured in the same laboratory by means of a phosphotungstic acid magnesium method using an MTP-32 device (Corona Electric, Ibaraki, Japan). The measurement of these lipids was standardized by the laboratory of the Osaka Medical Center for Health Science and Promotion under the laboratory network program of the US Centers for Disease Control and Prevention (Atlanta, Georgia) (12).

Baseline blood pressures were measured on the right arm of seated participants by trained observers using standard mercury sphygmomanometers. Height in stocking feet and weight in light clothing were measured. Body mass index was calculated as weight (kg) divided by the square of height (m). An interview was conducted to ascertain parental history of diabetes (yes, no, or unknown), alcohol intake (never, sometimes, <75 ml/day, or ≥75 ml/day), body mass index, systolic blood pressure, antihypertensive medication use (yes or no), fasting status (yes or no), plasma glucose level, serum total cholesterol level, high density lipoprotein cholesterol level, and log-transformed triglyceride level.

**Endpoint determination**

Plasma glucose level was measured by the glucose oxidase electrode method using a GA1140 device in 1994–1996 and by the hexokinase/glucose-6-phosphate dehydrogenase method using an H7170 device (Hitachi Ltd., Tokyo, Japan)

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**TABLE 1. Sex-specific risk ratios for type 2 diabetes mellitus according to smoking habits among 39,528 men and 88,613 women, Ibaraki-ken, Japan, 1993–2002**

<table>
<thead>
<tr>
<th>Sex and smoking status</th>
<th>No. of person-years</th>
<th>No. of subjects with incident diabetes</th>
<th>Age-adjusted RR*</th>
<th>95% CI*</th>
<th>Multivariate-adjusted RR†</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>42,718</td>
<td>748</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>54,305</td>
<td>1,125</td>
<td>1.15</td>
<td>1.05, 1.26</td>
<td>1.10</td>
<td>1.00, 1.20</td>
</tr>
<tr>
<td>Current smoker</td>
<td>80,317</td>
<td>1,831</td>
<td>1.31</td>
<td>1.20, 1.42</td>
<td>1.27</td>
<td>1.16, 1.38</td>
</tr>
<tr>
<td>&lt;20 cigarettes/day</td>
<td>4,326</td>
<td>109</td>
<td>1.51</td>
<td>1.23, 1.84</td>
<td>1.46</td>
<td>1.20, 1.79</td>
</tr>
<tr>
<td>≥20 cigarettes/day</td>
<td>75,991</td>
<td>1,722</td>
<td>1.30</td>
<td>1.19, 1.41</td>
<td>1.26</td>
<td>1.15, 1.37</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>419,375</td>
<td>4,067</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>2,202</td>
<td>23</td>
<td>1.08</td>
<td>0.71, 1.62</td>
<td>1.13</td>
<td>0.75, 1.70</td>
</tr>
<tr>
<td>Current smoker</td>
<td>15,394</td>
<td>196</td>
<td>1.38</td>
<td>1.20, 1.59</td>
<td>1.39</td>
<td>1.20, 1.61</td>
</tr>
<tr>
<td>&lt;20 cigarettes/day</td>
<td>7,354</td>
<td>90</td>
<td>1.41</td>
<td>1.15, 1.74</td>
<td>1.39</td>
<td>1.13, 1.72</td>
</tr>
<tr>
<td>≥20 cigarettes/day</td>
<td>8,040</td>
<td>106</td>
<td>1.36</td>
<td>1.12, 1.64</td>
<td>1.38</td>
<td>1.13, 1.68</td>
</tr>
</tbody>
</table>

* RR, risk ratio; CI, confidence interval.  
† Adjusted for age, parental history of diabetes (yes, no, or unknown), alcohol intake (never, sometimes, <75 ml/day, or ≥75 ml/day), body mass index, systolic blood pressure, antihypertensive medication use (yes or no), fasting status (yes or no), plasma glucose level, serum total cholesterol level, high density lipoprotein cholesterol level, and log-transformed triglyceride level.
in 1997–2002. Our laboratory participated in external standardization by the Ibaraki Association of Medical Scientists and successfully met the criteria for precision and accuracy for the measurement of plasma glucose levels. Plasma glucose values determined by means of the glucose oxidase electrode method were compared with those determined by the hexokinase method using 237 random samples of blood drawn in 1996. Compatibility between the two methods was maintained. In the linearity test between the glucose oxidase electrode method and the hexokinase method, the regression line was $Y = 1.017 \times X + 0.802$, where $Y$ is the hexokinase method value and $X$ is the glucose oxidase electrode method value (correlation coefficient = 0.999). On the basis of the linearity test, the calibration was performed every day.

We diagnosed incident type 2 diabetes when there was a fasting plasma glucose level of $\geq 7.0$ mmol/liter or a nonfasting plasma glucose level of $\geq 11.1$ mmol/liter and/or when a person had begun to receive treatment for diabetes. Fasting was defined as not having had a meal for at least 8 hours.

Statistical analysis

Participants were classified with regard to their smoking habits as never smokers, ex-smokers, current smokers of <20 cigarettes/day, or current smokers of $\geq 20$ cigarettes/day. Risk ratios for type 2 diabetes according to smoking habits were calculated with reference to never smokers using a multivariate Cox proportional hazards regression model. Covariates included age (years), parental history of diabetes (yes or no), alcohol intake (never, sometimes, <75 ml/day, or $\geq 75$ ml/day), body mass index, systolic blood pressure, antihypertensive medication use (yes or no), fasting status (yes or no), plasma glucose level, serum total cholesterol level, high density lipoprotein cholesterol level, and log-transformed triglyceride level.

RESULTS

During follow-up between 1994 and 2002, there were 3,704 incident cases of type 2 diabetes among the 39,528 men (177,340 person-years) and 4,286 cases among the 88,613 women (436,971 person-years). The incidence rate was 20.9 per 1,000 person-years for men and 9.8 per 1,000 person-years for women. The age-adjusted risk ratio for diabetes among current smokers as compared with never smokers was 1.31 (95 percent confidence interval (CI): 1.20,
Smoking and Type 2 Diabetes

1.42) in men and 1.38 (95 percent CI: 1.20, 1.59) in women (table 1). The respective multivariate risk ratios were 1.27 (95 percent CI: 1.16, 1.38) and 1.39 (95 percent CI: 1.20, 1.61), both of which reached statistical significance. No excess risk of diabetes for ex-smokers was found in either sex. There was no dose-response relation between the number of cigarettes smoked per day and the risk of diabetes in either sex. When male current smokers were divided according to the median number of cigarettes smoked per day, the multivariate risk ratios were 1.33 (95 percent CI: 1.20, 1.47) for \( <40 \) cigarettes/day and 1.29 (95 percent CI: 1.18, 1.42) for \( \geq 40 \) cigarettes/day.

Table 2 shows sex- and age-specific multivariate risk ratios for diabetes according to smoking habits. The multivariate risk ratio was 1.37 (95 percent CI: 1.18, 1.60) among men aged 40–59 years, 1.20 (95 percent CI: 1.08, 1.34) among men aged 60–79 years, 1.45 (95 percent CI: 1.18, 1.79) among women aged 40–59 years, and 1.34 (1.09, 1.66) among women aged 60–79 years. There was no significant excess risk of diabetes for ex-smokers in either sex or either age subgroup.

Table 3 shows sex-specific multivariate risk ratios for diabetes according to smoking habits, stratified by parental history of diabetes. The multivariate risk ratio was 1.84 (95 percent CI: 1.34, 2.53) among men with a parental history of diabetes and 1.21 (95 percent CI: 1.09, 1.33) among men without a parental history of diabetes \( (p \) for interaction = 0.02). The respective risk ratios among women were 1.12 (95 percent CI: 0.70, 1.80) and 1.44 (95 percent CI: 1.21, 1.71), with no significant interaction \( (p \) for interaction = 0.26).

**DISCUSSION**

This large prospective study showed that current smoking was associated with a 20–40 percent increased risk of diabetes mellitus, of which 99 percent was type 2 diabetes (13), among men and a 40–50 percent increased risk for both age subgroups (40–59 years and 60–79 years) among women. To our knowledge, this is the first prospective study showing a significant relation between smoking and risk of diabetes among elderly men and women and showing that the excess risk of diabetes for current smoking was more pronounced among men with a parental history of diabetes than among men without one.

Our study also showed a 50 percent excess risk of diabetes for current smoking among middle-aged women. The Nurses’ Health Study, a study of 114,247 US female nurses aged 30–55 years (11), and the Cancer Prevention Study I, a study of 434,637 women aged 30 years or more (8), reported a significant 20–70 percent excess risk among middle-aged women, while several other cohort studies failed to show an

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**TABLE 3.** Sex-specific multivariate-adjusted risk ratios for type 2 diabetes mellitus according to smoking habits, by parental history of diabetes, among 30,618 men and 70,440 women, Ibaraki-ken, Japan, 1993–2002*

<table>
<thead>
<tr>
<th>Sex, parental history of diabetes, and smoking status</th>
<th>No. of person-years</th>
<th>No. of subjects with incident diabetes</th>
<th>Multivariate-adjusted risk ratio†</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive parental history of diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>2,501</td>
<td>54</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>2,378</td>
<td>83</td>
<td>1.37</td>
<td>0.97, 1.95</td>
</tr>
<tr>
<td>Current smoker</td>
<td>4,050</td>
<td>167</td>
<td>1.84</td>
<td>1.34, 2.53</td>
</tr>
<tr>
<td>Negative parental history of diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>37,826</td>
<td>621</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>48,474</td>
<td>913</td>
<td>1.06</td>
<td>0.95, 1.17</td>
</tr>
<tr>
<td>Current smoker</td>
<td>70,184</td>
<td>1,413</td>
<td>1.21</td>
<td>1.09, 1.33</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive parental history of diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>27,115</td>
<td>425</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>185</td>
<td>4</td>
<td>2.29</td>
<td>0.84, 6.24</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1,353</td>
<td>19</td>
<td>1.12</td>
<td>0.70, 1.80</td>
</tr>
<tr>
<td>Negative parental history of diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>371,625</td>
<td>3,265</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1,848</td>
<td>15</td>
<td>0.94</td>
<td>0.56, 1.56</td>
</tr>
<tr>
<td>Current smoker</td>
<td>12,655</td>
<td>144</td>
<td>1.44</td>
<td>1.21, 1.71</td>
</tr>
</tbody>
</table>

* A total of 8,910 men and 18,173 women with unknown parental history of diabetes were excluded.
† Adjusted for age, alcohol intake (never, sometimes, <75 ml/day, or \( \geq 75 \) ml/day), body mass index, systolic blood pressure, antihypertensive medication use (yes or no), fasting status (yes or no), plasma glucose level, serum total cholesterol level, high density lipoprotein cholesterol level, and log-transformed triglyceride level.
association (9, 10, 14, 15). The magnitude of excess risk of diabetes for current smoking among middle-aged men was compatible with other findings from Caucasians and Japanese (5, 7, 8), though some other studies showed higher excess risks (70–230 percent) (2–4, 6, 9).

Our study failed to show a dose-response relation between number of cigarettes smoked per day and risk of diabetes. Some previous studies (5–8, 11), but not all (2, 4), showed a dose-response relation between the number of cigarettes smoked per day and the risk of diabetes.

A causal relation between smoking and type 2 diabetes is plausible, for several biologic reasons. Smoking increases the area under the curve of serum glucose level after an oral glucose load and impairs insulin sensitivity (16). Furthermore, smoking increases oxidative stress (17), which has been implicated in the causation of diabetes (18).

A strength of the present study is the use of a large cohort in which the incidence of diabetes was ascertained by blood glucose level, as opposed to many previous studies, which ascertained the incidence by questionnaire (2, 7–11, 15). On the other hand, our study had several limitations. First, approximately 28 percent of the subjects were lost to follow-up. However, mean plasma glucose levels did not differ between persons followed and persons not followed, and the potential bias due to the incomplete follow-up may have been small. Second, potential confounding by physical activity and dietary habits remained, since we did not assess these variables. However, inclusion of physical activity (2, 4–9, 11) and dietary intakes of fats and carbohydrates (8) as confounding variables did not substantially alter the relation between smoking and risk of diabetes.

In conclusion, in this study, cigarette smoking was associated with increased risk of type 2 diabetes mellitus among both middle-aged and elderly men and women.

REFERENCES