Smoking as an Independent Risk Factor for Hypertension: A 14-Year Longitudinal Study in Male Japanese Workers

MIREI DOCHI,1 KOUICHI SAKATA,1 MITSUHIRO OISHI,1 KUMIIKO TANAKA,1 ETSUKO KOBAYASHI1 and YASUSHI SUWAZONO1,2

1Department of Occupational and Environmental Medicine, Graduate School of Medicine, Chiba University, Chiba, Japan
2Center for Preventive Medical Science, Chiba University, Chiba, Japan

Many studies have described the effects of smoking on blood pressure, as well as the mechanism of this effect. The first study, which was conducted in Finland, indicated that blood pressure levels were slightly lower in smokers than non-smokers (Karvonen et al. 1959). Subsequently, numerous reports have found that smoking reduces blood pressure (Higgins and Kjelsberg 1967; Seltzer 1974; Berglund and Wilhelmsen 1975; Goldboult and Medalie 1977; Gofin et al. 1982; Agner 1983; Savdie et al. 1984; Green et al. 1986; Rosengren and Wilhelmsen 1987; Green et al. 1991; Imamura et al. 1996; Okubo et al. 2002; Nagahama et al. 2004; Okubo et al. 2004; Wang et al. 2006). In contrast, several reports have found that smoking raises blood pressure (Elliott and Simpson 1980; Dyer et al. 1982; Bolinder and de Faire 1998), while still others failed to confirm any effect on blood pressure (Arkwright et al. 1982; Criqui et al. 1982; Lang et al. 1983; Simons et al. 1984). Few large epidemiological studies on the effects of smoking on blood pressure have considered the confounding effects of such factors as age, obesity, blood chemistry, lifestyle or working conditions. Thus, results of these studies have been inconsistent, and were not sufficient in defining the effect of smoking on the onset of hypertension. Smoking is a direct cause of such fatal diseases as lung cancer, and is the most common risk factor of many preventable diseases. Since hypertension is one of the risk factors of cardiovascular disease, it is important to define the effect of smoking on blood pressure. This study revealed that smoking is independently related to the onset of hypertension and systolic hypertension in Japanese male workers. These results provide important information necessary to define the effect of smoking on blood pressure. ——— Smoking; Hypertension; Blood pressure; Cohort study; Epidemiology.

Patients and Methods

Subjects

This cohort study examined 8,251 male workers in a Japanese steel company, and was conducted between 1991 and 2005. The sub-
Table 1. Number of subjects examined and number of subjects who developed hypertension.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hypertension</th>
<th></th>
<th>Systolic hypertension</th>
<th></th>
<th>Diastolic hypertension</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-smokers</td>
<td>Smokers</td>
<td>Total</td>
<td>Non-smokers</td>
<td>Smokers</td>
<td>Total</td>
</tr>
<tr>
<td>Number of subjects examined</td>
<td>2,080</td>
<td>3,432</td>
<td>5,512</td>
<td>2,184</td>
<td>3,581</td>
<td>5,765</td>
</tr>
<tr>
<td>Number of subjects who developed hypertension</td>
<td>826</td>
<td>1,557</td>
<td>2,383</td>
<td>855</td>
<td>1,614</td>
<td>2,469</td>
</tr>
<tr>
<td>Incidence rate per 1,000 person years</td>
<td>71.0</td>
<td>77.2</td>
<td>74.9</td>
<td>68.5</td>
<td>75.4</td>
<td>72.8</td>
</tr>
<tr>
<td>Mean observed years per person</td>
<td>5.6</td>
<td>5.9</td>
<td>5.8</td>
<td>5.7</td>
<td>6.0</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Hypertension: systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, systolic hypertension: systolic blood pressure ≥ 140 mmHg, diastolic hypertension: diastolic blood pressure ≥ 90 mmHg, with initiation of antihypertensive medication

Subjects of this study were all male because there were very few female smokers. All of the workers were required to undergo a health examination once a year. At the same time, a self-administered questionnaire was administered to obtain information on their age, past history of disease, present illness, working conditions and lifestyle. In this study, hypertension [systolic blood pressure (SBP) ≥ 140 mmHg and diastolic blood pressure (DBP) ≥ 90 mmHg], systolic hypertension (SBP ≥ 140 mmHg), and diastolic hypertension (DBP ≥ 90 mmHg), with initiation of antihypertensive medication were defined as different endpoints of observation. It is useful to analyze SBP and DBP both together and separately since their progression may not be parallel. The following subjects were excluded from this study: subjects who received a health examination for the first time in the final year (2005) of the follow-up period (n = 504), subjects whose blood pressure was higher than each endpoint at entry and/or had initiated therapy for hypertension prior to or in the year of entry (hypertension: n = 1670, systolic hypertension: n = 1418, diastolic hypertension: n = 1133), subjects who did not undergo a health examination in the subsequent year (hypertension: n = 250, systolic hypertension: n = 255, diastolic hypertension: n = 259), subjects with any missing data in the year of entry (hypertension: n = 68, systolic hypertension: n = 62, diastolic hypertension: n = 45), and subjects for whom a diagnosis of hypertension could not be determined in the subsequent year, namely those whose blood pressure measurement or information on present illness of hypertension was missing (hypertension, systolic hypertension, and diastolic hypertension: n = 247). Finally, 5,512–6,063 workers were included for each endpoint (Table 1). The strict criteria for hypertension resulted in exclusion of more subjects, yielding smaller cohort for hypertension. More than 98% of the workers in this company underwent an annual health examination every year.

The study protocol was approved by the Ethical Review Board of the Graduate School of Medicine, Chiba University.

Smoking habits

A self-administered questionnaire at the annual health examination was used to determine smoking habits, which were confirmed by occupational physicians. During the first few years of the 14-year administration of the questionnaire, changes were made owing to changes in company policy. Originally, the questionnaire did not ask about daily frequency of smoking. Consequently, smoking habits were characterized simply as ‘smoking’ or ‘non-smoking’. Subjects who quit smoking before the study started were characterized as ‘non-smoking’ from the beginning of the follow-up period. Subjects who quit smoking during the follow-up period were characterized as ‘smoking’ prior to quitting and as ‘non-smoking’ after quitting. Similarly, subjects who started smoking during the follow-up period were characterized as ‘non-smoking’ prior to starting, and as ‘smoking’ after starting.

Blood pressure measurements

At the annual health examination, subjects’ blood pressure was measured once while in a sitting position using an automatic sphygmomanometer (BP203; COLIN Medical Instruments Co., Ltd, Komaki, Aichi, Japan) after 5 min of rest. Health examinations, including blood pressure measurement and blood sampling, were carried out between 0900 and 1500 h throughout the study period, and measurements that were within 30 min after smoking, eating a meal, or heavy physical activity were avoided. The blood pressure cuff automatically adjusted to the participants’ arm circumference, ranging from 23 to 32 cm. The accuracy of this automatic sphygmomanometer has been reported elsewhere (Sun and Jones 1999). Each subject’s medical history was taken at the annual health examination using a self-administered questionnaire. In addition, the content was confirmed by individual interviews conducted by occupational health physicians.

Other factors

Aspects of the subjects’ lifestyle such as drinking and exercise habits were also included in the questionnaire. Drinking habits were classified into two categories: drinking every day and not drinking every day. Habitual exercise was classified into two categories: regular exercise or no regular exercise. Job schedule type was determined using the company’s payment ledger for May of each year and subjects were categorized as shift workers and daytime workers. Workers who were engaged in irregular shift work such as 24-hour work and fixed night work were excluded. Age, body mass index (BMI, kg/m²), levels of glycosylated hemoglobin A1c (HbA1c, %), serum total cholesterol (T-CHO, mg/dl), creatinine (CRE, mg/dl), aspartic amino-transferase (AST, IU/l), γ-glutamyl transpeptidase (γ-GTP, IU/l), uric acid (UA, mg/dl), as well as job schedule type, drinking habits, and exercise habits were used as covariates. A meal was considered to affect the blood glucose level more than the HbA1c level; therefore, we adopted HbA1c as an indicator of glucose metabolism. Random blood sampling was performed without any restrictions regarding meals. All annual measurements of other factors during the follow-up period were incorporated into the analysis of the longitudinal observation. Thus, there were multiple endpoints (up to 13 points) for each subject.
**Statistical analysis**

For the univariate analysis, age, SBP, DBP, BMI, and levels of T-CHO, CRE, Hba1c, AST, γ-GTP, and UA were determined in the entry year and tested using the Mann-Whitney U test according to smoking status. Job schedule type, drinking habits, and habitual exercise were tested using the chi-square test according to smoking status. For the multivariate analysis, to evaluate the effect of smoking on each of three endpoints with consideration of confounding factors, a pooled logistic regression analysis was performed. This method was first described by Cupples et al. (1988). Levels of Hba1c, T-CHO, CRE, AST, γ-GTP, and UA were transformed logarithmically with a base of 1.1. After the transformation, the odds ratio corresponded to a 10% increase in those levels.

D’Agostino et al. (1990) has described pooled logistic regression analysis in detail. As an example, we consider a hypothetical study of 1000 persons at risk of a disease. All of the subjects have risk factors measured at time t₀ (exam 1). We follow them through the first interval of observation. During that time period, 40 subjects develop the disease and 10 others are lost to follow-up. We remove these 50 subjects from the population at time t₁ (exam 2), there are 950 subjects for whom risk factors are measured. Of these, 25 develop disease and 5 are lost to follow-up. The remaining 920 subjects have risk factors measured at time t₂ (exam 3), of which 20 develop the disease in the next period and 10 are lost to follow-up. This method pools the subjects at risk in each interval to yield 2870 (1000 + 950 + 920) person-exams and pools the 85 (40 + 25 + 20) observed years per person in the study.

A logistic regression with 2870 observations and 85 subjects have risk factors measured at time t₀ (exam 1). We follow them through the first interval of observation. During that time period, 40 subjects develop the disease and 10 others are lost to follow-up. We remove these 50 subjects from the population at time t₁ (exam 2), there are 950 subjects for whom risk factors are measured. Of these, 25 develop disease and 5 are lost to follow-up. The remaining 920 subjects have risk factors measured at time t₂ (exam 3), of which 20 develop the disease in the next period and 10 are lost to follow-up. This method pools the subjects at risk in each interval to yield 2870 (1000 + 950 + 920) person-exams and pools the 85 (40 + 25 + 20) observed years per person in the study.

Mathematically, the logistic regression model is written as follows (D’Agostino et al. 1990):

\[
\log \frac{q_i(X(t_i))}{1 - q_i(X(t_i))} = \alpha + \gamma_1 X_1(t_i) + \ldots + \gamma_p X_p(t_i)
\]

where \(q_i(X(t_i))\) is the conditional probability of observing an event by time \(t_i\) given that the individual is event-free at time \(t_{i-1}\), and

\[
X(t_i) = (X_1(t_i), ..., X_p(t_i))
\]

is the vector of risk factors measured at time \(t_i\). The parameters obtained are adjusted for the effects of other time-varying covariates (BMI, lifestyle, and laboratory data).

For our study, each examination interval of one year was treated as a mini follow-up study. If a subject developed hypertension during follow-up, subsequent data were excluded from the analyses. If data were missing, subsequent data were similarly excluded. The analyses were performed with SPSS 15.0J software (SPSS Japan Inc., Tokyo, Japan). \(P\)-values < 0.05 were considered to be statistically significant.

**RESULTS**

Table 1 shows the number of subjects and the number with onset of hypertension. In total, 2,383 (43.2%) participants developed hypertension, 2,469 (42.8%) developed systolic hypertension, and 1,830 (30.2%) developed diastolic hypertension. The incidence rates per 1000 person-years were 74.9 (hypertension), 72.8 (systolic hypertension), and 46.3 (diastolic hypertension). There were 5.8-6.5 mean observed years per person in the study.

Table 2 shows the characteristics of non-smokers and smokers in the year of entry. The mean BMI, T-CHO, CRE, AST, and UA levels were significantly lower, and the mean γ-GTP significantly higher in smokers than non-smokers. The percentages of those who drank every day, those who did not habitual exercise, and those who were shift workers, were significantly higher among smokers than non-smokers. The smoking rate in this company gradually decreased to 53.5% in 2005.

Table 3 shows the results of the pooled logistic regression analysis. The odds ratios (OR) and the 95% confidence intervals (95% CI) are presented for each risk factor. P-values < 0.05 were considered to be statistically significant.

**Table 2. Characteristics of non-smokers and smokers in the hypertension cohort at the entry year.**

<table>
<thead>
<tr>
<th></th>
<th>Non-smokers</th>
<th>Smokers</th>
<th>Total</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>121.1 (10.6)</td>
<td>120.9 (10.6)</td>
<td>121.0 (10.6)</td>
<td>0.392</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>74.1 (8.2)</td>
<td>73.8 (8.0)</td>
<td>73.9 (8.1)</td>
<td>0.051</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35.5 (10.9)</td>
<td>35.1 (9.8)</td>
<td>35.2 (10.3)</td>
<td>0.121</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.1 (2.6)</td>
<td>22.8 (2.8)</td>
<td>22.9 (2.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Glycated hemoglobin A1c (%)</td>
<td>4.64 (0.52)</td>
<td>4.66 (0.52)</td>
<td>4.65 (0.52)</td>
<td>0.090</td>
</tr>
<tr>
<td>Total serum cholesterol (mg/dl)</td>
<td>186.2 (34.4)</td>
<td>183.0 (34.6)</td>
<td>184.2 (34.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.89 (0.15)</td>
<td>0.88 (0.14)</td>
<td>0.88 (0.14)</td>
<td>0.001</td>
</tr>
<tr>
<td>Aspartate aminotransferase (IU/l)</td>
<td>21.5 (9.0)</td>
<td>21.2 (15.2)</td>
<td>21.3 (13.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>γ- glutamyl transpeptidase (IU/l)</td>
<td>25.1 (26.4)</td>
<td>29.3 (35.2)</td>
<td>27.7 (32.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.65 (1.16)</td>
<td>5.49 (1.19)</td>
<td>5.55 (1.18)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Drinking habit (every day)</td>
<td>32.6%</td>
<td>39.9%</td>
<td>37.2%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Habitual exercise (absence)</td>
<td>39.4%</td>
<td>46.9%</td>
<td>44.1%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Job schedule type (shift)</td>
<td>34.3%</td>
<td>45.5%</td>
<td>41.3%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

M: mean, SD: standard deviation. *P value for comparison between non-smokers and smokers.
Intervals (CI) for the factors of interest, i.e., hypertension, systolic hypertension, and diastolic hypertension, are summarized in Table 3. Smoking was significantly associated with the onset of hypertension and systolic hypertension. The odds ratios of smokers compared with non-smokers were 1.13 (95% confidence interval: 1.03-1.23) for hypertension, and 1.15 (95% confidence interval: 1.05-1.25) for systolic hypertension. In addition, BMI, T-CHO, γ-GTP, drinking habit, and shift work were positively associated with the onset of hypertension, systolic hypertension, and diastolic hypertension. AST was positively associated with the onset of hypertension and diastolic hypertension. Age was positively associated with the onset of diastolic hypertension. On the other hand, HbA1c was negatively associated with the onset of diastolic hypertension.

**Discussion**

In this study, we found that smoking was independently and significantly associated with the onset of hypertension and systolic hypertension. The results of the present study also suggested that smoking affects SBP more than DBP. This is in accordance with results from a study by Dyer et al. (1982), which showed a stronger association between smoking and pure systolic hypertension. However, numerous epidemiological studies have shown that blood pressure is lower in smokers than non-smokers (Karvonen et al. 1959; Higgins and Kjelsberg 1967; Seltzer 1974; Berglun and Wilhelmsen 1975; Goldbourt and Medalie 1977; Gofin et al. 1982; Agner 1983; Savdie et al. 1984; Green et al. 1986; Rosengren and Wilhelmsen 1987; Green et al. 1991; Imamura et al. 1996; Okubo et al. 2002; Nagahama et al. 2004; Okubo et al. 2004; Wang et al. 2006), although several other reports have found that smoking raises blood pressure (Elliott and Simpson 1980; Dyer et al. 1982; Bolinder and de Faire 1998). Moreover, other studies have speculated about the effects of smoking on blood pressure on the basis of changes in blood pressure that were observed after smoking cessation, and one of these studies reported that blood pressure rose after smoking cessation (Wilhelmsen et al. 1986), while others reported that smoking cessation had no clear-cut effect on blood pressure level (Schoenenberger 1982; Puddey et al. 1985; Tuomilehto et al. 1986; Green and Harari 1995) . Thus, the effect of smoking on blood pressure remains controversial.

Previous studies on smoking and hypertension have relied on simple statistical analysis and failed to account for the effects of confounding factors. To our knowledge, few sizable longitudinal studies of this issue have been performed. Okubo et al. (2004) followed a group of 2107 normotensive male steel workers, aged 40-54 years, for 5 years, and analyzed the relationship between changes in smoking habits and blood pressure using analysis of covariance (ANCOVA). After adjusting for the effects of anthropometric factors, biochemical factors, and drinking habits, they deduced that chronic smoking reduces changes in blood pressure and in the 5-year cumulative incidence of hypertension. Nagahama et al. (2004) followed 4489 individual (2927 men and 1562 women) who did not have hypertension and had not used antihypertensive medication for the previous 3 years. Multivariate analysis was performed for development of hypertension adjusted for age, family history of hypertension, alcohol consumption, cigarette smoking, obesity, hypercholesterolemia, hypertriglyceridemia, hyperuricemia, low high-density lipoprotein cholesterol, and diabetes mellitus. They found that habitual smoking had a significant negative correlation on the development of hypertension, but only in men (OR: 0.66, 95% CI: 0.48-0.91). Wang et al. (2006) followed 4549 Native
American men and women, aged 45 to 74 years. The estimated hypertension incidences from their cohort were also the 4-year cumulative hypertension incidences, and generalized linear models for SBP and DBP were used. Smoking was significantly and negatively related to both SBP and DBP in this group of Native Americans (Regression coefficient for SBP: −1.210, DBP: −1.287). In comparison with the present study, all of the previous studies had a smaller number of subjects and a shorter follow-up period. Furthermore, they compared only two sets of data (at baseline and after several years) and did not take into account changes in working conditions and lifestyle. In this study, we performed a pooled logistic regression analysis, which is a recently adopted and validated method (D’Agostino et al. 1990; Watanabe et al. 2002; Solomon et al. 2003; Schett et al. 2004). The advantage of this method is that it can be applied to repeated measures of working conditions and lifestyle, which may change over time in multivariate models. Therefore, this method can be used to eliminate the effect of confounders and their fluctuations on the onset of hypertension and thereby clarify the effect of smoking. We propose that the present study is currently the most reliable epidemiological investigation to assess this issue because of four notable features: a large cohort (n ≥ 5500), longitudinal data collected during a 14-year period, adjustment for confounding influences, and relevant statistical analysis.

The acute and chronic blood pressure response to smoking remains paradoxical. Previously, several reports described the relationship between malignant hypertension and smoking (Bloxham et al. 1979; Isles et al. 1979; Elliott and Simpson 1980; Isles 1980; Petitti and Klatsky 1983). The underlying mechanism was attributed to the association of smoking with lower concentrations of a stable metabolite of prostacyclin (PGI₂), which plays a role in limiting the extent of thrombus formation at sites of endothelial injury. Perhaps smokers who have impaired vessel wall PGI₂ synthesis or enhanced degradation, demonstrate malignant hypertension because of the absence of this protective mechanism. This might also explain the results of the present study. Furthermore, the pharmacologic effects of nicotine are undeniable. Experimental studies in men and animals have shown that smoking or nicotine administration produces small acute increases in blood pressure and heart rate, presumably due to release of catecholamines (United States Department of Health and Education and Welfare; Public Health Service 1979). This acute blood pressure increase has been attributed to smoking-induced vasoconstriction and accelerated heart rate (Aronow et al. 1971; Cellina et al. 1975; Cryer et al. 1976; Benowitz et al. 1982; Benowitz et al. 1984; De Cesaris et al. 1991; De Cesaris et al. 1992; Gropelli et al. 1992). Moreover, Istvan et al. (1999) reported that the level of salivary cotinine, a nicotine metabolite, was positively correlated with blood pressure in long-term smokers, suggesting that long-term nicotine exposure might be related to modest elevations in blood pressure. The paradoxical difference between the acute and long-term effects of smoking may have a number of possible causes. Firstly, smoking affects body weight, i.e., it is associated with a 2-4 Kg reduction of body weight. Secondly, lower blood pressure might be explained by reduced myocardial contractility due to coronary heart disease, which is more common among smokers than nonsmokers. Thirdly, the sympathetic reflex mechanism may be dysregulated. Findings from studies performed in rats indicate that prolonged exposure to nicotine induces an increase in nicotine receptors that leads to dysregulation of the nicotine receptors (Di Chiara 2000; Stitzel et al. 2000). Fourthly, compared to nonsmokers, smokers may have higher sympathetic reflex activity, since their rise in blood pressure is greater during the morning hours (Omvik 1996). Finally, the cadmium in tobacco might reduce blood pressure (Kurihara et al. 2004). Though reduction in blood pressure might also be an effect of nicotine, the results of epidemiological studies are inconsistent on this point. In the present study, the impacts of daily frequency of smoking and quantity of drinking were not considered. At the beginning of the 14-year observation period, the questionnaire did not ask in detail about smoking and drinking habits. To keep the independent variables consistent throughout the observation period, smoking habits were characterized simply as ‘smoking’ and ‘non-smoking’ and drinking habits were classified as ‘drinking every day’ and ‘not drinking every day’. Thus, we could not determine the dose-response relationship. However, it remains epidemiologically meaningful that we showed an effect of smoking on blood pressure in a long-term longitudinal study focusing on a large cohort.

In this study, different results were shown between the onset of systolic and diastolic hypertension. The odds ratios of hypertension and systolic hypertension were 1.13 (95% confidence interval: 1.03-1.23) and 1.15 (95% confidence interval: 1.05-1.25), respectively. The odds ratios of HbA1c and AST were significant for diastolic hypertension, but not for systolic hypertension. Therefore, the diastolic blood pressure may be more affected by these variables than the systolic blood pressure. Further investigation is necessary to establish these predispositions.

In conclusion, this study revealed that smoking is independently related to the onset of hypertension and systolic hypertension. These results provide important information necessary to define the effect of smoking on blood pressure.

Acknowledgments

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References


