

Cigarette Smoking and Risk for Impaired Fasting Glucose and Type 2 Diabetes in Middle-Aged Japanese Men

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Background: The contribution of cigarette smoking to development of impaired fasting glucose and type 2 diabetes remains unclear.

Objective: To investigate the association of cigarette smoking with development of impaired fasting glucose and type 2 diabetes.

Design: Prospective cohort study.

Setting: Work site in Osaka, Japan.

Participants: 1266 Japanese male office workers 35 to 59 years of age who did not have impaired fasting glucose or type 2 diabetes and were not taking medication for hypertension at study entry.

Measurements: Fasting plasma glucose levels were measured at annual health examinations from May 1994 through May 1999. Impaired fasting glucose was defined as a fasting glucose level of at least 6.1 mmol/L (110 mg/dL) but less than 7.0 mmol/L (126 mg/dL). Type 2 diabetes was defined as a fasting glucose level of 7.0 mmol/L or more or current receipt of hypoglycemic medication.

Results: 87 and 54 men developed impaired fasting glucose and type 2 diabetes during 5817 and 5937 person-years follow-up, respectively. After controlling for potential predictors of diabetes, the relative risk for impaired fasting glucose compared with never-

smokers was 1.62 (95% CI, 0.85 to 3.10) for ever-smokers, 1.14 (CI, 0.58 to 2.25) for persons who smoked 1 to 20 cigarettes/d, 1.33 (CI, 0.63 to 2.80) for those who smoked 21 to 30 cigarettes/d, and 2.56 (CI, 1.32 to 4.95) for those who smoked 31 or more cigarettes/d (*P* for trend for current smokers only = 0.013). The respective multivariate-adjusted relative risks for type 2 diabetes compared with never-smokers were 1.08 (CI, 0.34 to 3.42), 1.88 (CI, 0.71 to 5.00), 3.02 (CI, 1.15 to 7.94), and 4.09 (CI, 1.62 to 10.29) (*P* for trend for current smokers only < 0.001). The number of pack-years of exposure was also positively related to development of impaired fasting glucose and type 2 diabetes (*P* for trend = 0.039 and 0.002, respectively). The relative risk for impaired fasting glucose and type 2 diabetes in current smokers versus never-smokers was stronger among men with a body mass index less than 24.2 kg/m² than among men with a body mass index of 24.2 kg/m² or more, although the absolute risk was greater in more obese men.

Conclusion: The number of cigarettes smoked daily and the number of pack-years of exposure seem to be associated with development of impaired fasting glucose and type 2 diabetes in middle-aged Japanese men.

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The prevalence of type 2 diabetes in Japan has increased in the past decade, in tandem with the rapid westernization of lifestyle (1). This disorder of impaired insulin secretion and insulin resistance is associated with increased risk for cardiovascular disease, renal disease, and retinopathy (2–4). Although age, family history of diabetes, obesity, alcohol consumption, and reduced physical activity are well-known risk factors for type 2 diabetes (5–12), the association of smoking with development of type 2 diabetes is not well understood.

Longitudinal studies from the Netherlands, the United States, and Japan (11–14) have reported that cigarette smoking may be an independent risk factor for type 2 diabetes. However, one study found a monotonic association between cigarette smoking and type 2 diabetes (14), but two found a nonmonotonic association (12, 13). Furthermore, a cohort study in the United Kingdom failed to

show an independent association between cigarette smoking and type 2 diabetes (15). These inconclusive results may have resulted in part from ethnic or lifestyle differences in the study samples but also may have been strongly influenced by different methods used to diagnose type 2 diabetes. In the western studies (11, 12, 15), the diagnosis of type 2 diabetes was ascertained by a mailed questionnaire. In one Japanese study (13), type 2 diabetes was diagnosed by measuring the 75-g oral glucose tolerance test in persons with both glucosuria and a fasting plasma glucose level of 6.1 mmol/L (110 mg/dL) or more. In another Japanese study (14), type 2 diabetes was defined according to newer criteria (a fasting plasma glucose level \geq 7.0 mmol/L [126 mg/dL]) (16, 17) or a physician diagnosis of type 2 diabetes.

Because the American Diabetes Association (ADA) in 1997 (16) and the World Health Organization (WHO) in

1998 (17) recommended that estimates of diabetes incidence in epidemiologic studies be based on the fasting plasma glucose level, type 2 diabetes can be inexpensively and easily diagnosed in a large population. Using serial annual health examinations at the workplace and the new ADA and WHO criteria (16, 17), we performed a longitudinal population study to prospectively examine the association of cigarette smoking with development of impaired fasting glucose and type 2 diabetes in middle-aged Japanese men.

Methods

Study Cohort

Our study is an ongoing cohort investigation designed to clarify risk factors for major diseases, including hypertension, dyslipidemia, and diabetes, among Japanese male office workers at T Corporation, one of the biggest building contractors in Osaka, Japan. The Industrial Safety and Health Law in Japan requires the employer to conduct annual health examinations of all employees; the employee data, which are anonymous, are available for research with the approval of the employer. To evaluate the association of cigarette smoking with development of impaired fasting glucose and type 2 diabetes, surveillance of the incidence of impaired fasting glucose and type 2 diabetes was conducted between 1994 and 1999. All Japanese male office workers 35 to 59 years of age in May 1994 were invited to complete a survey ($n = 1581$); the participation rate was 99.9% ($n = 1580$).

Of 1580 potential participants, 269 (17.0%) were excluded: One hundred six (6.7%) had type 2 diabetes, 67 (4.2%) had impaired fasting glucose, and 114 (7.2%) were taking antihypertensive medication. Thus, the baseline sample consisted of 1311 men. We also excluded 45 men who did not participate in consecutive annual health examinations during follow-up. The final study sample for analysis therefore consisted of 1266 men. Men in whom impaired fasting glucose and type 2 diabetes were found during repeated surveys through May 1999 were defined as having incidental cases of impaired fasting glucose and type 2 diabetes. To determine the incidence of type 2 diabetes, incidental cases of impaired fasting glucose were followed and were considered type 2 diabetes if this condition developed. Fourteen participants who started taking medication for diabetes during the observation period were considered to have incidental cases of type 2 diabetes. Owing

to the age range of the study sample, all cases of impaired fasting glucose and type 2 diabetes were diagnosed after 35 years of age and were therefore classified as impaired fasting glucose and type 2 diabetes.

Study Design

Fasting plasma glucose levels were measured at annual health examinations in May from 1994 to 1999. The participants were asked to fast for at least 8 hours and to avoid smoking and heavy physical activity for more than 2 hours before the examinations. Blood samples were drawn from an antecubital vein. Fasting plasma glucose levels were measured by glucose dehydrogenase spectrophotometry with Olympus AU-5000 equipment in 1994 and Olympus AU-5200 equipment in 1995 to 1999 (Olympus Japan Co., Ltd., Tokyo, Japan) at FALCO Biosystems Tokyo Ltd., Tokyo, Japan. Quality control of the laboratory was maintained by an internal method, and the interassay and intra-assay coefficients of variation for plasma glucose were no more than 3% from 1994 to 1999. Normal fasting glucose, impaired fasting glucose, and type 2 diabetes were defined by using the ADA and WHO criteria (16, 17). Normal fasting glucose was defined as a fasting plasma glucose level less than 6.1 mmol/L (110 mg/dL). Impaired fasting glucose was defined as a fasting plasma glucose level of at least 6.1 but less than 7.0 mmol/L (126 mg/dL). Type 2 diabetes was defined as a fasting plasma glucose level of 7.0 mmol/L or greater or receipt of hypoglycemic medications (because not every participant underwent an oral glucose tolerance test).

Annual health examinations included medical history; physical examination; anthropometric measurements; blood pressure measurement; biochemical measurements; and a questionnaire on health-related behaviors, such as smoking, alcohol consumption, and physical activity. Medical history and history of use of prescription drugs were assessed by the examining physicians. Family history of diabetes was defined as a mother, father, sister, or brother with diagnosed diabetes. Body mass index was used as a measure of overall obesity and was calculated as body weight/height² (kg/m²). After a 5-minute rest in a quiet room, systolic and diastolic blood pressures were measured on the right arm by using a standard mercury sphygmomanometer. The Olympus AU-5000 spectrophotometer was also used to measure total cholesterol, high-density lipoprotein cholesterol, triglycerides, and uric acid. The

hematocrit was determined by using a Sysmex E-4000 autoanalyzer (Toa Medical Electronics Co., Ltd., Tokyo, Japan).

With regard to health-related behaviors, the questionnaire asked about smoking habits (never, past, or current smoker); past or current smokers were asked about the number of cigarettes smoked per day and the duration of smoking in years. Current smokers were subdivided into three groups by the number of cigarettes smoked daily: 1 to 20 cigarettes/d, 21 to 30 cigarettes/d, and 31 or more cigarettes/d. A pack-year was defined as smoking 20 cigarettes/d for 1 year. Participants were categorized by number of pack-years into five groups: 0 pack-years, 0.1 to 20.0 pack-years, 20.1 to 30.0 pack-years, 30.1 to 40.0 pack-years, and 40.1 or more pack-years. The questions about alcohol intake included items about the type of alcoholic beverage, the frequency of alcohol consumption per week, and the usual amount consumed daily. Weekly alcohol intake was calculated and converted to daily alcohol consumption (grams of ethanol per day) by using standard Japanese tables. Participants were asked about the type and weekly frequency of leisure-time physical activity. Physical exercise was defined as participation in any physical activity, such as jogging, bicycling, swimming or tennis, that was performed long enough to work up a sweat.

Statistical Analysis

The chi-square test and one-way analysis of variance were used to analyze the statistical differences among participant characteristics at enrollment according to smoking status. For each participant, person-years of follow-up were calculated from 1) the date of enrollment to the date of diagnosis of impaired fasting glucose or type 2 diabetes or 2) the date of follow-up, whichever came first. The follow-up rate was 95.6% of the total potential person-years of follow-up. Cox proportional hazards models (18) were used to evaluate the association between smoking status and the development of impaired fasting glucose or type 2 diabetes. Data were adjusted first for age alone, then for the following multiple covariates: age; body mass index; alcohol consumption; physical activity; family history of diabetes; systolic and diastolic blood pressure; levels of fasting plasma glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and uric acid; and hematocrit. Potential confounding factors were treated as categorical variables: age, body mass index, systolic and diastolic blood

pressure, fasting plasma glucose level, total cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, uric acid level, and hematocrit (all graded from 1 through 5 [first through fifth quintiles]); alcohol consumption (graded as 1 [none] or as quartile 1 [grade of 2] to quartile 4 [grade of 5] for drinkers); regular physical exercise (graded from 1 to 3 [hardly ever, once per week, or twice or more per week]); and family history of diabetes (no or yes). The linear trends in risks were evaluated by using the median value for each category of smoking status.

Data were analyzed by using the SPSS/PC statistical package (SPSS Inc., Chicago, Illinois). All reported *P* values are two-tailed; those less than 0.05 were considered statistically significant.

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The funding agencies did not participate in the collection, analysis, or interpretation of data or in the decision to submit the manuscript for publication.

Results

Table 1 shows the baseline characteristics of the study sample according to smoking status. Mean age, body mass index, daily alcohol consumption, diastolic blood pressure, high-density lipoprotein cholesterol level, triglyceride level, and hematocrit and the percentage of participants who exercised twice or more per week differed significantly by smoking status. Ex-smokers and current smokers were slightly older than never-smokers. Current smokers who smoked 1 to 30 cigarettes/d had the lowest body mass index, and past smokers and current smokers consumed more alcohol than never-smokers. The percentage of current smokers who exercised twice or more per week was lower than among never-smokers and ex-smokers. Ex-smokers had the highest diastolic blood pressure, and participants who smoked 31 or more cigarettes/d had the lowest. Ex-smokers and current smokers had lower high-density lipoprotein levels than did never-smokers; the lowest levels were found in participants who smoked 31 or more cigarettes/d. In contrast, triglyceride levels and hematocrit were lowest among never-smokers and highest among participants who smoked 31 or more cigarettes/d. The percentage of participants with family history of diabetes and the mean systolic blood pressure, fasting plasma

Table 1. Baseline Characteristics of 1266 Japanese Male Office Workers, according to Smoking Status*

Characteristic	Never-Smokers (n = 407)	Former Smokers (n = 213)	Current Smokers			P Value
			1–20 Cigarettes/d (n = 257)	21–30 Cigarettes/d (n = 198)	≥31 Cigarettes/d (n = 191)	
Mean age, y	46.1 ± 6.5	47.4 ± 5.9	46.5 ± 6.6	47.5 ± 5.7	46.7 ± 5.1	0.05
Body mass index, kg/m ²	23.2 ± 2.4	23.7 ± 2.4	22.9 ± 2.5	22.9 ± 2.7	23.5 ± 3.1	0.004
Family history of diabetes, %	5.9	9.4	10.9	8.1	11.5	0.102
Alcohol consumption (ethanol), g/d	25.9 ± 22.8	33.1 ± 25.3	32.9 ± 23.4	34.8 ± 26.2	39.5 ± 28.6	<0.001
Physical exercise, %						
Hardly ever	45.9	41.8	47.1	47.5	53.9	0.184
Once per week	35.9	36.2	40.9	43.4	38.2	>0.2
Twice or more per week	18.2	22.1	12.1	9.1	7.9	<0.001
Systolic blood pressure, mm Hg	128.2 ± 15.4	129.3 ± 14.6	127.2 ± 14.9	128.5 ± 15.3	126.6 ± 14.5	>0.2
Diastolic blood pressure, mm Hg	76.9 ± 11.7	78.7 ± 10.7	76.7 ± 11.0	77.4 ± 11.0	74.8 ± 9.9	0.009
Fasting plasma glucose level, mmol/L (mg/dL)	5.07 ± 0.40 (91 ± 7)	5.04 ± 0.40 (90 ± 7)	5.04 ± 0.44 (90 ± 8)	5.01 ± 0.41 (90 ± 7)	5.01 ± 0.46 (90 ± 8)	>0.2
Total cholesterol level, mmol/L (mg/dL)	5.08 ± 0.79 (196 ± 31)	5.12 ± 0.82 (198 ± 32)	5.01 ± 0.80 (193 ± 31)	5.01 ± 0.88 (193 ± 34)	5.08 ± 0.80 (196 ± 31)	>0.2
HDL cholesterol level, mmol/L (mg/dL)	1.47 ± 0.32 (57 ± 12)	1.41 ± 0.32 (54 ± 12)	1.35 ± 0.28 (52 ± 11)	1.35 ± 0.32 (52 ± 11)	1.29 ± 0.31 (50 ± 12)	<0.001
Triglyceride level, mmol/L (mg/dL)	1.24 ± 0.83 (110 ± 73)	1.49 ± 1.06 (132 ± 94)	1.54 ± 1.14 (136 ± 101)	1.51 ± 1.09 (134 ± 96)	1.78 ± 1.56 (158 ± 138)	<0.001
Uric acid level, μmol/L	350.6 ± 82.5	358.6 ± 80.7	354.9 ± 88.9	342.9 ± 81.3	351.6 ± 81.7	>0.2
Hematocrit, %	44.1 ± 2.5	44.6 ± 2.8	45.3 ± 2.8	45.1 ± 2.9	45.5 ± 3.1	<0.001

* Unless otherwise indicated, values are expressed as the mean (± SD). HDL = high-density lipoprotein.

glucose level, total cholesterol level, and uric acid level did not differ significantly among the five groups.

During 5 years of follow-up representing 5817 person-years, 87 men developed impaired fasting glucose (Table 2). The multivariate-adjusted relative risk for impaired fasting glucose compared with never-smokers was 1.62 (95% CI, 0.85 to 3.10) for ever-smokers, 1.14 (CI, 0.58 to 2.25) for those who smoked 1 to 20 cigarettes/d, 1.33 (CI, 0.63 to 2.80) for those who smoked 21 to 30 cigarettes/d, and 2.56 (CI, 1.32 to 4.95) for those who smoked 31 or more cigarettes/d. The test for trend across increasing categories of cigarette smoking for current smokers was statistically significant ($P = 0.013$).

Type 2 diabetes was diagnosed in 54 men during 5 years of follow-up representing 5937 person-years. The multivariate-adjusted relative risk for type 2 diabetes compared with never-smokers was 1.08 (CI, 0.34 to 3.42) for ever-smokers, 1.88 (CI, 0.71 to 5.00) for those who smoked 1 to 20 cigarettes/d, 3.02 (CI, 1.15 to 7.94) for those who smoked 21 to 30 cigarettes/d, and 4.09 (CI, 1.62 to 10.29) for those who smoked 31 or more cigarettes/d (P for trend for current smokers < 0.001).

To evaluate the long-term effect of cigarette smoking on development of impaired fasting glucose and type 2 diabetes, we assessed the relation between pack-years of

exposure and risk for impaired fasting glucose and type 2 diabetes (Table 3). The multivariate-adjusted relative risk for impaired fasting glucose compared with never-smokers was 1.03 (CI, 0.42 to 2.50) for those whose cumulative lifetime exposure was 0.1 to 20.0 pack-years, 1.10 (CI, 0.49 to 2.50) for those whose cumulative lifetime exposure was 20.1 to 30.0 pack-years, 1.75 (CI, 0.47 to 2.47) for those whose cumulative lifetime exposure was 30.1 to 40.0 pack-years, and 2.01 (CI, 1.05 to 3.837) for those whose cumulative lifetime exposure was 40.1 or more pack-years. The number of pack-years was positively related to the risk for impaired fasting glucose in a dose-dependent manner (P for trend = 0.039). The respective multivariate-adjusted relative risks for type 2 diabetes compared with never-smokers were 2.25 (CI, 0.73 to 6.91), 2.40 (CI, 0.82 to 7.05), 2.39 (CI, 0.80 to 7.16), and 4.18 (CI, 1.66 to 10.50) (P for trend = 0.002).

To evaluate the effect of obesity on the association between cigarette smoking and risk for diabetes, we assessed the relation between smoking status and development of impaired fasting glucose and type 2 diabetes according to body mass index (Table 4). Among men with a body mass index less than 24.2 kg/m², the multivariate-adjusted relative risk for impaired fasting glucose and type 2 diabetes compared with never-smokers was 0.94 (CI,

0.40 to 2.23) for ever-smokers, 1.49 (CI, 0.73 to 3.06) for those who smoked 1 to 20 cigarettes/d, 2.21 (CI, 1.06 to 4.58) for those who smoked 21 to 30 cigarettes/d, and 3.84 (CI, 1.94 to 7.60) for those who smoked 31 or more cigarettes/d (P for trend for current smokers only < 0.001). Among men with a body mass index of 24.2 kg/m² or more, the respective multivariate-adjusted relative risks for impaired fasting glucose and type 2 diabetes compared with never-smokers were 2.03 (CI, 0.91 to 4.50), 1.29 (CI, 0.54 to 3.11), 1.70 (CI, 0.66 to 4.37), and 2.38 (CI, 1.01 to 5.61) (P for trend for current smokers = 0.031). Among men with a body mass index less than 24.2 kg/m², the multivariate-adjusted relative risk for impaired fasting glucose and type 2 diabetes compared with never-smokers was 1.40 (CI, 0.58 to 3.40) for those whose cumulative lifetime exposure was 0.1 to 20.0 pack-years, 1.81 (CI, 0.81 to 4.03) for those whose cumulative lifetime exposure was 20.1 to 30.0 pack-years, 1.78 (CI, 0.78 to 4.05) for those whose cumulative lifetime exposure was 30.1 to 40.0 pack-years, and 3.01 (CI, 1.53 to 5.89) for those whose cumulative lifetime exposure was 40.1 or more pack-years (P for trend = 0.001) (data not shown). Among men with a body mass index of 24.2 kg/m² or more, the respective multivariate-adjusted relative risks for impaired fasting glucose and type 2 diabetes compared with never-smokers were 1.27 (95% CI, 0.43 to 3.73), 1.36 (CI, 0.45 to 4.11), 1.50 (CI, 0.50 to 4.50), and 2.60 (CI, 1.12 to 6.06) (P for trend = 0.03).

Discussion

We found that the risk for impaired fasting glucose and type 2 diabetes increased in a dose-dependent manner as the number of cigarettes smoked per day and the number of pack-years of exposure (the long-term effect of cigarette smoking for current smokers) increased. Being a past smoker was associated with a nonsignificantly higher risk for impaired fasting glucose compared with never-smokers but was not associated with risk for type 2 diabetes. Analyses of risk for impaired fasting glucose and type 2 diabetes according to body mass index revealed that leaner men who were current smokers had higher relative risk for impaired fasting glucose and type 2 diabetes than did never-smokers, although the absolute risk was greater in obese men. Furthermore, the absolute and relative risks for impaired fasting glucose and type 2 diabetes for ex-smokers compared with never-smokers were larger among more obese men.

Most (11–14) but not all (15) previous epidemiologic studies found smoking to be positively associated with risk for type 2 diabetes. However, the studies conflicted; one found that the relation between the number of cigarettes smoked per day and the risk for type 2 diabetes was monotonic (14), and two found that it was not monotonic (12, 13). Our results are consistent with the findings of an earlier Japanese study (14) that used the new ADA and WHO criteria (16, 17) for an epidemiologic study. Our data also

Table 2. Smoking Status and Risk for Impaired Fasting Glucose and Type 2 Diabetes in the Study Sample

Condition	Never-Smokers	Former Smokers	Current Smokers			P Value for Trend*
			1–20 Cigarettes/d	21–30 Cigarettes/d	≥31 Cigarettes/d	
Impaired fasting glucose						
Cases, <i>n</i>	20	18	16	12	21	
Person-years	1877	979	1206	892	863	
Rate per 1000 person-years	10.7	18.4	13.3	13.4	24.3	
Age-adjusted relative risk (95% CI)	1.00 (referent)	1.61 (0.85–3.04)	1.20 (0.62–2.32)	1.21 (0.59–2.48)	2.20 (1.19–4.07)	0.019
Multivariate-adjusted relative risk (95% CI)†	1.00 (referent)	1.62 (0.85–3.10)	1.14 (0.58–2.25)	1.33 (0.63–2.80)	2.56 (1.32–4.95)	0.013
Type 2 diabetes						
Cases, <i>n</i>	7	5	11	12	19	
Person-years	1906	1014	1227	899	892	
Rate per 1000 person-years	3.7	4.9	9.0	13.3	21.3	
Age-adjusted relative risk (95% CI)	1.00 (referent)	1.29 (0.41–4.06)	2.38 (0.92–6.15)	3.54 (1.39–9.01)	5.60 (2.35–13.32)	<0.001
Multivariate-adjusted relative risk (95% CI)†	1.00 (referent)	1.08 (0.34–3.42)	1.88 (0.71–5.00)	3.02 (1.15–7.94)	4.09 (1.62–10.29)	<0.001

* Calculated across increasing categories of smoking for current smokers only.

† Controls for age, body mass index, alcohol consumption, regular physical exercise, family history of diabetes, systolic and diastolic blood pressure, fasting plasma glucose level, total cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, uric acid level, and hematocrit at study entry.

agree with those from a U.S. study (12) in which the relative risk for diabetes associated with cigarette smoking was stronger in leaner men. Thus, obesity may modify the association between smoking and the risk for impaired fasting glucose and type 2 diabetes, and the impact of smoking on risk for impaired fasting glucose and type 2 diabetes may be stronger in leaner men. The U.S. study (12) also reported that the risk for type 2 diabetes was higher among past smokers than among never-smokers but decreased with years since quitting smoking. Because we could not examine years since quitting smoking among past smokers or smoking behaviors during follow-up, the effects of smoking cessation on impaired fasting glucose and type 2 diabetes in our study are less clear. However, we found that ex-smokers had a higher average body mass index during follow-up than did never-smokers ($24.2 \pm 2.5 \text{ kg/m}^2$ compared with $23.4 \pm 2.4 \text{ kg/m}^2$). This tendency was more pronounced among obese men with a body mass index of 24.2 kg/m^2 or more (average body mass index during follow-up, $27.0 \pm 1.8 \text{ kg/m}^2$ for ex-smokers and $25.8 \pm 1.7 \text{ kg/m}^2$ for never-smokers). Smoking cessation commonly results in weight gain, which increases the risk for diabetes (7). Inclusion of persons who were smokers at baseline but who quit and became more obese during follow-up might have falsely elevated the risk associated with smoking at baseline; however, this would not explain fully the increased risk seen in ex-smokers. These results suggest that

we need not only encourage smoking cessation but also concomitantly help patients avoid obesity.

The mechanism of how cigarette smoking increases the risk for impaired fasting glucose and type 2 diabetes remains to be elucidated. Higher levels of glycosylated hemoglobin in current smokers than in nonsmokers have been reported (19). Recent laboratory studies have indicated that cigarette smoking may cause insulin resistance in peripheral tissues, whereas insulin secretion may be unimpaired or somewhat overstimulated (20–23). It has also been reported that insulin resistance among smokers is normal in the abstinence phase of cigarette smoking, suggesting that effects of smoking are acute and are reversible (19, 24). In an experimental control trial using two oral glucose tolerance tests, smoking acutely impaired glucose tolerance and acutely increased serum insulin and C-peptide levels (25). In addition, cigarette smoking is known to stimulate release of counter-regulatory hormones and consequently cause temporary elevation in plasma glucose levels (26, 27).

Our study had several limitations. First, smokers were less healthy than never-smokers in several other ways that might explain their higher risk for impaired fasting glucose and type 2 diabetes. For example, smokers were slightly older, more frequently had family history of diabetes, were considerably less active, and had increased risks for atherogenic lipid profiles. Furthermore, we did not assess participants' dietary habits. Dietary lipids, fibers, or carbohy-

Table 3. Pack-Years of Cigarette Smoking and Risk for Impaired Fasting Glucose and Type 2 Diabetes in the Study Sample

Condition	Exposure to Cigarette Smoking					P Value for Trend*
	0 Pack-Years	0.1–20.0 Pack-Years	20.1–30.0 Pack-Years	30.1–40.0 Pack-Years	≥40.1 Pack-Years	
Impaired fasting glucose						
Cases, <i>n</i>	20	7	9	9	24	
Person-years	1877	644	670	611	1037	
Rate per 1000 person-years	10.7	10.9	13.4	14.7	23.2	
Age-adjusted relative risk (95% CI)	1.00 (referent)	1.11 (0.47–2.63)	1.23 (0.56–2.70)	1.32 (0.60–2.90)	1.95 (1.07–3.55)	0.032
Multivariate-adjusted relative risk (95% CI)†	1.00 (referent)	1.03 (0.42–2.50)	1.10 (0.49–2.50)	1.75 (0.47–2.47)	2.01 (1.05–3.83)	0.039
Type 2 diabetes						
Cases, <i>n</i>	7	6	7	7	22	
Person-years	1906	654	678	612	1074	
Rate per 1000 person-years	3.7	9.2	10.3	11.4	20.5	
Age-adjusted relative risk (95% CI)	1.00 (referent)	2.52 (0.84–7.53)	2.79 (0.98–7.95)	3.08 (1.08–8.80)	5.42 (2.29–12.82)	<0.001
Multivariate-adjusted relative risk (95% CI)†	1.00 (referent)	2.25 (0.73–6.91)	2.40 (0.82–7.05)	2.39 (0.80–7.16)	4.18 (1.66–10.50)	0.002

* Calculated across increasing categories of pack-years of cigarette smoking.

† Controls for age, body mass index, alcohol consumption, regular physical exercise, family history of diabetes, systolic and diastolic blood pressure, fasting plasma glucose level, total cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, uric acid level, and hematocrit at study entry.

Table 4. Risk for Impaired Fasting Glucose and Type 2 Diabetes by Body Mass Index and Smoking Status

Characteristic	Never-Smokers	Former Smokers	Current Smokers			P Value for Trend*
			1–20 Cigarettes/d	21–30 Cigarettes/d	≥31 Cigarettes/d	
Body mass index < 24.2 kg/m ²						
Cases, <i>n</i>	16	8	17	16	23	
Person-years	1282	624	858	606	542	
Rate per 1000 person-years	12.5	12.8	19.8	26.4	42.4	
Age-adjusted relative risk (95% CI)	1.00 (referent)	0.96 (0.41–2.24)	1.55 (0.78–3.07)	2.02 (1.01–4.04)	3.23 (1.71–6.12)	<0.001
Multivariate-adjusted relative risk (95% CI)†	1.00 (referent)	0.94 (0.40–2.23)	1.49 (0.73–3.06)	2.21 (1.06–4.58)	3.84 (1.94–7.60)	<0.001
Body mass index ≥ 24.2 kg/m ²						
Cases, <i>n</i>	11	14	10	8	15	
Person-years	584	350	330	265	295	
Rate per 1000 person-years	18.8	40.0	30.3	30.2	50.8	
Age-adjusted relative risk (95% CI)	1.00 (referent)	2.03 (0.92–4.49)	1.54 (0.65–3.63)	1.56 (0.63–3.89)	2.63 (1.21–5.73)	0.018
Multivariate-adjusted relative risk (95% CI)†	1.00 (referent)	2.03 (0.91–4.50)	1.29 (0.54–3.11)	1.70 (0.66–4.37)	2.38 (1.01–5.61)	0.031

* Calculated across increasing categories of smoking for current smokers only.

† Controls for age, body mass index, alcohol consumption, regular physical exercise, family history of diabetes, systolic and diastolic blood pressure, fasting plasma glucose level, total cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, uric acid level, and hematocrit at study entry.

drates may influence fasting insulin levels (28–30), and diets with a high glycemic load and a low cereal fiber content may be associated with risk for type 2 diabetes (31). Research is needed to clarify the causal relation between cigarette smoking and risk for impaired fasting glucose and type 2 diabetes.

Second, smoking status during follow-up was not included in the analysis. Smoking status was recorded at entry, before impaired fasting glucose and type 2 diabetes were diagnosed; however, smoking status probably did not change as a result of disease status. If participants had stopped smoking during follow-up, the impact of smoking on risk for impaired fasting glucose and type 2 diabetes would have been underestimated.

Third, bias in case-finding may have occurred. Smokers are more likely to visit a physician for reasons other than diabetes, which could result in a greater chance that diabetes would be diagnosed (11). However, because all incident cases were found by periodic annual screening in our study, such bias is unlikely.

Finally, persons in our normoglycemic cohort, particularly those in the older age groups, may not be typical of the general population. Persons whose plasma glucose level was already elevated beyond borderline values or who reported taking drugs for hypertension during the initial examination were excluded. Because hypertension is a recognized risk factor for diabetes (32, 33), exclusion of hypertensive persons would bias the study toward a particularly healthy study population at low risk for diabetes. Thus, a “healthy worker effect” may have occurred.

Despite these potential limitations, our findings, which were obtained from a cohort of middle-aged Japanese men, support the conclusion that the number of cigarettes smoked daily and the number of pack-years of exposure are closely associated with the risk for impaired fasting glucose and type 2 diabetes according to the new ADA and WHO criteria for epidemiologic studies. Our findings provide evidence that cigarette smoking is a modifiable risk factor that could be targeted for prevention of diabetes.

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