Impact of cigarette smoking on impaired insulin secretion and insulin resistance in Japanese men: The Saku Study

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ABSTRACT

Aims/Introduction: To assess the impact of smoking on impaired insulin secretion and insulin resistance in Japanese men.

Materials and Methods: This study included 1,199 men aged 30–79 years without diabetes, impaired insulin secretion and insulin resistance at baseline who underwent a comprehensive medical check-up between April 2006 and March 2007 at Saku Central Hospital. Smoking status was categorized as current, ex-smoker and never-smoker. Insulinogenic index and homeostasis model assessment-insulin resistance were determined using a standard 75-g oral glucose tolerance test. The Japan Diabetes Society criteria were used to define impaired insulin secretion and insulin resistance. Participants were followed up until March 2011.

Results: A total of 449 and 99 men developed impaired insulin secretion and insulin resistance during 3,403 and 4,092 person-years follow up, respectively. The multivariable-adjusted hazard ratios (HRs) for impaired insulin secretion were 1.06 (95% confidence interval [CI] 0.84–1.33) in ex-smokers and 1.95 (95% CI 1.44–2.63) in current smokers compared with never-smokers after adjustment for age, familial history of diabetes, alcohol consumption, exercise, systolic blood pressure, triglyceride, γ-glutamyltransferase, waist circumference, leukocyte count, changes in smoking status and changes in waist circumference. The number of pack-years was positively associated with the risk for impaired insulin secretion in a dose-dependent manner (P-values for trend <0.001). The multivariable-adjusted HRs for insulin resistance were 0.95 (95% CI 0.56–1.61) in ex-smokers and 1.11 (95% CI 0.67–1.79) in current smokers compared with never-smokers.

Conclusions: Cigarette smoking is a modifiable risk factor for impaired insulin secretion. The findings might also be important for other Asian populations, which have low insulin secreting ability. (J Diabetes Invest doi: 10.1111/jdi.12019, 2013)

KEY WORDS: Cigarette smoking, Impaired insulin secretion, Insulin resistance

INTRODUCTION

Cigarette smoking is positively associated with the incidence of type 2 diabetes mellitus[1]. Notably, the population-attributable fraction of current smoking for diabetes was much higher than that of obesity in Japanese men[2]. Therefore, smoking is an important risk factor for diabetes in Japanese men with a high prevalence of smoking[3].

Impaired insulin secretion and insulin resistance are the main pathophysiological components of type 2 diabetes mellitus. The link between smoking and diabetes might involve the effects of smoking on β-cells. Smoking might have direct, harmful effects on pancreatic tissue, which is consistent with the elevated risk of pancreatic cancer among smokers[4]. Furthermore, clinical studies have implicated smoking to have a direct effect on β-cells[5,6]. However, the impact of smoking on impaired insulin secretion has never been assessed in a large-scale study. Although clinical and community-based studies on healthy individuals have previously linked smoking with insulin resistance[7,8], other studies did not report that smoking had an effect on insulin resistance[9,10]. Thus, the risks associated with smoking on impaired insulin secretion and insulin resistance remain controversial.

In the present study, we assessed the impact of smoking on impaired insulin secretion and insulin resistance. Specifically, annual insulin secretion and insulin resistance were determined in Japanese men using a standard 75-g oral glucose tolerance test (OGTT).

MATERIALS AND METHODS

Participants

The Saku Study included community residents who underwent annual comprehensive medical check-ups. The cohort consisted of 3,005 men, aged 30–79 years, who underwent a baseline comprehensive medical check-up over 2 days and one night between April 2006 and March 2007 at Saku Central Hospital (Nagano, Japan). Of these individuals, our investigation included 1,434 men based on the following six exclusion

criteria at baseline examination: (i) history of diabetes, as determined by an interview carried out by the physicians ($n = 200$); (ii) a fasting plasma glucose level ≥ 7.0 mmol/L ($n = 241$); (iii) a 2-h post-load plasma glucose level ≥ 11.1 mmol/L ($n = 75$); (iv) a glycated hemoglobin (HbA_{1c}) level (National Glycohemoglobin Standardization Program [NGSP]) $\geq 6.5\%$ ($n = 33$); (v) a homeostasis model assessment of insulin resistance (HOMA-IR) level ≥ 3.0 ($n = 150$); and (vi) an insulinogenic index ($\Delta I_{30}/\Delta G_{30}$) level ≤ 51.7 pmol/mmol ($n = 872$). Additionally, our investigation included 1,200 men who underwent at least one follow-up examination by the end of the follow-up period in March 2011. Furthermore, a man who was missing data was excluded. A total of 1,199 men, aged 30–79 years, were eligible for our analysis. Of these 1,199 men, 1,012 (84.4%) men had annual comprehensive medical check-ups regularly for 3 years ($n = 143$) or 4 years ($n = 869$) after the baseline examination.

The study protocol was in accordance with the Helsinki Declaration, and approved by the Ethical Committee of Saku Central Hospital. The informed consent was obtained from all participants at each examination.

Study Procedure

In the morning after an overnight fast (12 h), all participants underwent a standard 75-g OGTT. Venous samples were collected for the measurement of serum insulin concentrations before and 30 min after glucose ingestion. Blood samples were examined at the clinical laboratory of the Saku Central Hospital. Serum insulin levels were determined by a chemiluminescence enzyme immunoassay (Lumipulse Presto Insulin; Fujirebio Inc., Tokyo, Japan). The insulinogenic index ($\Delta I_{30}/\Delta G_{30}$) was calculated using the formula: $\Delta I_{30}/\Delta G_{30}$ = (insulin$_{30}$ [pmol/L]–insulin$_0$ [pmol/L])/(glucose$_{30}$ [mmol/L]–glucose$_0$ [mmol/L])[11,12]. HOMA-IR was calculated using the formula: HOMA-IR = insulin$_0$ (pmol/L) × glucose$_0$ (mmol/L)/135[13]. Blood glucose, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, serum triglyceride and uric acid concentrations were measured by enzymatic methods. The leukocyte count was determined with automated cell counters. High-sensitive C-reactive protein (hsCRP) was measured by the latex immunity turbidimetric method. HbA_{1c} was assessed by high-performance liquid chromatography. HbA_{1c} (%) was estimated as a NGSP equivalent value (%), and calculated using the formula: HbA_{1c} (%) = HbA_{1c} (Japan Diabetes Society; %) + 0.4%[14].

Bodyweight, height, waist circumference and body fat percentage were measured in the morning in the fasting state. The body mass index was calculated as the weight (kg) divided by the height squared (m^2). Waist circumference was measured around the abdomen at the level of the navel during the late expiratory phase with a tape measure. Body fat percentage was evaluated using the bioelectric impedance method with an automatic scale. Blood pressure was measured by trained nurses using an automatic sphygmomanometer in the sitting position after at least a 5-min rest.

Additionally, the examination included standard questionnaires on demographic characteristics, medical history, family history and health-related habits. Smoking status was categorized as current, ex-smoker and never-smoker. Current smokers were asked to report on their average number of cigarettes smoked per day and the duration of smoking in years. A pack-year was defined as smoking 20 cigarettes/day for 1 year. Current smokers and never-smokers were categorized by the number of pack-years into the following four groups: 0 pack-years, 0.1–20.0 pack-years, 20.1–30.0 pack-years and 30.1 or more pack-years. Alcohol consumption (ethanol) was categorized into 0, 1–139 or ≥ 140 g/week, and exercise was categorized into 0, 1–119 or ≥ 120 min/week.

The Japan Diabetes Society criteria were used to define impaired insulin secretion and insulin resistance for Japanese individuals[15,16]. Impaired insulin secretion was defined as $\Delta I_{30}/\Delta G_{30} \leq 51.7$ pmol/mmol, and insulin resistance was defined as HOMA-IR ≥ 3.0[15,16].

A total of 1,199 Japanese men were followed up annually until they developed impaired insulin secretion or insulin resistance or March 2011. Participants underwent annual comprehensive medical check-ups over 2 days and one night, which included the 75-g OGTT, at Saku Central Hospital. Individuals who did not undergo all examinations during the follow-up period were censored on the date of their last examination.

Statistical Analysis

Differences in baseline characteristics between current smokers, ex-smokers and never-smokers were determined by using an age-adjusted analysis of covariance for continuous data with a normal distribution, a Kruskal–Wallis H-test for continuous data with a non-normal distribution and a chi-squared-test for dichotomous and categorical data. In addition, we calculated changes in smoking status between the baseline and final examinations.

The Cox proportional hazards regression was used to estimate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the incidence of impaired insulin secretion and insulin resistance in current smokers and ex-smokers compared with never-smokers. Multicollinearity between covariates was examined by calculating the mean and individual covariate variance inflation factors. Data was adjusted for age, familial history of diabetes (yes or no), alcohol consumption (0, 1–139 or ≥ 140 g/week), exercise (0, 1–119 or ≥ 120 min/week), systolic blood pressure, log-transformed triglyceride, log-transformed γ-glutamyltransferase, waist circumference, leukocyte count, change in smoking status between the baseline and final examinations (no change, started smoking, or quitted smoking), and Δ waist circumference (Δ = final examination minus baseline examination). The assumptions required for proportional hazards were met, and these were assessed with graphs of log–log plots.

Additionally, the Cox proportional hazards regression was used to estimate adjusted HRs and 95% CIs for the incidence

of impaired insulin secretion and insulin resistance, according to pack-years of cigarette smoking. In the Cox proportional hazards regression, we adjusted for the same covariates.

All data were analyzed using the SAS statistical package software version 9.1 (SAS Institute Inc., Cary, NC, USA) and SPSS statistical software Version 17.0J (SPSS Japan Inc., Tokyo, Japan). All reported *P*-values are two-tailed, and those less than 0.05 were considered statistically significant.

RESULTS

At baseline, 263 (21.9%) men were current smokers, 583 (48.6%) men were ex-smokers and 353 (29.4%) men were never-smokers. Table 1 presents the baseline characteristics of 1,199 Japanese men, according to smoking status. Age, alcohol consumption, exercise, waist circumference, body fat percentage, systolic blood pressure, diastolic blood pressure, HDL cholesterol, triglyceride, γ-glutamyltransferase, uric acid, leukocyte

count, hsCRP and 2-h post-load plasma glucose significantly differed among the three groups. Current smokers had high waist circumference, body fat percentage, triglyceride, γ-glutamyltransferase, leukocyte count and hsCRP, and low HDL cholesterol.

The mean follow up was 2.8 years (total person-years: 3,403), and 449 men developed impaired insulin secretion during this period, which represents an incidence rate of 131.9 per 1,000 person-years. The mean follow up was 3.4 years (total person-years: 4,092), and 99 men developed insulin resistance during this period, which represents an incidence rate of 24.2 per 1,000 person-years. Changes in smoking status between the baseline and final examinations are presented in Table 2.

Table 3 presents the incidence rates and HRs for impaired insulin secretion and insulin resistance, according to smoking status. The incidence rates (per 1,000 person-years) for impaired insulin secretion were 120.9 in never-smokers, 125.1

Table 1 | Baseline characteristics of 1,199 Japanese men according to smoking status

	Never-smokers	Ex-smokers	Current smokers	*P*-value
n	353	583	263	
Age (years)*	57.3 (10.5)	59.6 (10.2)	55.1 (8.5)	<0.001
Familial history of diabetes, *n* (%)	52 (14.7)	87 (14.9)	29 (11.0)	0.290
Alcohol consumption (ethanol), *n* (%) g/week				
0	72 (20.4)	92 (15.8)	48 (18.3)	<0.001
1–139	194 (55.0)	277 (47.5)	92 (35.0)	
≥140	87 (24.6)	214 (36.7)	123 (46.8)	
Exercise, *n* (%) min/week				
0	153 (43.3)	243 (41.7)	155 (58.9)	<0.001
1–119	98 (27.8)	194 (33.3)	81 (30.8)	
≥120	102 (28.9)	146 (25.0)	27 (10.3)	
Body mass index (kg/m^2)	23.6 (23.3–23.9)	23.8 (23.6–24.0)	23.8 (23.6–24.0)	0.426
Waist circumference (cm)	84.6 (83.9–85.4)	85.9 (85.3–86.4)	86.2 (85.3–87.1)	0.011
Body fat percentage (%)	22.0 (21.5–22.4)	22.8 (22.5–23.2)	23.0 (22.4–23.5)	0.005
Systolic blood pressure (mmHg)	120.5 (119.0–122.1)	121.6 (120.4–122.8)	118.7 (116.9–120.5)	0.028
Diastolic blood pressure (mmHg)	74.9 (73.9–76.0)	75.6 (74.7–76.4)	73.1 (71.8–74.4)	0.006
HDL cholesterol (mmol/L)	1.38 (1.35–1.42)	1.41 (1.38–1.43)	1.30 (1.26–1.34)	<0.001
LDL cholesterol (mmol/L)	3.22 (3.15–3.30)	3.20 (3.13–3.26)	3.21 (3.11–3.30)	0.853
Triglycerides (mmol/L)†	1.08 (0.77–1.57)	1.20 (0.88–1.66)	1.30 (0.96–1.89)	<0.001
γ-Glutamyltransferase (IU/L)†	27.0 (20.0–44.5)	33.0 (22.0–59.0)	38.0 (25.0–64.0)	<0.001
Uric acid (μmol/L)	356.5 (349.1–364.0)	371.8 (365.9–377.6)	365.8 (357.0–374.5)	0.007
Leukocyte count (×10^9/L)	5.2 (5.0–5.3)	5.3 (5.2–5.4)	6.3 (6.1–6.4)	<0.001
High-sensitivity CRP (μg/mL)†	0.5 (0.3–0.8)	0.5 (0.3–1.1)	0.6 (0.3–1.2)	<0.001
Insulinogenic index (ΔI$_{30}$/ΔG$_{30}$)‡ (pmol/mmol)	136.5 (107.4–165.6)	148.7 (125.9–171.5)	123.2 (103.5–142.9)	0.472
HOMA-IR	1.17 (1.11–1.22)	1.17 (1.12–1.21)	1.13 (1.06–1.19)	0.581
HbA$_{1c}$ (%)	5.46 (5.43–5.49)	5.47 (5.44–5.49)	5.54 (5.50–5.58)	0.203
Fasting plasma glucose (mmol/L)	5.49 (5.44–5.53)	5.49 (5.45–5.52)	5.48 (5.43–5.53)	0.954
2-h plasma glucose (mmol/L)	6.48 (6.35–6.61)	6.69 (6.58–6.79)	6.39 (6.24–6.54)	0.003

*Age was analyzed with the analysis of variance, and is shown in the mean (standard deviation). Continuous data with a normal distribution were analyzed with the analysis of covariance with adjustments for age, and are shown in the mean (95% confidence interval).
†Continuous data with a non-normal distribution were analyzed with the Kruskal–Wallis *H*-test, and are shown in the median (25th to 75th percentile). Dichotomous and categorical data were analyzed with the Chi-squared test, and are shown in the number (%).
‡(insulin$_{30}$–insulin$_0$)/(glucose$_{30}$–glucose$_0$).
CRP, C-reactive protein; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein.

Table 2 | Changes in smoking status between the baseline and final examinations

	Never-smokers	Ex-smokers	Current smokers
n	353	583	263
Outcome: impaired insulin secretion, n (%)*			
No change	353 (100.0)	565 (96.9)	197 (74.9)
Started smoking	0 (0.0)	18 (3.1)	0 (0.0)
Quit smoking	0 (0.0)	0 (0.0)	66 (25.1)
Outcome: insulin resistance, n (%)†			
No change	353 (100.0)	561 (96.2)	193 (73.4)
Started smoking	0 (0.0)	22 (3.8)	0 (0.0)
Quit smoking	0 (0.0)	0 (0.0)	70 (26.6)

*The mean follow up was 2.8 years (total person-years: 3,403).
†The mean follow up was 3.4 years (total person-years: 4,092).

in ex-smokers and 165.0 in current smokers. The adjusted HRs and 95% CIs for impaired insulin secretion were 1.06 (0.84–1.33) in ex-smokers and 1.95 (1.44–2.63) in current smokers compared with never-smokers after adjustment for age, familial history of diabetes, alcohol consumption, exercise, systolic blood pressure, log-transformed triglyceride, log-transformed γ-glutamyltransferase, waist circumference, leukocyte count, changes in smoking status and changes in waist circumference (Table 3; model 6). These results were the same as when we excluded 99 men who developed insulin resistance (Table 3; model 7). Additionally, the adjusted HRs and 95% CIs for impaired insulin secretion in ex-smokers who had quit ≤3 (n = 96), 4–9 (n = 105) and ≥10 (n = 382) years before baseline were 1.15 (0.90–1.45), 1.06 (0.73–1.55), and 0.97 (0.64–1.48), respectively, compared with never-smokers after adjustment for the same confounding factors.

The incidence rates (per 1,000 person-years) for insulin resistance were 18.1 in never-smokers, 21.9 in ex-smokers and 38.2 in current smokers. The adjusted HRs and 95% CIs for insulin resistance were 1.04 (0.62–1.75) in ex-smokers and 1.93 (1.10–3.38) in current smokers compared with never-smokers after adjustment for age, familial history of diabetes,

Table 3 | Incidence rates and hazard ratios for impaired insulin secretion and insulin resistance according to smoking status

	Never-smokers	Ex-smokers	Current smokers
n	353	583	263
Impaired insulin secretion			
Cases (n)/person-years	122/1,009	213/1,703	114/691
Incidence rate (per 1,000 person-years)	120.9	125.1	165.0
HR (95% CI)			
Model 1	1.0	1.00 (0.80–1.25)	1.38 (1.07–1.79)
Model 2	1.0	1.03 (0.82–1.29)	1.51 (1.16–1.97)
Model 3	1.0	1.06 (0.84–1.32)	1.55 (1.18–2.02)
Model 4	1.0	1.04 (0.83–1.30)	1.54 (1.16–2.03)
Model 5	1.0	1.02 (0.82–1.29)	1.89 (1.42–2.51)
Model 6	1.0	1.06 (0.84–1.33)	1.95 (1.44–2.63)
Model 7*	1.0	1.02 (0.81–1.29)	1.94 (1.42–2.65)
Insulin resistance			
Cases (n)/person-years	22/1,216	44/2,011	33/865
Incidence rate (per 1,000 person-years)	18.1	21.9	38.2
HR (95% CI)			
Model 1	1.0	1.19 (0.71–1.99)	2.15 (1.25–3.69)
Model 2	1.0	1.04 (0.62–1.75)	1.93 (1.10–3.38)
Model 3	1.0	0.92 (0.54–1.57)	1.59 (0.91–2.78)
Model 4	1.0	1.00 (0.59–1.69)	1.59 (0.88–2.85)
Model 5	1.0	1.03 (0.61–1.74)	1.42 (0.74–2.72)
Model 6	1.0	0.95 (0.56–1.61)	1.11 (0.67–1.79)
Model 7†	1.0	0.94 (0.43–2.06)	1.06 (0.58–1.72)

Model 1: Adjusted for age. Model 2: Adjusted for age, familial history of diabetes (yes or no), alcohol consumption (0, 1–139 or ≥140 g/week), exercise (0, 1–119 or ≥120 min/week), systolic blood pressure, log-transformed triglyceride and log-transformed γ-glutamyltransferase. Model 3: Adjusted for all factors in model 2 plus waist circumference. Model 4: Adjusted for all factors in model 2 plus leukocyte count. Model 5: Adjusted for all factors in model 2 plus changes in smoking status between the baseline and final examinations (no change, started smoking or quit smoking) and Δ waist circumference (Δ = final examination–baseline examination). Model 6: Adjusted for all factors in model 2 plus waist circumference, leukocyte count, changes in smoking status and Δ waist circumference.
Model 7: *Adjusted for all factors in model 6 among 1,100 men excluding 99 men who developed insulin resistance. †Adjusted for all factors in model 6 among 750 men excluding 449 men who developed impaired insulin secretion.
CI, confidence interval; HR, hazard ratio.

Table 4 | Incidence rates and hazard ratios for impaired insulin secretion and insulin resistance according to pack-years of cigarette smoking

	Never-smokers	Current smokers			*P* for trend†
	0 Pack-years	0.1–20.0 Pack-years	20.1–30.0 Pack-years	≥30.1 Pack-years	
n	353	68	70	125	
Impaired insulin secretion					
Cases (*n*)/person-years	122/1,009	24/181	30/182	60/328	
Incidence rate (per 1,000 person-years)	120.9	132.6	164.8	182.9	
Age-adjusted HR (95% CI)	1.0	1.17 (0.75–1.82)	1.42 (0.95–2.13)	1.46 (1.07–1.99)	0.003
Multivariable-adjusted HR (95% CI)*	1.0	1.74 (1.09–2.76)	1.92 (1.25–2.96)	2.09 (1.46–2.99)	<0.001
Insulin resistance					
Cases (*n*)/person-years	22/1216	6/215	9/237	18/413	
Incidence rate (per 1,000 person-years)	18.1	27.9	38.0	43.6	
Age-adjusted HR (95% CI)	1.0	1.60 (0.64–3.97)	2.16 (0.99–4.73)	2.40 (1.29–4.47)	<0.001
Multivariable-adjusted HR (95% CI)*	1.0	0.97 (0.40–1.79)	1.07 (0.55–2.55)	1.18 (0.65–2.19)	0.39

*Adjusted for age, familial history of diabetes (yes or no), alcohol consumption (0, 1–139 or ≥140 g/week), exercise (0, 1–119 or ≥120 min/week), systolic blood pressure, log-transformed triglyceride, log-transformed γ-glutamyltransferase, waist circumference, leukocyte count, changes in smoking status between the baseline and final examinations (no change or quitted smoking) and Δ waist circumference (Δ = final examination minus baseline examination).
†Calculated across increasing categories of pack-years of cigarette smoking. Pack-years: one pack has 20 cigarettes.
CI, confidence interval; HR, hazard ratio.

alcohol consumption, exercise, systolic blood pressure, log-transformed triglyceride and log-transformed γ-glutamyltransferase (Table 3; model 2). Adjustment for waist circumference, leukocyte count or changes in smoking status and changes in waist circumference attenuated the risk relationships in current smokers (Table 3; models 3, 4 and 5). When simultaneously adjusted for waist circumference, leukocyte count, changes in smoking status and changes in waist circumference, the risk for insulin resistance was markedly attenuated in current smokers (Table 3; model 6). These results were the same as when we excluded 449 men who developed impaired insulin secretion (Table 3; model 7).

The incidence rates and HRs for impaired insulin secretion and insulin resistance according to pack-years of cigarette smoking are presented in Table 4. The multivariable-adjusted HRs and 95% CIs for impaired insulin secretion were 1.74 (1.09–2.76) in current smokers whose cumulative lifetime exposure was 0.1–20.0 pack-years, 1.92 (1.25–2.96) in those whose cumulative lifetime exposure was 20.1–30.0 pack-years and 2.09 (1.46–2.99) in those whose cumulative lifetime exposure was 30.1 or more pack-years compared with never-smokers. The number of pack-years was positively associated with the risk for impaired insulin secretion in a dose-dependent manner (*P*-value for trend <0.001). Conversely, the multivariable-adjusted HRs and 95% CIs for insulin resistance were 0.97 (0.40–1.79) in current smokers whose cumulative lifetime exposure was 0.1–20.0 pack-years, 1.07 (0.55–2.55) in those whose cumulative lifetime exposure was 20.1–30.0 pack-years and 1.18 (0.65–2.19) in those whose cumulative lifetime exposure was 30.1 or more pack-years compared with never-smokers. All results were the same as when our analysis included just 1,012 men who had annual comprehensive

medical check-ups regularly for 3 years or 4 years after the baseline examination.

DISCUSSION
The main findings of the present study indicated that after adjustment for baseline confounding factors, changes in smoking status and changes in waist circumference, current smokers had a twofold higher risk for impaired insulin secretion compared with never-smokers. Additionally, we found that the risk for impaired insulin secretion increased in a dose-dependent manner with an increasing number of pack-years of exposure (i.e. the long-term effect of cigarette smoking for current smokers). However, when simultaneously adjusted for waist circumference, leukocyte count, changes in smoking status and changes in waist circumference, the risk for insulin resistance was markedly attenuated in current smokers.

The present study showed that current smoking was a risk factor for impaired insulin secretion, and there was a dose–response relationship between impaired insulin secretion and the number of pack-years of exposure in Japanese men. These findings are in accordance with previous clinical studies, which reported that smoking directly affects β-cells[5,6]. Additionally, these findings support the hypothesis that cigarette smoking might suppress insulin secretion. The mechanism responsible for the risk of impaired insulin secretion among current smokers might be attributed to the effects of nicotine on insulin secretion[17]. It has been previously reported that nicotine influences insulin secretion through nicotinic acetylcholine receptors on β-cells and that nicotine increases apoptosis of islet β-cells[18]. Insulin secretion in Japanese individuals is less than half of that of Caucasians[19,20]. Therefore, to prevent type 2 diabetes in Japan, the low insulin secretion of Japanese individuals needs to be considered.

However, the modifiable risk factors of impaired insulin secretion are not yet determined. In the present study, ex-smokers did not increase the risk for impaired insulin secretion. The present findings provide evidence that cigarette smoking is a modifiable risk factor of impaired insulin secretion that could be targeted for the prevention of type 2 diabetes. In the present study, we excluded the participants with impaired insulin secretion at baseline examination because the outcome of this prospective study was impaired insulin secretion. Current smokers with impaired insulin secretion might be prone to deterioration of glucose tolerance and development of diabetes. Therefore, we will examine the risk of current smokers with impaired insulin secretion for the incidence of diabetes in the future.

There was no association between current smoking and insulin resistance after adjustment for waist circumference, leukocyte count, changes in smoking status and changes in waist circumference in the present study. Some previous studies have reported that smokers are insulin resistant[7,8]. This idea was questioned, and conflicting or negative results on the relationship between cigarette smoking and insulin resistance have been reported[9,10]. Waist circumference is an indicator of the amount of visceral adipose tissue. A greater amount of visceral adipose tissue is related to insulin resistance and diabetes[21]. Smokers tend to have a larger waist circumference than non-smokers[22,23]. The impact of current smoking on insulin resistance might be, in part, mediated by visceral adipose tissue, visceral adipose tissue gain and systemic inflammation.

The strengths of the present study were the large-scale data that included changes in smoking exposure and the extensive data on potential confounders. Furthermore, the 12-h overnight fast before OGTT was managed by being hospitalized from the day before, and impaired insulin secretion and insulin resistance cases were screened every year. There were several limitations that should also be considered. First, the estimates of insulin secretion and resistance were made by using calculations based on the OGTT and not the 'gold standard' test, the glucose clamp technique. However, a clamp study is not feasible in large-scale studies, and we believe that these proxy measures are reliable with large datasets. Second, we cannot deny the possibility of selection bias, as the study participants were those that underwent routine comprehensive medical check-ups, and thus might have paid more attention to their health. Generally, the comprehensive medical check-up is expensive, but the comprehensive medical check-up at Saku Central Hospital is free or inexpensive, as administrations and companies provide subsidies for these examinations. Therefore, many community residents undergo such examinations. Furthermore, the prevalence of diabetes and obesity were similar to those found in the general population, according to previous reports in Japan[24]. However, individuals who did not undergo the annual comprehensive medical check-ups after the baseline examination were excluded from our analysis. As individuals that developed severe diseases or died during the follow-up period were not assessed, we cannot deny the possibility of selection bias.

Despite these potential limitations, the present findings, which were obtained from a cohort of Japanese men, support the conclusion that cigarette smoking is a modifiable risk factor for impaired insulin secretion. Additionally, the number of pack-years of exposure was closely associated with the risk for impaired insulin secretion. The study findings might also be important for other Asian populations, which have low insulin secreting ability.

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