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Cumulative Number of Cigarettes Smoked Is an Effective Marker to Predict Future Diabetes

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To estimate a cutoff level for cumulative number of cigarettes smoked critical for diabetes prevention, we examined health-check data for 121 male residents in Shimane Prefecture, Japan, from 1998 to 2005. We used the Brinkman Index (BI) calculated as the number of cigarettes smoked per day multiplied by the number of years of smoking for the index of cumulative number of cigarettes smoked. Multivariate logistic-model analysis was conducted to determine the relationship between BI and the diabetes risk. We documented 26 new cases during the observation period. Multivariate-adjusted odds ratio (OR) for diabetes risk compared with BI of 0 was 3.52 (95% CI: 0.84-14.71) for BIs of 1-600 and 10.19 (95% CI: 2.38-43.64) for BI ≥ 601 (p-trend=0.002). We found that the BI is an effective marker for predicting future risk for diabetes, and indicated a BI of 600 as a useful cutoff value.

Key words: Brinkman index, diabetes mellitus, glucose intolerance, smoking, longitudinal study

INTRODUCTION

Cigarette smoking has been linked to cardiovascular disease, cerebrovascular disease, diabetic retinopathy, diabetic nephropathy, dyslipidemia, obesity, cancer, and tooth loss among others [1-9]. Komiya *et al*. reported significantly increased visceral fat levels in obese heavy smokers [5]. Additionally, evidence shows that smoking exacerbates some aspects of diabetes. The development of complications in patients with diabetes is largely dependent on the effectiveness of its management. In particular, smokers suffer more severe diabetic complications [10, 11], and smoking adversely affects blood-glucose levels in these patients [10-13].

A consensus regarding the relationship between cigarette smoking and diabetes risk has not been reached. The MONICA Project reported that compared to non-smokers, odds ratios (ORs) for the development of type 2 diabetes in male smokers who smoked 15-19 cigarettes per day was 1.78, and 2.43 for those who smoked more than 20 cigarettes per day [14]. Several studies in the US, Europe, and Japan have shown that smokers display higher risk and hazard ratios for impaired glucose tolerance (IGT) than non-smokers [7, 15-20]. In the Framingham studies, in contrast, no relationship between cigarette smoking or the development of diabetes was observed [21]. Moreover, Hu *et al*. also reported that current smokers were not more likely to suffer from impaired glucose regulation [22].

We propose that these discrepancies arise because smoking status was not estimated accurately or consistently across studies, and that the cumulative number of cigarettes smoked is a useful measure for predicting diabetes risk. The Brinkman Index (BI) is such a measure, and has already been used to relate smoking to poor health [23-26]. Further, Anan *et al*. reported that BI values have a dose-response relationship with insulin resistance [27]. The purpose of this study was to estimate a cutoff level for BI values critical for diabetes prevention.

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METHODS

Study population

Health checks were conducted on 273 male residents aged 20 years or older in a single town in Shimane Prefecture, Japan, in 1998. Fifty-seven subjects either suspected of being at risk for diabetes or who had medical histories related to diabetes were excluded, and thus the original cohort group consisted of 216 men. This group was tracked from 2002 to 2005, and 121 subjects provided written consent to participate in the study. The data from 1998 were used as baseline, and the development of diabetes risk was determined using the results from check-ups conducted between 2002 and 2005.

This study was approved by the ethics committee of Shimane University Faculty of Medicine in 2003 (Notification no. 85).

Health checks

Baseline health checks were conducted in 1998 based on the Health and Medical Service Law for the Aged. After fasting overnight, the subject's height, weight, and blood pressure were measured, and a blood profile and urine analysis were performed. A medical history interview was conducted by a public health nurse, a questionnaire for health-related lifestyle issues (smoking, alcohol consumption, and physical activity) was given, and patients were examined by a physician. The blood profile included total cholesterol (TC), HDL-cholesterol (HDL-C), triglycerides (TG), AST, ALT, γ-GTP, blood glucose (BS), hemoglobin A1c (HbA1c), and creatinine. The urine profile included protein, occult blood, and urinary glucose. The HbA1c value was determined by Japan Diabetes Society (JDS) method which is 0.4% lower than National Glycohemoglobin Standardization Program (NGSP) value [28]. Body-mass index (BMI) was calculated as weight/height^2 (kg/m^2). All health checks were carried out at the same hospital, by the same organization.

Definition of diabetes risk

We used the diabetes-management classifications [29] found in the Law of Health and Medical Services for the Aged, and observed levels of HbA1c to assess diabetes risk. Subjects were diagnosed with diabetes risk if they were classified as "in need of observation" (5.5% $\leq$ HbA1c $<$ 6.0% or 100 mg/dl $\leq$ BS $<$ 126 mg/dl) or "in need of medical care" (HbA1c $\geq$ 6.0%, BS $\geq$ 126 mg/dl, or under medication). If diabetes-management classification data could not be obtained, those with HbA1c levels $\geq$ 5.5% were said to have diabetes risk.

Smoking status

Smoking status was determined by questionnaire during the health checks between 2002 and 2005. Current smokers and former smokers were asked how many cigarettes they smoked per day and the number of years spent smoking. Brinkman Index (BI) values were calculated as the number of cigarettes smoked per day multiplied by the number of years of smoking [23].

Statistical analysis

Mean and standard deviations for each value obtained from the 1998 health check were calculated, and the diabetes-risk group and the no-risk group were compared using Student's *t*-tests. The median, 25% quartile, and 75% quartile scores were calculated for TG and compared using the Mann-Whitney U test.

Subjects were grouped by smoking category. Multivariate logistic-model analysis was conducted for the development of diabetes risk, with odds ratios (ORs) and 95% confidence intervals (CIs) calculated and p-trends derived with logistic models. Confounding factors were determined from the results of the 1998 health checkup. The respective cutoff values were defined as laboratory test values that increase the risk of cardiovascular disease or a major complication of diabetes [30, 31], and laboratory test values used as a standard in diabetes screening [32]. Finally, we selected age, BMI, blood pressure, HDL-C, TG, alcohol consumption, physical exercise, and follow-up year as confounding factors.

ORs for the development of diabetes risk were obtained by age-adjusted logistic regression analysis for each confounding factor. Multivariate-adjusted logistic analysis was conducted with the confounding factors of age, BMI ≥ 25 kg/m^2, hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg), HDLC < 40 mg/dl, TG ≥ 150 mg/dl, current drinking, exercise less than three times/week, and the follow-up year, and ORs and p values were also obtained. The cutoff level of BI was changed from 400 to 800 and the ORs were again compared.

The SAS software version 9.0 (SAS Institute, Inc., Cary, NC) was used to perform all statistical analyses.

RESULTS

Of the 216 people in the cohort group established in 1998, 121 were followed from 2002 to 2005 and gave consent to participate in the study, giving a follow-up rate of 56.0%.

The mean age (SD) was 61.9 (13.6) years, ranging from 21 to 88 years. We documented 26 new cases of diabetes risk during the observation period. Cumulative incidence rate was 21.5%. At baseline level results obtained in 1998, HbA1c was significantly higher in those who later developed diabetes risk (p<0.001, Table 1). Among the 121 subjects, there were 53 BIs of 0,36 ranged from 1-600, and 32 were > 600. Of these, 19 were former smokers, with BIs ranging from 1-600 in 13 and > 600 in 6. Table 2 shows the diabetes-risk status for each confounding factor. The group with BMI ≥ 25 showed a significant relationship with diabetes-risk development (p=0.018), with an age-adjusted OR of 4.08 (95% CI: 1.27-13.10). BI values and diabetes-risk status are shown in Table 3. Smokers had higher incidence rates for developing IGT than nonsmokers at every BI grade.

Adjusted odds ratios with cutoffs of BI values for the development of diabetes risk are presented in Table 4. A significant dose-response relationship was found for each cutoff value. Heavy smokers showed a significantly higher OR until the cutoff BI-value reaches 600, but after the cutoff value ex-

Table 1. Baseline data (case vs. control)

	case (n = 26)	control (n = 95)	P-value*
Age (years) †	66.1 (8.9)	60.8 (14.5)	0.08
Body mass index (kg/m^2) †	23.0 (3.2)	22.1 (2.5)	0.21
Systolic blood pressure (mm Hg) †	124.3 (19.6)	127.2 (16.0)	0.47
Diastolic blood pressure (mm Hg) †	76.2 (10.3)	77.7 (10.7)	0.50
HDL-cholesterol (mg/dl) †	48.7 (13.8)	49.7 (13.6)	0.72
Blood sugar (mg/dl) †	101.9 (11.4)	97.2 (9.6)	0.06
Hemoglobin A1c (%)†	5.1 (0.2)	4.8 (0.2)	< 0.01
Triglyceride (mg/dl) ‡	124 (90 - 169)	112 (7 - 153)	0.29
Alcohol consumption §			
Non-drinker	15 (57.6)	51 (53.7)	
Ex-drinker	1 (3.9)	1 (1.1)	
Current drinker	10 (38.5)	43 (45.2)	0.54
Brinkman Index§			
0	7 (26.9)	46 (48.4)	
1–600	8 (30.8)	28 (29.5)	
601+	11 (42.3)	21 (22.1)	0.07

*P-values are from student t-tests or Mann-Whitney U test or χ^2 (chi-square) tests comparing cases against Without IGT

† Mean (SD)

‡ Median (25% quartile – 75% quartile)

§ n (%)

Table 2. Adjusted odds ratio for diabetes risk

	case (%)	control (%)	Age-adjusted OR* (95% CI†)
Body mass index			
< 25 kg/m^2	19 (18.5)	84 (81.5)	1.0 (reference)
≥ 25 kg/m^2	7 (38.9)	11 (61.1)	4.08 (1.27–13.10)
Blood pressure (BP)			
Systolic BP < 140 mm Hg and diastolic BP < 90 mm Hg	21 (22.6)	72 (77.4)	1.0 (reference)
Systolic BP > 140 mm Hg and/or diastolic BP ≥ 90 mm Hg	5 (17.9)	23 (82.1)	0.54 (0.17–1.69)
HDL cholesterol			
≥ 40 mg/dl	19 (21.6)	69 (78.4)	1.0 (reference)
< 40 mg/dl	7 (21.2)	26 (78.7)	0.97 (0.39–2.41)
Triglyceride			
< 150 mg/dl	17 (19.5)	70 (80.5)	1.0 (reference)
≥ 150 mg/dl	9 (26.5)	25 (73.5)	1.87 (0.70–5.01)
Alcohol consumption			
non-drinker or ex-drinker	11 (20.0)	44 (80.0)	1.0 (reference)
current drinker	15 (22.7)	51 (77.3)	1.34 (0.53–3.31)
Physical exercise			
≥ 3 times/week	9 (25.7)	26 (74.3)	1.0 (reference)
< 3 times/week	17 (19.8)	69 (80.2)	0.80 (0.31–2.05)

*OR: odds ratio
†CI: confidence interval

Table 3. Relationship between Brinkman Index and diabetes risk

Brinkman Index	Total (n)	case (%)	control (%)
0	53	7 (13.2)	46 (86.8)
1–400	24	5 (20.8)	19 (79.2)
401–500	5	1 (20.0)	4 (80.0)
501–600	7	2 (28.6)	5 (71.4)
601–700	7	3 (42.9)	4 (57.1)
701–800	5	1 (20.0)	4 (80.0)
801–	20	7 (35.0)	13 (65.0)

ceeded 600, the OR for heavy smokers and other smokers was reversed. Multivariate-adjusted OR for diabetes risk compared with a BI of 0 was 3.52 (95% CI: 0.84-14.71) for BIs of 1-600 and 10.19 (95% CI: 2.38-43.64) for BI ≥ 601 (p-trend=0.002). For confounding factors, only BMI produced a significant OR. Thus, only BI and BMI remained as significant predictors of diabetes risk when a BI cutoff-value of 600 was used.

DISCUSSION

In this analysis of the relationship between diabetes risk and cigarette smoking, we found that the BI is an effective marker for predicting diabetes risk. A BI value > 600 indicated a significant risk for diabetes. To our knowledge, this is the first study to estimate successfully the risk of developing diabetes by using BI as an indicator of the cumulative number of cigarettes smoked.

Our study revealed that cigarette smoking increases the risk of developing diabetes in all smokers. Although previous studies have related smoking to diabetes risk [6, 14-19], our study provides a useful quantification of smoking history, and a cutoff value above which the risk of developing diabetes

Table 4. Adjusted odds ratio of the Brinkman Index for the development of diabetes risk

Brinkman Index	n	Diabetes risk (%)	Adjusted OR* (95% CI†) Age-adjusted	p-trend	multivariate-adjusted‡	p-trend
0	53	7 (13.2)	1.0 (reference)		1.0 (reference)	
1–400	24	5 (20.8)	4.07 (0.92–17.97)		3.24 (0.64–16.36)	
401–	44	14 (31.8)	4.45 (1.47–13.50)	0.010	7.92 (2.01–31.22)	0.003
0	53	7 (13.2)	1.0 (reference)		1.0 (reference)	
1–500	29	6 (20.7)	3.53 (0.89–13.95)		3.30 (0.73–15.04)	
501–	39	13 (33.3)	4.77 (1.54–14.76)	0.007	8.76 (2.17–35.43)	0.002
0	53	7 (13.2)	1.0 (reference)		1.0 (reference)	
1–600	36	8 (22.2)	3.68 (1.02–13.27)		3.52 (0.84–14.71)	
601–	32	11 (34.4)	4.90 (1.53–15.74)	0.008	10.19 (2.38–43.64)	0.002
0	53	7 (13.2)	1.0 (reference)		1.0 (reference)	
1–700	43	11 (25.6)	4.76 (1.37–16.61)		5.34 (1.37–20.83)	
701–	25	8 (32.0)	4.06 (1.20–13.76)	0.020	6.55(1.54–27.84)	0.009
0	53	7 (13.2)	1.0 (reference)		1.0 (reference)	
1–800	48	12 (25.0)	4.29 (1.29–14.34)		4.97(1.30–18.97)	
801–	20	7 (35.0)	4.49 (1.26–16.01)	0.014	7.65 (1.72–34.09)	0.005

*OR: odds ratio

† CI: confidence interval

‡ adjusted for age, BMI ≥ 25 kg/m^2, hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg), HDL cholesterol < 40 mg/dl, triglyceride ≥ 150 mg/dl, current drinker, physical exercise (< 3 times/week), and follow-up year

sharply rises. This can be helpful when educating smokers about the dangers of cigarettes.

The BI, calculated as the number of cigarettes smoked per day multiplied by the number of years of smoking, is a useful index for estimating the cumulative number of cigarettes smoked over an entire lifetime. In previous studies, the BI was primarily used as a marker of respiratory syndromes such as pneumonia and lung cancer [23-26]. Brinkman determined that individuals with BIs > 600 are heavy smokers [23]. However, this determination varies depending on the specific disease, with heavy smokers having BIs > 400 for respiratory disease, and 500 for arteriosclerosis [24-26]. Our present data suggest that a BI of 600 is the appropriate cutoff value for heavy smoking with regard to diabetes. This supports similar conclusions reached by Anan *et al.* , who indicate that a BI of 600 is the cutoff level for increased insulin resistance [27]. Further, heavy smoking is related to both the development of IGT and type-2 diabetes [14, 17, 20]. This study predicts that smoking cessation before BI reaches 600 may reduce the risk of developing diabetes.

Results also indicate that increased BMI is independently related to diabetes risk. Other factors such as age, blood pressure, dyslipidemia, and lack of exercise are linked to type-2 diabetes [21, 22, 34-36]. Indeed, obese people display elevated insulin resistance, which is factor in the development of diabetes [3, 27]. Some studies have reported that many young people smoke for the purpose of losing weight [37, 38], although other studies indicate that smoking is likely a risk factor for future obesity [5]. Peltzer *et al.* reported that smoking history is significantly related to high weight and obesity among school children [39]. Our data provide a clear and useful example of health risks that increase with smoking, and can be used to educate younger people. Further evidence that smoking leads to a risk for diabetes is required.

Cigarette smoking causes increases in insulin resistance [10, 11, 40-44] and postprandial blood-glucose levels [5]. Our results suggest that BI values may predict diabetes-risk development, and that early guidance to quit smoking can be an important factor in preventing diabetes risk. We consider that this result is particularly useful for adolescents who have not yet reached high BI values.

This study shows the usefulness of the BI as a means to quantify smoking consistently. Currently, different health checks assess smoking status with different questions. Some merely ask whether or not a subject smokes, others ask about the daily number of cigarettes that the subject currently smokes, and still others ask about both the number of cigarettes smoked daily and number of years spent smoking. Other alternatives include asking subjects to select from categories relating to smoking status (as in the present study), or asking subjects about the actual number of cigarettes smoked. In health checks performed in Japan since April 2008, all subjects have been asked whether or not they smoke, but confirming the number of cigarettes smoked per day or the number of years spent smoking has not been necessary [29]. The present results indicate that this practice may not be sufficient, and that ascertaining the cumulative number of cigarettes smoked will more likely accurately estimate the risk of developing lifestyle-related diseases.

Several methodological limitations to the present study warrant mention. First, this study was targeted for male, second, many confounding factors are used for the small subjects, finally, we determined the diabetes risk from the health check. Although a Ministry of Health, Labour and Welfare survey in 2007 showed that 38.2% of men and 33.7% of women potentially have diabetes, our study only surveyed males. Because diabetes is a common disease found in Japanese men, with a 2010 survey showing that men smoke more than women (smoking rate: males, 32.2%; women, 8.4%), we deemed it worthwhile to limit our efforts to examining the association between smoking and glucose tolerance specifically in men. Additionally, despite a small sample size and a BI calculated from data at the follow-up health check, results revealed a significant cut-off value at which the cumulative number of cigarettes smoked can predict elevated blood-glucose levels. The meaning and effectiveness of this cut-off value should be further investigated. Further, the number of confounding factors analyzed was relatively high. Past studies have also used more than five confounding factors to estimate the relationship between cigarette smoking and diabetes, and experts think that developing diabetes results from a combination of many factors [4, 13, 17, 19, 20]. Therefore, even with small sample sizes, testing many confounding factors is necessary. We determined risk for diabetes using data from medical histories and HbA1c levels, information commonly available through health checks in Japan. Although both blood-glucose and HbA1c levels are commonly used in Japan [29], because the Ministry of Health, Labor, and Welfare allows blood tests a short time after eating, HbA1c data are more accurate [45].

Here, we found that the BI is an effective marker for predicting future risk for diabetes, and indicated a BI of 600 as a useful cutoff value. These findings may indicate the effectiveness of anti-smoking measures as one way of preventing diabetes, and the importance of guiding young smokers to quit smoking as soon as possible.

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