# 学 位 論 文 の 要 旨

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学　位　論　文　名　Cumulative Number of Cigarettes Smoked Is an Effective Marker to Predict Future Diabetes

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## 論 文 内 容 の 要 旨

### INTRODUCTION

A consensus regarding the relationship between cigarette smoking and diabetes risk has not been reached. Several studies in the US, Europe, and Japan have shown that smokers displayed higher risk and hazard ratios for impaired glucose tolerance (IGT) than non-smokers. However, in the other study, no relationship between cigarette smoking and the development of diabetes was observed.

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. The purpose of this study was to estimate a cutoff level for BI values critical for diabetes prevention.

### MATERIALS AND METHODS

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.

Baseline health checks were conducted in 1998. After fasting overnight, the subject's height, weight, and blood pressure were measured, and a blood profile and urine analysis were

performed. A questionnaire for health-related lifestyle issues (smoking, alcohol consumption, and physical activity) was given. 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. Body-mass index (BMI) was calculated as weight/height$^2$ (kg/m$^2$) from check-ups conducted between 2002 and 2005.

Subjects were diagnosed with diabetes risk if they were classified as "in need of observation" (5.5% ≤ HbA1c < 6.0% or 100 mg/dl ≤ BS < 126 mg/dl) or "in need of medical care" (HbA1c ≥ 6.0%, BS ≥ 126 mg/dl, or under medication).

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. BI values were calculated as the number of cigarettes smoked per day multiplied by the number of years of smoking.

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 and the Mann-Whitney U test for TG.

Subjects were grouped by smoking category. Age-adjusted logistic-model and Multivariate logistic-model analysis were 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, and laboratory test values used as a standard in diabetes screening. 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-trends were also obtained. The cut-off level of BI was changed from 400 to 800 and the ORs were again compared.

## RESULTS AND DISCUSSION

The mean age (SD) was 61.9 (13.6) years, ranging from 21 to 88 years. We documented 26 (21.5%) new cases of diabetes risk during the observation period. At baseline level results obtained in 1998, HbA1c was significantly higher in those who later developed diabetes risk

(case: 5.1%, control: 4.8%, $p < 0.001$). For each confounding factor, the group with BMI $\geq 25$ 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).

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 exceeded 600, the OR for heavy smokers and other smokers was reversed. Among the 121 subjects, there were 53 BIs of 0, 36 ranged from 1–600, and 32 were > 600. 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 $\geq$ 601 (p-trend = 0.002). For confounding factors, only BMI produced a significant OR. The OR for IGT compared with a BMI < 25 was 3.57 (95% CI: 0.89–14.40) for BMI $\geq$ 25.

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. 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. 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.

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. 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.

## CONCLUSION

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. This study predicts that smoking cessation before BI reaches 600 may reduce the risk of developing diabetes. 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.