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Dose–response relationship between tobacco or alcohol consumption and the development of diabetes mellitus in Japanese male workers

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ABSTRACT

Background: The aim of this study was to examine the dose–response relationships between tobacco or alcohol consumption and the development of diabetes mellitus.
Methods: An 8-year prospective cohort study was conducted in 8423 male workers who received annual health check-ups between 2002 and 2010 at a Japanese steel company. The endpoints were defined as an $HbA_{1c} \geq 6.1\%$ or taking any anti-diabetic medication. The dose–response relationships of tobacco or alcohol consumption were investigated using a proportional hazards regression with time-dependent covariates selected from baseline age, body mass index, mean arterial pressure, total serum cholesterol, aspartate aminotransferase, creatinine and uric acid, shift work or day work, and habitual exercise by stepwise selection method.
Results: A positive dose–response relationship between tobacco consumption and the development of diabetes mellitus was observed, with a significantly higher hazard ratio (HR) seen with higher tobacco consumption (11–20 cigarettes/day, HR 1.26 [95% confidence interval (CI), 1.00–1.59], ≥21 cigarettes/day, HR 1.54 [95%CI, 1.20–1.97]). In contrast, we observed a negative dose–response relationship between alcohol consumption and the development of diabetes mellitus, with a significantly lower HR with higher weekly alcohol consumption (7.0–13.9 gou/week [154–307 g/week], HR 0.73 [95% CI, 0.55–0.97], ≥14.0 gou/week [308 g/week], HR 0.75 [95% CI, 0.57–0.98]).
Conclusions: The results indicated that decreasing tobacco consumption will achieve significant prevention of diabetes mellitus. On the other hand, we observed a significant, negative dose–response relationship between alcohol consumption and the development of diabetes mellitus, in contrast to previous studies that reported a positive relationship in the Japanese population.

1. Introduction

Tobacco smoking has been shown to be a significant risk factor for cerebro- and cardiovascular diseases, aortic aneurysms, chronic obstructive pulmonary disease, lung cancer and acute myeloid leukemia, as well as numerous cancers of the larynx, oral cavity, pharynx, esophagus, bladder, stomach, cervix, kidney, and pancreas (U.S. Department of Health and Human Services, 2004). Numerous prospective studies have shown that tobacco smoking is also associated with an increased risk of diabetes mellitus in both men and women (U.S. Department of Health and Human Services, 2010; Willi et al., 2007). In terms of the dose–relationship between tobacco consumption and development of diabetes mellitus, several studies reported a significantly greater risk in heavy smokers, indicating a significant dose–response relationship (Manson et al., 2000; Meisinger et al., 2006; Nakanishi et al., 2000; Patja et al., 2005; Uchimoto et al., 1999; Will et al., 2001). However, several studies did not observe such a clear dose–response relationship due to a decreased risk in heavy smokers (Kawakami et al., 1997; Rimm et al., 1995; Sairenchi et al., 2004; Wannamethee et al., 2001) or solitary significant risk in single, smoking groups (Nagaya et al., 2008; Rimm et al., 1993).

Alcohol consumption is another lifestyle factor that may possibly be associated with the risk of diabetes mellitus. In general, excessive drinking habits are assumed to have a harmful effect on glucose metabolism, as alcohol itself is high in calories, with drinkers also tending to eat high-calorie meals. Contrary to usual expectations, the results of various studies in Western countries

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(Carlsson et al., 2005; Howard et al., 2004; Koppes et al., 2005; Pietraszek et al., 2010) indicate that moderate alcohol consumption is associated with a decreased incidence of diabetes mellitus. This suggests there may be a U-shaped relationship between alcohol and diabetes mellitus. A similar U-shaped relationship has been reported in one study in the Japanese population (Nakanishi et al., 2003). In contrast, other studies in the Japanese population showed that moderate to high alcohol consumption was associated positively with the incidence of diabetes mellitus (Kiyohara et al., 2003; Sawada et al., 2003; Sugimori et al., 1998; Waki et al., 2005), while meta-analysis of the Japanese population indicated that alcohol intake was a risk factor for diabetes in Japanese men who had a relatively low body mass index (Seike et al., 2008).

We therefore consider that a dose–response relationship between tobacco or alcohol consumption and the development of diabetes mellitus has been established, especially in the Japanese population. On the other hand, in our previous studies (Suwazono et al., 2006, 2009), we showed that shift work was also a significant risk factor for the development of diabetes mellitus and increased glycated hemoglobin A_{1c} (HbA_{1c}) in Japanese workers. Analysis of lifestyles in that study showed that drinking every day decreased the risk of either a 20%, 25% or 30% increase in HbA_{1c} (Suwazono et al., 2009). These results suggest that alcohol consumption may protect against increases in HbA_{1c} level. However, we could not obtain detailed information on tobacco or alcohol consumption due to the simple questions regarding smoking and drinking in the questionnaires. From 2002, detailed information about lifestyle became available because of the revised questionnaire. This prompted us to conduct new longitudinal study in different follow-up period compared to those in our previous studies (Suwazono et al., 2006, 2009). The aim of the present study was therefore to examine the relationship of tobacco and alcohol consumption on diabetes mellitus using a more stratified dose–response relationship based on longitudinal observation over 8 years.

2. Methods

2.1. Participants

This cohort study included observations made over an 8-year period from 2002 to 2010. The study protocol was approved by the ethical review boards of the Graduate School of Medicine, Chiba University. A total of 8423 participants out of a possible 10,900 male workers at a Japanese steel company were enrolled in the study. The cohort consisted of more than 98% of the workers who attended annual health examinations during the observation period. New participants could be enrolled during the follow-up period. The following individuals were excluded from the study; those who did not have a health examination in the subsequent year ($n = 1339$), those who did not have an HbA_{1c} measurement in the subsequent year ($n = 571$), those who were diagnosed with diabetes mellitus based on the criteria in the present study at entry ($n = 495$), and those with any missing data in the year of entry ($n = 72$). At baseline, all the participants excluded from the study had a lower mean age (40.5 yrs vs. 42.3 yrs), higher percentage of non-smokers (49.7% vs. 43.5%), and a higher percentage of abstainers (43.6% vs. 23.7%) than the enrolled participants. Therefore, exclusion of young participants in the control group may have resulted in a loss of detection power. On the other hand, the geometric mean (5.0%) of HbA_{1c} level in the excluded participants without diabetes mellitus ($n = 1225$) was the same as the target participants (5.0%). This suggests that exclusion of these participants did not cause significant bias on the incidence of diabetes mellitus in the target participants.

2.2. Measurements

Diagnosis of diabetes mellitus was based on two data sources: the results of the annual health examination and individual medical histories. Health examination data included the results of a laboratory test for HbA_{1c} (normal: 4.3–5.8%) measured using a latex agglutination kit (RAPIDIA Auto HbA1c-L, Fujirebio inc., Tokyo, Japan). The presence of diabetes mellitus was based on an $HbA_{1c} \geq 6.1\%$ (Kuzuya et al., 2002) or taking any antidiabetic medication. Participants were censored upon developing diabetes mellitus. The health examinations, including blood sampling, were carried out between 9 a.m. and 3 p.m. throughout the study period. None of the measurements were taken within 30 min after a meal or heavy physical activity. Although blood glucose levels were also measured during screening, fasting samples were not always obtainable, and therefore fasting blood glucose level was not used as a diagnostic criterion. The medical history of the workers was recorded during the annual health examination using a self-administered questionnaire. The responses were confirmed during individual interviews conducted by occupational physicians. Age, body mass index (BMI), mean arterial pressure, and the levels of total serum cholesterol, aspartate aminotransferase (AST), creatinine, and uric acid were measured during the study. Mean arterial pressure was calculated using the following equation: ((diastolic blood pressure $\times$ 2 + systolic blood pressure)/3) (Meaney et al., 2000). In Japan, the measurement of these items is legally required at annual health examinations as objective indicators for various lifestyle-related diseases. To avoid co-linearity in the statistical model, we chose, as much as possible, covariates from the items listed in the annual health examinations, without overlapping other measurements such as AST and alanine aminotransferase for liver dysfunction. The tests were conducted in comprehensive clinical testing laboratories that met the requirements of official certification organizations. Drinking and smoking habits, job schedule type, and habitual exercise were used as covariates in the analyses. Information on drinking and smoking habits, job schedule type, and habitual exercise, were recorded at the annual health examination and obtained from self-administered questionnaires. Smoking status was classified as non-smokers, smoking 1–10 cigarettes/day, 11–20 cigarettes/day, and $\geq$21 cigarettes/day. As the questionnaire enquired about current smoking status, the participants who had quit smoking before the follow-up period were classified as non-smokers. The participants who changed their answer from "smoker" to "non-smoker" during the follow-up period were classified as ex-smokers. The quantity of alcohol in each type of alcoholic beverage was calculated based on the unit "gou". In Japan, "gou" is the most popular unit used to measure alcohol consumption, with 180 mL of Japanese sake (rice wine) usually containing 15% of ethanol. 1 gou (180 mL) of Japanese sake which contains approximately 22 g of ethanol is equivalent to 500 mL of beer, 60 mL of whiskey, 180 mL of wine, or 110 mL of shochu (white spirits). This unit was used in the questionnaire as it is easily comprehensible for the general Japanese population to determine the amount of alcohol beverages they consumed. To calculate the total quantity of alcohol consumed per day, we assigned a score to each category as follows: 0 for 0 gou, 0.5 for <1 gou, 1 for about 1 gou, 2 for about 2 gou, 3 for about 3 gou, and 5 for >4 gou. Weekly alcohol intake was estimated by multiplying the quantity by frequency. The subjects were then divided into the following 5 groups with abstainers as controls: Abstainers (0.0 gou, 0.0 g), 0.1–3.4 gou (0.1–76.9 g), 3.5–6.9 gou (77.0–153.9 g), 7.0–13.9 gou (154.0–307.9 g), and 14.0 gou (308.0 g) or more. The other variables were categorized as follows: Job schedule type (Daytime, shift work), Habitual exercise (None, once-twice/month, once-twice/week, 3 times/week or more).

2.3. Statistical analyses

For the multivariate analysis, a proportional hazards regression with time-dependent covariates (Therneau and Grambsch, 2000) was used to evaluate the dose–response relationships between annual measurements of tobacco or alcohol consumption and the development of diabetes mellitus. Using this method, the derived hazard ratios (HR) for the endpoints were adjusted for the effects of the other time-variable covariates. Tobacco and alcohol consumption were included simultaneously in the statistical model to obtain HRs adjusted for each other. For baseline age and other covariates, stepwise model selection based on Akaike's information criterion (Akaike, 1974; Venables and Ripley, 2002) was performed to construct the most desirable statistical model. As the data on total serum cholesterol, AST, creatinine, and uric acid were not normally distributed, the values were transformed logarithmically using a base of 1.5. This transformation resulted in the HR for the variables increasing by 50%. The proportional hazards assumption for tobacco or alcohol consumption was not violated based on the Schoenfeld residuals. The analyses were performed with IBM SPSS 19J (IBM Business Analytics, Tokyo), survival (Therneau, 2011) and MASS (Venables and Ripley, 2002) packages in R version 2.14.1 (R Development Core Team, 2011). A P value < 0.05 was considered statistically significant.

3. Results

The number of person-years studied and incidence rates grouped according to tobacco consumption at entry to the study are shown in Table 1. The incidence rates per 1000 person years were 11.7 (nonsmokers), 8.6 (1–10 cigarettes/day), 11.4 (11–20 cigarettes/day), and 17.1 ($\geq$21 cigarettes/day).

Table 2 summarizes the characteristics of the participants grouped according to tobacco consumption at entry to the study. Participants smoking 1–10 cigarettes/day were younger and had lower BMI, systolic blood pressure, diastolic blood pressure, mean arterial pressure, and total serum cholesterol than nonsmokers or participants smoking either 11–20 or $\geq$21 cigarettes/day. The percentage of shift workers, participants who drank $\geq$14.0 gou/week or those who did not exercise regularly was higher in participants