A Prospective Study of Cigarette Smoking and the Incidence of Diabetes Mellitus among US Male Physicians

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PURPOSE: To determine the association between cigarette smoking and the incidence of type 2 diabetes mellitus.

SUBJECTS AND METHODS: We studied 21,068 US male physicians aged 40 to 84 years in the Physicians’ Health Study who were initially free of diagnosed diabetes mellitus, cardiovascular disease, and cancer. Information about cigarette smoking and other risk indicators was obtained at baseline. The primary outcome was reported diagnosis of type 2 diabetes mellitus.

RESULTS: During 255,830 person-years of follow-up, 770 new cases of type 2 diabetes mellitus were identified. Smokers had a dose-dependent increased risk of developing type 2 diabetes mellitus: compared with never smokers, the age-adjusted relative risk was 2.1 (95% confidence interval [CI]: 1.7 to 2.6) for current smokers of ≥20 cigarettes per day, 1.4 (95% CI: 1.0 to 2.0) for current smokers of <20 cigarettes per day, and 1.2 (95% CI: 1.0 to 1.4) for past smokers. After multivariate adjustment for body mass index, physical activity, and other risk factors, the relative risks were 1.7 (95% CI: 1.3 to 2.3) for current smokers of ≥20 cigarettes per day, 1.5 (95% CI: 1.0 to 2.2) for current smokers of <20 cigarettes per day, and 1.1 (95% CI: 1.0 to 1.4) for past smokers. Total pack-years of cigarette smoking was also associated with the risk of type 2 diabetes mellitus (P for trend <0.001).


Type 2 (noninsulin-dependent) diabetes mellitus is one of the most prevalent chronic diseases worldwide and affects more than 15 million people in the United States (1). The morbidity associated with diabetes is substantial, including markedly increased risks of cardiovascular disease, renal failure, and blindness; economic costs have been estimated to approach $100 billion annually in the United States (2). Four large-scale prospective studies have raised the possibility that cigarette smoking may increase the risk of type 2 diabetes mellitus (3–6), while three others found no association between smoking and diabetes (7–9).

A causal association between cigarette smoking and type 2 diabetes mellitus is biologically plausible for several reasons. Smoking increases blood glucose levels after an oral glucose challenge (10–12) and may impair insulin sensitivity (12). Smokers are more resistant than nonsmokers to insulin-mediated glucose uptake and are more hyperinsulinemic in response to an oral glucose load. This insulin resistance associated with smoking may account, in part, for the dyslipidemia (decreased high-density lipoprotein [HDL] cholesterol and increased triglyceride concentrations) and increased risk of coronary heart disease among smokers (13). Although smokers tend to be thinner, cigarette smoking has also been linked to increased abdominal fat distribution and greater waist-to-hip ratio (14,15), which may affect glucose tolerance (16). Vascular changes and reduced blood flow to skeletal muscles in smokers may contribute to the insulin resistance (13). Further, smoking increases free radical oxidative damage and oxidative stress (17), factors that have been implicated in causing diabetes (18). Finally, nicotine, carbon monoxide, or other chemical components of tobacco may have direct toxic effects on the pancreas, beta-cell function, and insulin receptor sensitivity (19–21).

In a large prospective cohort study of US male physicians, we investigated the relation between cigarette smoking and the incidence of type 2 diabetes mellitus. Participants in the Physicians’ Health Study were 40 to 84 years of age at entry and were observed for an average of 12 years.

METHODS

Study Sample

The Physicians’ Health Study (22,23) was a randomized, double-blind, placebo-controlled trial designed to test whether low-dose aspirin and beta-carotene reduce the...
risks of cardiovascular disease and cancer. Briefly, 22,071 US male physicians 40 to 84 years of age at entry in 1982 and free from prior myocardial infarction, stroke, and transient cerebral ischemia were assigned at random using a 2 × 2 factorial design to aspirin, beta carotene, both drugs, or placebo. A total of 1,003 men who reported having diabetes mellitus, coronary heart disease, cerebrovascular disease, or cancer before entry were excluded from the analyses.

**Questionnaires**
Information was collected at baseline by mailed questionnaires about previously diagnosed medical conditions, including diabetes mellitus, as well as about cigarette smoking, height and weight, history of hypertension and high cholesterol levels, parental history of myocardial infarction, frequency of vigorous exercise, alcohol use, and other health habits. Information about family history of diabetes was not ascertained. Study participants provided information about whether they had ever smoked cigarettes regularly (never, past only, or current) and, if currently smoking, how many cigarettes per day on average they smoked.

**Follow-up**
Every 6 months for the first year and annually thereafter, participants were mailed brief questionnaires asking about their compliance with the randomized treatment assignment and any new medical diagnoses, including diabetes (with the approximate date of diagnosis). Because the participants are physicians, medical records were not requested to confirm self-reports of diagnosed diabetes. Owing to the age structure of the sample, all incident cases of diabetes were diagnosed after the age of 40 years and were therefore classified as type 2 diabetes mellitus. For these analyses, follow-up was continued until October 1995. Vital status was known for all physicians, and follow-up information on morbidity was 99.7% complete.

**Statistical Analyses**
Participants were classified at baseline into one of the following categories: never smoker, past smoker, or current smoker (subclassified into ≥20 cigarettes per day and <20 cigarettes per day). Incidence rates for type 2 diabetes mellitus were obtained by dividing incident cases by person-years in each category of cigarette smoking, after adjustment for age. Age-adjusted relative risks were computed as the rate of occurrence of type 2 diabetes mellitus in a specific category of cigarette smoking divided by the corresponding rate among never smokers, after adjustment for age (1-year categories) and randomized treatment assignment. Proportional hazards regression models were used to adjust for age, treatment assignment, body mass index (defined as weight in kilograms divided by height in meters squared), history of hypertension, family history of diabetes, parental history of myocardial infarction before age 60 years, episodes of vigorous exercise per week (<1, 1 to 2, or 4, and 5 or more times per week), and alcohol consumption (daily, weekly, or never). As the presence of coronary risk factors may lead to increased medical surveillance, these covariates were included in the model to minimize confounding by these variables. The Mantel-extension test was used to assess the overall trend between greater levels of smoking and the risk of diabetes (24). Multivariate analyses of body mass index, physical activity, and history of hypertension as predictors of type 2 diabetes mellitus were also performed. In all multivariate models, we included available covariates that have been shown to be important risk factors for type 2 diabetes mellitus. The population attributable-risk of diabetes from cigarette smoking was calculated as the difference between the incidence rate for type 2 diabetes mellitus in the total sample and that in never smokers, divided by the incidence rate in the total sample (×100%). We calculated the 95% confidence intervals (CI) for each relative risk, and all P values were two-sided.

**RESULTS**
The prevalence of current smoking in the cohort was 11%. Never smokers tended to be slightly younger, somewhat thinner, more active physically, and less likely to consume alcohol than either past or current smokers (Table 1). Other risk factors did not differ appreciably by smoking status.

During 12 years of follow-up (255,830 person-years), a total of 770 incident cases of diabetes were reported. Compared with never smokers, men who currently smoked ≥20 cigarettes per day were about twice as likely to develop diabetes as never smokers; current smokers of <20 cigarettes per day were also at increased risk (Table 2). A linear test for trend for increasing risk of diabetes with increasing category of cigarettes was highly significant (P for trend <0.001). In multivariate analyses, the relative risks of type 2 diabetes mellitus among current smokers remained substantially elevated. Past smokers had only a modest and nonsignificantly elevated risk (Table 2). Further control for body mass index in finer categories (as a continuous variable) did not appreciably alter these relative risk estimates.

Total pack-years of smoking was a strong predictor of the risk of diabetes (Table 3). However, regardless of total pack-years of smoking, men who had quit smoking at least 10 years before study entry did not have an increased risk of type 2 diabetes mellitus, with relative risks of 1.3 (95% CI: 0.9 to 2.0) for those who quit smoking ≤5 years before baseline, 1.3 (95% CI: 0.9 to 1.8) for those who quit 5 to 10 years before baseline, and 1.1 (95% CI: 0.9 to 1.3) for those who quit >10 years before baseline, as compared with never smokers.
The multivariate-adjusted relative risk of diabetes associated with current smoking (≥20 cigarettes daily) was 1.7 (95% CI: 1.3 to 2.3), which was similar to the relative risk associated with mild overweight (body mass index 24.4 to 26.4 kg/m²), which had a relative risk of 2.1 (95% CI: 1.5 to 2.8), and history of hypertension, which had a relative risk of 1.7 (95% CI: 1.4 to 2.0).

Because of the possibility that physicians who smoke may have been more likely to be diagnosed with (asymptomatic) diabetes mellitus as the result of an incidental

Table 1. Age-Adjusted Distribution of Baseline Variables by Cigarette Smoking Status in a Cohort of US Male Physicians 40 to 84 Years of Age in 1982

<table>
<thead>
<tr>
<th>Age group</th>
<th>Never Smokers (n = 10,511)</th>
<th>Past Smokers (n = 8,258)</th>
<th>Current Smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percent or Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–49 years</td>
<td>47.6 ± 35.9</td>
<td>35.9 ± 43.5</td>
<td>43.5 ± 39.9</td>
</tr>
<tr>
<td>50–59 years</td>
<td>31.6 ± 36.3</td>
<td>20.5 ± 14.8</td>
<td>35.3 ± 36.8</td>
</tr>
<tr>
<td>60–69 years</td>
<td>15.6 ± 20.5</td>
<td>14.8 ± 19.2</td>
<td>35.3 ± 36.8</td>
</tr>
<tr>
<td>70–84 years</td>
<td>5.3 ± 7.3</td>
<td>6.4 ± 4.0</td>
<td>4.0 ± 4.0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.8 ± 9.3</td>
<td>54.2 ± 9.4</td>
<td>52.4 ± 9.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.8 ± 2.9</td>
<td>25.0 ± 3.0</td>
<td>24.9 ± 3.2</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>12.4 ± 13.7</td>
<td>12.6 ± 13.8</td>
<td>13.8 ± 13.8</td>
</tr>
<tr>
<td>History of high cholesterol</td>
<td>6.2 ± 7.1</td>
<td>6.9 ± 5.8</td>
<td>5.8 ± 5.8</td>
</tr>
<tr>
<td>Parental history of myocardial infarction before age 60 years</td>
<td>13.0 ± 12.6</td>
<td>12.6 ± 12.6</td>
<td>14.6 ± 14.6</td>
</tr>
<tr>
<td>Vigorous exercise</td>
<td>Less than once a week</td>
<td>26.2 ± 26.3</td>
<td>29.8 ± 39.2</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>Daily</td>
<td>18.1 ± 30.1</td>
<td>31.2 ± 38.0</td>
</tr>
<tr>
<td></td>
<td>Weekly</td>
<td>49.4 ± 51.9</td>
<td>50.0 ± 39.7</td>
</tr>
</tbody>
</table>

* Defined as reported systolic blood pressure of 160 mm Hg or greater, diastolic blood pressure of 95 mm Hg or greater, or history of treatment for high blood pressure.
† Defined as reported high cholesterol, reported blood cholesterol level of 260 mg/dL (6.8 mmol/L) or greater, or history of treatment with cholesterol-lowering medication.
‡ Defined as physical activity long enough to work up a sweat.

Table 2. Cigarette Smoking and Risk of Type 2 Diabetes Mellitus during 12 Years of Follow-up

<table>
<thead>
<tr>
<th>Cigarette Smoking Category</th>
<th>Person-Years</th>
<th>Cases</th>
<th>Incidence per 1000 Person-Years</th>
<th>Age-Adjusted*</th>
<th>Multivariate Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smokers</td>
<td>129,090</td>
<td>323</td>
<td>2.5</td>
<td>1.0 (Referent)</td>
<td>1.0 (Referent)</td>
</tr>
<tr>
<td>Past smokers</td>
<td>99,827</td>
<td>320</td>
<td>3.2</td>
<td>1.2 (1.0–1.4)</td>
<td>1.1 (1.0–1.4)</td>
</tr>
<tr>
<td>Current smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 cigarettes/day</td>
<td>9,685</td>
<td>35</td>
<td>3.6</td>
<td>1.4 (1.0–2.0)</td>
<td>1.5 (1.0–2.2)</td>
</tr>
<tr>
<td>≥20 cigarettes/day</td>
<td>17,228</td>
<td>92</td>
<td>5.3</td>
<td>2.1 (1.7–2.6)</td>
<td>1.7 (1.3–2.3)</td>
</tr>
<tr>
<td>P for trend‡</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Adjusted for age (1-year categories) and treatment assignment (aspirin and beta-carotene).
† Adjusted for age (1-year categories), body mass index (quartiles), physical activity (<1, 1, 2–4, and 5 or more times per week), history of hypertension, history of high cholesterol, parental history of myocardial infarction at age <60, alcohol consumption (<monthly, monthly, weekly, daily), and treatment assignment.
‡ Trend by smoking categories as listed in the Table.
Table 3. Association between Pack-Years of Cigarette Smoking and Risk of Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Pack-Years of Smoking</th>
<th>Cases</th>
<th>Age-Adjusted*</th>
<th>Multivariate Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (never smoker)</td>
<td>323</td>
<td>1.0 (Referent)</td>
<td>1.0 (Referent)</td>
</tr>
<tr>
<td>1 to 19.9</td>
<td>148</td>
<td>1.0 (0.8–1.2)</td>
<td>1.0 (0.8–1.3)</td>
</tr>
<tr>
<td>20 to 39.9</td>
<td>116</td>
<td>1.4 (1.1–1.7)</td>
<td>1.3 (1.0–1.6)</td>
</tr>
<tr>
<td>≥40</td>
<td>122</td>
<td>2.1 (1.7–2.5)</td>
<td>1.6 (1.3–2.1)</td>
</tr>
<tr>
<td>P for trend‡</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Adjusted for age (1-year categories) and treatment assignment (aspirin and beta-carotene).
† Adjusted for age (1-year categories), body mass index (quartiles), physical activity (<1, 1, 2–4, and 5 or more times per week), history of hypertension, history of high cholesterol, parental history of myocardial infarction at age <60, alcohol consumption (<monthly, monthly, weekly, daily), and treatment assignment.
‡ Trend by smoking categories as listed in the Table.

In this prospective study of US male physicians, current cigarette smoking was associated with a substantial increase in the incidence of type 2 diabetes mellitus. A dose-response gradient between increased smoking and the risk of diabetes was observed. These increased risks persisted after adjustment for body mass index and other measured risk factors and health habits. The risk elevation associated with cigarette smoking was similar to that attributable to mild overweight or hypertension. Assuming the association between cigarette smoking and type 2 diabetes mellitus is causal, our results suggest that in the general US population—i.e., in which approximately 25% of adults smoke (25)—about 10% (95% CI: 6% to 14%) of the incidence of type 2 diabetes mellitus may be attributable to cigarette smoking. For populations in which smoking is (or was) more common, greater population-attributable risks are likely. Cigarette smoking, therefore, may contribute to the increased risk of type 2 diabetes mellitus observed with the adoption of habits that are, or once were, common in developed countries.

Some but not all prospective studies have observed a positive association between smoking and risk of type 2 diabetes. In a 25-year prospective study among 841 middle-aged Dutch men, the relative risk of diabetes was 3.3 (95% CI: 1.4 to 7.9) among men who smoked >20 ciga-

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rate of corroboration by medical record review (26). Information about family history of diabetes was not available, but adjusting for this variable in the Nurses’ Health Study analyses did not materially alter the results (4).

Increased medical surveillance of smokers remains a potential explanation for their greater risk of being diagnosed with diabetes as an incidental finding. We addressed this concern in part by repeating the analysis after excluding participants who developed diabetes during the first 2 years of follow-up—which gave asymptomatic participants more time to develop symptomatic diabetes—and the results of our analyses were similar. In addition, we previously found that smoking was a risk factor for symptomatic diabetes in the Nurses’ Health Study (4). However, the strictest interpretation of our results is that, in our cohort, smoking was associated with the clinical diagnosis of diabetes, rather than the development of diabetes.

In conclusion, these prospective data from the Physicians’ Health Study support the hypothesis that cigarette smoking is an independent and modifiable determinant of type 2 diabetes mellitus. The biologic plausibility of this association lends further credence to a causal interpretation, and we believe that type 2 diabetes can be added to the list of major adverse health outcomes linked to smoking. Strategies to prevent the adoption of cigarette smoking or to facilitate smoking cessation may also reduce the incidence of diabetes and its complications. Populations at high risk of type 2 diabetes mellitus should be considered for special targeted smoking interventions. Guidelines for physicians (27) to ask about tobacco use and to assist smokers to quit could help reduce the burden of diabetes as well as the even larger burdens of cardiovascular disease and cancer.

ACKNOWLEDGMENT

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REFERENCES


