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INTERACTION BETWEEN CIGARETTE SMOKING AND DIABETES MELLITUS IN THE PREDICTION OF DEATH ATTRIBUTED TO CARDIOVASCULAR DISEASE

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Previous studies have shown that the increased risk of cardiovascular disease in adults with diabetes is independent of heart disease risk factors and have suggested that the effect of these risk factors is similar in diabetics compared with nondiabetics. To determine whether there was interaction between diabetes and the classic heart disease risk factors (cholesterol, blood pressure, and cigarette smoking) in the prediction of cardiovascular death, the etiologic fraction due to interaction was assessed in a nine-year follow-up of 2,620 older Caucasian adults (60–79 years) who resided in Rancho Bernardo, California, 8.7% of whom had diabetes by history or fasting hyperglycemia. In these older adults, the frequency of categoric hypertension, hypercholesterolemia, or current cigarette smoking did not differ significantly among diabetics compared with nondiabetics. Overall, the age-adjusted relative cardiovascular mortality risk among diabetics was similar to that in nondiabetics for all risk factors except cigarette smoking, for which the relative risk for diabetics was 2.2 compared with 1.2 for nondiabetics. High cholesterol and systolic blood pressure levels showed no interaction with diabetes, but cigarette smoking had a large and significant interaction with diabetes, such that an estimated 65% of the cardiovascular disease deaths among diabetics could be attributed to the interaction of diabetes and cigarette smoking. If confirmed, these data have important implications for the prevention of cardiovascular death in older diabetics.

cardiovascular diseases; diabetes mellitus; smoking

Adults with diabetes mellitus have an increased risk of cardiovascular disease that persists after adjusting for the classic coronary risk factors, cholesterol, systolic blood pressure, and cigarette smoking (1). Most of the prospective studies of coronary disease and diabetes have not reported a greater impact of cardiovascular risk factors in diabetics than in nondiabetics (2, 3). For example, analysis of the Framingham data showed no significant differences in univariate logistic coefficients for cholesterol, systolic blood pressure, or cigarette smoking in diabetics versus nondiabetics of either sex (2). Similarly, both univariate and multivariate logistic analysis of data from the Whitehall study of male civil servants aged 40–64 years showed coefficients for choles-

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terol, systolic blood pressure, and cigarette smoking on coronary heart disease mortality to be of the same magnitude in normoglycemic and hyperglycemic groups (3).

Two studies are inconsistent with these reports. Among 1,603 Tecumseh residents, including 11 diabetics, blood glucose and cholesterol were highly predictive of coronary heart disease as an interaction pair in a multiple logistic model (4). However, this significant interaction of blood glucose and cholesterol was one of 21 interaction terms tested. In addition, a study restricted to all-cause mortality showed higher relative risks for systolic blood pressure among diabetics compared with age-, sex-, and race-matched controls. The same study found no evidence of interaction between diabetes and cigarette smoking on all-cause mortality (5).

These studies compared coefficients or relative risks for diabetics and nondiabetics from linear models: Excess risk due to an interaction or synergistic effect of risk factors with diabetes might not be obvious with these methods. We used a technique based on the additivity of attributable risks to examine the interaction of diabetes with cholesterol, systolic blood pressure, and cigarette smoking on the nine-year cardiovascular disease mortality in a defined population of older adults.

Methods

Eighty-two per cent of all adult residents of a geographically defined, upper-middle-class Caucasian community in southern California were surveyed for heart disease risk factors in 1972–1974 (6). All participants had a standardized interview that included questions about cigarette smoking, personal history of diabetes, and the use of selected medications. Blood pressure was measured with a standard mercury sphygmomanometer after the subject had been seated for at least five minutes. Blood was obtained by venipuncture from fasting subjects. Plasma cholesterol was measured in a standardized Lipid Research Clinic laboratory by means of an autoanalyzer. Plasma glucose was measured in a hospital diagnostic laboratory by the hexokinase method for true glucose.

Vital status was determined annually to the present for an average of nine years of follow-up and is known for 99.9 per cent of the cohort (7). Death certificates were obtained for all decedents and coded by a certified nosologist using the Eighth Revision of the *International Classification of Diseases, Adapted* for use in the United States. Cardiovascular deaths were those coded 400 to 438. In a subset of this population, interviews with next of kin and physicians and review of hospital records supported the death certificate diagnosis of cardiovascular disease in about 85 per cent.

All 2,620 subjects aged 60–79 years who had fasted at least 12 hours before venipuncture and who had data for all relevant variables were included in the analysis. All persons with a personal history of diabetes, whether or not they were taking antidiabetic medications, or who had a fasting plasma glucose $\geq$140 mg/dl were classified as diabetic. All others were considered nondiabetic. Cholesterol and systolic blood pressure were dichotomized into low and high categories with clinically reasonable cutpoint criteria (cholesterol $\geq$230 mg/dl and systolic blood pressure $\geq$160 mmHg) assigned prior to the analysis. Current cigarette smokers were compared with all others. Age-adjusted cardiovascular death rates per 1,000 person-years were calculated by the direct method based on 10-year age-at-risk categories and by using the total population as a standard. Differences between age-adjusted death rates for each category of risk factor among diabetics

and nondiabetics were tested by means of the Mantel-Haenszel summary chi-square.

To estimate the degree of interaction between diabetes and each risk factor, a technique based on the additivity of attributable risks described by Walker was used (8). Briefly, an estimate is made of the fraction of cardiovascular disease deaths among those with diabetes and a risk factor (doubly exposed) which is attributable to interaction or nonadditivity of rates. This proportion is referred to as the etiologic fraction due to interaction (I). The etiologic fraction due to interaction of diabetes and each risk factor was adjusted for age using the 10-year distribution of person-years in the doubly exposed. Methods outlined by Walker were used to determine 95 per cent confidence limits. Estimates of the etiologic fraction due to interaction close to zero indicate no effect, while estimates closer to unity indicate synergy. Given the limited number of cardiovascular deaths and because each of the risk factors made a similar contribution to the risk of cardiovascular disease mortality in men and women, data for men and women were combined to obtain stable estimates of the proportion of disease among diabetics due to interaction.

Results

At baseline, there were 229 (8.7 per cent) diabetics and 2,391 nondiabetics aged 60–79 years; as previously reported, diabetes was more common in men (11.2 per cent) than in women (6.5 per cent) in this population (9). The distribution of three risk factors, cholesterol, blood pressure, and cigarette smoking, among diabetics and nondiabetics by sex is shown in table 1. The frequency of high cholesterol, high systolic blood pressure, and current cigarette smokers was not significantly different among diabetics and nondiabetics in both sexes.

Age-adjusted cardiovascular disease death rates per 1,000 person-years among diabetics and nondiabetics for each dichotomized risk factor are presented for men and women in table 2. In both sexes, age-adjusted cardiovascular death rates were higher in persons with high cholesterol, in hypertensives, and in current cigarette smokers. Differences in age-adjusted death rates were significant only in men and only for cholesterol and systolic blood pressure. The age-adjusted relative cardiovascular mortality risk was similar to or lower among diabetics than nondiabetics for cholesterol in men and for systolic blood pressure in both men and women. High cholesterol had a slightly higher relative risk in diabetic women than in nondiabetic women. In contrast, the relative risk for smoking is nearly 2.5-fold in diabetic men (2.6, $p < 0.05$) and women (2.4, $p > 0.05$) compared with less than 1.5 in nondiabetics. To obtain stable estimates of the fraction of cardiovascular disease due to interaction among those with diabetes and a risk factor, data for men and women were combined. Estimates of the etiologic fraction and 95 per cent confidence limits are shown in table 3. High cholesterol and systolic blood pressure levels showed no interaction with diabetes ($I = 0.08$ for cholesterol and -0.01 for blood pressure). Current cigarette smoking, however, had a large and significant interaction with diabetes ($I = 0.65$; 95 per cent confidence limits = 0.21, 0.84). In other words, an estimated 65 per cent of the cardiovascular disease deaths among diabetics was due to the interaction of diabetes and cigarette smoking.

Discussion

Previous efforts to assess the relationship of the major cardiovascular risk factors to the excess risk of cardiovascular disease in diabetics have concluded that the effect of these factors is similar in di-

TABLE 1

Distribution of heart disease risk factors, person-years, and cardiovascular (CVD) deaths among Rancho Bernardo, CA, nondiabetics and diabetics aged 60–79 years at entry

	Nondiabetics			Diabetics		
	No. (%)	Person-years	CVD deaths	No. (%)	Person-years	CVD deaths
			Men			
Cholesterol (mg/dl)						
<230	799 (72.2)	6,143.0	86	100 (71.4)	725.3	15
≥230	307 (27.8)	2,301.4	54	40 (28.6)	289.6	6
Systolic blood pressure (mmHg)						
<160	801 (72.4)	6,273.6	73	98 (70.0)	716.8	13
≥160	305 (27.6)	2,170.6	67	42 (30.0)	298.1	8
Cigarette smoking						
Nonsmoker	921 (83.3)	7,051.1	119	119 (85.0)	890.4	15
Current	185 (16.7)	1,393.3	21	21 (15.0)	124.6	6
			Women			
Cholesterol (mg/dl)						
<230	694 (54.0)	5,764.7	31	51 (57.3)	397.1	6
≥230	591 (46.0)	4,860.0	29	38 (42.7)	296.5	6
Systolic blood pressure (mmHg)						
<160	1,006 (78.3)	8,366.1	41	64 (71.9)	509.3	7
≥160	279 (21.7)	2,258.5	19	25 (28.1)	184.3	5
Cigarette smoking						
Nonsmoker	1,031 (80.2)	8,560.7	48	66 (74.2)	535.7	8
Current	254 (19.8)	2,063.9	12	23 (25.8)	157.9	4

abetics and nondiabetics (2, 3). We were unable to show a significant interaction between diabetes and cholesterol or blood pressure. However, in contrast to the results in Framingham (2), Whitehall (3), Washington County (5), and Tecumseh (10), the present study suggests a strong interaction between diabetes and cigarette smoking, such that an estimated 65 per cent of cardiovascular deaths in diabetics was related to an interaction of diabetes and smoking. This association was so strong that it was apparent despite the small number of cardiovascular deaths (n = 10) among diabetics who smoked. Failure to find this interaction previously may relate to the informal comparison of linear coefficients insensitive to detection of synergistic effects, or to the study of younger cohorts for which the relative risk associated with cigarette smoking is stronger than that seen in older nondiabetic adults. Although the assessment of interaction of risk factors and diabetes in this study was based on an additive model, there is evidence of an interaction effect between smoking and diabetes whether an additive or multiplicative model is assumed. Overall, the age-adjusted cardiovascular disease death rates (per 1,000 person-years) were 34.1 for diabetics who smoked, 15.8 for diabetics who did not smoke, 11.9 for nondiabetics who smoked, and 10.3 for nondiabetics who did not smoke. Multiplying the relative risk (RR) associated with smoking alone (RR = 11.9/10.3 = 1.2) and diabetes alone (RR = 15.8/10.3 =

TABLE 2

Cardiovascular disease death rates (per 1,000 person years) among Rancho Bernardo, CA, nondiabetics and diabetics aged 60–79 years at entry, by risk factor levels

	Nondiabetics		Diabetics		Total	
	Rate	No. of deaths	Rate	No. of deaths	Rate	No. of deaths
			Men			
Cholesterol (mg/dl)						
<230	13.3	86	20.4	15	14.1	101
≥230	23.2*	54	24.5	6	23.1*	60
Relative risk	1.7		1.2			
Systolic blood pressure (mmHg)						
<160	11.7	73	18.4	13	12.3	86
≥160	27.6*	67	27.5	8	27.9*	75
Relative risk	2.4		1.5			
Cigarette smoking						
Nonsmoker	16.0	119	16.5	15	16.0	134
Current	17.0	21	43.5*	6	19.7	27
Relative risk	1.1		2.6			
			Women			
Cholesterol (mg/dl)						
<230	5.6	31	15.6	6	6.3	37
≥230	6.1	29	24.9	6	7.0	35
Relative risk	1.1		1.6			
Systolic blood pressure (mmHg)						
<160	5.5	41	19.4	7	6.1	48
≥160	7.3	19	22.8	5	8.5	24
Relative risk	1.3		1.2			
Cigarette smoking						
Nonsmoker	5.5	48	15.2	8	6.0	56
Current	7.6	12	36.5	4	9.1	16
Relative risk	1.4		2.4			

* Significantly higher than for individuals in the normal or nonsmoker category at $p < 0.05$.

1.5) predicts a lower risk (RR = 1.5 × 1.2 = 1.8) than is observed in the presence of both factors (RR = 34.1/10.3 = 3.3) (11).

The mechanism whereby either cigarette smoking or diabetes increases the risk of atherosclerosis is poorly understood. The majority of older diabetics have noninsulin-dependent type II diabetes, and both type II diabetes and cigarette smoking are associated with lower levels of high density lipoprotein cholesterol (12, 13), a lipoprotein that is inversely and independently predictive of cardiovascular disease in nondiabetics (14). Similarly, both smoking and diabetes are associated with alterations in the clotting mechanism that could cause cardiovascular death (15). Unfortunately, high density lipoprotein cholesterol and platelet function were not measured at the baseline visit, and we cannot explore these possible explanations for the observed interaction in this cohort. Finally, our data only address mortality: It is pos-

TABLE 3

Proportion of cardiovascular disease (CVD) deaths attributable to the interaction of diabetes and risk factors among Rancho Bernardo, CA, adults aged 60–79 years at entry

	Fraction of CVD rate due to interaction of diabetes and risk factor		
	Crude	Age-adjusted	95% confidence limits
Cholesterol (mg/dl) ≥230	0.000	0.075	−0.882, 0.545
Systolic blood pressure (mmHg) ≥160	−0.037	−0.007	−0.905, 0.467
Current cigarette smoking	0.577	0.650	0.211, 0.844

sible that smoking precipitates a fatal event in diabetics who have a compromised circulation due to vascular disease.

Although the mechanism for the interaction is obscure, its public health significance is apparent. If the estimated 65 per cent of cardiovascular disease deaths in diabetics attributed to cigarette smoking can be confirmed by others, theoretically the majority of these deaths could be prevented if diabetics did not smoke.

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