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# Abnormal Glucose Metabolism and Pancreatic Cancer Mortality

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**I**N THE UNITED STATES, PANCREATIC cancer is the fifth most common cause of death due to cancer.<sup>1</sup> Because it is difficult to diagnose and tumors are usually detected after they have metastasized,<sup>2</sup> the prognosis for pancreatic cancer is poor. Therefore, identification of risk factors amenable to modification could have a marked impact on reducing pancreatic cancer morbidity and mortality.

Apart from age and cigarette smoking, the risk factors for pancreatic cancer are not well established.<sup>2,3</sup> Numerous epidemiologic studies have reported a positive association between diabetes mellitus and pancreatic cancer risk<sup>4</sup>; however, there has been some concern that diabetes may be a consequence, rather than a cause, of this neoplasia.<sup>2-4</sup> Assessment of the relationship between diabetes and pancreatic cancer is further complicated by use of self-reported diabetes, which could result in exposure misclassification. Moreover, heterogeneity among individuals with diabetes in terms of physiologic status (ie, type 1 vs type 2 diabetes), sequelae, and treatment could also confound this relationship.

The study of postload plasma glucose concentration in the absence of self-reported diabetes provides an alternative approach for addressing the possible effect of abnormal glucose metabolism on pancreatic cancer. This approach has

**Context** Previous studies reported an increased risk of pancreatic cancer among persons with diabetes. Few data exist, however, on the association of postload plasma glucose concentration with pancreatic cancer, which could provide insight into the role of abnormal glucose metabolism in the etiology of pancreatic cancer.

**Objective** To determine the independent association between postload plasma glucose concentration and risk of pancreatic cancer mortality among persons without self-reported diabetes.

**Design** Prospective cohort study.

**Setting and Participants** Employees of 84 Chicago-area organizations, with an average age of 40 years at baseline, were screened from 1963 to 1973 and followed up for an average of 25 years. A total of 96 men and 43 women died of pancreatic cancer among 20475 men and 15183 women, respectively.

**Main Outcome Measures** Relationship of pancreatic cancer mortality with postload plasma glucose levels.

**Results** Compared with a postload plasma glucose level of 6.6 mmol/L (119 mg/dL) or less and after adjusting for age, race, cigarette smoking, and body mass index, the relative risks (95% confidence intervals) of pancreatic cancer mortality were 1.65 (1.05-2.60) for postload plasma glucose levels between 6.7 (120) and 8.8 (159) mmol/L (mg/dL); 1.60 (0.95-2.70) for levels between 8.9 (160) and 11.0 (199); and 2.15 (1.22-3.80) for levels of 11.1 (200) or more; *P* for trend = .01. An association appeared to be stronger for men than women. Estimates were only slightly lower after excluding 11 men and 2 women who died of pancreatic cancer during the first 5 years of follow-up. In men only, higher body mass index and serum uric acid concentration also were independently associated with an elevated risk of pancreatic cancer mortality.

**Conclusion** These results suggest that factors associated with abnormal glucose metabolism may play an important role in the etiology of pancreatic cancer.

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the advantage of reducing potential errors inherent in studying self-reported diabetes and allows for a more objective investigation of the biologically plausible hypothesis that excess insulin or related growth factors stimulate pancreatic carcinogenesis.<sup>5-7</sup>

Two previous studies assessed the possible association of postload plasma glucose level with risk of pancreatic cancer mortality. In a study of the Chicago Heart Association Detection Project in Industry (CHA) cohort, involving 12 years of follow-up, only 21 men and 6 women died of pancreatic cancer.<sup>8</sup> Baseline postload plasma glu-

cose concentration was higher among men who died of pancreatic cancer compared with survivors; no difference was observed for women. In the Whitehall Study,<sup>9</sup> postload plasma glu-

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glucose concentration and pancreatic cancer mortality were inversely associated among men with normal glycemic levels. In that study, potential confounding effects of cigarette smoking, body mass index (BMI), and other risk factors were not considered.

We have expanded on the earlier analysis of the CHA cohort<sup>8</sup> by determining the independent association between postload plasma glucose concentration and risk of pancreatic cancer mortality among participants who did not report diabetes at baseline; this analysis included 139 pancreatic cancer deaths after 25 years of follow-up. In addition, we considered the potential confounding effects of age, race, cigarette smoking, BMI, and serum uric acid level. We also assessed the association between self-reported diabetes and pancreatic cancer mortality.

## METHODS

### The Chicago Heart Association Detection Project in Industry Cohort

Detailed methods for recruitment and data collection in CHA were reported previously.<sup>10</sup> Between 1967 and 1973, nearly 75 000 employees of 84 Chicago-area companies and organizations were invited to participate in a large screening program of cardiovascular disease risk. The number of participants screened was 39 573.

In the primary analyses, 888 participants with self-reported diabetes were excluded. We also excluded 2857 participants who at baseline (1) did not have diabetes and did not receive a 50-g oral glucose load, (2) were missing glucose data, (3) did not answer the question on history of diabetes, or (4) had blood drawn more than 65 minutes after the administration of glucose or whose time of blood draw was unknown. Individuals missing data for height, weight, smoking, or education (n=81) or for whom vital status was unknown (n=89) also were excluded. For analyses involving postload glucose, there were 20 475 men and 15 183 women aged 15 to 90 years at baseline. In analyses for diabetes, partici-

pants who reported diabetes at baseline were included.

### Measurement of Postload Plasma Glucose Level and Other Risk Factors

Data were collected using a standard protocol and uniform methods of measurement. Height and weight were measured, and BMI was computed as weight in kilograms divided by height in meters squared. Serum uric acid concentration was determined for all participants except those examined prior to March 1970. A self-administered questionnaire was used to collect demographic data, smoking history, and information on previous medical diagnoses and treatment.

A 50-g oral glucose load was administered without regard to fasting status or time of day. Blood was drawn for measurement of plasma glucose approximately 1 hour after loading. Plasma glucose concentration was determined using the method described by Hoffman.<sup>11</sup> We excluded persons whose blood was drawn more than 65 minutes after the glucose load, because their mean glucose level was more than 0.6 mmol/L (10 mg/dL) lower than that of all other participants.<sup>12</sup>

### Follow-up of Cohort and Identification of Pancreatic Cancer Deaths

Through December 1995, men and women enrolled in the CHA cohort were followed up to determine vital status. Before 1979, deaths were ascertained annually through direct mailings to individuals, submission of records to the Social Security Administration, mailings to employers, and direct telephone or neighborhood contact. After 1979, records were matched periodically to the National Death Index. Death certificates were obtained from state health departments for all decedents. Physicians, blinded to baseline data, coded certificates for underlying and multiple causes of death based on the *International Classification of Diseases, Eighth Revision*, adapted for use in the United States.<sup>13</sup> Deaths due to pancre-

atic cancer were assigned code 157, which excludes islet cell tumors. Pancreatic cancer was listed as the underlying cause of death for 96 men and 43 women among the 35 658 individuals included in the primary analyses. Additionally, 9 men and no women died of pancreatic cancer among participants who reported diabetes at baseline.

### Statistical Analysis

Participants were classified according to 4 postload plasma glucose levels: 6.6 and lower, 6.7-8.8, 8.9-11.0, and 11.1 and higher mmol/L ( $\leq 119$ , 120-159, 160-199, and  $\geq 200$  mg/dL). There are no standard criteria for defining asymptomatic hyperglycemia for a 50-g challenge at 1 hour; however, a cut point of 11.1 mmol/L (200 mg/dL) was used in previous publications of this cohort.<sup>14,15</sup> The next 2 lower categories each represent the range for approximately 1 SD (2.2 mmol/L [40 mg/dL]) and 2 SD lower postload plasma glucose levels, respectively. The reference group is the lowest glucose level. Education was classified as less than high school, high school graduate, or more than high school. Cigarette smoking status was classified as never, past, currently smoking less than 20 cigarettes per day, or at least 20 cigarettes per day. Race was categorized as African American or white/other. Cut points for quartiles of BMI and serum uric acid level were computed for men and women separately.

Person-years of follow-up for each individual were computed as the amount of time from baseline examination date to death date or until December 31, 1995. Sex-specific, age-adjusted relative risks (RRs) and 95% confidence intervals (CIs) were computed using Cox proportional hazards regression. Possible confounding was examined by comparing the prevalence or mean level of covariates across postload plasma glucose categories.

Independent associations of postload plasma glucose levels and other risk factors with pancreatic cancer mortality were determined for men, women, and men and women combined using

**Table 1.** Selected Baseline Characteristics of Men and Women Screened in the Chicago Heart Association Detection Project in Industry

Characteristic	Men (n = 20 475)	Women (n = 15 183)
Age, mean (SD), y	40.0 (12.4)	39.8 (14.1)
Plasma glucose level, mean (SD), mmol/L*	7.4 (2.5)	7.2 (2.3)
Education, %		
Less than high school	19.6	21.0
High school	30.8	49.8
More than high school	49.5	29.2
Smoking, %		
Never	26.5	44.7
Past	29.8	15.8
Current	43.7	39.5
Race, %		
White	90.3	84.1
African American	6.6	13.3
Other	3.1	2.6
Body mass index, mean (SD), kg/m <sup>2</sup>	26.6 (3.7)	24.0 (4.4)
Serum uric acid level, mean (SD), μmol/L†	366.4 (76.1)	265.9 (67.8)

\*To convert glucose from mmol/L to mg/dL, multiply by 18.

†Analysis included 13 889 men and 11 935 women for whom serum uric acid concentration was determined.

proportional hazards regression. The models included age, race, plasma glucose levels, cigarette smoking status, and BMI quartiles. Trend tests were conducted by assigning to each individual the mean value of a risk factor in its category and modeling this as a continuous variable. Because BMI and plasma glucose concentration might be on the same causal pathway, risk of pancreatic cancer mortality associated with glucose level was determined in models excluding BMI; similarly, the association with BMI was determined in models excluding glucose levels. Because serum uric acid concentration was not measured on the 9834 participants examined prior to March 1970, RRs for uric acid were determined in

**Table 2.** Age-Adjusted Relative Risk of Pancreatic Cancer Mortality Associated With Potential Risk Factors in the Chicago Heart Association Detection Project in Industry\*

Risk Factor	Men			Women		
	No. of Deaths	Total Person-Years	Relative Risk (95% CI)	No. of Deaths	Total Person-Years	Relative Risk (95% CI)
Postload plasma glucose level, mmol/L‡						
≤6.6	17	206 782	1.0	13	172 904	1.0
6.7-8.8	37	154 110	1.86 (1.04-3.34)	18	110 952	1.54 (0.74-3.19)
8.9-11.0	24	69 137	2.08 (1.09-3.94)	7	47 338	1.18 (0.46-3.04)
≥11.1	18	31 821	2.84 (1.42-5.68)	5	20 910	1.75 (0.60-5.07)
Education						
Less than high school	26	83 796	1.0	12	71 857	1.0
High school	32	141 957	1.09 (0.65-1.85)	17	177 039	0.88 (0.41-1.88)
More than high school	38	236 096	0.90 (0.54-1.50)	14	103 207	1.41 (0.64-3.12)
Cigarette smoking						
Never	13	126 177	1.0	17	158 542	1.0
Past	36	138 485	2.06 (1.09-3.88)	6	56 197	1.16 (0.46-2.96)
Current, <20/d	11	51 373	2.60 (1.16-5.80)	10	63 360	2.04 (0.93-4.49)
Current, ≥20/d	36	145 814	2.94 (1.56-5.56)	10	74 005	1.73 (0.78-3.82)
Race						
White/other	89	432 113	1.0	40	304 164	1.0
African American	7	29 736	1.51 (0.70-3.26)	3	47 939	0.94 (0.28-3.18)
Body mass index, by quartile‡						
1	10	117 330	1.0	9	88 835	1.0
2	21	116 766	1.76 (0.83-3.74)	6	89 604	0.48 (0.17-1.36)
3	23	115 788	1.68 (0.80-3.53)	16	87 571	1.09 (0.47-2.51)
4	42	111 965	3.04 (1.52-6.08)	12	86 093	0.73 (0.30-1.80)
Serum uric acid level, by quartile§						
1	10	81 224	1.0	10	74 168	1.0
2	9	68 504	1.10 (0.45-2.70)	6	65 841	0.56 (0.20-1.55)
3	21	82 106	2.12 (1.00-4.50)	9	62 447	0.78 (0.31-1.94)
4	30	71 881	3.30 (1.61-6.75)	9	68 964	0.58 (0.23-1.45)

\*Relative risks adjusted for age as a continuous variable using Cox proportional hazards regression. CI indicates confidence interval.

‡To convert glucose from mmol/L to mg/dL, multiply by 18.

‡Cut points for quartiles of body mass index (kg/m<sup>2</sup>) for men were ≤24.128, 24.129-26.292, 26.293-28.630, and ≥28.631; for women, ≤20.977, 20.978-23.240, 23.241-26.156, and ≥26.157.

§Cut points for quartiles of serum uric acid concentration (μmol/L) for men were ≤316, 317-357, 358-411, and ≥412; for women, ≤221, 222-256, 257-298, and ≥299. Analysis included 13 889 men and 11 935 women for whom serum uric acid level was determined.

separate models. Interactions with sex were evaluated using cross-product terms with categories of postload plasma glucose level, BMI, and serum uric acid concentration. Analyses were performed using PROC PHREG of the SAS-PC statistical software package (SAS Institute Inc, Cary, NC).

## RESULTS

TABLE 1 shows baseline characteristics by sex. Average age and concentration of postload plasma glucose were similar in men and women. A higher percentage of men than women completed more than a high school education. At baseline, more than 39% of these men and women were current smokers; among smokers, men smoked an average of 22 cigarettes per day and women, 17. The cohort was predominantly white. Body mass index and serum uric acid concentration were higher for men than women. Over the average 25 years of follow-up, the 35658 persons contributed 813952 total person-years.

Sex-specific, age-adjusted RRs for postload plasma glucose levels and other potential risk factors are shown in TABLE 2. For men, postload plasma glucose level was significantly and

positively associated with pancreatic cancer mortality ( $P$  for trend = .004). No association with education was observed. Past cigarette smokers had a 2-fold greater risk of pancreatic cancer mortality than those who had never smoked, and among current smokers, risk increased with number of cigarettes smoked. Risk was slightly but not significantly higher for African American men than for other men. Pancreatic cancer mortality was significantly and positively associated with both BMI and serum uric acid concentration ( $P$  for trend < .001 for both).

For women, there was a positive association between postload plasma glucose level and pancreatic cancer mortality; however, this association was not statistically significant ( $P$  for trend = .39). Current cigarette smokers were at a higher risk than women who had never smoked. There was no association for education, race, BMI, or serum uric acid concentration.

TABLE 3 shows the variation for several potential confounding factors across strata of postload plasma glucose level. For men and women, mean age, BMI, and serum uric acid concentration were higher with higher levels of plasma glucose. Across glucose

groups, the percentage of individuals who did not have serum uric acid level assessed at baseline ranged from 19% to 22% and from 29% to 34% for women and men, respectively. Across increasing strata of postload plasma glucose level, the proportion of participants with less than a high school education was higher, and the proportion of African Americans was lower.

The multivariate-adjusted RRs of pancreatic cancer mortality increased with higher levels of postload plasma glucose concentration ( $P$  for trend = .01) for men and women combined (TABLE 4). Although this association appeared to be stronger for men than for women, there was no evidence of statistically significant effect modification by sex ( $P$  for interaction = .64). After excluding BMI in the model, the RR of pancreatic cancer for the highest category of postload plasma glucose was 2.35 ( $P$  for trend = .005). Relative risks also were computed after exclusion of 11 men and 2 women who died of pancreatic cancer within 5 years of baseline. Compared with participants with glucose levels less than or equal to 6.6 mmol/L (119 mg/dL), RRs of pancreatic cancer mortality across the 3 groups of successively higher glucose levels were 1.59

**Table 3.** Selected Baseline Characteristics, by Glycemia Status

Characteristic	Postload Plasma Glucose Level, mmol/L*							
	Men (n = 20 475)				Women (n = 15 183)			
	≤6.6	6.7-8.8	8.9-11.0	≥11.1	≤6.6	6.7-8.8	8.9-11.0	≥11.1
No.	8847	6838	3184	1606	7311	4799	2101	972
Mean age, y	34.9	41.6	46.1	49.7	34.6	42.3	46.9	51.1
Mean postload plasma glucose level, mmol/L	5.5	7.6	9.8	13.2	5.4	7.6	9.8	12.9
Education, %								
Less than high school	16.7	20.4	22.1	27.8	16.3	23.1	27.5	31.6
High school	29.8	31.4	31.7	32.3	50.9	49.9	48.3	44.6
More than high school	53.5	48.2	46.2	39.9	32.8	26.9	24.3	23.8
Cigarette smoking, %								
Never	28.2	26.3	24.7	21.5	42.2	46.7	48.6	46.0
Past	26.2	31.7	33.1	34.7	16.7	15.2	14.8	13.6
Current	45.6	42.0	42.2	43.8	41.1	38.1	36.6	40.4
Race, %								
White/other	91.9	93.6	95.6	96.3	81.1	90.0	94.0	96.7
African American	8.1	6.4	4.4	3.7	18.9	10.0	6.0	3.3
Mean body mass index, kg/m <sup>2</sup>	25.9	26.7	27.3	27.9	23.3	24.4	25.0	25.5
Mean serum uric acid level, μmol/L†	356.9	368.8	378.3	384.8	251.6	270.0	285.5	305.7

\*To convert glucose from mmol/L to mg/dL, multiply by 18.

†Includes 13 889 men and 11 935 women for whom serum uric acid concentration was determined.

(95% CI, 1.00-2.54), 1.40 (95% CI, 0.81-2.42), and 1.97 (95% CI, 1.08-3.57), respectively (*P* for trend=.05). Past and current cigarette smoking were also independently associated with risk of pancreatic cancer mortality. There was a statistically significant interaction between BMI and sex for risk of pancreatic cancer mortality (*P* for interaction=.02). Relative risks of pancreatic cancer for individuals in the highest vs lowest BMI quartiles were 3.1 for men and 0.8 for women. In models excluding plasma glucose level, the corresponding RRs were 3.2 (*P* for trend <.001) for men and 0.8 (*P* for trend=.99) for women. Similar to BMI, serum uric acid concentration was also strongly associated with risk of pancreatic cancer mortality in men but not in women; the test for interaction be-

tween sex and serum uric acid level was statistically significant (*P* for interaction=.04).

For men who reported diabetes at baseline compared with those who did not, the age-adjusted RR of pancreatic cancer mortality was 2.48 (95% CI, 1.25-4.49), whereas the RR was 4.51 (95% CI, 1.97-10.33) when compared with those whose postload plasma glucose level was less than or equal to 6.6 mmol/L (119 mg/dL). There were no pancreatic cancer deaths among women who reported diabetes.

**COMMENT**

In this study, there was a positive association between postload plasma glucose level and risk of pancreatic cancer mortality. Risk was 2.2-fold higher for participants whose postload plasma

glucose level was at least 11.1 mmol/L (200 mg/dL) at baseline compared with those whose level was less than or equal to 6.6 mmol/L (119 mg/dL). This association was independent of other known and suspected pancreatic cancer risk factors (ie, age, race, cigarette smoking, BMI, serum uric acid concentration) and was essentially unchanged after exclusion of subjects who died due to this malignancy within the first 5 years of follow-up. Consistent with other studies,<sup>2,3</sup> our findings also indicate that cigarette smoking was related to pancreatic cancer mortality. For men, but not for women, BMI and serum uric acid concentration were significantly and positively associated with pancreatic cancer mortality even after adjustment for postload plasma glucose level. These sex differences should be interpreted cautiously, given the small number of women who died of pancreatic cancer.

An association between diabetes and pancreatic cancer has been shown in many studies. In some cases, diabetes appears to be a clinical manifestation of occult pancreatic cancer.<sup>4</sup> Indeed, a high proportion of pancreatic cancer patients present with impaired glucose tolerance or diabetes.<sup>16,17</sup> Among some patients with pancreatic cancer and peripheral insulin resistance, removal of the tumor improved glucose metabolism,<sup>18</sup> providing evidence that altered glucose metabolism may be a result of the tumor. Conversely, a considerable amount of data suggests that diabetes may be a predisposing factor in pancreatic carcinogenesis. In a meta-analysis including more than 20 epidemiologic studies, the pooled RR of pancreatic cancer for those whose diabetes was diagnosed at least 1 year prior to either diagnosis of pancreatic cancer or to pancreatic cancer death was 2.1 (95% CI, 1.6-2.8). In an analysis requiring 5 years' duration of diabetes, this association was similar (RR=2.0; 95% CI, 1.2-3.2). Recently, 2 large cohort studies examined the association of diabetes for up to 10 or more years' duration with subsequent pancreatic cancer risk.<sup>19,20</sup> In both studies, diabetes was positively associ-

**Table 4.** Multivariable-Adjusted Relative Risk of Pancreatic Cancer Mortality in the Chicago Heart Association Detection Project in Industry\*

Risk Factor	Relative Risk (95% CI)		
	Men	Women	Men and Women
Postload plasma glucose level, mmol/L			
≤6.6	1.0	1.0	1.0
6.7-8.8	1.74 (0.97-3.12)	1.56 (0.75-3.25)	1.65 (1.05-2.60)
8.9-11.0	1.85 (0.97-3.51)	1.17 (0.45-3.04)	1.60 (0.95-2.70)
≥11.1	2.39 (1.20-4.79)	1.68 (0.57-4.89)	2.15 (1.22-3.80)
<i>P</i> for trend†	.02	.43	.01
Cigarette smoking‡			
Never	1.0	1.0	1.0
Past	2.04 (1.08-3.84)	1.19 (0.47-3.02)	1.70 (1.04-2.75)
Current, <20/d	2.64 (1.18-5.94)	2.04 (0.92-4.51)	2.31 (1.32-4.07)
Current, ≥20/d	3.06 (1.62-5.81)	1.70 (0.76-3.77)	2.44 (1.52-3.93)
Body mass index, by quartiles§			
1	1.0	1.0	...
2	1.84 (0.87-3.92)	0.50 (0.18-1.41)	...
3	1.71 (0.81-3.61)	1.14 (0.49-2.65)	...
4	3.07 (1.53-6.15)	0.79 (0.32-1.95)	...
<i>P</i> for trend†	<.001	.95	...
Serum uric acid level, by quartile§			
1	1.0	1.0	...
2	1.04 (0.42-2.57)	0.56 (0.20-1.57)	...
3	1.93 (0.90-4.16)	0.75 (0.30-1.88)	...
4	2.82 (1.34-5.93)	0.55 (0.21-1.44)	...
<i>P</i> for trend†	.001	.30	...

\*Relative risk adjusted for age (continuous years), race (African American vs other), categories of postload plasma glucose concentration, cigarette smoking status, and quartiles of body mass index. For men and women combined, the model also included sex and the interaction term for sex and quartiles of body mass index. CI indicates confidence interval. To convert glucose from mmol/L to mg/dL, multiply by 18.

†*P* for trend was computed by modeling the within-category mean level of each risk factor as a continuous variable. ‡No *P* value is included for smoking because smoking categories cannot be ordered in the same way as other variables due to the inclusion of past smoking as a separate category.

§See Table 2 for cut points of quartiles for body mass index and serum uric acid. Ellipses indicate there is a statistically significant interaction between sex and each of these variables; combining the sex groups is not appropriate.

||Relative risks were adjusted for the same covariates listed above. This analysis included 13 889 men and 11 935 women for whom serum uric acid concentration was determined.

ated with risk, and this association was only marginally lower when restricted to longer duration of follow-up (ie,  $\geq 10$  years). In our study, we observed a 2.5-fold greater risk of pancreatic cancer mortality among men who reported diabetes compared with those without diabetes. Overall, it appears that diabetes could be both an early manifestation of pancreatic cancer as well as an etiologic factor.

In the earlier analysis of the CHA cohort,<sup>8</sup> there were too few pancreatic cancer deaths to examine the association of postload plasma glucose concentration with risk of this malignancy. In the only other cohort study to assess this association,<sup>9</sup> participants were classified as diabetic (ie, 2-hour postload plasma glucose level of  $\geq 11.1$  mmol/L [ $\geq 200$  mg/dL]), impaired glucose tolerant (ie, 5.3-11.0 mmol/L [96-199 mg/dL]), or normoglycemic (ie,  $\leq 5.2$  mmol/L [ $\leq 95$  mg/dL]). Both diabetes and impaired glucose tolerance were positively associated with pancreatic cancer mortality; however, these relationships were based on 4 and 8 deaths, respectively. For men with normal glycemic levels, among whom there were only 56 pancreatic cancer deaths, postload plasma glucose appeared to be inversely associated with pancreatic cancer mortality. Reasons for inconsistencies between results of the Whitehall Study<sup>9</sup> and the study described here are unclear. Results of the Whitehall Study may not be directly comparable to ours because, in that study, glucose was measured in capillary blood samples 2 hours after a 75-g glucose challenge among participants who had fasted. Furthermore, potential covariates such as BMI and cigarette smoking were not considered.

An association between obesity and pancreatic cancer has been shown in some<sup>21-23</sup> but not all studies.<sup>24-27</sup> Silverman et al<sup>28</sup> reported results from a large case-control study, in which pancreatic cancer risk was 50% greater for women in the highest quartile of BMI (ie,  $\geq 27.2$  kg/m<sup>2.5</sup>) and 60% greater for men in the highest quartile (ie,  $> 34.4$  kg/m<sup>2</sup>), compared with those women

and men in the lowest quartiles. In a more recent analysis of that study, a positive trend in risk of pancreatic cancer with higher BMI was noted only for individuals without diabetes.<sup>29</sup> In our study, men in the highest quartile of BMI (ie,  $\geq 28.6$  kg/m<sup>2</sup>) had a 3-fold greater risk of pancreatic cancer mortality compared with men in the lowest quartile, and there was no association in women.

Ames et al<sup>30</sup> hypothesized that uric acid might reduce oxygen toxicity and, therefore, provide an antioxidant defense mechanism against carcinogenesis. Few epidemiologic studies have investigated the association between serum uric acid concentration and cancer risk.<sup>31-36</sup> The findings from these studies are inconsistent, with some showing inverse associations<sup>31,35</sup> and others positive associations with either total or site-specific cancer incidence or mortality.<sup>32,34,36</sup> To our knowledge, there have been no previous studies of the relationship between serum uric acid concentration and pancreatic cancer risk. As discussed below, a positive association of serum uric acid concentration with risk of pancreatic cancer could reflect associated abnormalities of glucose metabolism. Hyperinsulinemia has been related to decreased renal clearance of uric acid.<sup>37</sup>

The biological mechanisms underlying the associations of hyperglycemia, greater BMI, and hyperuricemia with pancreatic cancer are unclear, but several intriguing possibilities exist. Elevated postload plasma glucose, BMI, and serum uric acid concentration have been associated with impaired glucose tolerance, insulin resistance, and the resultant hyperinsulinemia.<sup>38</sup> Exocrine cells of the pancreas, which give rise to most fatal pancreatic cancers,<sup>39</sup> are exposed to unusually high concentrations of insulin in the hyperinsulinemic state because their blood supply passes through the islet cell region.<sup>40</sup> Insulin has been shown to have a direct, dose-dependent, growth-promoting effect on pancreatic cancer cell lines in vitro.<sup>6</sup> Moreover, high concentrations of insulin are able to bind to and activate the insulin-like growth factor 1 (IGF-1)

receptor.<sup>41</sup> Activation of this receptor is known to have growth-promoting effects, including modulation of cell cycle progression.<sup>41</sup> Excess insulin also could affect development of pancreatic cancer indirectly, through down-regulation of insulin-like growth factor-binding protein 1 (IGFBP-1).<sup>42,43</sup> Reduced concentrations of IGFBP-1 could result in an increase in the bioavailable fraction of IGF-1, which has been shown to stimulate pancreatic cell proliferation in vitro.<sup>44</sup>

The strengths of this study include mortality follow-up for approximately 25 years and availability of data on response to a glucose challenge and on other potential risk factors from a large number of men and women without self-reported diabetes. We also recognize potential limitations. First, the ability of a single oral glucose tolerance test to characterize an individual's glycemic level is relatively low.<sup>45,46</sup> Therefore, a single measurement of postload plasma glucose, particularly one in which there was variation in the timing of blood collection, may result in misclassification, producing a conservative estimate of the association of glucose level with cancer risk. Misclassification also may have occurred for cause of death, because pancreatic cancer mortality was determined by death certificate; this malignancy is often misreported on death certificates.<sup>47</sup>

In conclusion, this study provides evidence for a positive, dose-response relationship between postload glycemia and pancreatic cancer mortality among individuals who did not report diabetes at baseline. Moreover, in men, BMI and serum uric acid concentration, factors also linked to abnormal glucose metabolism, were strongly and independently associated with pancreatic cancer mortality. Because the prevalence of type 2 diabetes and obesity, including childhood obesity, are steadily increasing,<sup>48-50</sup> identification of a potential causal association between hyperglycemia and pancreatic cancer could have important implications on the preventable fraction and future mortality due to this malignancy.

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