Insulin, Glucose, Insulin Resistance, and Pancreatic Cancer in Male Smokers

Rachael Z. Stolzenberg-Solomon, PhD
Barry I. Graubard, PhD
Suresh Chari, MD
Paul Limburg, MD
Philip R. Taylor, MD, ScD
Jarmo Virtamo, MD
Demetrius Albanes, MD

Context Obesity, diabetes mellitus, and glucose intolerance have been associated with increased pancreatic cancer risk; however, prediagnostic serum insulin concentration has not been evaluated as a predictor of this malignancy.

Objective To investigate whether prediagnostic fasting glucose and insulin concentrations and insulin resistance are associated with subsequent incidence of exocrine pancreatic cancer in a cohort of male smokers.

Design, Setting, and Participants A case-cohort prospective study within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (1985-1988) cohort of 29 133 male Finnish smokers ages 50 to 69 years. The study included 400 randomly sampled subcohort control participants and 169 incident pancreatic cancer cases that occurred after the fifth year of follow-up. All participants were followed up through December 2001 (up to 16.7 years of follow-up).

Main Outcome Measures Incident exocrine pancreatic cancer identified from the Finnish Cancer Registry.

Results After adjusting for age, smoking, and body mass index, higher baseline fasting serum concentrations of glucose, insulin, and insulin resistance were positively associated with pancreatic cancer. The presence of biochemically defined diabetes mellitus (glucose, ≥126 mg/dL [≥6.99 mmol/L]) and insulin concentration in the highest vs lowest quartile both showed a significant 2-fold increased risk (hazard ratio [HR], 2.13; 95% confidence interval [CI], 1.04-4.35; and HR, 2.01; 95% CI, 1.03-3.93; respectively). There were significant interactions for all the biomarker exposures by follow-up time, such that the positive associations were stronger among the cases that occurred more than 10 years after baseline (highest vs lowest quartile: glucose, HR, 2.16; 95% CI, 1.05-4.42; *P* for trend = .02; insulin, HR, 2.90; 95% CI, 1.22-6.92; *P* for trend = .005; and insulin resistance, HR, 2.71; 95% CI, 1.19-6.18; *P* for trend = .006).

Conclusions These results support the hypothesis that exposure to higher insulin concentrations and insulin resistance predicts the risk of exocrine pancreatic cancer.

JAMA. 2005;294:2872-2878 www.jama.com

Based on the findings from several retrospective and prospective observational studies, type 2 diabetes mellitus and glucose intolerance are fairly consistent, albeit somewhat controversial, risk factors for pancreatic cancer.[1-5] This is because it has been unresolved whether diabetes mellitus is etiologically involved in pancreatic carcinogenesis or the result of subclinical malignancy. One biologically plausible mechanism whereby type 2 diabetes mellitus may be related to pancreatic carcinogenesis is through the growth-regulatory effects of insulin.[6] Experimental studies show that insulin has growth promoting and mitogenic effects on pancreatic cancer cells[7] and patients with type 2 diabetes mellitus are known to exhibit hyperinsulinemia during the early stages of their disease.[8] The proposed hyperinsulinemia hypothesis is also indirectly supported by several studies of positive associations between obesity, lack of physical activity, and pancreatic cancer.[9-14]

We previously reported a significant 2-fold increased risk between self-reported diabetes mellitus and pancreatic cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study of male smokers.[14] In this case-cohort study, we evaluated whether fasting serum insulin and glucose concentrations were prospectively associated with risk for incident pancreatic cancer. To reduce the potential influence of subclinical cancer on insulin and glucose concentrations, only participants alive and without clinical evidence of cancer during the first 5 years of cohort follow-up were included.

See also Patient Page.

METHODS

Study Population

The ATBC Study was a double-blind, placebo-controlled, 2×2 factorial design, primary prevention trial that tested

Author Affiliations: Nutritional Epidemiology Branch (Drs Stolzenberg-Solomon and Albanes), Biostatistics Branch (Dr Graubard), and Genetic Epidemiology Branch (Dr Taylor), Division of Cancer Epidemiology and Genetics, National Cancer Institute, Department of Health and Human Services, Rockville, Md; Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minn (Drs Chari and Limburg); and Department of Epidemiology and Health Promotion, National Public Health Institute, Helsinki, Finland (Dr Virtamo).
Corresponding Author: Rachael Z. Stolzenberg-Solomon, PhD, Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Department of Health and Human Services, 6120 Executive Blvd, Suite 320, Rockville, MD 20852 (rs221z@nih.gov).

 ©2005 American Medical Association. All rights reserved.

Downloaded from www.jama.com at National Institute of Hlth, on January 18, 2006

whether α-tocopherol or beta carotene could reduce the incidence of cancer among male smokers. Study rationale, design, and methods have been previously described.[15] Between 1985 and 1988, 29 133 eligible men in southwestern Finland aged 50 to 69 years who smoked at least 5 cigarettes per day were randomized to receive active supplements (50 mg/d of α-tocopherol, 20 mg/d of beta carotene, or both) or placebo. Men were excluded from the study if they had a history of malignancy other than nonmelanoma cancer of the skin or carcinoma in situ, severe angina on exertion, chronic renal insufficiency, liver cirrhosis, chronic alcoholism, or other medical conditions that might limit long-term participation; or if they were receiving anticoagulant therapy or used supplements containing vitamin E (>20 mg/d), vitamin A (>20 000 IU/d), or beta carotene (>6 mg/d). All participants provided written informed consent before randomization into the study. The study was approved by the institutional review boards of both the National Public Health Institute, Helsinki, Finland, and the US National Cancer Institute, Bethesda, Md.

Participants completed questionnaires on general background characteristics, including medical, smoking, dietary, and physical activity history during their prerandomization baseline visit.[15] Trained study staff measured height and weight at baseline using standard methods. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Diet was assessed with a validated self-administered dietary history questionnaire that determined the frequency of consumption and usual portion size of 276 food items during the past year, using a color picture booklet as a guide for portion size.[16]

Selection of Case and Control Participants

To reduce the potential influence of subclinical cancer on insulin and glucose concentrations, all participants were alive and without clinical evidence of cancer during the first 5 years of cohort follow-up. Cases of pancreatic cancer occurring after their fifth year of cohort follow-up through December 2001 were identified from the Finnish Cancer Registry, which provides almost 100% case ascertainment in Finland.[17] As their etiology may be different from the exocrine tumors, islet cell carcinomas (*International Classification of Diseases, Ninth Revision* [*ICD-9*] code 157.4 and *ICD, 10th Revision* [*ICD-10*] code C254) were excluded. During the follow-up period, 169 exocrine pancreatic cancer cases (*ICD-9* code 157 and *ICD-10* code C25) were confirmed. We selected a random sample of 400 participants among all eligible cohort members alive without a cancer diagnosis as of 5 years of follow-up or subcohort control participants as the comparison group. The interval between serum collection and follow-up was up to 16.7 years (median follow-up time for diagnosis, 13.8 years).

Biomarkers

At their prerandomization visit, study participants had a venipuncture for serum after an overnight fast and serum was stored in the dark at –70°C. Frozen baseline serum samples were assayed for insulin and glucose concentration using the 2-site immunoenzymatic assay performed on an automated immunoassay system (Access, Beckman Instruments, Chaska, Minn) and a chemical analyzer and the hexokinase reagent (Hitachi 912 Chemistry Analyzer, Boehringer Mannheim, Indianapolis, Ind), respectively. Laboratory personnel were blinded to case and control sample status. Insulin resistance was estimated by using the Homeostasis Model Assessment–Insulin Resistance (HOMA-IR) formula {[fasting insulin (mIU/L) × fasting glucose (mmol/L)]/22.5}.[18]

In 2000, 93 participants with incident pancreatic cancer that occurred through 1997 and the 400 subcohort control participants had glucose and insulin values measured. In 2004, we measured glucose and insulin values at the same laboratory on an additional 76 case participants that occurred through 2001 to increase the sample size and power of the study. Blinded replicate quality control phantom samples from a pooled sample were placed randomly in all batches. Among the samples run in 2000, quality controls were 10% of each batch and had coefficient of variation percentages of less than 5% for both glucose and insulin. For the samples run in 2004, 27% of the samples tested were from our quality control pool. Unthawed samples from the same pooled quality control serum used in the batches run in 2000 were randomly placed throughout the 2004 study samples. Unthawed vials from 8 participants from the ATBC study who were control participants in the original study were also randomly placed throughout the study samples. Using a nested components of variance analysis, with logarithmically transformed quality control measurements across all batches,[19] the estimated overall (intrabatch and interbatch) coefficient of variation percentages of the assays for glucose and insulin were 2.46% and 4.83%, respectively. The interbatch coefficient of variation percentage for the repeated measurements on the 8 control participants was 2.22% for glucose and 4.25% for insulin. Given the low coefficient of variation percentage calculated from our quality control study, we were confident that there were no differences in the measurements of glucose or insulin measured at the 2 times.

Statistical Analysis

We compared the distribution of the characteristics of the case and subcohort control participants for continuous variables using the Wilcoxon rank sum test and for categorical variables using asymptotic χ^2 test. Generalized linear models and logistic regression adjusted for age, continuous factors, and proportions, respectively, were used to calculate means and 95% confidence intervals (CIs) of the cohort characteristics among the control participants by fasting serum insulin quartile to help identify potential confounders. SAS software version 8.2 (SAS Institute Inc, Cary, NC) was used for these analyses.

©2005 American Medical Association. All rights reserved.

Downloaded from www.jama.com at National Institute of Hlth, on January 18, 2006

To account for the differential sample rates of the case and subcohort control participants in a survival analysis, we used SUDAAN software version 9.0 (Research Triangle Institute, Research Triangle Park, NC) to perform weighted Cox proportional hazards regression analyses in which each participant's weight was the inverse of their sample fraction. Case participants were given weights of 1 because they were sampled with certainty and the subcohort control participants had weights of 61.77 (24 708/400). By chance, as pancreatic cancer is relatively rare, none of the subcohort sample developed pancreatic cancer during follow-up. In the survival analysis, follow-up time was used as the underlying time metric to calculate hazard ratios (HRs) and 95% CIs. Using age as an underlying time metric in the survival analysis to more tightly control for age conferred similar HRs; however, we chose to use the follow-up time metric to evaluate the effects of latent disease with stratified analyses by follow-up time. Serum glucose, insulin, and insulin resistance were categorized in quartiles based on the distribution of the control participants. Biochemically defined diabetes mellitus was defined as a glucose concentration of at least 126 mg/dL (≥6.99 mmol/L). Dose response trends were tested using a score variable based on the median value of each category. Multivariable models were developed for serum glucose, insulin, and insulin resistance by individually adding potential confounders into the model, which included baseline age at randomization; height, weight, and BMI; smoking history (years of smoking, cigarettes smoked per day, and pack-years); urban living; education; self-reported medical history of gallstones, pancreatitis, peptic and duodenal ulcers, and diabetes mellitus; trial intervention group (α-tocopherol or beta carotene); occupational and leisure activity; and dietary energy, energy-adjusted protein, fat, saturated fat, carbohydrate, fiber, starch, free sugars, sucrose, zinc, calcium, and folate intake, and alcohol consumption. Although none of the smoking variables were confounders of our associations in our smoker population, smoking duration was included in our models because smoking is a putative risk factor for pancreatic cancer. Other variables were included in the final model if they were associated with both the risk factor and the disease, changed the risk estimate to at least 10%, had $P \leq .20$ in the full model, and/or increased the precision of the risk estimate. The final multivariable models included continuous variables for age, years of smoking, and BMI.

We used a case-cohort design rather than a matched-nested, case-control design because it allows use of time-to-disease data and provides an unbiased estimate of the HR in our population. It also enabled us to examine interactions by time, which was one of our study goals. Because all participants in our study were smokers, the potentially relevant matching factors for which our cases differed from the subcohort control participants were age and smoking duration (years of smoking). We controlled for these differences by including both variables as covariates in the Cox proportional hazards regression analysis, as one would in a cohort study. This model adjustment approach worked especially well for our analysis because there was substantial overlap between our case and subcohort control participants in the distributions of these variables.

Effect modification of glucose, insulin, and insulin resistance by BMI, smoking intensity and duration, alcohol intake, trial intervention group, and follow-up time was tested through cross-product terms in multivariable models by using the serum biomarkers trend variables and dichotomized BMI, smoking, alcohol (based on the median split), and follow-up time from baseline (<8 years and ≥8, 10, 12, and 14 years, respectively). Analyses stratified by follow-up time were also conducted. All statistical tests were 2-sided and considered statistically significant at $P \leq .05$.

RESULTS

Selected characteristics of the case and subcohort control participants are shown in TABLE 1. Compared with the subcohort control participants, case participants were older ($P < .001$), had smoked for more years ($P = .002$), tended to have higher fasting glucose concentrations ($P = .06$), and more often reported a history of diabetes mellitus ($P = .07$).

TABLE 2 shows the age-adjusted means and 95% CIs of selected baseline characteristics of the subcohort control participants, according to quartile of fasting serum insulin concentration. With increasing quartiles of fasting serum insulin concentration, the mean levels of serum glucose, insulin resistance, weight, BMI, protein, and total and saturated fat intake, and the proportion of participants reporting a history of diabetes mellitus all increased (all $P \leq .02$), although the proportion of participants reporting living in a city ($P = .04$) and leisure activity of exercising to keep fit decreased ($P = .02$).

After adjustment for age, years of smoking, and BMI, higher concentrations of glucose, insulin, and insulin resistance tended to show positive dose-response associations with pancreatic cancer (all P for trend $\leq .05$) (TABLE 3). Biochemically defined diabetes mellitus and the highest insulin quartile demonstrated significant 2-fold increased risks. There were significant interactions between quartile-categorized glucose, insulin, and insulin resistance and pancreatic cancer by follow-up time, such that risks were greater among the cases that occurred with longer follow-up time (FIGURE). There was no interaction of the association between glucose, insulin, or insulin resistance and pancreatic cancer by BMI, smoking intensity and duration, alcohol intake, or trial intervention group, or interaction of the association for biochemically defined diabetes mellitus by follow-up time. Exclusion of participants who fasted less than 12 hours before blood collection and self-reported diabetes mellitus did not substantially change our results.

COMMENT

To our knowledge, this is the first study to show that higher prediagnostic fast-

 ©2005 American Medical Association. All rights reserved.

Downloaded from www.jama.com at National Institute of Hlth, on January 18, 2006

ing serum insulin and insulin resistance are associated with an increased risk for pancreatic cancer. The dose-response nature of the association, the 2-fold increase in risk of biochemically defined diabetes mellitus, and the substantially enhanced risk observed with longer follow-up support the veracity of our results.

Both the direction and magnitude of our findings confirm the positive association between higher glucose concentrations, biochemically defined diabetes mellitus, and pancreatic cancer reported in other prospective studies.[2-5] The Paris Prospective Study (all men)[5] with 17 years of follow-up and the Chicago Heart Association Detection Project in Industry cohort[3] and Whitehall study (all men)[4] both with 25 years of follow-up showed 2- to 5-fold increased relative risks for postload glucose-defined diabetes mellitus (glucose, ≥200 mg/dL [≥11.1 mmol/L]) and pancreatic cancer mortality.[3-5] The Chicago Heart Association study[3] demonstrated a significant positive linear association for postload glucose among men that corresponded with significant increased cancer risk with increasing BMI and serum uric acid levels; however, no association for these factors were observed in women. The Korean Cancer Prevention Study (KCPS), with 10 years of follow-up, showed a similar 1.5- to 2-fold increased pancreatic cancer risk with increased fasting serum glucose and biochemically defined diabetes mellitus (fasting glucose, ≥126 mg/dL [≥6.99 mmol/L]) for both men and women, and for both incident and fatal disease.[2] The majority of participants in KCPS are considered lean by western standards and the associations between fasting glucose and pancreatic cancer were unchanged after controlling for BMI and did not vary by BMI.[2] Body mass index is not associated with a greater pancreatic cancer risk in the ATBC study cohort despite the fact that approximately half of the population was overweight.[14] In addition, in our study, the glucose, insulin, and insulin resistance associations became stronger after controlling for BMI, and similar to KCPS, BMI did not modify our associations. Smokers tend to be more insulin resistant and have higher insulin levels compared with nonsmokers, independent of obesity.[20] In addition to BMI, our findings along with those of KCPS suggest that other factors independent of BMI may also contribute to the diabetes mellitus that is associated with pancreatic cancer.

The associations we observed for diabetes mellitus, insulin concentration, and insulin resistance are unlikely a consequence of pancreatic cancer, given our prospective study design that excluded

Table 1. Baseline Characteristics of Case and Subcohort Control Participants*

Characteristics	Case Participants (n = 169)	Subcohort Control Participants (n = 400)	*P* Value†
Demographics			
Age, y	58 (54-61)	56 (52-60)	<.001
Height, cm	174 (171-179)	174 (170-178)	.43
Weight, kg	78.8 (69.9-87.3)	79.5 (70.9-87.8)	.55
BMI	25.6 (23.5-28.3)	26.2 (23.9-28.9)	.25
Primary school education or less, No. (%)	125 (74.0)	314 (78.5)	.26
Living in a city, No. (%)	81 (47.9)	183 (45.8)	.63
Clinical characteristics			
Glucose, mg/dL	101.0 (94.0-109.0)	99.0 (93.0-107.0)	.06
Biochemically defined diabetes mellitus (glucose ≥126 mg/dL), No. (%)	16 (9.5)	24 (6.0)	.14
Insulin, μIU/mL	4.40 (2.80-6.50)	4.10 (2.75-6.10)	.35
Insulin resistance (HOMA-IR)	1.07 (0.67-1.65)	1.02 (0.69-1.53)	.28
Medical history			
History of diabetes mellitus, No. (%)	14 (8.3)	18 (4.5)	.07
History of pancreatitis, No. (%)	4 (2.4)	5 (1.3)	.33
Smoking history			
Total cigarettes/d	20 (15-25)	20 (15-25)	.47
Years of smoking	38 (32-43)	35 (30-40)	.002
Dietary intake per d‡			
Energy, kcal	2730 (2321-3194)	2721 (2314-3256)	.86
Fat, g	102.0 (94.3-113.4)	102.2 (92.8-111.4)	.24
Saturated fat, g	54.2 (47.0-63.9)	53.1 (44.4-61.6)	.15
Carbohydrate, g	302 (272-327)	292 (263-330)	.68
Sucrose, g	51.8 (36.0-71.8)	57.2 (40.3-73.7)	.10
Fiber, mg	24.5 (20.9-30.9)	25.3 (18.6-31.3)	.46
Alcohol, g	10.1 (2.42-26.3)	11.4 (2.2-26.9)	.65
Physical activity, No. (%)§			
Occupational			
Sedentary	28 (16.6)	54 (13.5)	.13
Light/moderate	57 (33.7)	161 (40.2)	
Heavy	9 (5.3)	36 (9.0)	
Nonworking	75 (44.4)	149 (37.2)	
Leisure			
Sedentary	72 (42.9)	172 (43.0)	.99
Light, moderate	86 (51.2)	204 (51.0)	
Exercise to keep fit	10 (6.0)	24 (6.0)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HOMA-IR, Homeostasis Model Assessment–Insulin Resistance.

SI conversions: To convert glucose to mmol/L, multiply by 0.0555; insulin to pmol/L, multiply by 6.945.

*Data are presented as median (interquartile range) unless otherwise specified.

†Categorical variables (primary school education, living in a city, biochemically defined diabetes mellitus, history of diabetes mellitus and pancreatitis, and physical activity) are based on χ^2 or Fisher exact test and continuous variables (age, height, weight, BMI, glucose, insulin, insulin resistance, smoking history, and dietary intake) are based on Wilcoxon rank sum test.

‡Dietary intake analysis was based on 166 cases and 383 control participants.

§Self-reported physical activity during the past 12 months. Occupational activities included sedentary (desk work), light/moderate (walking and lifting), heavy (heavy labor), and not working. Leisure activity variables were based on 168 cases and 400 control participants, and included sedentary (read, watch TV, go to movies), moderate (walk, fish, hunt, gardening), and heavy (exercising to keep fit).

©2005 American Medical Association. All rights reserved.

Downloaded from www.jama.com at National Institute of Hlth, on January 18, 2006

cases diagnosed within the first 5 years after blood collection. Moreover, our associations for glucose, insulin, and insulin resistance were stronger among cases that occurred at least 10 years after baseline blood draw from which the insulin and glucose were determined. Most of the participants in the highest insulin quartile have normal concentrations that do not correspond with hyperinsulinemia (>14 μIU/mL [>97.2 pmol/L]). Given the close proximity of the exocrine pancreatic tissue to the islets of Langerhans, exocrine pancreatic cells are estimated to be exposed to insulin concentrations that are 20-fold higher than the systemic circulation, which some have hypothesized may potentially have implications for pancreatic cancer promotion.[21] In vitro studies have shown that insulin promotes hamster, rat, and human pancreatic cancer cell lines.[8,21] In addition, a number of animal studies have shown that peripheral insulin resistance promotes ductal pancreatic carcinogenesis,[22-27] and treatment with metformin, a drug used to treat glucose intolerance that specifically reduces insulin production, prevented the development of malignant lesions.[27] The peripheral insulin resistance effect on pancreatic carcinogenesis in recently developed animal models, which more closely resemble human pancreatic cancer, however, have not yet been reported.[28] These experimental studies

Table 2. Selected Age-Adjusted Characteristics of Subcohort Control Participants by Quartile of Fasting Serum Insulin*

Characteristics	Fasting Serum Insulin, Quartile 1	2	3	4	*P* for Trend
Quartile, μIU/mL	2.05 (1.51-2.58)	3.47 (2.94-4.00)	5.04 (4.52-5.57)	10.22 (9.67-10.77)	
Demographics					
Age, y	56.6 (55.6-57.4)	56.1 (55.2-57.1)	56.1 (55.1-57.1)	56.7 (55.7-57.7)	.67
Height, cm	173.1 (171.9-174.2)	174.0 (172.8-175.1)	174.4 (173.2-175.5)	173.8 (175.0-172.6)	.54
Weight, kg	72.5 (70.4-74.7)	75.9 (73.8-78.1)	82.5 (80.4-84.7)	91.2 (89.0-93.5)	<.001
BMI	24.2 (23.6-24.8)	25.0 (24.4-25.7)	27.1 (26.5-27.8)	30.8 (29.5-30.8)	<.001
Primary school education or less	84.0 (75.5-90.0)	75.4 (66.1-82.8)	71.1 (61.6-79.0)	84.3 (75.6-90.3)	.66
Living in a city	54.1 (44.3-63.4)	46.4 (37.0 (56.2)	43.6 (34.3-53.4)	38.7 (29.5-48.7)	.04
Clinical characteristics					
Glucose, mg/dL	94.3 (89.9-98.8)	99.5 (95.1-103.9)	105.3 (100.9-109.7)	115.7 (111.2-120.3)	<.001
Insulin resistance (HOMA-IR)	0.48 (0.18-0.77)	0.85 (0.55-1.14)	1.31 (1.02-1.60)	3.14 (2.84-3.44)	<.001
Medical history					
History of diabetes mellitus	1.0 (0.1-6.7)	1.0 (0.1-6.7)	3.9 (1.5-9.9)	12.2 (7.0-20.5)	<.001
Smoking history					
Total cigarettes/d	20.6 (19.0-22.1)	20.7 (19.1-21.0)	19.4 (17.8-21.0)	21.3 (19.7-23.0)	.57
Years of smoking	35.5 (34.1-36.9)	34.5 (33.1-35.8)	34.1 (32.8-35.5)	35.3 (33.9-36.7)	.87
Dietary intake per d†					
Energy, kcal	2862.6 (2696-3029)	2760 (2597-2924)	2782 (2619-2944)	2942 (2775-3110)	.32
Protein, g	100.6 (97.8-103.5)	102.5 (99.7-105.3)	106.4 (103.6-109.2)	105.4 (102.5-108.2)	.02
Fat, g	98.6 (95.2-101.9)	100.7 (97.4-104.0)	102.8 (99.5-106.0)	104.2 (100.8-107.6)	.02
Saturated fat, g	51.6 (48.8-54.5)	52.7 (49.9-55.5)	52.6 (49.9-55.4)	56.5 (53.6-59.4)	.01
Carbohydrate, g	308 (299-318)	308 (299-316)	300 (291-309)	301 (292-311)	.26
Starch, g	145.4 (138.5-152.3)	146.9 (140.1-153.7)	145.0 (138.3-151.8)	142.8 (135.9-149.8)	.49
Free sugars, g	71.4 (65.0-77.7)	69.3 (75.5-63.1)	67.9 (61.7-74.0)	65.0 (58.6-71.4)	.16
Sucrose, g	64.4 (58.4-70.3)	61.1 (55.2-67.0)	58.1 (52.2-63.9)	56.8 (50.7-62.8)	.08
Fiber, g	26.1 (24.5-27.7)	25.7 (24.2-27.3)	25.1 (23.5-26.6)	25.3 (23.7-26.9)	.48
Alcohol, g	24.1 (19.4-28.8)	19.6 (14.9-24.2)	16.9 (12.3-21.4)	18.1 (13.4-22.8)	.10
Physical activity					
Occupational					
Sedentary	8.1 (4.1-15.1)	12.6 (7.5-20.5)	14.5 (8.9-22.8)	13.6 (8.1-22.1)	.29
Light/moderate	41.1 (31.3-51.6)	41.9 (32.3-52.2)	37.0 (27.7-47.3)	34.4 (25.2-44.9)	.29
Heavy	11.1 (6.2-19.0)	10.0 (5.5-17.5)	5.9 (2.8-12.3)	5.8 (2.6-12.5)	.13
Nonworking	36.1 (27.9-44.2)	32.9 (24.8-41.0)	38.3 (30.3-46.3)	42.0 (33.7-50.3)	.18
Leisure					
Sedentary	42.2 (31.9-53.2)	35.9 (26.2-47.0)	40.3 (30.2-51.2)	44.0 (33.6-55.0)	.12
Exercise to keep fit	10.8 (6.0-18.6)	6.9 (3.3-13.8)	2.9 (0.9-8.6)	3.0 (1.0-9.0)	.02
Walk, fishing, hunt, gardening	46.9 (37.3-56.7)	56.6 (46.8-65.9)	53.5 (43.9-62.9)	46.7 (37.9-56.7)	.64

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; HOMA-IR, Homeostasis Model Assessment–Insulin Resistance.
SI conversions: To convert glucose to mmol/L, multiply by 0.0555; insulin to pmol/L, multiply by 6.945.
*Generalized linear models and logistic regression, adjusted for age, continuous factors, and proportions, respectively, were used to calculate means and 95% CIs.
†Dietary variables were adjusted for energy, with the exception of alcohol.

 ©2005 American Medical Association. All rights reserved.

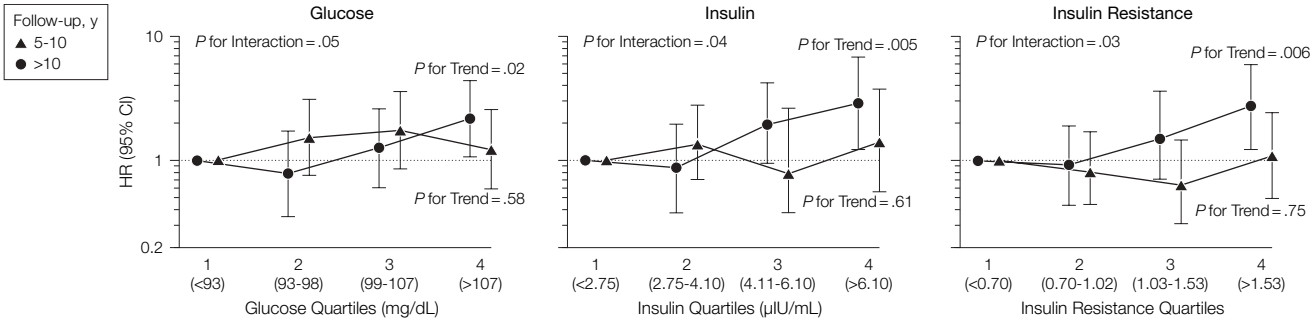
Downloaded from www.jama.com at National Institute of Hlth, on January 18, 2006

Table 3. Age- and Multivariable-Adjusted Hazard Ratios of Baseline Fasting Serum Insulin, Glucose, and Insulin Resistance and Pancreatic Cancer Among Cases (n = 169) and Subcohort Control Participants (n = 400)

	Quartiles				*P* for Linear Trend
	1	2	3	4	
Glucose, mg/dL	<93	93-98	99-107	>107	
No. of pancreatic cancer cases/ subcohort control participants	34/99	37/100	48/102	50/99	
HR (95% CI)					
Age-adjusted	1.00	1.12 (0.64-1.96)	1.45 (0.85-2.49)	1.60 (0.94-2.74)	.06
Multivariable-adjusted*	1.00	1.15 (0.66-2.02)	1.49 (0.86-2.59)	1.69 (0.97-2.94)	.05
	Cut Point				
Biochemically defined diabetes mellitus, glucose, mg/dL	<126	≥126			
No. of pancreatic cancer cases/ subcohort control participants	153/376	16/24			
HR (95% CI)					
Age-adjusted	1.00	2.06 (1.02-4.15)			
Multivariable-adjusted*	1.00	2.13 (1.04-4.35)			
Insulin, μIU/mL	<2.75	2.75-4.10	4.11-6.10	>6.10	
No. of pancreatic cancer cases/ subcohort control participants	38/100	40/101	41/103	50/96	
HR (95% CI)					
Age-adjusted	1.00	1.09 (0.63-1.86)	1.07 (0.63-1.84)	1.53 (0.90-2.60)	.09
Multivariable-adjusted*	1.00	1.14 (0.66-1.96)	1.27 (0.72-2.22)	2.01 (1.03-3.93)	.03
Insulin resistance (HOMA-IR)†	<0.70	0.70-1.02	1.03-1.53	>1.53	
No. of pancreatic cancer cases/ subcohort control participants	44/100	36/100	37/100	52/100	
HR (95% CI)					
Age-adjusted	1.00	0.84 (0.49-1.43)	0.85 (0.50-1.45)	1.34 (0.81-2.24)	.15
Multivariable-adjusted*	1.00	0.85 (0.50-1.47)	0.99 (0.56-1.73)	1.69 (0.92-3.14)	.049

Abbreviations: CI, confidence interval; HOMA-IR, Homeostasis Model Assessment–Insulin Resistance; HR, hazard ratio.
SI conversions: To convert glucose to mmol/L, multiply by 0.0555; insulin to pmol/L, multiply by 6.945.
*Adjusted for age, years of smoking, and body mass index.
†Estimated by using the HOMA-IR formula {[fasting insulin (mIU/L) × fasting glucose (mmol/L)]/22.5}.

Figure. Hazard Ratios of Baseline Fasting Serum Glucose, Insulin, and Insulin Resistance and Pancreatic Cancer Stratified by Time



Follow-up													
5-10 y	No. of Cases	17	24	27	18	21	28	15	22	27	21	15	23
	No. of Controls	99	100	102	99	100	101	103	96	100	100	100	100
	HR (95% CI)	1.00	1.54 (0.76-3.12)	1.75 (0.86-3.59)	1.23 (0.59-2.57)	1.00	1.35 (0.71-2.56)	0.78 (0.38-1.61)	1.37 (0.56-3.38)	1.00	0.82 (0.43-1.57)	0.65 (0.31-1.37)	1.09 (0.50-2.37)
>10 y	No. of Cases	17	13	21	32	16	13	26	28	17	15	22	29
	No. of Controls	89	88	89	79	89	89	91	76	89	88	90	78
	HR (95% CI)	1.00	0.79 (0.35-1.74)	1.26 (0.60-2.63)	2.16 (1.05-4.42)	1.00	0.87 (0.38-1.96)	1.95 (0.92-4.14)	2.90 (1.22-6.92)	1.00	0.91 (0.42-1.98)	1.50 (0.71-3.17)	2.71 (1.19-6.18)

HR indicates hazard ratio; CI, confidence interval. Adjusted for age, years of smoking, and body mass index; n = 86 cases developing during 5 to 10 years of follow-up; n = 83 cases developing more than 10 years of follow-up (up to 16.7 years). Hazard ratios are plotted on a log scale with error bars indicating 95% CIs. Insulin resistance was estimated by using the Homeostasis Model Assessment–Insulin Resistance formula {[fasting insulin (mIU/L) × fasting glucose (mmol/L)]/22.5}.

©2005 American Medical Association. All rights reserved.

Downloaded from www.jama.com at National Institute of Hlth, on January 18, 2006

support the biological plausibility of higher insulin concentrations and insulin resistance promoting pancreatic cancer development and our observed associations in humans.

In conclusion, our results support the hypothesis that higher insulin concentrations and insulin resistance may be a mechanism that explains the associations between diabetes mellitus, higher glucose concentration, and pancreatic cancer observed in previous studies.[1-5,14] Although based solely on male smokers, our findings for glucose and biochemically defined diabetes mellitus are consistent with previous studies conducted in diverse populations that have included women and nonsmokers.[2-5] As with any cause-specific analysis, competing causes of death were treated as censored at the time they occurred and assumed to be independent of occurrence of pancreatic cancer. If the censored events were related to occurrence of pancreatic cancer, there is potential for biased relative hazards. However, we have no reason to believe that such dependency exists, particularly because pancreatic cancer has few strong risk factors that result in higher mortality. The associations for insulin and insulin resistance reported herein require confirmation and along with observations of other studies[1-5,14,27] could potentially have important implications for nutrition and treatment-related cancer preventive strategies that modify or interfere with the insulin resistance pathway to help decrease the burden from this devastating disease. Lifestyle changes to decrease glucose and insulin concentrations through weight reduction, increasing physical activity, and diet, such as decreasing saturated fat intake, and identification of other modifiable factors that may contribute to higher glucose and insulin concentrations could possibly impact pancreatic cancer development, as well as other cancer and chronic disease.[29-33]

Author Contributions: Dr Stolzenberg-Solomon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Stolzenberg-Solomon, Albanes.
Acquisition of data: Stolzenberg-Solomon, Limburg, Taylor, Virtamo, Albanes.
Analysis and interpretation of data: Stolzenberg-Solomon, Graubard, Chari, Limburg.
Drafting of the manuscript: Stolzenberg-Solomon.
Critical revision of the manuscript for important intellectual content: Stolzenberg-Solomon, Graubard, Chari, Limburg, Taylor, Virtamo, Albanes.
Statistical analysis: Stolzenberg-Solomon, Graubard.
Obtained funding: Stolzenberg-Solomon, Limburg, Taylor, Virtamo, Albanes.
Administrative, technical, or material support: Limburg, Taylor, Virtamo, Albanes.
Study supervision: Taylor, Albanes.
Financial Disclosures: None reported.
Funding/Support: This study was supported by the Intramural Research Program of the National Institutes of Public Health, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Department of Health and Human Services with Public Health Service contracts N01-CN-45165, N01-RC-45035, and N01-RC-37004.
Role of the Sponsor: The National Cancer Institute is responsible for the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the manuscript.

REFERENCES

1. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer*. 2005;92:2076-2083.
2. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. *JAMA*. 2005;293:194-202.
3. Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, Dyer A. Abnormal glucose metabolism and pancreatic cancer mortality. *JAMA*. 2000;283:2552-2558.
4. Batty GD, Shipley MJ, Marmot M, Smith GD. Diabetes status and post-load plasma glucose concentration in relation to site-specific cancer mortality: findings from the original Whitehall study. *Cancer Causes Control*. 2004;15:873-881.
5. Balkau B, Barrett-Connor E, Eschwege E, Richard JL, Claude JR, Ducimetiere P. Diabetes and pancreatic carcinoma. *Diabetes Metab*. 1993;19:458-462.
6. Kaaks R, Lukanova A. Energy balance and cancer: the role of insulin and insulin-like growth factor-I. *Proc Nutr Soc*. 2001;60:91-106.
7. Kazakoff K, Cardesa T, Liu J, et al. Effects of voluntary physical exercise on high-fat diet-promoted pancreatic carcinogenesis in the hamster model. *Nutr Cancer*. 1996;26:265-279.
8. Wang F, Herrington M, Larsson J, Permert J. The relationship between diabetes and pancreatic cancer. *Mol Cancer*. 2003;2:4.
9. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *N Engl J Med*. 2003;348:1625-1638.
10. Coughlin SS, Calle EE, Patel AV, Thun MJ. Predictors of pancreatic cancer mortality among a large cohort of United States adults. *Cancer Causes Control*. 2000;11:915-923.
11. Friedman GD, van den Eeden SK. Risk factors for pancreatic cancer: an exploratory study. *Int J Epidemiol*. 1993;22:30-37.
12. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height, and the risk of pancreatic cancer. *JAMA*. 2001;286:921-929.
13. Berrington de Gonzalez A, Sweetland S, Spencer E. A meta-analysis of obesity and the risk of pancreatic cancer. *Br J Cancer*. 2003;89:519-523.
14. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D. A prospective study of medical conditions, anthropometry, physical activity, and pancreatic cancer in male smokers (Finland). *Cancer Causes Control*. 2002;13:417-426.
15. The ATBC Cancer Prevention Study Group. The Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study: design, methods, participant characteristics, and compliance. *Ann Epidemiol*. 1994;4:1-10.
16. Pietinen P, Hartman AM, Haapa E, et al. Reproducibility and validity of dietary assessment instruments, I: a self-administered food use questionnaire with a portion size picture booklet. *Am J Epidemiol*. 1988;128:655-666.
17. Korhonen P, Malila N, Pukkala E, Teppo L, Albanes D, Virtamo J. The Finnish Cancer Registry as follow-up source of a large trial cohort: accuracy and delay. *Acta Oncol*. 2002;41:381-388.
18. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412-419.
19. Fears TR, Ziegler RG, Donaldson JL, et al. Reproducibility studies and interlaboratory concordance for androgen assays in female plasma. *Cancer Epidemiol Biomarkers Prev*. 2000;9:403-412.
20. Reaven G, Tsao PS. Insulin resistance and compensatory hyperinsulinemia: the key player between cigarette smoking and cardiovascular disease? *J Am Coll Cardiol*. 2003;41:1044-1047.
21. Hennig R, Ding XZ, Adrian TE. On the role of the islets of Langerhans in pancreatic cancer. *Histol Histopathol*. 2004;19:999-1011.
22. Bell RH Jr, McCullough PJ, Pour PM. Influence of diabetes on susceptibility to experimental pancreatic cancer. *Am J Surg*. 1988;155:159-164.
23. Pour PM, Kazakoff K, Carlson K. Inhibition of streptozotocin-induced islet cell tumors and N-nitrosobis (2-oxopropyl)amine-induced pancreatic exocrine tumors in Syrian hamsters by exogenous insulin. *Cancer Res*. 1990;50:1634-1639.
24. Pour PM, Stepan K. Modification of pancreatic carcinogenesis in the hamster model, VIII: inhibitory effect of exogenous insulin. *J Natl Cancer Inst*. 1984;72:1205-1208.
25. Zendehdel K, Nyren O, Ostenson CG, Adami HO, Ekbom A, Ye W. Cancer incidence in patients with type 1 diabetes mellitus: a population-based cohort study in Sweden. *J Natl Cancer Inst*. 2003;95:1797-1800.
26. Hjalgrim H, Frisch M, Ekbom A, Kyvik KO, Melbye M, Green A. Cancer and diabetes: a follow-up study of two population-based cohorts of diabetic patients. *J Intern Med*. 1997;241:471-475.
27. Schneider MB, Matsuzaki H, Haorah J, et al. Prevention of pancreatic cancer induction in hamsters by metformin. *Gastroenterology*. 2001;120:1263-1270.
28. Leach SD. Mouse models of pancreatic cancer: the fur is finally flying! *Cancer Cell*. 2004;5:7-11.
29. Wei EK, Ma J, Pollak MN, et al. A prospective study of C-peptide, insulin-like growth factor-I, insulin-like growth factor binding protein-1, and the risk of colorectal cancer in women. *Cancer Epidemiol Biomarkers Prev*. 2005;14:850-855.
30. Ma J, Giovannucci E, Pollak M, et al. A prospective study of plasma C-peptide and colorectal cancer risk in men. *J Natl Cancer Inst*. 2004;96:546-553.
31. Lukanova A, Zeleniuch-Jacquotte A, Lundin E, et al. Prediagnostic levels of C-peptide, IGF-I, IGFBP-1, -2 and -3 and risk of endometrial cancer. *Int J Cancer*. 2004;108:262-268.
32. Kaaks R, Toniolo P, Akhmedkhanov A, et al. Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. *J Natl Cancer Inst*. 2000;92:1592-1600.
33. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005;365:1415-1428.

 ©2005 American Medical Association. All rights reserved.

Downloaded from www.jama.com at National Institute of Hlth, on January 18, 2006