Fasting Serum Glucose Level and Cancer Risk in Korean Men and Women

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Context Diabetes is a serious and costly disease that is becoming increasingly common in many countries. The role of diabetes as a cancer risk factor remains unclear.

Objective To examine the relationship between fasting serum glucose and diabetes and risk of all cancers and specific cancers in men and women in Korea.

Design, Setting, and Participants Ten-year prospective cohort study of 1 298 385 Koreans (829 770 men and 468 615 women) aged 30 to 95 years who received health insurance from the National Health Insurance Corp and had a biennial medical evaluation in 1992-1995 (with follow-up for up to 10 years).

Main Outcome Measures Death from cancer and registry-documented incident cancer or hospital admission for cancer.

Results During the 10 years of follow-up, there were 20 566 cancer deaths in men and 5907 cancer deaths in women. Using Cox proportional hazards models and controlling for smoking and alcohol use, the stratum with the highest fasting serum glucose (≥140 mg/dL [≥7.8 mmol/L]) had higher death rates from all cancers combined (hazard ratio [HR], 1.29; 95% confidence interval [CI], 1.22-1.37 in men and HR, 1.23; 95% CI, 1.09-1.39 in women) compared with the stratum with the lowest level (<90 mg/dL [<5.0 mmol/L]). By cancer site, the association was strongest for pancreatic cancer, comparing the highest and lowest strata in men (HR, 1.91; 95% CI, 1.52-2.41) and in women (HR, 2.05; 95% CI, 1.43-2.93). Significant associations were also found for cancers of the esophagus, liver, and colon/rectum in men and of the liver and cervix in women, and there were significant trends with glucose level for cancers of the esophagus, colon/rectum, liver, pancreas, and bile duct in men and of the liver and pancreas in women. Of the 26 473 total cancer deaths in men and women, 848 were estimated as attributable to having a fasting serum glucose level of less than 90 mg/dL. For cancer incidence, the general patterns reflected those found for mortality. For persons with a diagnosis of diabetes or a fasting serum glucose level greater than 125 mg/dL (6.9 mmol/L), risks for cancer incidence and mortality were generally elevated compared with those without diabetes.

Conclusion In Korea, elevated fasting serum glucose levels and a diagnosis of diabetes are independent risk factors for several major cancers, and the risk tends to increase with an increased level of fasting serum glucose.

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DIABETES MELLITUS IS A SERIOUS and costly disease that is becoming increasingly common in many countries, including Korea.[1] Recent data show that approximately 150 million people have diabetes mellitus worldwide, and this number may double by 2025, especially in developing countries, because of population growth, aging, unhealthy diets, obesity, and sedentary lifestyles.[2] The association between diabetes mellitus and cardiovascular mortality is well established.[3] However, while the role of diabetes as a risk factor for cancer is still uncertain, having diabetes or an elevated glucose level is of interest because of the effect of insulin on cell growth and of the systemic inflammation associated with diabetes and the metabolic syndrome.[4,5]

Recent observational studies have provided consistent evidence on associations of diabetes with increased risk of cancers of the pancreas,[5] liver,[6] endometrium,[7] and colon/rectum.[8] Data on cancers of the esophagus, stomach, prostate, and breast are more limited and have been inconsistent.[8,9] This lack of consistency may be attributable to the limited number of studies and their small sample sizes.

For editorial comment see p 235.

We conducted a prospective cohort investigation, the Korean Cancer Prevention Study (KCPS), among more than 1 million Koreans to assess associations of fasting serum glucose and of a diagnosis of diabetes with cancer risk.[10] In addition, we explored modification of this risk by obesity in a population with a low average body weight compared with those of Western countries.

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METHODS

Study Participants

The National Health Insurance Corp (NHIC), previously the Korean Medical Insurance Corp, provides health insurance to government employees, teachers, and their dependents. Of the Korean population (approximately 43.7 million in 1992), 10.7% were insured by this organization, including 1 297 833 workers and 3 364 605 dependents. All workers were required to participate in biennial medical examinations.[11] In 1992, 94% of the insured workers completed examinations; a total of 95% completed biennial examinations in 1994. For dependents, the numbers were 37% in 1993 and 24% in 1995. This examination included a lifestyle and medical questionnaire, along with measurement of blood chemistries in a fasting blood sample.

The KCPS cohort includes 1 329 525 Koreans (846 907 men and 482 618 women) aged 30 to 95 years who received health insurance from NHIC and who had biennial medical evaluations during the period 1992 to 1995. By year, 784 870 (59.0%) were enrolled in 1992, 367 903 (27.7%) in 1993, 98 417 (7.4%) in 1994, and 78 335 (5.9%) in 1995.[10] Of the 1 329 525 participants, 27 192 (2.1%) with missing information were excluded. A total of 3719 people reporting a history of any form of cancer and 229 who died in the interval between questionnaire completion and start of follow-up on January 1 of the subsequent year were also excluded, leaving a final sample size of 1 298 385.

Data Collection

The NHIC biennial examinations, conducted by medical staff at local hospitals, follow a standard procedure. In the 1992, 1993, 1994, and 1995 questionnaires, participants were asked (1) to describe their smoking habits, along with some other health habits, including alcohol consumption, and (2) if they were being treated for diabetes, with the date of diagnosis if they answered yes. Serum glucose measurements were obtained under fasting conditions for routine clinical purposes. Each hospital had internal and external quality control procedures directed by the Korean Association of Laboratory Quality Control. All follow-up time of the participants was assigned to the first recorded serum glucose level.

The follow-up period was up to 10 years, through December 31, 2002. The exact dates of completion of the survey form were not recorded. Consequently, follow-up accrual began on January 1 of the calendar year following the year in which the survey form was completed. Because the study involved routinely collected medical data, participant consent was not specifically obtained. The study was approved by the institutional review boards of Yonsei University and the Johns Hopkins Bloomberg School of Public Health.

Cancer Outcomes

The principal outcome variables were mortality from cancer by site and cancer incidence, based on national cancer registry data and hospitalization records. Although Korea has a national cancer registry, reporting was not complete during the time of follow-up and, consequently, hospital admission files were used to identify a first admission event for cancer. An incident cancer case was coded as occurring based on either a positive report from the national cancer registry or on a hospital admission for a cancer diagnosis. Outcomes for mortality were ascertained from the causes of death on the death certificates. A computerized search of death certificate data from the National Statistical Office in Korea was performed using the unique identification number assigned at birth. Causes of death are assigned by trained hospital abstractors; for this analysis, we used underlying cause.

Statistical Analysis

Fasting serum glucose levels were categorized as less than 90, 90 to 109, 110 to 125, 126 to 139, and 140 or more mg/dL (<5.0, 5.0-6.0, 6.1-6.9, 7.0-7.7, and ≥7.8 mmol/L). For some analyses, the upper categories of fasting glucose levels were combined into a single stratum because of small numbers. In all primary analysis, the fasting glucose category of less than 90 mg/dL (<5.0 mmol/L) was the reference group. Additionally, we created a category for diabetes combining participants with self-reported treatment for diabetes or with fasting serum glucose levels greater than 125 mg/dL (6.9 mmol/L).[12,13]

Age-adjusted death and cancer incidence rates were calculated for each category of fasting serum glucose level and directly standardized to the age distribution of the 1995 Korean national population. All analyses were stratified by sex. We computed hazard ratios (HRs; the hazard for mortality in a specific fasting glucose category divided by the corresponding hazard in the reference category [<90 mg/dL]) using Cox proportional hazards modeling[14] to adjust for age and other potential confounding factors. In the Cox model, smoking status was included as a dummy variable for previous smokers and current smokers, with 3 categories of amount smoked (1-9, 10-19, and ≥20 cigarettes/d), and alcohol use as 5 categories (none, 1-24, 25-49, 50-99, and ≥100 g/d). We also calculated the attributable numbers of deaths associated with having elevated serum glucose levels, using standard methods.[15] All analyses were conducted using SAS statistical software, version 8.0 (SAS Institute Inc, Cary, NC).

RESULTS

The population was primarily middle-aged, with approximately twice as many men as women (TABLE 1). By the criteria of self-report and fasting serum glucose level, the prevalence rates of diabetes were about 5% in men and 4.5% in women. The population had a low body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) on average, and only 23.8% and 0.8% of men and 27.0% and 2.5% of women had BMI values of 25 or above and above 30, respectively. Both smoking and alcohol use were substantially more common in men.

Overall Pattern of All-Cause Mortality and Fasting Serum Glucose Level

During the 10 years of follow-up, 54 385 deaths occurred among men and 20 362 among women. As shown in FIGURE 1, fasting serum glucose level was positively associated with all-cause mortality rates. In the adjusted Cox proportional hazards model, this effect persisted, with persons in the highest stratum of fasting serum glucose (≥140 mg/dL) having a higher HR for all causes combined (HR, 2.09; 95% confidence interval [CI], 2.03-2.16 in men and HR, 2.35; 95% CI, 2.24-2.48 in women) compared with the lowest stratum (<90 mg/dL) (TABLE 2 and TABLE 3).

Table 1. Baseline Characteristics of Korean Cancer Prevention Study Participants*

Characteristics	Men (n = 829 770)	Women (n = 468 615)
Age, y	45.3 (11.1)	49.6 (12.1)
Body mass index†	23.2 (2.6)	23.2 (3.2)
Fasting serum glucose, mg/dL	92.9 (25.2)	90.7 (24.4)
Alcohol drinking, g/d	17.1 (32.1)	0.2 (1.9)
Smoking status, %		
Never	20.8	93.8
Previous	20.7	2.1
Current	58.5	4.1
Any alcohol use, %	76.1	14.1
Diabetes, %‡	5.1	4.5

*Data are expressed as mean (SD) unless otherwise indicated.
†Body mass index was calculated as weight in kilograms divided by the square of height in meters.
‡Diabetes was defined as fasting blood glucose level of at least 126 mg/dL (7.0 mmol/L) or medication.

Cancer Mortality

A total of 20 566 cancer deaths occurred among men and 5907 deaths occurred among women during the 10 years of follow-up. In general, HR estimates were above unity for male participants in the higher strata of serum glucose level and among those with a diagnosis of diabetes (Table 2). In fact, all point estimates were somewhat elevated in association with a diagnosis of diabetes. We explored the relationship between duration of diabetes and cancer risk and did not find consistent associations, with the exception of pancreatic cancer in men. Among men with diabetes, the HRs for pancreatic cancer death with diabetes durations of less than 4.9 years, 5.0 to 9.9 years, and 10 years or more were 2.0 (95% CI, 1.2-3.3), 2.4 (95% CI, 1.4-4.3), and 3.0 (95% CI, 1.8-5.0), respectively, compared with those without diabetes.

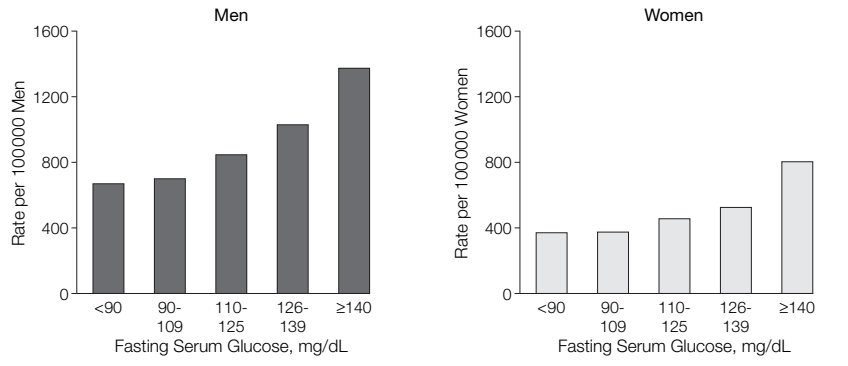
We observed linear trends in mortality with increasing fasting serum glucose level for all cancers combined and for cancers of several sites (Table 2). Compared with the reference category (<90 mg/dL), men with a fasting serum glucose level above 140 mg/dL had significantly elevated HRs of death from cancers of the esophagus (HR, 1.44; 95% CI, 1.08-1.93), liver (HR, 1.57; 95% CI, 1.40-1.76), pancreas (HR, 1.91; 95% CI, 1.52-2.41), and colon/rectum (HR, 1.31; 95% CI, 1.03-1.67). Significant associations were also found for bladder cancer and leukemia for those with a fasting serum glucose level of 126 mg/dL or higher. Men with a fasting serum glucose level of 110 to 125 mg/dL had significantly elevated HRs of death from esophageal, stomach, colon/rectal, liver, and pancreatic cancers. Of the total of 20 566 cancer deaths in men, 802 were estimated as attributable to having a fasting serum glucose level of less than 90 mg/dL.

For women, the overall pattern of association was similar to that in men (Table 3), with all point estimates increased for those with diabetes. Significant positive linear trends in death rates were observed for pancreatic cancer; HRs ranged from 1.70 (95% CI, 1.17-2.46) at fasting serum glucose levels of 110 to 125 mg/dL to 2.05 (95% CI, 1.43-2.93) at fasting serum glucose levels of 126 mg/dL or higher (Table 3). Significant associations with diabetes were also found for cancers of the liver, lung, breast, and cervix, while associations were not observed for risk of death from cancers of the stomach or colon/rectum. Of the total 5907 cancer deaths in women, 46 were estimated as attributable to having a fasting serum glucose level less than 90 mg/dL.

Cancer Incidence

The numbers of incident cases during the 10 years of follow-up were 37 759 among men and 16 074 among women. Trends were generally similar for mortality and incidence. We observed positive linear trends in cancer incidence with increasing fasting serum glucose levels for cancers of the liver, pancreas, and kidney (TABLE 4). However, fasting serum glucose level was inversely associated with prostate cancer incidence among men with a fasting glucose level of at least 126 mg/dL. The association of fasting serum glucose level and cancer incidence was similar whether the analysis was based on the total population or on those who had at least a 5-year follow-up period (data not shown). Furthermore, the incidence findings were unchanged with adjustment for BMI. For example, men with diabetes had similar HRs of death

Figure 1. Age-Adjusted Rate per 100 000 for Death Due to All Causes by Fasting Serum Glucose Level



from pancreatic cancer before (HR, 1.71; 95% CI, 1.42-2.06) and after (HR, 1.73; 95% CI, 1.42-2.07) BMI adjustment.

In women, positive linear trends were observed in incidence of pancreatic cancer with increasing fasting serum glucose level (TABLE 5). We observed a significant association for liver cancer for the stratum with fasting serum glucose levels of 110 to 125 mg/dL. The observed associations in women were

Table 2. Age-Adjusted Mortality Rate per 100 000 Men for Death Due to All Causes, All Cancers, and Various Cancers by Fasting Serum Glucose Level in Korean Men, 1993-2002*

	Fasting Serum Glucose Level, mg/dL†						
Type of Cancer	<90 (n = 429 370)	90-109 (n = 304 362)	110-125 (n = 58 020)	126-139 (n = 11 459)	≥140 (n = 26 559)	*P* Value for Trend	Diabetes (n = 41 868)‡
All causes							
Death rate§	677.3	697.7	847.2	1029.2	1371.6		1207.7
HR (95% CI)‖	1.00	1.04 (1.02-1.06)	1.28 (1.24-1.32)	1.50 (1.42-1.58)	2.09 (2.03-2.16)	.01	1.83 (1.79-1.88)
All cancer							
Death rate§	266.0	270.9	303.7	334.5	341.0		333.0
HR (95% CI)‖	1.00	1.04 (1.01-1.07)	1.17 (1.11-1.23)	1.25 (1.14-1.36)	1.29 (1.22-1.37)	.003	1.27 (1.22-1.33)
Esophagus							
Death rate§	8.9	9.0	11.7	11.7	14.4		12.6
HR (95% CI)‖	1.00	1.05 (0.89-1.24)	1.30 (1.01-1.68)	1.36 (0.87-2.11)	1.44 (1.08-1.93)	.007	1.36 (1.08-1.71)
Larynx							
Death rate§	3.4	3.1	4.6	4.0			3.9
HR (95% CI)‖	1.00	0.95 (0.72-1.27)	1.33 (0.88-2.02)	1.37 (0.89-2.10)		.12	1.41 (0.96-2.07)
Stomach							
Death rate§	57.3	56.9	66.5	62.8	63.8		63.1
HR (95% CI)‖	1.00	1.01 (0.95-1.08)	1.17 (1.05-1.30)	1.15 (0.94-1.40)	1.11 (0.97-1.27)	.17	1.16 (1.04-1.28)
Colon/rectum							
Death rate§	14.8	16.2	18.8	20.0	19.2		20.2
HR (95% CI)‖	1.00	1.07 (0.95-1.22)	1.27 (1.04-1.55)	1.23 (0.84-1.79)	1.31 (1.03-1.67)	.03	1.28 (1.06-1.55)
Liver							
Death rate§	58.7	60.3	70.6	103.7	93.1		96.5
HR (95% CI)‖	1.00	1.04 (0.97-1.10)	1.24 (1.12-1.37)	1.69 (1.43-2.00)	1.57 (1.40-1.76)	.03	1.59 (1.45-1.74)
Bile duct							
Death rate§	7.8	8.4	9.1	12.6	10.4		11.0
HR (95% CI)‖	1.00	1.09 (0.91-1.30)	1.18 (0.89-1.57)	1.42 (0.88-2.28)	1.30 (0.93-1.82)	.05	1.26 (0.97-1.63)
Pancreas							
Death rate§	12.2	12.4	14.6	16.9	21.5		19.0
HR (95% CI)‖	1.00	1.08 (0.93-1.24)	1.28 (1.02-1.59)	1.45 (0.99-2.13)	1.91 (1.52-2.41)	.009	1.71 (1.42-2.06)
Lung							
Death rate§	60.9	60.6	63.6	67.0	59.5		59.0
HR (95% CI)‖	1.00	1.02 (0.96-1.09)	1.09 (0.97-1.21)	1.08 (0.89-1.31)	1.00 (0.87-1.14)	.74	1.01 (0.91-1.13)
Prostate							
Death rate§	3.7	3.7	3.1	4.3			3.6
HR (95% CI)‖	1.00	0.96 (0.73-1.26)	0.85 (0.52-1.38)	1.14 (0.74-1.77)		.61	1.13 (0.75-1.70)
Kidney							
Death rate§	3.0	2.9	3.6	4.4			4.3
HR (95% CI)‖	1.00	0.93 (0.69-1.24)	1.17 (0.75-1.84)	1.44 (0.92-2.25)		.09	1.41 (0.94-2.13)
Bladder							
Death rate§	2.6	3.4	2.8	4.1			3.7
HR (95% CI)‖	1.00	1.22 (0.90-1.65)	1.12 (0.68-1.87)	1.57 (1.00-2.50)		.14	1.45 (0.96-2.19)
Brain							
Death rate§	3.4	3.0	3.2	3.5			3.3
HR (95% CI)‖	1.00	0.92 (0.70-1.21)	0.95 (0.59-1.52)	1.04 (0.63-1.72)		.58	1.02 (0.64-1.63)
Leukemia							
Death rate§	4.9	4.5	3.7	6.6			6.6
HR (95% CI)‖	1.00	0.92 (0.74-1.16)	0.71 (0.45-1.12)	1.42 (1.00-2.01)		.49	1.53 (1.08-2.15)

Abbreviations: CI, confidence interval; HR, hazard ratio.
SI conversion: To convert glucose from mg/dL to mmol/L, multiply by 0.0555.
*Participants with any of the following features at study entry were excluded: missing data on fasting blood glucose level, existing cancer, and missing data on smoking status.
†The highest fasting blood glucose category examined varies for cancer at different sites; higher categories have been combined when necessary because of small numbers.
‡Diabetes was defined as fasting blood glucose level of at least 126 mg/dL (7.0 mmol/L) or medication.
§The rate per 100 000 men is given, standardized to the age distribution of men in the 1995 Korean national population.
‖The Cox proportional hazards model was adjusted for age, age squared, amount of smoking, and alcohol use.

unchanged with adjustment for BMI (data not shown).

Cancer Mortality and Incidence and Fasting Glucose Levels According to BMI in Men

To control for potential confounding by obesity and to evaluate effect modification, the data were further stratified by BMI (<20, 20 to <23, and ≥23). Because of limited numbers for some cancer sites, the analyses were carried out for all sites combined and for cancers of the colon/rectum, liver, and pancreas. For all cancers, a trend was evident in mortality risk by fasting serum glucose level in each stratum of BMI (FIGURE 2). Positive trends in death rates were observed for cancers of the liver and pancreas in all BMI groups as well. The risk of death due to liver and pancreatic cancers associated with fasting serum glucose level was not modified by BMI. For cancer incidence, the association of fasting serum glucose level with risk for liver cancer remained consistent and lacked evidence of effect modification by obesity. The association of pancreatic cancer incidence with fasting serum glucose level was not as consistent as for mortality, although all strata showed increased risk compared with the reference category.

We also assessed potential modification of the effect of serum glucose level by smoking and alcohol consumption. We did not find significant interactions for cancer incidence or mortality in either men or women.

COMMENT

This cohort of Koreans, in comparison with Western populations, is notable for the low frequency of obesity in its participants. The average BMI was 23.2, and only one fourth of participants had a BMI above 25. Based on other studies in Korea, almost all cases of diabetes could be expected to be type 2.[16] Nonetheless, we documented, as in Western populations, that serum glucose level and presence of diabetes are associated with cancer incidence and mortality.

Other studies have addressed diabetes or glucose intolerance and risk for

Table 3. Age-Adjusted Mortality Rate per 100 000 Women for Death Due to All Causes, All Cancers, and Various Cancers by Fasting Serum Glucose Level in Korean Women, 1993-2002*

	Fasting Serum Glucose Level, mg/dL†						
Type of Cancer	<90 (n = 270 157)	90-109 (n = 157 940)	110-125 (n = 22 578)	126-139 (n = 5657)	≥140 (n = 12 283)	*P* Value for Trend	Diabetes (n = 21 056)‡
All causes							
Death rate§	371.7	374.5	453.5	525.1	803.4		698.6
HR (95% CI)‖	1.00	1.01 (0.98-1.05)	1.24 (1.17-1.30)	1.42 (1.30-1.55)	2.35 (2.24-2.48)	.04	1.99 (1.91-2.07)
All cancer							
Death rate§	118.8	117.7	121.9	143.9	150.5		159.0
HR (95% CI)‖	1.00	1.00 (0.95-1.06)	1.01 (0.96-1.18)	1.12 (0.91-1.28)	1.23 (1.09-1.39)	.03	1.31 (1.20-1.44)
Stomach							
Death rate§	24.7	25.0	28.3	16.5	22.2		24.1
HR (95% CI)‖	1.00	1.01 (0.89-1.14)	0.98 (0.77-1.24)	0.99 (0.82-1.14)	1.00 (0.74-1.32)	.65	1.09 (0.88-1.36)
Colon/rectum							
Death rate§	11.4	11.2	11.1	10.4			13.2
HR (95% CI)‖	1.00	0.96 (0.80-1.14)	1.05 (0.75-1.45)	0.85 (0.58-1.24)		.42	1.11 (0.81-1.51)
Liver							
Death rate§	15.0	12.2	13.5	15.5	19.3		17.0
HR (95% CI)‖	1.00	0.85 (0.73-1.00)	1.04 (0.75-1.35)	1.22 (0.75-1.98)	1.33 (1.01-1.81)	.045	1.28 (1.00-1.66)
Pancreas							
Death rate§	5.9	8.7	9.8	12.2			12.2
HR (95% CI)‖	1.00	1.45 (1.16-1.81)	1.70 (1.17-2.46)	2.05 (1.43-2.93)		.01	1.71 (1.25-2.34)
Lung							
Death rate§	15.5	16.9	13.3	23.0	21.6		22.2
HR (95% CI)‖	1.00	1.10 (0.95-1.27)	0.90 (0.67-1.22)	1.60 (1.13-2.55)	1.50 (0.94-1.78)	.14	1.39 (1.10-1.76)
Breast							
Death rate§	6.0	7.5	5.2	6.1			9.8
HR (95% CI)‖	1.00	1.15 (0.90-1.47)	0.89 (0.49-1.60)	1.24 (0.65-1.92)		.59	2.23 (1.49-3.33)
Cervix							
Death rate§	3.3	2.7	2.6	4.9			6.1
HR (95% CI)‖	1.00	0.87 (0.61-1.24)	1.04 (0.54-2.02)	1.81 (1.03-3.15)		.17	2.50 (1.58-3.95)

Abbreviations: CI, confidence interval; HR, hazard ratio.
SI conversion: To convert glucose from mg/dL to mmol/L, multiply by 0.0555.
*Participants with any of the following features at study entry were excluded: missing data on fasting blood glucose level, existing cancer, and missing data on smoking status.
†The highest fasting blood glucose category examined varies for cancer at different sites; higher categories have been combined when necessary because of small numbers.
‡Diabetes was defined as fasting blood glucose level of at least 126 mg/dL (7.0 mmol/L) or medication.
§The rate per 100 000 women is given, standardized to the age distribution of women in the 1995 Korean national population.
‖The Cox proportional hazards model was adjusted for age, age squared, amount of smoking, and alcohol use.

cancer. Although diverse in design and in their measures of glucose intolerance, the majority have shown that increased cancer risk, either overall or for particular cancer sites, is associated with glucose intolerance. The magnitude of the association of glucose intolerance or diabetes with risk for all cancers was small in the KCPS but was within the range found in some studies.[5,6,17] The multicancer site effect is consistent with postulated mechanisms of systemic consequences of hyperinsulinemia.[4,5] In interpreting the findings of these studies and of the KCPS, potential confounding by obesity is of concern. In the KCPS, we found that the increased cancer risk associated with high serum glucose or diabetes was unchanged when controlling for BMI; additionally, most KCPS participants were

Table 4. Age-Adjusted Incidence Rate per 100 000 Men for All Cancer and Various Cancers by Fasting Serum Glucose Level in Korean Men, 1993-2002*

	Fasting Serum Glucose Level, mg/dL						
Type of Cancer	<90 (n = 429 370)	90-109 (n = 304 362)	110-125 (n = 58 020)	126-139 (n = 11 459)	≥140 (n = 26 559)	*P* Value for Trend	Diabetes (n = 41 868)†
All cancer							
Incidence rate‡	484.9	487.8	547.5	565.6	608.0		619.6
HR (95% CI)§	1.0	1.01 (0.99-1.04)	1.13 (1.09-1.17)	1.16 (1.08-1.24)	1.22 (1.16-1.27)	.005	1.24 (1.20-1.28)
Esophagus							
Incidence rate‡	12.3	13.6	16.1	14.9	16.3		15.6
HR (95% CI)§	1.0	1.10 (0.96-1.26)	1.37 (1.20-1.80)	1.19 (0.64-1.53)	1.26 (0.89-1.52)	.21	1.11 (0.90-1.37)
Larynx							
Incidence rate‡	8.3	8.3	11.9	9.5	9.3		10.5
HR (95% CI)§	1.0	1.05 (0.88-1.25)	1.36 (1.05-1.76)	1.19 (0.72-2.00)	1.12 (0.80-1.58)	.48	1.28 (0.99-1.64)
Stomach							
Incidence rate‡	126.3	125.2	137.3	134.4	129.3		140.3
HR (95% CI)§	1.0	0.98 (0.94-1.03)	1.05 (0.98-1.13)	1.08 (0.94-1.24)	1.00 (0.91-1.10)	.53	1.11 (1.04-1.20)
Colon/rectum							
Incidence rate‡	52.4	57.8	63.1	53.5	58.2		60.1
HR (95% CI)§	1.0	1.08 (1.01-1.15)	1.14 (1.02-1.27)	1.03 (0.82-1.28)	1.13 (0.98-1.30)	.35	1.11 (1.00-1.24)
Liver							
Incidence rate‡	80.8	80.9	92.0	125.1	149.9		144.9
HR (95% CI)§	1.0	1.01 (0.95-1.06)	1.16 (1.07-1.27)	1.45 (1.24-1.70)	1.72 (1.56-1.89)	.01	1.66 (1.53-1.79)
Bile duct							
Incidence rate‡	11.1	13.7	12.8	15.9	13.5		14.9
HR (95% CI)§	1.0	1.22 (1.06-1.41)	1.15 (0.90-1.46)	1.47 (0.99-2.19)	1.29 (0.90-1.57)	.15	1.22 (0.98-1.52)
Pancreas							
Incidence rate‡	13.7	14.2	17.6	18.3	28.6		25.6
HR (95% CI)§	1.0	1.08 (0.95-1.24)	1.34 (1.09-1.64)	1.37 (0.94-2.00)	2.09 (1.70-2.58)	.03	1.78 (1.50-2.11)
Lung							
Incidence rate‡	78.0	76.0	85.1	91.9	82.3		84.8
HR (95% CI)§	1.0	0.98 (0.93-1.04)	1.09 (1.00-1.20)	1.14 (0.96-1.34)	1.01 (0.90-1.14)	.49	1.06 (0.96-1.16)
Prostate							
Incidence rate‡	16.9	16.8	17.5	13.5	14.8		13.8
HR (95% CI)§	1.0	0.98 (0.87-1.12)	1.06 (0.87-1.31)	0.58 (0.35-0.95)	0.86 (0.66-1.13)	.33	0.80 (0.64-0.99)
Kidney							
Incidence rate‡	10.5	11.4	11.2	16.0	15.4		14.7
HR (95% CI)§	1.0	1.08 (0.93-1.25)	1.07 (0.84-1.38)	1.24 (0.78-1.96)	1.26 (0.94-1.71)	.02	1.21 (0.98-1.53)
Bladder							
Incidence rate‡	17.1	18.2	18.7	22.9	20.3		22.3
HR (95% CI)§	1.0	1.08 (0.96-1.21)	1.06 (0.87-1.30)	1.36 (0.97-1.90)	1.23 (0.97-1.56)	.11	1.32 (1.10-1.57)
Brain							
Incidence rate‡	5.5	5.5	5.8	6.1	7.1		6.6
HR (95% CI)§	1.0	1.03 (0.84-1.26)	1.06 (0.74-1.51)	1.28 (0.66-2.50)	1.21 (0.77-1.91)	.06	1.16 (0.81-1.67)
Leukemia							
Incidence rate‡	6.5	6.2	5.3	12.8	10.3		11.1
HR (95% CI)§	1.0	1.06 (0.73-1.11)	0.87 (0.63-1.11)	1.68 (1.01-2.80)	1.58 (1.12-2.24)	.13	1.62 (1.23-2.13)

Abbreviations: CI, confidence interval; HR, hazard ratio.
SI conversion: To convert glucose from mg/dL to mmol/L, multiply by 0.0555.
*Participants with any of the following features at study entry were excluded: missing data on fasting blood glucose level, existing cancer, and missing data on smoking status.
†Diabetes was defined as fasting blood glucose level of at least 126 mg/dL (7.0 mmol/L) or medication.
‡The rate per 100 000 men is given, standardized to the age distribution of men in the 1995 Korean national population.
§The Cox proportional hazards model was adjusted for age, age squared, amount of smoking, and alcohol use.

not overweight. The association of serum glucose level with cancer risk did not vary by BMI (Figure 2).

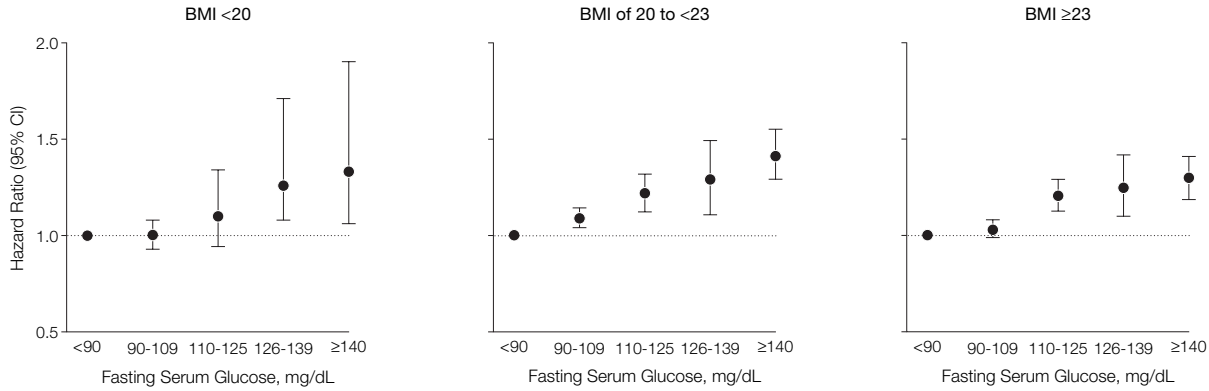
The study confirmed the excess risk of digestive cancers reported in several studies,[5,6,8] particularly of cancers of the pancreas, liver, esophagus, and colon among persons with diabetes. For pancreatic cancer, a 1995 meta-analysis of cohort and case-control studies estimated a 2-fold increase in risk of pancreatic cancer, comparing patients with and without diabetes.[18] The KCPS estimates were similar, and the HR increased with increasing fasting serum glucose level (Table 2 and Table 3), as found in a Chicago cohort study.[4] Our prospective results, along with the

Table 5. Age-Adjusted Incidence Rate per 100 000 Women for Various Cancers by Fasting Glucose Level in Korean Women, 1993-2002*

	Fasting Serum Glucose Level, mg/dL						
Type of Cancer	<90 (n = 270 157)	90-109 (n = 157 940)	110-125 (n = 22 578)	126-139 (n = 5657)	≥140 (n = 12 283)	*P* Value for Trend	Diabetes (n = 21 056)†
All cancer							
Incidence rate‡	352.2	354.3	351.4	320.2	342.7		457.2
HR (95% CI)§	1.0	1.02 (0.99-1.06)	1.03 (0.96-1.10)	1.03 (0.93-1.13)	1.15 (1.01-1.25)	.08	1.33 (1.25-1.41)
Stomach							
Incidence rate‡	55.9	56.0	54.6	54.4	54.8		54.2
HR (95% CI)§	1.0	1.02 (0.94-1.11)	0.96 (0.81-1.13)	0.99 (0.87-1.12)	1.01 (0.88-1.19)	.90	1.15 (0.99-1.34)
Colon/rectum							
Incidence rate‡	36.8	38.0	36.5	45.1	54.2		51.8
HR (95% CI)§	1.0	1.04 (0.94-1.15)	1.11 (0.92-1.34)	0.80 (0.53-1.20)	1.07 (0.84-1.36)	.84	1.17 (0.98-1.40)
Liver							
Incidence rate‡	21.1	19.5	26.4	24.5	27.3		24.0
HR (95% CI)§	1.0	0.90 (0.79-1.03)	1.23 (1.00-1.55)	1.05 (0.94-1.28)	1.22 (0.91-1.63)	.22	1.18 (1.00-1.43)
Pancreas							
Incidence rate‡	7.4	9.3	11.0	14.6	11.9		12.7
HR (95% CI)§	1.0	1.27 (1.03-1.57)	1.39 (0.96-2.02)	1.99 (1.13-3.49)	1.67 (1.09-2.56)	.04	1.56 (1.14-2.14)
Lung							
Incidence rate‡	23.0	26.2	22.5	24.8	27.2		28.0
HR (95% CI)§	1.0	1.14 (0.99-1.29)	0.99 (0.78-1.27)	1.30 (0.88-1.93)	1.13 (0.85-1.51)	.38	1.16 (0.94-1.44)
Breast							
Incidence rate‡	60.2	63.8	68.7	65.2	55.4		76.9
HR (95% CI)§	1.0	1.11 (0.92-1.34)	1.12 (0.92-1.34)	1.05 (0.71-1.55)	0.82 (0.61-1.21)	.33	1.51 (1.26-1.80)
Cervix							
Incidence rate‡	51.4	52.6	46.5	40.0	58.9		101.1
HR (95% CI)§	1.0	1.03 (0.94-1.13)	0.87 (0.71-1.08)	0.97 (0.66-1.43)	1.24 (0.98-1.58)	.40	2.20 (1.90-2.54)

Abbreviations: CI, confidence interval; HR, hazard ratio.
SI conversion: To convert glucose from mg/dL to mmol/L, multiply by 0.0555.
*Participants with any of the following features at study entry were excluded: missing data on fasting blood glucose level, existing cancer, and missing data on smoking status.
†Diabetes was defined as fasting blood glucose level of at least 126 mg/dL (7.0 mmol/L) or medication.
‡The rate per 100 000 women is given, standardized to the age distribution of women in the Korean Cancer Prevention Study.
§The Cox proportional hazards model was adjusted for age, age squared, amount of smoking, and alcohol use.

Figure 2. Hazard Ratios for All Cancer Deaths by Fasting Serum Glucose Levels in Korean Men by BMI, 1993-2002



Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. CI indicates confidence interval.

unchanged findings with exclusion of the first 5 years of follow-up, weigh against the possibility that the presence of pancreatic cancer increases blood glucose levels; ie, reverse causality. In the KCPS, we observed a significant positive linear trend for risk of pancreatic cancer with fasting glucose level: the HR was 1.7 (95% CI, 1.4-2.1) in men with diabetes and 1.5 (95% CI, 1.2-1.9) when data were restricted to men with at least 5 years of follow-up time. The complementary findings with these exposure measures, serum glucose level, and report of diabetes, and the presence of a dose-response relationship with fasting serum glucose level support a causal interpretation of these associations.

The findings for several other cancer sites further support this interpretation. In men, we found increased risks of cancers of the esophagus, liver, stomach, colon/rectum, kidney, and bladder and leukemia (Table 2), while in women, risk was increased for cancers of the liver, lung, breast, and cervix (Table 3). Other studies have also found increased risk for these cancer sites.[19,20] In Korea, hepatitis B infection is common and is an important cause of liver cancer.[21] Serum glucose level was not associated with hepatitis B surface antigen status in the subset of participants with assay results, indicating that hepatitis B does not confound the results for liver cancer. On hospital admission diagnoses, we found little mention of nonalcoholic steatotic hepatitis, suggesting that the increased risk of liver cancer associated with higher serum glucose level reflects a direct pathway rather than an indirect pathway through obesity and fatty liver damage.

For prostate cancer, for both incidence and mortality, we found no evidence for an association with either fasting serum glucose level or diabetes (Tables 2 and 4), consistent with other reports. One large, population-based Swedish cohort study found that men with diabetes had a 10% lower risk of developing prostate cancer than the general male population.[22] A reduced risk for men with diabetes was found in a case-control study in New York.[23] In contrast, the American Cancer Society's Cancer Prevention Study showed no association between diabetes at baseline and prostate cancer mortality,[24] and a study of incidence in 823 participants in the Baltimore Longitudinal Study of Aging also found association with fasting insulin and glucose levels.[20] The lack of association for prostate cancer weighs against observation bias as contributing to the positive associations for other sites; the medical care and frequent blood chemistries associated with diabetes might be expected to increase the opportunity for detecting prostate cancer, but the negative association is inconsistent with such bias.

Hyperinsulinemia has been cited as a possible risk factor for breast cancer, and supporting laboratory findings have been reported,[5] but results of epidemiological studies have been mixed.[25] In a recent publication based on the Nurses' Health Study, women with type 2 diabetes had a small increase in risk (HR, 1.17; 95% CI, 1.01-1.35). The association was apparent among postmenopausal women but not among premenopausal women.[25] We did not find an association, although 95% CIs for our estimates covered the value from the Nurses' Health Study. With stratification at age 55 years, we did not find increased risk in the older stratum, corresponding to an age range when most women would be postmenopausal.

The potential limitations of our study result primarily from using data collected for clinical purposes. Serum glucose was measured under fasting conditions using clinical laboratories operating with standard quality assurance and control protocols in place. A single measurement of fasting serum glucose made for clinical purposes is used as a diagnostic standard and matches the World Health Organization's recommended approach for epidemiological studies.[26] We further relied on self-report of a diagnosis of diabetes; the serum glucose level of those with reported history of diabetes was 66 mg/dL higher than for those not reporting diabetes, suggesting that the self-reported information was valid. We do not anticipate that these clinical data would artifactually introduce association of cancer risk with fasting serum glucose level.

Cancer mortality is subject to misclassification on death certificates, particularly with regard to attribution to a particular site. The limitations of death certificate data on cancer have been characterized in some countries,[27,28] but we are uncertain as to the applicability of the findings of these studies in Korea. A small study within KCPS showed high validity for a death certificate listing of lung cancer.[29] Additionally, we have found that of KCPS participants with incident liver cancer, 73% of their deaths were attributed to liver cancer over a follow-up interval of at least 5 years. In Korea, cancer registration is not yet complete nationwide; it is currently estimated at 90%.[30] Consequently, we used hospital admission for cancer as a further indication of cancer incidence. We were able to take potential confounding by smoking and alcohol consumption into account and explored effect modification by obesity. We cannot attribute the associations of fasting serum glucose level and diabetes to uncontrolled confounding, particularly given the dose-response relationships observed with glucose.

While the generalizability of the findings is uncertain, we have shown that fasting serum glucose level and diabetes are associated with cancer risk in a population far leaner than the Western populations in other studies. These associations do not reflect confounding by obesity, suggesting that the mechanism of increased cancer risk reflects the consequences of hyperinsulinemia. Glucose intolerance may be one pathway by which obesity increases cancer risk, and rising obesity may increase future cancer rates.

Author Contributions: Dr Jee 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: Jee, Ohrr, Samet.
Acquisition of data: Jee, Yun.
Analysis and interpretation of data: Jee, Sull, Ji, Samet.
Drafting of the manuscript: Jee, Yun, Ji, Samet.

Critical revision of the manuscript for important intellectual content: Ohrr, Sull.
Statistical analysis: Jee, Sull, Yun, Ji.
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Study supervision: Ohrr, Samet.
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