Glucose Tolerance Status and 20 year Cancer Incidence

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Abstract

Background: Type 2 diabetes, an extreme state of glucose intolerance, has been found to be associated with cancer mortality; less is known about impaired glucose tolerance and cancer incidence.

Objectives: To examine the association between fasting and post-load plasma glucose and insulin, and the 20 year incidence of cancer.

Methods: We followed a sample of the Jewish Israeli population (n=2780), free of cancer at baseline, from 1977-1980 to 1999 for cancer incidence and mortality. Baseline fasting and 1 and 2 hour post-load plasma glucose levels were recorded, as was insulin, in 1797 of them.

Results: During 20 years, 329 individuals (11.8%) developed cancer. Cancer incidence for all sites differed between men and women (13.0% and 10.7%, $P = 0.03$), and among different glucose tolerance status groups ($P = 0.01$). Cancer incidence hazard ratio, by glucose status adjusted for gender, age, ethnicity, smoking and body mass index, was 1.24 (95%CI 0.96–1.62, $P = 0.10$) for impaired fasting glucose or impaired glucose tolerance, and 1.32 (95%CI 0.96–1.81, $P = 0.09$) for type 2 diabetes mellitus, compared with those who were normoglycemic at baseline. Fasting insulin and cancer incidence were not associated.

Conclusions: An increased long-term cancer risk for individuals with impaired fasting glucose or glucose tolerance, or diabetes, is suggested. Even this modest association could have substantial public health consequences.

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The association between type 2 diabetes mellitus and cancer, two prevalent diseases of old age, has attracted much interest for many years [1,2]. In a study published in 1934, about 2.6% of 10,000 diabetic patients were diagnosed with or died from malignant diseases [3].

In recent years several studies have addressed the co-morbidity of cancer and T2DM by studying all-cause mortality or cancer mortality, separately or together, in cohorts followed for relatively long periods and following the ascertainment of their glucose tolerance status. Although these studies produced inconsistent results, most of them have shown a positive relationship between the GTS and cancer-related mortality [1,2,4,5]. Recently, a large-scale prospective American cohort of approximately 1.2 million subjects demonstrated that T2DM is an independent predictor of

mortality from cancer of the colon, pancreas, female breast, and male liver and bladder [6].

The carcinogenic effect of diabetes, perhaps mediated specifically by insulin, is one of the hypotheses forwarded to explain this putative association [7]. However, also insulin-like growth factor 1 has been associated with increased risk of several common cancers [8]. Several studies have reported elevated risk for specific cancers among diabetic patients and compared them with non-diabetics, but only few evaluated prospectively the association between incident cancers and blood glucose [9-11]. Therefore, we investigated the association between fasting and post-load plasma glucose, plasma insulin, and the 20 year incidence of cancer, in a representative sample of the Israeli population.

Subjects and Methods

Population and measurements

A cohort of 5710 Jewish men and women was randomly sampled from the Central Israeli Population Registry from three age strata of those born between 1912 and 1941. Ethnic origin was categorized as those originating from the Middle East, North Africa, America or Europe, and Yemen. This study group was followed from 1969 until 1999, comprising the Israeli Study of Glucose Intolerance, Obesity and Hypertension (the GOH study) [12] – a longitudinal study of the inter-relationship between these conditions and consequent morbidity and mortality in the adult Israeli Jewish population. A representative sub-sample of 2845 individuals was examined for fasting glucose, 1 and 2 hour blood glucose, and insulin post-100 g glucose load, together with blood pressure, weight, height, and smoking status, from 1977 until 1980 (baseline of the current study). Individuals with a diagnosis of cancer prior to the date of the oral glucose tolerance test examination were excluded (n=65). The Sheba Medical Center Review Board approved the study, and all participants gave their informed consent.

The Israeli National Cancer Registry maintains records of all malignancies diagnosed since 1960 and is updated annually from mortality records. A law mandating this reporting to the Registry from multiple sources, such as pathological reports, hospital discharge files, oncology institutes, and outpatient and private clinics, assures full coverage of the entire population. Indeed, the comprehensiveness of reporting was demonstrated to have reached 95% for solid tumors [13]. The GOH database

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T2DM = type 2 diabetes mellitus
GTS = glucose tolerance status

was linked to the Cancer Registry updated to 1999 in order to obtain information about 20 year cancer morbidity and mortality of the cohort.

Glucose status definitions

GTS was categorized into: a) normoglycemic, with fasting plasma glucose < 110 mg/dl and 2 hour post-load plasma glucose < 140 mg/dl; b) impaired fasting glucose or impaired glucose tolerance, when fasting glucose was in the range of 110–125 mg/dl and 2 hour post-load plasma glucose < 200 mg/dl, or with fasting glucose < 110 mg/dl and 2 hour post-load plasma glucose within the range of 140–199 mg/dl; c) T2DM, when fasting glucose > 125 mg/dl or 2 hour post-load plasma glucose ≥ 200 mg/dl.

Laboratory procedures

Plasma glucose was measured by automated Auto-analyzer II (Technion Instrument Corp, Israel), using potassium ferricyanide reduction. Plasma insulin levels were determined in duplicate by Phadebas radioimmunoassay (Pharmacia Diagnostics, UK); the intra-assay and inter-assay coefficients of variation were 4% and 8%, respectively.

Insulin measurements were added to the study protocol later in the data collection phase, and therefore are available for only 1797 (63.1%) of the 2845 participants. One and 2 hour post-glucose load insulin measurements were available for a smaller sample of 1241 subjects (44%), who completed the OGTT.

In addition, the association between all-site cancer incidence and the HOMA index (**Ho**meostasis **M**odel **A**ssessment) – i.e., fasting insulin (U/ml) × fasting glucose (mmol/L)/22.5 – was examined applying the categorization of < 2, 2–3.9, and ≥ 4.

Statistical analysis

The chi-square test was used for comparison of categorical variables; one-way and two-way analysis of variance (ANOVA) was applied for continuous variables between the three categories of individuals according to their GTS. Cox proportional hazard regression model was performed to assess the effect of being diabetic or being IFG/IGT on the incidence of cancer, controlling for demographic variables and lifestyle habits. Separate Cox models were applied to examine the effect of insulin levels (after logarithmic transformation) or the HOMA index on the incidence of all-sites cancer. Cumulative cancer incidence curves were calculated based on the Kaplan-Meier method and compared using the Log-Rank test.

Results

A total of 1410 males and 1435 females participated in this follow-up study. At baseline, 62% of the study group was in the normoglycemic glucose range, 22.6% were IGT or IFG, and 15.4% had T2DM. Table 1 shows the significant differences be-

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OGTT = oral glucose tolerance test
IFG = impaired fasting glucose
IGT = impaired glucose test
HOMA = Homeostasis Model Assessment

Table 1. Baseline (~1980) characteristics of the GOH cohort according to glucose tolerance status

	Glucose tolerance status			
	Normoglycemia n=1765 (62.0%)	IGT or IFG n=643 (22.6%)	T2DM n=437 (15.4%)	*P*
Age (mean ± SD)	51.9 ± 8.0	54.9 ± 7.8	57.6 ± 7.0	< 0.001
Gender (%)				
Male	59.2	24.5	16.3	0.01
Female	64.9	20.7	14.4	
Ethnic origin (%)				
Yemen	60.2	22.1	17.7	0.04
Europe/America	62.6	24.3	13.1	
Middle East	63.5	23.0	13.5	
North Africa	61.5	20.3	18.2	
BMI (mean ± SD)				
Male	25.0 ± 3.2	25.3 ± 3.7	26.9 ± 4.1	< 0.001
Female	25.9 ± 4.4	27.5 ± 5.0	29.1 ± 5.2	
Smoking (%)	40.1	38.6	39.2	0.8

Table 2. Cancer incidence rates in the three glucose tolerance groups

		Glucose tolerance status		
Site of cancer	Total* (N=2780) n (%)	Normoglycemia (N=1740) n (%)	IGT or IFG (N=626) n (%)	T2DM (N=414) n (%)
All sites**	329 (11.8)	182 (10.5)	89 (14.2)	58 (14.0)
Colon-rectum	48 (1.7)	24 (1.4)	14 (2.2)	10 (2.4)
Pancreas	10 (0.4)	6 (0.3)	3 (0.5)	1 (0.2)
Breast (female)	47 (3.3)	29 (3.2)	14 (4.8)	4 (2.0)
Prostate	29 (2.1)	18 (2.2)	9 (2.7)	2 (0.9)

* 65 individuals were excluded due to cancer diagnosed prior to the date of the OGTT.
** *P* = 0.01.

tween these three groups in age, gender, and body mass index. Individuals who had T2DM at baseline were older and had higher BMI values, in both genders. T2DM was more prevalent among Yemenites and North Africans as compared to subjects of European/American and Middle Eastern origin. No differences were observed in smoking habits of the three GTS groups.

Table 2 lists the site-specific cancer incidence rates classified according to GTS. During the 20 year follow-up period, 329 of the 2780 individuals who were free of cancer on the date of OGTT developed cancer. The most prevalent site was prostate in males and breast in females (16.2% and 30% of the cancer cases, respectively), followed by colorectal cancer in both genders (15.6% and 12.7% in males and females, respectively). Individuals with normoglycemia exhibited lower site-specific incidence rates as compared to those in the other two glucose tolerance groups, yet statistical significance was reached only for all sites combined (*P* = 0.01).

BMI = body mass index

Table 3. Adjusted Cox proportional hazard ratios for cancer

	Hazard ratio	95% CI	P
GTS (compared to normoglycemia)			
T2DM	1.32	0.96–1.81	0.09
IFG/IGT	1.24	0.96–1.62	0.10
Smoking (yes vs. no)	1.20	0.95–1.51	0.13
Age (1 year increment)	1.07	1.05–1.08	< 0.001
BMI (1 unit increment)	0.99	0.96–1.02	0.4
Gender (female compared to male)	0.93	0.73–1.17	0.5
Ethnic origin (compared to European/American)			
Yemen	0.52	0.38–0.71	< 0.001
Middle East	0.68	0.51–0.91	0.008
North Africa	0.74	0.55–1.01	0.06

Twelve percent of the males in the normoglycemic glucose range developed cancer, compared to 13.7% and 16.1% of those with IFG/IGT and with T2DM, respectively. Among females, the highest incidence rate was found in the IFG/IGT group, 14.8%, compared to 9.1% and 11.7% among the normoglycemic and diabetic groups, respectively (not shown).

Respective increases in the hazard ratios for the total cancer incidence of 32% and 24% (95%confidence interval = 0.96–1.81 and 0.96–1.62), relative to the normoglycemic group, were observed in the T2DM and IFG/IGT groups, controlling for age, gender, ethnic origin, smoking and BMI [Table 3]. As expected, age was highly related to the incidence of cancer in all sites combined. Yemenites and Middle Easterners had significantly lower adjusted hazard ratio for incidence of cancer.

Figure 1 depicts the cumulative cancer incidence curves for the normoglycemic, IFG/IGT, and T2DM groups. Normoglycemic individuals had lower 20 year cancer incidence rates as compared to those with improved glucose tolerance.

No significant associations were found between the logarithmic transformed values of insulin levels (fasting and 1 and 2 hour post-load) and the incidence of cancer adjusted for age,
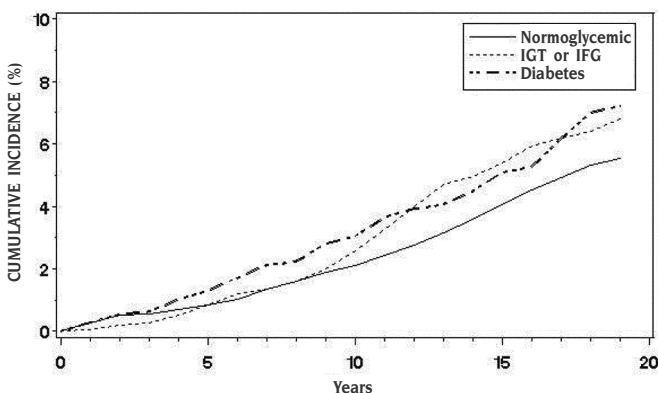

Figure 1. Twenty year cumulative cancer incidence in the cohort by Cox proportional hazard model according to glucose tolerance status at baseline, adjusted for gender, age, origin, smoking and BMI.

gender, origin, smoking and BMI for the normoglycemic, T2DM and IFG/IGT groups. The respective hazard ratios were 0.98 (95%CI 0.67–1.44), 1.01 (0.69–1.47) and 1.10 (0.78–1.56). Nor was such an association found for the HOMA-index categories (data not shown).

Discussion

In the present 20 year cohort study of a stratified random sample of 2780 Israeli men and women, a modest association between GTS and cancer incidence at all sites was observed. Increased hazard ratios were found for people with T2DM and IFG/IGT compared to those with normal glucose tolerance at baseline.

Fasting blood glucose was shown to be weakly associated with the incidence of all cancers combined, in men and women of a large cohort study of Austrian adults with a mean follow-up of 8.4 years [9]. In the Paris Prospective Study, after 20 years of follow-up, death rates from cancer in diabetic men, diagnosed from a post-challenge measurement, were three times higher than in non-diabetic men, and double in diabetic men diagnosed by fasting hyperglycemia but with normal 2 hour glucose values [14]. On the other hand, no association was noted between post-load glucose and cancer mortality, except for pancreatic cancer, in the Whitehall study of 18,274 male civil servants, where a much larger number of cancer deaths in the 18–20 year follow-up was recorded [15].

About 20,000 men and women in the Chicago Heart Association Detection Project in Industry, who had plasma glucose measurements done 1 hour after a non-fasting 50 g glucose challenge, were followed for 12 years. The post-challenge plasma glucose levels were positively related to cancer mortality in men but not in women [16]. The 12 year total number of cancer deaths was rather small in this cohort. Cancer mortality rates were also higher for those with a clinical diagnosis of T2DM than for those without it. After about 25 years of follow-up of this cohort, a modest association was found linking post-load plasma glucose, elements of the metabolic syndrome, colorectal cancer mortality in men [17], and pancreatic cancer mortality [18].

In two Japanese cohorts of men undergoing colonoscopy, T2DM, but not IGT or fasting insulin, carried a significantly increased risk of colon adenomas [19].

Mortality studies fail to cover all prevalent cancer cases in the community, especially when improved and effective cancer treatments considerably increase patient survival. A substantial strength of the present study stems from it being an incidence study in which cancer diagnosis was ascertained objectively through the National Cancer Registry, which was validated to include at least 95% of the malignant tumors of all sites [13].

In a recent prospective mortality study, 1.2 million U.S. men and women, with a mean age at enrollment of 57, were followed for 16 years in the Cancer Prevention Study II [6]. T2DM was found to be an independent predictor of mortality from cancer of the colon and pancreas in both genders, breast in females, and liver and bladder in men. These associations were not

IGF = insulin growth factor
CI = confidence interval

explained by BMI, and concur with our findings that the association between glucose intolerance or T2DM and the incidence of cancer is independent of BMI. Another very recently published prospective Swedish study of 33,293 women and 31,304 men reported an association of hyperglycemia with total cancer risk in women only, and an increase in risk of cancer at selected sites (pancreas, malignant melanoma, and urinary tract) in both men and women, independently of BMI [10]. This study had no data regarding baseline insulin levels.

In some studies, the diagnosis of T2DM was made based on responses in self-administered questionnaires, and thus did not include individuals unaware of their T2DM, who usually comprise one-third to one-half of the individuals with T2DM in the community [20]. The pre-diabetic state of glucose intolerance, which is similar in prevalence to T2DM, was also not considered. In our study, GTS was objectively determined by the OGTT, and reported T2DM cases were verified from the use of oral hypoglycemic medication, thus fully and objectively accounting for the entire spectrum of glucose tolerance.

Insulin was often implicated in the attempt to explain the association between all forms of glucose intolerance and malignancy. Currently available data do not lend unequivocal support to the insulin theory, nor do the findings of the present study, which failed to detect a relationship between plasma insulin levels and cancer. Only the Paris Prospective Study demonstrated a role for plasma insulin levels in the etiopathogenesis of cancer [21], but even there the association was positive for cancer of the liver and inverse for other types of cancer.

A limitation of the present study was the omission of data on IGF-1 that was linked to an increased risk of several cancers [8]. This factor was not routinely assayed during the late 1970s when the study started. Another limitation is that some of the individuals, especially those with IFG/IGT at baseline, developed overt T2DM during the long follow-up period. A sub-sample of survivors of this cohort had 30% of the cumulative incidence of T2DM documented in a 25 year follow-up study. The 3 year cumulative incidence of T2DM seen in the control arm of IFG/IGT in the Diabetes Prevention Program was 29% as well [22]. Unfortunately, in our study no glucose measurements or information regarding status of T2DM after baseline were available, thus it is not known whether changes in glucose tolerance status that might have occurred impacted on the risk of cancer.

A 100 g oral glucose load was used instead of the standard 75 g because the additional load has little effect on blood glucose levels but enhances insulin response [23].

Recent research suggested that the type of anti-diabetic medication for T2DM might be associated with cancer and cancer-related mortality. Bowker et al. [24] reported increased risk of cancer mortality among T2DM patients using exogenous insulin. Since no continuous follow-up of the baseline cohort was performed, it was not possible to control for medications used in the diabetic participants of our study.

Our findings demonstrate a modest association between glucose intolerance or T2DM and 20 year cancer incidence, based on well-ascertained exposure and outcome measures. The prevalence of abnormal glucose tolerance is increasing rapidly worldwide – both the "pre-diabetic" states, namely IFG and IGT, and T2DM. All ages are affected, but the prevalence increases in an age-dependent manner, where between 15% and 25% of the population in the 7th and 8th decades of life have abnormal glucose tolerance and T2DM [25]. Therefore, even the modest association that we observed could have a substantial public health impact and possibly also preventive implications. This implies that additional incidence studies on this relationship are needed. Elucidating the possible etiologic mechanism of glucose intolerance in malignancy generation would enable early detection of cancer among high risk glucose-intolerant populations. A lifestyle that decreases plasma glucose levels may reduce overall cancer risk.

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