Abnormal Glucose Tolerance and the Risk of Cancer Death in the United States

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Although abnormal glucose tolerance is a well-established risk factor for cardiovascular disease, its relation to cancer risk is less certain. Therefore, the authors performed a prospective cohort study using data from the Second National Health and Nutrition Examination Survey and the Second National Health and Nutrition Examination Survey Mortality Study to determine this relation. This analysis focused upon a nationally representative sample of 3,054 adults aged 30–74 years who underwent an oral glucose tolerance test at baseline (1976–1980). Deaths were identified by searching national mortality files through 1992. Adults were classified as having either previously diagnosed diabetes (*n* = 247), undiagnosed diabetes (*n* = 180), impaired glucose tolerance (*n* = 477), or normal glucose tolerance (*n* = 2250). There were 195 cancer deaths during 40,024 person-years of follow-up. Compared with those having normal glucose tolerance, adults with impaired glucose tolerance had the greatest adjusted relative hazard of cancer mortality (relative hazard = 1.87, 95% confidence interval (CI): 1.06, 3.31), followed by those with undiagnosed diabetes (relative hazard = 1.31, 95% CI: 0.48, 3.56) and diabetes (relative hazard = 1.13, 95% CI: 0.49, 2.62). These data suggest that, in the United States, impaired glucose tolerance is an independent predictor for cancer mortality.

diabetes mellitus; glucose tolerance test; mortality; neoplasms; nutrition surveys

Abnormal glucose tolerance is a well-established risk factor for increased all-cause mortality and cardiovascular disease mortality (1–3). Less well appreciated is growing evidence that abnormal glucose tolerance may predict an increased risk of cancer (4–6). Possible mechanisms include adiposity-related hormonal effects (7–9), dietary carcinogenesis associated with diets high in fats and energy (10–12), hyperlipidema (13), and dysregulation of cell growth related to high levels of insulin (11, 14–16) and insulin-like growth factors (17–24). Results from previous epidemiologic studies of the association of abnormal glucose tolerance and cancer are mixed (1, 4–6, 25–32). A few positive studies have reported relative risks ranging from 1.5 to 8.0 related to impaired glucose tolerance (4–6, 28). However, the majority of studies have reported no associations (1, 25, 27, 29–32). Methodological limitations that may account for the variability in prior studies include the nonstandard oral glucose tolerance test (28, 32), failure to control for obesity (31), samples not typical of the general US population (1, 4, 6, 25–27, 30, 32), and lack of attention to impaired glucose tolerance as a category distinct from undiagnosed or diagnosed diabetes (1, 26, 27, 29, 31, 32).

Therefore, to determine if abnormal glucose tolerance predicts cancer mortality in the general US population, we analyzed data from the Second National Health and Nutrition Examination Survey (NHANES II) Mortality Study

with the following two objectives: first, to compare cancer mortality among individuals with diagnosed type 2 diabetes, undiagnosed diabetes, and impaired glucose tolerance with that among individuals who had normal glucose tolerance; and second, to determine whether excess cancer mortality in adults with abnormal glucose tolerance is independent of adiposity and other potential cancer risk factors.

MATERIALS AND METHODS

Data source

Data were taken from the NHANES II Mortality Study, a prospective cohort study that passively followed participants over 30 years of age who underwent a detailed physical examination in NHANES II ($n = 9,250$). NHANES II was conducted between 1976 and 1980 by the National Center for Health Statistics. A stratified, multistage sample design was used to produce a representative sample of the noninstitutionalized US civilian population between the ages of 6 months and 74 years (33). The survey included a physical examination, laboratory tests, and questionnaires on health and nutrition-related topics. The response rate for adults aged 20–74 years selected for the examination was 68 percent (34).

Participants

Of the NHANES II participants, half the adults aged 30–74 years ($n = 4,664$) were selected at random and asked to undergo an oral glucose tolerance test. Individuals were excluded from analysis if they attended the afternoon examination session ($n = 14$), had a 2-hour oral glucose tolerance test duration of less than 105 minutes or greater than 135 minutes ($n = 2$), had a missing 2-hour blood glucose value ($n = 1,402$), or reported race as "other" (i.e., neither White nor African American) ($n = 62$). Participants who had type 1 diabetes (age of diagnosis < 30 years and current insulin use; $n = 10$) were also excluded. Thus, the analysis sample included 3,174 White or African-American adults with known glucose tolerance status. For the mortality and proportional hazards analysis, participants with a history of cancer at baseline ($n = 162$) were excluded, and participants with missing values for blood pressure, high density lipoprotein cholesterol, education, smoking, or physical activity ($n = 306$) were excluded from the multivariate analysis.

Glucose tolerance classification

Glucose tolerance was classified according to 1985 World Health Organization criteria (33). These criteria were chosen because they were in wide use at the time of the baseline examination and follow-up and because they had been applied in most studies of glucose tolerance in NHANES II (34). After a fasting blood sample was taken, participants ingested 75 g of glucose (33). Subsequent blood samples were taken at 120 minutes postchallenge, within 15 minutes of specified times. Participants were classified as having previously diagnosed diabetes ($n = 248$) if they answered "yes" to both of the following questions: "Do you have sugar diabetes?" and "Did a doctor tell you that you had it?"; they were classified as having undiagnosed diabetes ($n = 183$) if their fasting plasma glucose level was greater than or equal to 140 mg/dl or if their 2-hour plasma glucose level was greater than or equal to 200 mg/dl. Participants were classified as having impaired glucose tolerance if their 2-hour plasma glucose level was between 140 mg/dl and 199 mg/dl and their fasting plasma glucose level was less than 140 mg/dl ($n = 480$). All other participants were classified as having normal glucose tolerance ($n = 2,263$).

Baseline assessments

Information on age at interview, sex, race, years of education (less than high school, high school or greater), and personal health characteristics was obtained by interview. Cigarette smoking status was categorized as current, past, or never. Alcohol intake was categorized as zero drinks per week, 1–2 drinks per week, or three or more drinks per week. Participants were asked to rate both their own recreational and nonrecreational physical activity as "much," "moderate," or "little to no activity." Responses for both types of physical activity questions were summed and recoded to yield the following classification: 1 (high in one and moderate in the other), 2 (moderate in both), 3 (moderate in one and low in the other), and 4 (low activity in both). There were no participants who reported high physical activity in both categories. Participants were classified as having a history of cancer if they answered "yes" to the following question: "Has a doctor ever told you that you had cancer?"

Height, measured using standardized bar, and weight, measured using a balance bar scale, were used to calculate the body mass index (weight (kg)/height (m)^2) for each participant. Using a mercury sphygmomanometer, a physician recorded each participant's resting blood pressure twice in the sitting position. The average of the two blood pressure (mmHg) readings for each participant was used in this study. Laboratory measures, including standard blood assays for serum total cholesterol, high density lipids, triglycerides, and plasma glucose levels, were obtained after participants fasted overnight for 10–16 hours (33, 35).

Outcomes

Mortality status was ascertained for the years 1976–1992 by searching the National Death Index and the Social Security Administration Death Master File (36). There was no censoring in this cohort; participants not found to be deceased by December 31, 1992, were assumed to be alive.

Deaths were ascribed to cancer if cancer was coded as the underlying cause of death on the death certificate (*International Classification of Diseases,* Ninth Revision (ICD-9), codes 146.0–239.9). There were a total of 195 cancer deaths in the oral glucose tolerance test group. In subsidiary analyses of specific types of cancer, cancer deaths were subdivided as follows: colon (ICD-9 codes 153.0–153.9), breast (ICD-9 codes 174.0–175.9), prostate (ICD-9 codes 185.0–185.9), lung (ICD-9 codes 162.0–162.9), and pancreas (ICD-9 codes 157.0–157.9).

Analysis

Analyses were weighted to the US population using the standard National Center for Health Statistics-derived sample weights for the midpoint of NHANES II (March 1, 1978) and SUDAAN statistical software, version 6.4, to account for the complex survey design and provide nationally representative estimates (33, 37, 38).

Baseline comparisons by glucose tolerance groups for demographics (age, sex, race, education) and behavioral (physical activity, smoking, alcohol intake) and biologic (total cholesterol, high density lipoprotein cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, body mass index, history of cancer at baseline) risk factors were completed using analysis of variance or Pearson's χ^2 test. All tests of significance were two tailed, and no corrections for multiple comparisons were made.

The weighted number of person-years was summed separately for each glucose tolerance group. The weighted number of deaths from cancer was also summed for each group. Mortality was calculated for each group using these weighted sums. The Poisson distribution was used to calculate 95 percent confidence intervals (39).

Cumulative mortality was determined using a life-table method (40). For each 5-year age group, the weighted population based on age at death or at end of follow-up was calculated along with the weighted number of deaths from all cancers and the specific cancers for each glucose tolerance group. A life table was developed, and the probability of mortality based on age was calculated. Cumulative mortality was determined for all cancers and specific cancers and plotted as cumulative mortality curves by glucose tolerance group. Cumulative mortality curves were compared using log-rank tests (39, 41).

Proportional hazard analyses (41) were performed to determine whether the observed relative hazards could be explained by other potentially confounding variables including age, sex and race, education, behavioral risk factors (physical activity and smoking), and biologic risk factors (body mass index, systolic blood pressure, and high density lipoprotein cholesterol). Graphs of the log-log plot of the relative hazards by time were used to confirm the assumption of proportional hazards. There were no significant first-order interactions between glucose tolerance status and any other covariate (all p values > 0.05).

Analysis was repeated using the 1998 World Health Organization criteria (42). On the basis of these criteria, participants were classified as having diagnosed diabetes ($n = 248$), undiagnosed diabetes if the fasting glucose level was greater than or equal to 126 mg/dl or if the 2-hour plasma glucose level was greater than or equal to 200 mg/dl ($n = 206$), impaired glucose tolerance if the fasting plasma glucose level was less than 126 mg/dl and the 2-hour glucose level was 140–200 mg/dl ($n = 465$), or impaired fasting glucose if the fasting glucose level was greater than or equal to 110 mg/dl and less than 126 mg/dl and the 2-hour glucose level was less than 140 mg/dl ($n = 71$). Because of the small number of participants with impaired fasting glucose and the small number of deaths in this group, we combined the impaired fasting glucose and the impaired glucose tolerance groups

into an abnormal glucose tolerance group. All other participants were classified as having normal glucose tolerance ($n = 2,184$). To attempt to exclude participants who may have had subclinical cancer prior to examination in NHANES II, we also repeated the analysis excluding deaths during the first 3 and 5 years of follow-up.

RESULTS

Baseline characteristics

Table 1 summarizes the characteristics of the cohort by glucose tolerance status at baseline. Expected trends were observed across the groups from normal glucose tolerance to diagnosed diabetes. Specifically, compared with their counterparts who had normal glucose tolerance, those with abnormal glucose tolerance were older and more likely to be female, less educated, and sedentary. They also were less likely to be current smokers or to drink one or more drinks per week compared with those having normal glucose tolerance. Further, they had greater adiposity, lower high density lipoprotein cholesterol, higher total cholesterol and triglycerides, and higher blood pressure. The reported history of cancer at baseline was highest for participants with diagnosed diabetes, but it was not statistically different compared with other groups.

All-cause mortality

As we previously reported, there were 737 deaths (23 percent) during 42,130 person-years of follow-up. The all-cause death rate per 1,000 person-years was highest for the diagnosed diabetes group at 40.9, followed by the undiagnosed diabetes group at 33.2, the impaired glucose tolerance group at 20.8, and the normal glucose tolerance group at 10.6 (p for trend < 0.001) (43). Likewise, cumulative all-cause mortality was strongly associated with the glucose tolerance group, rising from 20.3 percent in the normal glucose tolerance group at age 70 years to 26.7 percent in the impaired glucose tolerance group, 33.9 percent in the undiagnosed diabetes group, and 41.2 percent in the diagnosed diabetes group (overall log-rank $p < 0.001$) (43) (detailed findings not presented).

Cancer mortality

Patterns of cancer mortality differed from all-cause mortality. Of the 737 deaths, 206 (28 percent) were attributable to cancer. The highest cancer death rate per 1,000 person-years was for the impaired glucose tolerance group at 8.1, followed by undiagnosed diabetes at 5.7, diagnosed diabetes at 5.4, and the normal glucose tolerance group at 4.1 (table 2).

At age 70 years, the cumulative mortality for cancer was highest for the impaired glucose tolerance group (12.4 percent), followed by the normal glucose tolerance group (7.9 percent), undiagnosed diabetes (7.1 percent), and diagnosed diabetes (5.2 percent) (figure 1).

To determine whether the excess risk of mortality associated with abnormal glucose tolerance might be explained by the presence of cancer risk factors or biologic factors that commonly accompany diabetes and abnormal glucose toler-

TABLE 1.   Baseline characteristics of 3,174 adults aged 30–74 years in the Second National Health and Nutrition Examination Survey (1976–1980) by glucose tolerance status*

	Normal glucose tolerance (*n* = 2,263)	Impaired glucose tolerance (*n* = 480)	Undiagnosed diabetes (*n* = 183)	Diagnosed diabetes (*n* = 248)
Age (mean years)†	47.9 (0.3)‡	54.3 (0.7)	58.3 (1.0)	58.4 (0.7)
Female (%)†	53.2	55.6	61.6	60.2
White (%)†	92.1	90.5	87.0	85.5
Education, less than high school (%)†	33.5	41.5	53.7	51.7
Physical activity (%)†				
1 (high)	22.2	18.1	14.9	10.2
2	46.4	39.5	42.6	33.2
3	21.3	29.2	28.5	29.1
4 (low)	10.0	13.3	13.9	27.5
Smoking status (%)†				
Current	36.4	27.8	29.6	22.9
Past	26.4	29.7	26.2	36.0
Never	37.2	42.5	44.2	41.1
Alcohol intake (%)†				
0 drinks/week	34.6	41.4	47.5	66.6
1–2 drinks/week	62.4	53.8	46.3	32.2
≥3 drinks/week	3.0	4.9	6.2	1.2
Body mass index (mean kg/m²)†	25.3 (0.1)	27.8 (0.3)	29.8 (0.9)	27.7 (0.4)
Systolic blood pressure (mean mmHg)†	125.7 (0.8)	138.5 (1.7)	142.0 (1.7)	143.4 (2.2)
Diastolic blood pressure (mean mmHg)	78.4 (0.6)	83.8 (0.9)	83.9 (0.9)	83.4 (1.1)
Total cholesterol (mean mg/dl)†	219 (1.4)	231 (3.0)	238 (4.0)	229 (3.4)
High density lipoprotein cholesterol (mean mg/dl)†	50.9 (0.6)	48.5 (1.2)	47.7 (1.6)	46.2 (1.5)
Triglyercides (mean mg/dl)†	129 (2.2)	174 (7.7)	216 (20.3)	196 (6.3)
Prior history of cancer (%)	3.7	5.1	6.1	9.0

  * All results weighted to the US population in 1978 using SUDAAN software (Research Triangle Institute, Inc., Research Triangle Park, NC).
  † Overall *p* value < 0.05 (tests null hypothesis of homogeneity across all four glucose tolerance groups).
  ‡ Numbers in parentheses, standard error.

TABLE 2.   Cancer mortality during follow-up (1976–1992) by glucose tolerance status for 3,054 adults aged 30–74 years in the Second National Health and Nutrition Examination Survey (1976–1980)*

	Normal glucose tolerance (*n* = 2,250	Impaired glucose tolerance (*n* = 477)	Undiagnosed diabetes (*n* = 180)	Diagnosed diabetes (*n* = 247)
Cancer deaths (no.)	122	47	12	14
Deaths per 1,000 person-years	4.1	8.1	5.7	5.4
Adjusted relative hazard†	1.00	1.67	1.00	1.03
95% confidence interval	Referent	0.96, 2.88	0.41, 2.42	0.56, 1.89

  * All results weighted to the US population in 1978 using SUDAAN software (Research Triangle Institute, Inc., Research Triangle Park, NC).
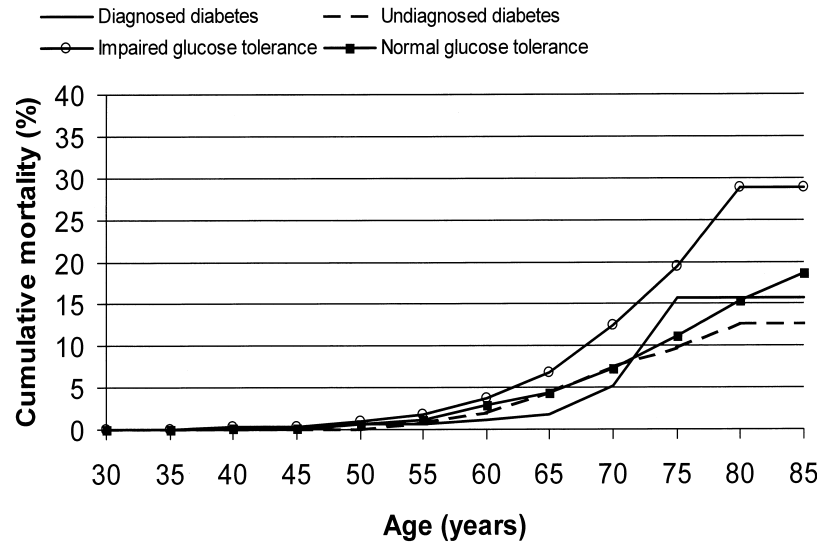 † Adjusted for age, sex, and race.

FIGURE 1. Cumulative cancer mortality in 3,054 adults aged 30–74 years in the Second National Health and Nutrition Examination Survey (1976–1980) by glucose tolerance group at baseline. Cumulative mortality was calculated using a life-table approach after weighting to the US population in 1978. The solid line indicates mortality in adults with diagnosed diabetes at baseline, the dashed line indicates mortality in adults with undiagnosed diabetes at baseline, the circles indicate mortality in adults with impaired glucose tolerance at baseline, and the squares indicate mortality in adults with normal glucose tolerance at baseline. The overall log-rank test p value was less than 0.001.

ance, we constructed proportional hazards models. After simultaneous adjustment for age, sex, race, education, smoking, alcohol intake, physical activity, body mass index, systolic blood pressure, and high density lipoprotein cholesterol, abnormal glucose tolerance remained strongly associated with cancer mortality. Compared with their counterparts who had normal glucose tolerance, participants with impaired glucose tolerance had a fully adjusted relative risk

for cancer mortality that was 1.87 times higher (table 3). There was also a 1.13-fold increased risk for participants with diagnosed diabetes and a 1.31-fold increased risk for participants with undiagnosed diabetes; however, neither was statistically significant (table 3). We repeated the analysis excluding deaths during the first 3 and 5 years of follow-up to determine if the increased cancer mortality was due to undiagnosed or subclinical cancer at baseline. This did not

TABLE 3. Adjusted relative hazard of cancer mortality during follow-up (1976–1992) by glucose tolerance status for 3,054 adults aged 30–74 years in the Second National Health and Nutrition Examination Survey (1976–1980)*

Lag time†	Normal glucose tolerance (n = 2,250)	Impaired glucose tolerance (n = 477)	Undiagnosed diabetes (n = 180)	Diagnosed diabetes (n = 247)
0 years (no.)‡	122	47	12	14
Relative hazard§	1.00	1.87	1.31	1.13
95% confidence interval	Referent	1.06, 3.31	0.48, 3.56	0.49, 2.62
3 years (no.)‡	109	41	9	9
Relative hazard§	1.00	1.85	1.41	1.17
95% confidence interval	Referent	0.97, 3.55	0.46, 4.29	0.44, 3.13
5 years (no.)‡	95	35	9	9
Relative hazard§	1.00	1.84	1.55	1.30
95% confidence interval	Referent	0.93, 3.65	0.50, 4.84	0.48, 3.52

* All results weighted to the US population in 1978 using SUDAAN software (Research Triangle Institute, Inc., Research Triangle Park, NC).

† Lag time: 0 years indicates that no events were excluded from the analysis; 3 years indicates that events in the first 3 years were excluded from the analysis; 5 years indicates that events in the first 5 years of follow-up were excluded from the analysis.

‡ Number of deaths, unweighted.

§ Adjusted for age, sex, race, education, smoking, alcohol intake, physical activity, high-density lipids, systolic blood pressure, and body mass index.

appreciably change the increased risk of cancer mortality for participants with impaired glucose tolerance compared with those who had normal glucose tolerance (table 3).

We repeated the analysis using the 1998 World Health Organization definition for undiagnosed diabetes and abnormal glucose tolerance. Similar trends were observed for cancer mortality. Compared with those who had normal glucose tolerance, the fully adjusted relative risk of cancer death for participants with abnormal glucose tolerance was 1.53 (95 percent confidence interval (CI): 0.95, 3.13). This increased risk was also observed for participants with undiagnosed diabetes (relative risk (RR) = 1.25, 95 percent CI: 0.50, 3.13) and diagnosed diabetes (RR = 1.19, 95 percent CI: 0.51, 2.75).

Specific types of cancer

To determine if a specific type of cancer was primarily responsible for increased cancer mortality in the impaired glucose tolerance group, we compared specific cancers by glucose tolerance group. The most commonly reported cancer sites were the lung ($n = 67$), colon ($n = 19$), pancreas ($n = 13$), breast ($n = 9$), and prostate ($n = 10$). Compared with that of the participants who had normal glucose tolerance, the relative hazard (adjusted for age, sex, and race) of colon cancer mortality for participants with impaired glucose tolerance ($n = 8$) was 4.24 (95 percent CI: 1.25, 14.41). Compared with that of the participants who had normal glucose tolerance, the relative hazard (adjusted for age, sex, and race) of lung cancer mortality for participants with impaired glucose tolerance ($n = 14$) was 1.57 (95 percent CI: 0.70, 3.54). Participants with undiagnosed or diagnosed diabetes did not appear to have an increased risk of cancer mortality by specific cancer site. However, the small number of events within each of these groups precludes us from drawing any inferences (44).

DISCUSSION

These data suggest that, in the general US population, impaired glucose tolerance is a strong predictor of death due to cancer, particularly colon cancer. This association was independent of adiposity, smoking, and a variety of other potentially confounding factors. In contrast, for adults with diabetes, whether undiagnosed or diagnosed, there was little or no association with subsequent risk of cancer death. The strengths of this study that lend weight to the conclusions include a nationally representative sample, long follow-up, and use of a standard 75-g oral glucose tolerance test.

Nonetheless, several limitations should be kept mind. First, we cannot exclude the possibility that unsuspected cancer at the time of baseline assessment led to abnormal glucose tolerance (45–47). However, there was no appreciable difference in mortality risk when deaths during the first 5 years of follow-up were excluded. If preclinical cancer were driving the results, one would expect the risk of cancer mortality to decrease significantly when these deaths were excluded. Second, there was nonresponse in NHANES II and, in addition, people in nursing homes, long-term-care hospitals, and prisons were not included. However, previous

investigation of nonresponse in the oral glucose tolerance group revealed that respondents and nonrespondents did not differ significantly in demographic or health-related characteristics (34). Participants who completed and those who did not complete the oral glucose tolerance test did not differ by mortality experience: The all-cause death rate per 1,000 person-years for oral glucose tolerance test respondents was 17.3 (95 percent CI: 16.1, 18.7), and for oral glucose tolerance test nonrespondents, it was 18.0 (95 percent CI: 16.1, 20.2); the cancer mortality per 1,000 person-years for respondents was 4.3 (95 percent CI: 3.8, 4.9), and for nonrespondents, it was 5.0 (95 percent CI: 4.5, 5.6). Third, there was also potential for misclassification of glucose tolerance status at baseline. Previous studies have found that, although day-to-day variation of glucose tolerance may occur, these variations are not the result of changes in insulin response and are similar to the variations found with other biologic measurements such as cholesterol (48–50). If misclassification occurred, it was likely to be nondifferential and would therefore have produced a conservative bias. In addition, only 6.7 percent of the impaired glucose tolerance group who died had diabetes coded on their death certificates (43). Fourth, because mortality follow-up was passive, misclassification of vital status was possible. It is unknown whether the validity of cancer recorded on death certificates differs by diabetes status. However, autopsy studies have found that the recording of deaths from cancer on death certificates is highly accurate (51, 52). Previous studies indicate that deaths may be underascertained in Blacks (36). Insofar as Blacks were overrepresented in the abnormal glucose tolerance groups, this may have produced an underestimate of the mortality risk. Finally, the small numbers of specific cancer deaths limited the power for analyses by cancer types, so relative hazards estimates for specific types of cancer should be interpreted with caution (44).

Results from previous studies regarding abnormal glucose tolerance and cancer risk are mixed. Of 13 prospective cohort studies published since 1980 concerning glucose tolerance and cancer, four examined only the increased risk of incident cancer for people with diagnosed diabetes, neglecting individuals with impaired glucose tolerance or undiagnosed diabetes. Of those four studies, three found no evidence of increased risk for incident cancer (29), colorectal cancer mortality (31), or prostate cancer (30), and one study (27) found a slightly increased risk of colorectal cancer for women with diagnosed diabetes. Three studies that combined participants with diagnosed diabetes and undiagnosed diabetes into a single exposure category reported that there was a slightly increased risk of cancer mortality and, specifically, pancreatic cancer (25, 26, 32).

Of the six prospective studies examining the association of abnormal glucose tolerance and cancer, five provide the strongest evidence to date linking abnormal glucose tolerance and an increased risk of cancer (4–6, 28, 53). Stengard et al. (53) did not find an association between abnormal glucose tolerance and cancer; however, the study had less than 5 years of follow-up. Levine et al. (28) examined different plasma glucose categories after a 1-hour oral glucose tolerance test and the risk of cancer in the Chicago Heart Association Detection Project cohort. The relative risk

of cancer for participants with a 1-hour plasma glucose level greater than 205 mg/dl was statistically significant for men (RR = 1.47, 95 percent CI: 1.09, 1.99) but not for women (RR = 1.08, 95 percent CI: 0.67, 1.72). Shaw et al. (5) pooled data from three separate cohort studies from Mauritius, Fiji, and Nauru to determine the association of known diabetes, impaired fasting hyperglycemia, and isolated postchallenge hyperglycemia with mortality in 9,179 adults. The relative risk of cancer mortality was greatest for individuals with isolated postchallenge hyperglycemia (RR = 8.0, 95 percent CI: 3.6, 17.9). Individuals with diabetes did not have an increased risk of cancer mortality. Schoen et al. (4) conducted a nested case-control study using the Cardiovascular Health Study cohort with a mean follow-up time for cases and controls of 6.5 years. All participants underwent a 75-g oral glucose tolerance test at baseline, and exposure categories were designated as normal glucose tolerance, impaired glucose tolerance, and diabetes. Cases were selected from participants who had incident colon cancer. There was an increased risk of cancer for impaired glucose tolerance and diabetes, although it was not statistically significant. However, analysis of 2-hour glucose categories by quartiles, excluding people with diabetes, found an increased risk of cancer for the highest quartile compared with the lowest of 2.4 (95 percent CI: 1.2, 4.7). In a prospective study of prostate cancer mortality, Gapstur et al. (6) found that, compared with participants with a postload plasma glucose level of less than 6.6 mmol/liter, those with levels of 6.7–8.8 mmol/liter had a 1.64-fold (95 percent CI: 1.1, 2.6) increased risk.

The exact mechanism underlying the increased risk of cancer mortality in general, and colorectal cancer mortality in particular, for individuals with impaired glucose tolerance is not clear. Previous studies have suggested that compensatory hyperinsulinemia (4–6, 54) may promote carcinogenesis, since insulin has been shown to be an important growth factor, especially for colonic epithelial cells. Impaired glucose tolerance corresponds to increased insulin levels (55). These increased insulin levels also correspond to increased levels of growth factor and insulin-like growth factor binding proteins and decreased levels of insulin-like growth factors, all of which inhibits cell apoptosis (13, 17, 56). Impaired glucose tolerance and hyperinsulinemia also correspond to increased adiposity, which has also been linked to increased risk of cancer, especially for colon cancer and endometrial and postmenopausal breast cancer in women (4, 7–9, 57).

In light of these hypothesized mechanisms, why should impaired glucose tolerance be more strongly related to cancer death than diabetes itself? One possible explanation is that, as individuals progress from impaired glucose tolerance to diabetes, insulin levels decrease from the highest values for individuals with impaired glucose tolerance to levels well below normal for individuals with diabetes who have β-cell failure (55). However, since participants with diagnosed diabetes in this study had type 2 diabetes, it less likely that they had progressed to β-cell failure and were more likely insulin resistant. Another possible explanation is that of competing causes of death, whereby individuals with diabetes may be more likely to die from cardiovascular

disease than from cancer. A third is that diabetes offers some type of protective effect as observed by De Giorgino et al. (58), who observed that diabetes was associated with longer survival rates for individuals with malignant tumors. This observation, along with recent evidence that the vessels of individuals with diabetes may impede neoplastic cell spread and metastasis (59), may also explain the lower cancer mortality observed in participants with undiagnosed and diagnosed diabetes. Each of these observations may contribute to the explanation of why a greater risk of cancer mortality is observed for individuals with impaired glucose tolerance than for individuals with diabetes.

There are three main implications of our study. First, impaired glucose tolerance may identify individuals who are at high risk of developing colon cancer to target for increased participation in screening programs and for rational triage of invasive or expensive screening. Second, individuals with impaired glucose tolerance may also serve as a high-risk group from which to recruit for cancer prevention trials. Finally, although these results do not necessarily have implications for cancer prognosis, they do for cancer incidence and etiology by identifying impaired glucose tolerance and related physiologic determinants as potential mechanisms and risk factors for cancer.

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