EBioMedicine 21 (2017) 117–122

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

Response to Intravenous Glucose-Tolerance Test and Risk of Cancer: A Long-Term Prospective Cohort Study

R.S. Falk [a], S. Tretli [b,c], J.E. Paulsen [d], L. Sandvik [a], J. Erikssen [e], T. Heir [e,f,*]

[a] Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway
[b] Department of Research, Cancer Registry of Norway, Oslo, Norway
[c] Department of Public Health and General Practice, Norwegian University of Science and Technology, Trondheim, Norway
[d] Department of Food Safety and Infection Biology, Norwegian University of Life Sciences, Oslo, Norway
[e] Oslo Ischemia study, Oslo University Hospital, Oslo, Norway
[f] Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Norway

ARTICLE INFO

Article history:
Received 23 April 2017
Received in revised form 14 June 2017
Accepted 19 June 2017
Available online 21 June 2017

Keywords:
Glucose tolerance
Cancer incidence
Cohort study
Healthy men
Polymorphism
Plasma glucose

ABSTRACT

Background: Impaired glucose regulation, measured with an oral glucose-tolerance test, has been associated with the risk of cancer. Here, we explored whether the response to an intravenous glucose-tolerance test (IVGTT) is associated with the risk of cancer.
Methods: A cohort of 945 healthy men, aged 40–59 years in 1972–75, was followed for 40 years. An IVGTT was performed at baseline. Blood samples for glucose determinations were drawn immediately before glucose injection and thereafter every 10 min for 1 h. Associations were assessed with incidence rate ratios (IRR) and Cox models.
Findings: Cancer incidence was higher among men with 10-min glucose levels below the median than in men with levels above the median (IRR: 1.5, 95% CI: 1.2–1.9). This association remained significant after adjusting for relevant confounders (HR: 1.6, 95% CI: 1.3–2.1) and when excluding the first 10 years of follow-up to minimize the possibility of reverse causality (HR: 1.5, 95% CI: 1.2–2.0).
Interpretation: Healthy middle-aged males that responded to an intravenous glucose injection with rapid glucose elimination during the first phase had an elevated risk of cancer during 40 years of follow-up. First phase response to a glucose load might be related to cancer development.

1. Introduction

Previous studies suggest that impaired glucose regulation may be associated with cancer incidence or cancer-related death. This association was found among patients with diabetes mellitus (Hirakawa et al., 2012; Jee et al., 2005; Levine et al., 1990; Saydah et al., 2003), pre-diabetic levels of impaired fasting glycemia (Hirakawa et al., 2012; Jee et al., 2005; Huang et al., 2014; Rapp et al., 2006), or impaired glucose tolerance (Hirakawa et al., 2012; Huang et al., 2014; Zhou et al., 2010). In those studies, impaired glucose regulation was detected with the oral glucose-tolerance test (OGTT), where 2-h post-load glucose levels were measured after a standardized dose of oral glucose (Hirakawa et al., 2012; Zhou et al., 2010).

Impaired glucose tolerance can also be detected with the intravenous glucose-tolerance test (IVGTT), where an artificial increase in plasma glucose induces insulin secretion from pancreatic β cells. The characteristic biphasic insulin secretion response is a rapid, transient first phase, which lasts a few minutes, followed by a more sustained second phase (Seino et al., 2015). In contrast, the insulin secretion response of β cells during an OGTT is more complex; it can produce variable results, due to the combined influences of plasma glucose, hormones, neurotransmitters, and nutrients.

In the present study, we investigated the relationship between glucose tolerance and cancer risk in a 40-year follow-up study of initially healthy middle-aged men. We implemented the IVGTT, with plasma glucose measurements every 10 min for 1 h. We aimed to explore the association between cancer risk and the responses to an IVGTT, including the first phase (plasma glucose at 10 min) and second phase (plasma glucose at 10–60 min) of the glucose induced insulin response.

2. Materials and Methods

2.1. Data Sources

The Oslo Ischemia Study is a comprehensive health survey that was established in 1972. A total of 2341 men, aged 40–59 years, were invited

* Corresponding author at: Oslo Ischemia Study, Oslo University Hospital, N-0407 Oslo, Norway.
E-mail address: trond.heir@medisin.uio.no (T. Heir).

http://dx.doi.org/10.1016/j.ebiom.2017.06.018

to participate from five companies in Oslo, Norway. The men were apparently healthy (i.e., free from somatic diseases and no need for drugs) according to a physical examination and a review of medical records. Among those invited, 2014 (86%) agreed to participate, provided informed consent in accordance with the Declaration of Helsinki, and completed the study protocol. At inclusion, after at least 12 h fasting and 8 h abstaining from smoking, participants underwent a comprehensive review of medical history, clinical and physical examinations, a panel of blood tests, an IVGTT, and a maximal exercise tolerance bicycle test. In addition, information on lifestyle variables (i.e., smoking habits) was collected with a questionnaire. The detailed selection procedures and implementation procedures were reported previously (Erikssen and Enger, 1977; Erikssen et al., 1998; Heir et al., 2011).

Information on cancer and vital status were obtained by linking the cohort data to the Cancer Registry of Norway, which has stored data on all malignancies diagnosed in the Norwegian population since 1953. Mandatory reporting to the Registry from several independent sources ensures data completeness and high data quality (Larsen et al., 2009). The cancer data comprised information on the cancer site (ICD-10 code) and the date of diagnosis. Cohort data were linked to the Registry through the unique personal identification number assigned to every individual that has resided in Norway from 1960 to present. Permission to link the data was provided by the Regional Committees for Medical and Health Research Ethics, Norway.

2.2. Variables

The IVGTT was originally implemented as part of a prospective study on cardiovascular disease and diabetes. The test was performed with an intravenous injection of 25 g glucose (50 mL 50% glucose solution) during 2–3 min, via an inlaid cannula (venflon) with subjects in a semiprone position. Completion of the injection was defined as time zero. Blood samples for glucose determinations were taken right before the glucose injection, then after the injection, at time zero, and thereafter, every 10 min for 1 h. The first phase responses was defined as the level of glucose at 10 min (Seino et al., 2015), and further categorized into two groups; 10-min glucose levels ≤ the cohort median were considered "low" and levels > the cohort median were considered "high". The second phase response was assessed by the slope of a linear regression analysis performed on a plot of logarithmic glucose values over time (i.e., the derived glucose disappearance rate [K_G], log(mmol/L)/min), when four or more measurements were available (Bjørnholt et al., 2001).

Baseline measurements included the individual's body height and weight, measured objectively, and physical fitness (kJ/kg), measured as the total work (sum of the work performed in a bicycle test) divided by body weight. Information on smoking was extracted from the questionnaire, and individuals were categorized as "never", "former", or "present" smokers. Information about the year of a diabetes mellitus diagnosis was obtained from surveys and patient records for the period of 1979 to 2008 (Bjørnholt et al., 2001; Grundvold et al., 2012). Information on diet and alcohol consumption, which are factors associated with risk of cancers in men (World Cancer Research Fund, 2007), was not available.

The protocol was followed strictly through the first part of data collection period with blood sampling every 10 min. Because of reduction in workforce the procedure was changed to blood collection every 15 min in the second part. Only those who have followed the original protocol were included in the present study. Thus, 1016 men were excluded because of changes in the data collection procedures. Furthermore, 36 men did not perform the IVGTT at all, 15 men were excluded due to a cancer diagnosis prior to the date of the first examination and two men were lost to follow-up. A total of 945 men were included in the analyses (see Appendix A Flowchart). This cohort was followed for cancer and death to the end of 2012.

2.3. Statistical Analyses

Descriptive analyses of individual baseline characteristics are expressed as the means and standard deviations (SD). Graphically, during the IVGTTs, glucose levels are expressed as the median for each group (low and high), according to the assessments every 10 min. In addition, to illustrate the variation among individuals, the glucose level of the men that represent the 25th and 75th percentiles of the area under the curve, are presented for each group.

Incidence rates of cancer were computed for groups with different levels of glucose at 10 min. Individual person-years were calculated from the date of examination to the date of cancer diagnosis, death, emigration, or the end of follow-up (December 31st 2012). We calculated the cancer incidences for all-sites combined, and then separately, for the eight most prevalent sites in the study cohort. To evaluate cancer risk in the low versus high glucose groups, we computed the incidence rate ratios (IRR) with accompanying 95% confidence intervals (CI). Adjustments for age (5-year age groups) were performed with the method of Mantel-Haenszel. Furthermore, to study the risk over time, the follow-up period was divided into four decades. To evaluate cancer risk in low versus high glucose groups at the sequential follow-up times, separate IRR analyses were also performed for levels of glucose at 20, 30, 40, 50 and 60 min.

Cox regression models were used to evaluate the relationship between the glucose level and the risk of all-site cancer. Hazard ratios (HR) with 95% CIs were calculated. The men were followed longitudinally from the date of examination to the date of cancer diagnosis, death, emigration, or the end of follow-up. Potential confounding covariates included in the final models were age, fasting glucose level, smoking, physical fitness, body weight, and height, all measured at baseline. Furthermore, to examine the influence of a diabetes mellitus diagnosis, the model included a time-varying covariate, according to the date of diagnosis. The Cox proportional hazards assumption was checked for glucose and other covariates, and it was adequately met for all covariates, except smoking. Thus, we performed a stratified Cox model on smoking, where the baseline hazards were allowed to differ between smokers and non-smokers. Statistical interactions between the glucose levels and the covariates were checked by including product terms, one at a time. No significant interactions were found.

We also examined the possibility of reverse causality; i.e., where low glucose levels could result from an ongoing cancer disease. For this assessment, we performed a sensitivity analysis restricted to men that remained alive and cancer-free 10 years after baseline, i.e. first 10 years of observation was excluded.

An alternative measure of the first phase was the change in blood glucose from fasting levels to 10-min levels. Thus, we performed Cox regression models similar to those described above to study an association between the risk of all-site cancer and the change, both absolute and relative, in glucose levels within the first 10-min of the IVGTT.

Lastly, we studied the association between the second phase and the risk of all-site cancer. Here, Cox regression analyses were performed for groups with two different glucose disappearance rates (K_G below and above the median rate).

An association was considered statistically significant when $p < 0.05$. All statistical analyses were performed with Stata (StataCorp, 2015).

3. Results

The baseline characteristics of the included study population are presented in Table 1. Overall, the mean age at inclusion was 49.8 years, and the median glucose value at 10 min was 11.66 mmol/L. The mean glucose levels at 10 min were 10.65 and 12.74 mmol/L among men below and above the median, respectively. Men with high 10-min glucose levels had higher glucose levels during the entire IVGTT than men with low 10-min glucose levels, despite considerable variation between individuals (Fig. 1). The median K_G was 1.86 (interquartile range 1.42–2.50).

Table 1
Baseline characteristics, stratified by whether the 10-min glucose level was above or below the cohort median.

Characteristic	10-min glucose ≤ median (n = 496)	10-min glucose > median (n = 449)	p-Value[a]
Age at inclusion (years)	50.0 (5.7)	49.6 (5.5)	0.27
Fasting blood glucose (mmol/L)	4.3 (0.46)	4.7 (0.49)	<0.0001
Weight (kg)	79.4 (10.0)	74.8 (8.6)	<0.0001
Height (cm)	178.3 (6.0)	175.7 (6.0)	<0.0001
Body mass index (kg/m^2)	25.0 (2.7)	24.2 (2.6)	<0.0001
Physical fitness (kJ/kg)	149.6 (61.0)	146.3 (54.4)	0.38
Smoking, never	118 (23.8%)	114 (25.4%)	0.22
Former	154 (31.0%)	157 (35.0%)	
Present	224 (45.2%)	178 (39.6%)	

Data are the mean (SD) or n (%). No missing data.
For 10-min glucose ≤ median group, the mean was 10.65, range: 7.66–11.66 mmol/L.
For 10-min glucose > median group, the mean was 12.74, range: 11.67–15.54 mmol/L.
[a] T-test for continuous variables and chi-square test for categorical variables.

There were no significant differences in baseline characteristics (except for height) and cancer incidence between men included (blood sampling every 10 min) and not included (blood sampling every 15 min) in the analyses (Appendix Table 1A and 1B).

During the 40-year follow-up (median 26.3 years, range 0.1–40.3 years), 376 men were diagnosed with cancer. A higher cancer incidence was observed among men with low than those with high 10-min glucose levels (Fig. 2, Table 2). There was a significant inverse association between 10-min glucose levels and all-site cancer (IRR: 1.5, 95% CI: 1.2–1.9). This association remained significant, when we divided the follow-up times into four sequential decades. The corresponding IRRs [95% CIs] were as follows: first decade: 3.0 [1.4–6.4]; second decade: 1.6 [1.1–2.4]; third decade: 1.6 [1.1–2.2]; and fourth decade: 1.5 [1.01–2.2]. Additionally, the IRRs were significantly higher in digestive organs (i.e., liver, gallbladder and bile ducts, and pancreas; IRR: 3.5, 95% CI: 1.3–9.4) and colon (IRR: 1.9, 95% CI: 1.1–3.5). We observed no association between fasting glucose and the incidence of cancer. Moreover, at the sequential follow-up times, we found no association between glucose levels at 20, 30, 40, 50, and 60 min after the IVGTT and the incidence of cancer (data not shown). Furthermore, the K_G was not associated with the incidence of all-site cancer.

The Cox regression analysis showed that the risk of all-site cancer in men with low 10-min glucose levels was significantly higher than in those with high 10-min glucose levels (HR: 1.6, 95% CI: 1.3–2.0; Table 3). This difference remained significant after adjusting for age at inclusion, fasting glucose level, smoking, physical fitness, body weight, and height (HR: 1.6, 95% CI: 1.3–2.1). Diabetes mellitus was diagnosed in 91 men during follow-up; however, we detected no significant association with cancer risk (Model III, HR: 1.3, 95% CI: 0.8–1.9).

The sensitivity analyses were restricted to men that had remained alive and cancer-free after 10 years of follow-up. The results were similar to those obtained when the entire 40-year follow-up was included (Table 3).

Alternatively, studying the change from fasting glucose to the level at 10 min showed a higher risk of all-site cancer among men with a rapid decline (above the median change) than among men with a slower decline (below the median change) in glucose levels (Model III, HR: 1.4, 95% CI: 1.2–1.8). The risk was similarly elevated, when considering either the absolute or the relative change from fasting to 10-min glucose levels (data not shown).

Lastly, the K_G was not associated with all-site cancer risk, either in the univariate or in the multivariate Cox regression analysis (Table 3).

4. Discussion

In this prospective study of initially healthy, middle-aged men, we examined the association between plasma glucose levels at 10 min (first phase) and at 10–60 min (second phase), after an intravenous glucose infusion, and the risk of cancer in a 40-year follow-up. We found that low levels of plasma glucose at 10 min were associated with a higher incidence of cancer. In contrast, the risk of cancer was not associated with the slope of plasma glucose elimination in the 10–60 min period after infusion. Furthermore, the risk of cancer was not associated with the fasting glucose level or with any of the glucose levels at 20, 30, 40, 50, and 60 min.

The strong negative association we found between the 10-min plasma glucose and the risk of cancer may appear contradictory to previous prospective studies on cancer incidence and OGTT responses. In those studies, a higher risk was associated with higher levels of plasma glucose at 2-h post-loading (Jee et al., 2005; Huang et al., 2014; Rapp et al., 2006). However, we studied a quite different aspect of glucose metabolism, which manifests itself in the first minutes after an intravenous glucose load, namely the efficiency of first phase glucose disposal. The low 10-min glucose level after an intravenous glucose load was most

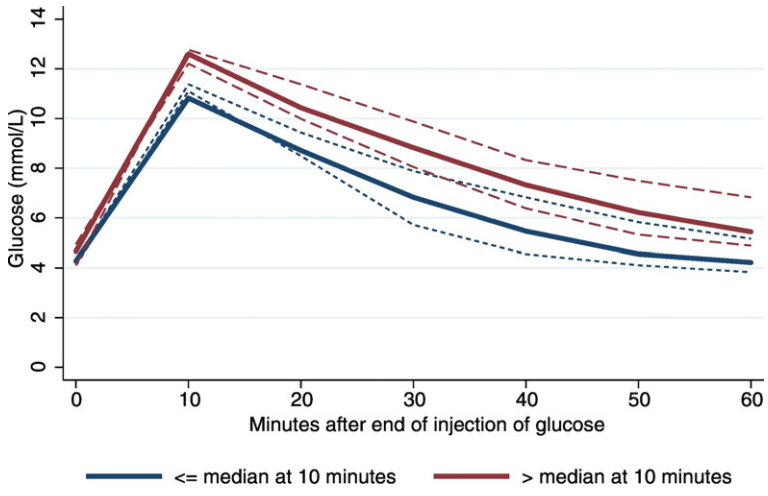


Fig. 1. Plasma glucose levels measured at 10-min intervals for 1 h after an intravenous glucose load (25 g glucose). Plasma glucose was measured in the fasting state before injection, and at 10, 20, 30, 40, 50, and 60 min after the injection. The two groups comprise men with 10-min glucose levels above (red) or below (blue) the cohort median at 10 min (11.66 mmol/L). Solid lines are median glucose levels, and dashed lines show the glucose level of the men that represent the first and third quartiles of the area under the curve in each group.

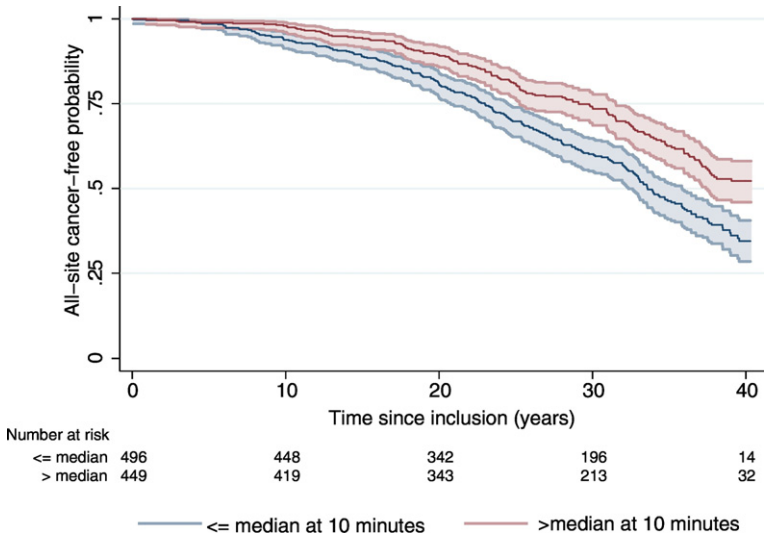


Fig. 2. All-site cancer-free survival (solid lines) with 95% confidence bands are shown for men with 10-min glucose levels above (red) or below (blue) the cohort median. The difference between groups was significant, with a p-value < 0.0001, based on a log rank test.

likely due to an effective first-phase glucose-induced insulin secretion (GIIS) response from β cells, which led to an effective insulin-stimulated elimination of plasma glucose. In principle, increased glucose disposal at 10 min could also be due to increased general insulin sensitivity, or increased general insulin independent glucose uptake by various GLUTs. However, it was less likely that high insulin sensitivity, or high insulin independent glucose uptake, could be responsible for this first phase effect, because neither the fasting glucose nor the glucose disappearance rate was found to be associated with cancer risk. Therefore, we focused on specific mechanisms associated with the first phase GIIS. The key proteins in the first phase GIIS include the facilitated glucose transporters (GLUT 1 and GLUT 2) and hexokinase, which are responsible for pancreatic glucose sensing and the immediate release of predocked insulin granules (Seino et al., 2015). These proteins are also rate limiting for the uptake and utilization of glucose in tumors. Cancer cells generally have enhanced glucose utilization and a metabolic shift towards aerobic glycolysis, which generate sustained metabolic changes that favor tumor growth and progression, and require a constant supply of high glucose (Jang et al., 2013). Thus, more efficient glucose uptake may be particularly advantageous for cancer cells.

Low 10-min plasma glucose levels were associated with a higher incidence of cancer, considering all cancer sites combined. Our site-specific analyses could not exclude the possibility that similar mechanisms may apply to all the cancer sites studied. Nevertheless, some cancer sites appeared to be more strongly associated with the rates of plasma glucose absorption, such as digestive organs and the colon. Those findings were consistent with data that showed that GLUT 1 or GLUT 2 levels were relatively high in cancer cells at those sites (Barron et al., 2016). In light of the argument that it is critical for cancer cells to obtain glucose, it is notable that GLUT 1 polymorphisms have been linked to cancers in the lung (Fan et al., 2016), liver (Amann et al., 2011), and kidney (Page et al., 2005).

The estimates of cancer-free survival for the groups with 10-min glucose levels below and above the median showed an increasing divergence over the 40-year follow-up (Fig. 2). Thus, it is unlikely that causal factors related to glucose disposal at baseline were temporary in nature. It is more likely that causality was related to some individual characteristics that were substantially constant throughout life. An example of an individual characteristic might be a polymorphism in a gene that is critical for insulin-independent uptake of plasma glucose into cells.

This study had several strengths. We analyzed multiple measurements of plasma glucose, which made it possible to examine both the first and the second phase responses to an IVGTT, in a healthy cohort. In addition, we implemented a long-term prospective study design, where individuals were followed over a 40-year period to determine cancer incidence. Moreover, the data retrieved from the Cancer Registry of Norway provided complete, valid information on cancer diagnoses

Table 2
Comparison of cancer incidence (all-sites and the eight most prevalent subsites) among men with 10-min glucose levels below and above the median glucose level at 10 min, n = 945.

		10-min glucose ≤ median			10-min glucose > median			
Cancer site	ICD-10 code	Events	PY	IR (per 1000 PY)	Events	PY	IR (per 1000 PY)	Age-adjusted IRR (95% CI)[b]
Cancer, all-sites		228	12,671	18.0	148	12,542	11.8	1.52 (1.24–1.87)
Digestive organs[a]	C22–25	18	13,834	1.3	5	13,249	0.4	3.45 (1.27–9.38)
Colon	C10	33	13,713	2.4	16	13,196	1.2	1.94 (1.07–3.53)
Lymphoma/leukemia	C81–95	20	13,793	1.5	10	13,229	0.8	1.85 (0.87–3.91)
Lung	C33–34	25	13,820	1.8	15	13,242	1.1	1.59 (0.83–3.03)
Rectum	C19–20	13	13,792	0.9	8	13,204	0.6	1.57 (0.66–3.73)
Bladder and kidney	C64,C66–68	32	13,576	2.4	21	13,113	1.6	1.46 (0.84–2.54)
Melanoma	C43–44	25	13,727	1.8	18	13,157	1.4	1.31 (0.72–2.40)
Prostate	C61	61	13,532	4.5	50	12,988	3.9	1.17 (0.81–1.71)

The cohort median glucose value at 10 min was 11.66 mmol/L.
Events = number of incident cancer cases by site; PY = person-years; IR = incidence rate; IRR = incidence rate ratio; CI = confidence interval.
[a] Digestive organs include the liver (C22, n = 4), gallbladder and bile ducts (C23–24, n = 3), and the pancreas (C25, n = 16).
[b] Low compared to high levels of glucose, after adjusting for age by the method of Mantel-Haenszel.

Table 3
Comparison of all-site cancer risk between men with 10-min glucose levels below and above the median 10-min glucose measurement, and between men with glucose disappearance rates (K_G) above and below the median rate.

	Events	Crude HR (95% CI)	Model I[a]: adjusted HR (95% CI)	Model II[b]: adjusted HR (95% CI)	Model III[c]: adjusted HR (95% CI)
First phase (10 min glucose)					
40-year follow-up (n = 945)					
>median	148	1.00	1.00	1.00	1.00
≤median	228	1.64 (1.33–2.01)	1.66 (1.35–2.05)	1.61 (1.26–2.04)	1.61 (1.27–2.05)
Excluding first 10 years (n = 867)					
>median	139	1.00	1.00	1.00	1.00
≤median	198	1.54 (1.24–1.91)	1.57 (1.26–1.95)	1.53 (1.19–1.98)	1.54 (1.19–1.99)
Second phase (K_G)					
40-year follow-up (n = 945)					
≤median rate	176	1.00	1.00	1.00	1.00
>median rate	200	1.08 (0.88–1.32)	1.18 (0.96–1.45)	1.10 (0.88–1.36)	1.10 (0.89–1.37)

Median glucose at 10 min was 11.66 mmol/L. Ranges: 7.66–11.66 and 11.67–15.54 mmol/L for groups with 10-min glucose levels ≤ and > the median 10-min glucose, respectively.
Median K_G was 1.86. Ranges: 0.44–1.86 and 1.87–7.69 for groups with rates ≤ and > the median rate, respectively.
Events = number of incident cancer cases; HR = hazard ratio; CI = confidence interval
[a] Model I: Adjusted for age at inclusion.
[b] Model II: Model I with added adjustments for fasting glucose, physical fitness, smoking, body weight, and height.
[c] Model III: Model II with added an adjustment for the diagnosis of diabetes mellitus as a time-varying covariate.

and vital status (i.e., death) during the time-span covered. Lastly, the cohort was representative of the age-group of men within the given time-period, with regard to cancer incidence in their counties of residence (Oslo and Akershus) (Heir et al., 2016).

This study had some limitations. First, the study protocol was originally designed for estimating the risk of cardiovascular disease and diabetes, not for the aims of the present study. Therefore, the sample size was relatively small, and no information was available on variables related to the glucose load response, other than plasma glucose. Second, despite the need to exclude many individuals when studying the first phase response, there was no clinical difference between included and excluded men in the study population. Third, to achieve appropriate statistical power, we dichotomized the men based on the median plasma glucose, which may have concealed some non-linear relationships. However, post hoc analyses using tertiles showed similar results, which suggested that it was appropriate to assume a linear relationship.

In summary, we found that rapid elimination of plasma glucose during the first phase response following an intravenous glucose load was associated with an elevated 60% risk of cancer compared to those with a slower elimination. Plasma glucose uptake during the first-phase GIIS response may depend on the effectiveness of the molecular glucose-sensing apparatus. Polymorphisms that are critical for plasma glucose sensing, in general, may also be important for transporting glucose into cancer cells. Our findings highlight crucial aspects of cancer cell proliferation, and they point to future avenues of research. Future studies on the ability of cancer cells to take up glucose are warranted for a better understanding of the mechanisms underlying cancer development.

Funding Sources

No funding resources.

Conflicts of Interests

The authors declare no competing interests.

Data Availability

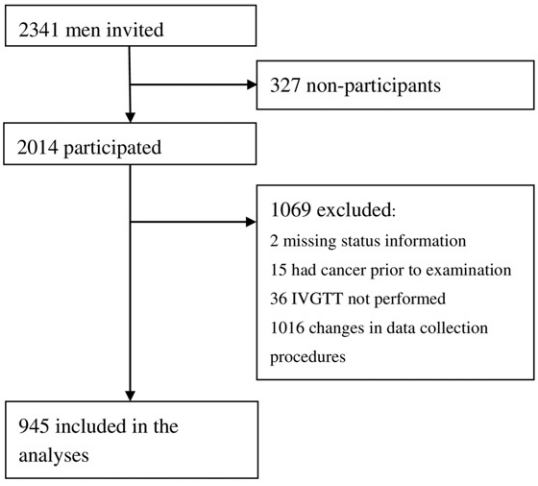
Data are from the Oslo Ischemia Study. Public availability would compromise privacy of the respondents. According to the approval from the Norwegian Regional committees for medical and health research ethics, the data is to be stored properly and in line with the Norwegian Law of privacy protection. However, provision can be made for inspection of the data, pending ethical approval from our Ethics committee. Interested researchers can contact first author Ragnhild S Falk (r.s.falk@medisin.uio.no) or Prof. Trond Heir (trond.heir@medisin.uio.no) with requests for the data underlying our findings.

Author Contributions

JE was the principal investigator of the study and provided the materials. RSF, ST, LS and TH conceived of and designed the study. RSF performed the statistical analysis. RSF, JEP and TH wrote the first draft of the manuscript. All authors interpreted the data and wrote and approved the manuscript.

Appendix A. Flowchart

Oslo Ischemia Study. An intravenous glucose-tolerance test (IVGTT) was performed with an intravenous injection of 25 g glucose.



Appendix Table 1A
Baseline characteristics of men with blood glucose measured every 10 (included) and 15 (not included) min during the intravenous glucose-tolerance test.

	Included n = 945	Not included n = 1016	p-Value[a]
Age at inclusion (years)	49.8 (5.6)	49.8 (5.4)	0.96
Weight (kg)	77.2 (9.6)	76.4 (10.1)	0.06
Height (cm)	177.1 (6.1)	176.4 (6.2)	0.03
Body mass index (kg/m^2)	24.6 (2.7)	24.5 (2.8)	0.40

(continued on next page)

Appendix Table 1A (*continued*)

	Included n = 945	Not included n = 1016	p-Value[a]
Physical fitness (kJ/kg)	148.1 (57.9)	145.3 (57.3)	0.29
Cholesterol (mmol/L)	6.7 (1.2)	6.6 (1.2)	0.13
Triglycerides (mmol/L)	1.3 (0.6)	1.3 (0.7)	0.23
Smoking, never	232 (24.6%)	260 (25.6%)	0.25
Former	311 (32.9%)	299 (29.4%)	
Present	402 (42.5%)	457 (45.0%)	

Data are mean (SD) or n (%).
[a] T-test for continuous variables and chi-square test for categorical variables.

Appendix Table 1B
All-site cancer incidence among men with glucose measurements at 10 (included) and 15 (not included) min intervals in the intravenous glucose-tolerance test.

	Included n = 945	Not included n = 1016
Cancer cases, all-sites	376	372
Person-years	25,158	26,327
Incidence rate (IR) per 1000 person-years	14.95	14.13
95% confidence interval of IR	13.51–16.54	12.76–15.64

References

Amann, T., Kirovski, G., Bosserhoff, A.K., Hellerbrand, C., 2011. Analysis of a promter polymorphism of the GLUT1 gene in patients with hepatocellular carcinoma. Mol. Membr. Biol. 28, 182–186.

Barron, C.C., Bilan, P.J., Tsakiridis, T., Tsiani, E., 2016. Facilitative glucose transporters: implications for cancer detection, prognosis and treatment. Metabolism 65, 124–139.

Bjørnholt, J.V., Erikssen, G., Liestøl, K., Jervell, J., Erikssen, J., Thaulow, E., 2001. Prediction of Type 2 diabetes in healthy middle-aged men with special emphasis on glucose homeostasis. Results from 22.5 years' follow-up. Diabet. Med. 18, 261–267.

Erikssen, J., Enger, S.C., 1977. Intravenous glucose tolerance test in middle-aged men with and without latent coronary heart disease. Acta Med Scand. 202, 357–362.

Erikssen, G., Liestøl, K., Bjørnholt, J., Thaulow, E., Sandvik, L., Erikssen, J., 1998. Changes in physical fitness and changes in mortality. Lancet 352, 759–762.

Fan, R., Hou, W.J., Zhao, Y.J., Liu, S.L., Qiu, X.S., Wang, E.H., Wu, G.P., 2016. Overexpression of HPV16 E6/E7 mediated HIF-1α upregulation of GLUT1 expression in lung cancer cells. Tumour Biol. 37, 4655–4663.

Grundvold, I., Skretteberg, P.T., Liestøl, K., Erikssen, G., Kjeldsen, S.E., Arnesen, H., Erikssen, J., Bodegard, J., 2012. Upper normal blood pressures predict incident atrial fibrillation in healthy middle-aged men: a 35-year follow-up study. Hypertension 59, 198–204.

Heir, T., Erikssen, J., Sandvik, L., 2011. Overweight as predictor of long-term mortality among healthy, middle-aged men: a prospective cohort study. Prev. Med. 52, 223–226.

Heir, T., Falk, R.S., Robsahm, T.E., Sandvik, L., Erikssen, J., Tretli, S., 2016. Cholesterol and prostate cancer risk: a long-term prospective cohort study. BMC Cancer 16, 643.

Hirakawa, Y., Ninomiya, T., Mukai, N., Doi, Y., Hata, J., Fukuhara, M., Iwase, M., Kitazono, T., Kiyohara, Y., 2012. Association between glucose tolerance level and cancer death in a general Japanese population: the Hisayama Study. Am. J. Epidemiol. 176, 856–864.

Huang, Y., Cai, X., Qiu, M., Chen, P., Tang, H., Hu, Y., Huang, Y., 2014. Prediabetes and the risk of cancer: a meta-analysis. Diabetologia 57, 2261–2269.

Jang, M., Kim, S.S., Lee, J., 2013. Cancer cell metabolism: implications for therapeutic targets. Exp. Mol. Med. 45, e45.

Jee, S.H., Ohrr, H., Sull, J.W., Yun, J.E., Ji, M., Samet, J.M., 2005. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 293, 194–202.

Larsen, I.K., Småstuen, M., Johannesen, T.B., Langmark, F., Parkin, D.M., Bray, F., Møller, B., 2009. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur. J. Cancer 45, 1218–1231.

Levine, W., Dyer, A.R., Shekelle, R.B., Schoenberger, J.A., Stamler, J., 1990. Post-load plasma glucose and cancer mortality in middle-aged men and women. 12-year follow-up findings of the Chicago Heart Association Detection Project in Industry. Am. J. Epidemiol. 131, 254–262.

Page, T., Hodgkinson, A.D., Ollerenshaw, M., Hammonds, J.C., Demaine, A.G., 2005. Glucose transporter polymorphisms are associated with clear-cell renal carcinoma. Cancer Genet. Cytogenet. 163, 151–155.

Rapp, K., Schroeder, J., Klenk, J., Ulmer, H., Concin, H., Diem, G., Oberaigner, W., Weiland, S.K., 2006. Fasting blood glucose and cancer risk in a cohort of more than 140,000 adults in Austria. Diabetologia 49, 945–952.

Saydah, S.H., Loria, C.M., Eberhardt, M.S., Brancati, F.L., 2003. Abnormal glucose tolerance and the risk of cancer death in the United States. Am. J. Epidemiol. 157, 1092–1100.

Seino, S., Shibasaki, T., Minami, K., 2015. β-Cell biology of insulin secretion. In: DeFronzo, R.A., Ferrannini, E., Alberti, K.G.M.M., Zimmet, P. (Eds.), International Textbook of Diabetes Mellitus, 4th edn Wiley, UK, pp. 96–107.

StataCorp, 2015. Stata Statistical Software: Release 14. StataCorp LP, College Station, TX.

World Cancer Research Fund, American Institute for Cancer Research, 2007. Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. AICR, Washington D.C.

Zhou, X.H., Qiao, Q., Zethelius, B., Pyörälä, K., Söderberg, S., Pajak, A., Stehouwer, C.D., Heine, R.J., Jousilahti, P., Ruotolo, G., Nilsson, P.M., Calori, G., Tuomilehto, J., DECODE Study Group, 2010. Diabetes, prediabetes and cancer mortality. Diabetologia 53, 1867–1876.