Prospective Study of Hyperglycemia and Cancer Risk

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OBJECTIVE — To investigate whether hyperglycemia is associated with increased cancer risk.

RESEARCH DESIGN AND METHODS — In the Västerbotten Intervention Project of northern Sweden, fasting and postload plasma glucose concentrations were available for 33,293 women and 31,304 men and 2,478 incident cases of cancer were identified. Relative risk (RR) of cancer for levels of fasting and postload glucose was calculated with the use of Poisson models, with adjustment for age, year of recruitment, fasting time, and smoking status. Repeated measurements 10 years after baseline in almost 10,000 subjects were used to correct RRs for random error in glucose measurements.

RESULTS — Total cancer risk in women increased with rising plasma levels of fasting and postload glucose, up to an RR for the top versus bottom quartile of 1.26 (95% CI 1.09–1.47) (P_{trend} <0.001) and 1.31 (1.12–1.52) (P_{trend} = 0.001), respectively. Correction for random error in glucose measurements increased these risks up to 1.75 (1.32–2.36) and 1.63 (1.26–2.18), respectively. For men, corresponding uncorrected RR was 1.08 (0.92–1.27) (P_{trend} = 0.25) and 0.98 (0.83–1.16) (P_{trend} = 0.99), respectively. Risk of cancer of the pancreas, endometrium, urinary tract, and of malignant melanoma was statistically significantly associated with high fasting glucose with RRs of 2.49 (1.23–5.45) (P_{trend} = 0.006), 1.86 (1.09–3.31) (P_{trend} = 0.02), 1.69 (0.95–3.16) (P_{trend} = 0.049), and 2.16 (1.14–4.35) (P_{trend} = 0.01), respectively. Adjustment for BMI had no material effect on risk estimates.

CONCLUSIONS — The association of hyperglycemia with total cancer risk in women and in women and men combined for several cancer sites, independently of obesity, provides further evidence for an association between abnormal glucose metabolism and cancer.

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Type 2 diabetes, an extreme state of glucose intolerance, is associated with elevated plasma levels of glucose and insulin, both before and after its diagnosis, and is associated with an increased risk of cancers of the liver, pancreas, colon, endometrium, kidney, and breast (1,2). Less is known, however, about the effect on cancer risk of moderately elevated glucose levels among nondiabetic subjects.

Recently, total cancer risk was reported to be modestly increased in women and men with elevated levels of fasting glucose in a very large cohort study of 1.3 million Korean men and women with 53,833 incident cases of cancer (3). Five substantially smaller prospective studies (4–8) with a total number of ~11,000 incident cases of cancer also have reported data on associations between fasting or postload glucose and cancer incidence or mortality. Here, we report the results from a prospective study in northern Sweden, with the aim to estimate the relationship of hyperglycemia, as measured by fasting and postload glucose, with the risk of cancer overall and the risk of cancer at specific organ sites.

RESEARCH DESIGN AND METHODS

The Northern Sweden Health and Disease Cohort

The Västerbotten Intervention Project is a subcohort of the Northern Sweden Health and Disease Cohort and has been described in detail previously (9). In brief, all residents in the county of Västerbotten in northern Sweden were invited to a health survey, in the years in which they become 40, 50, or 60 years old since 1985. An abbreviated oral glucose tolerance test was performed, according to the World Health Organization standard (10) in all participants who had a fasting glucose level <7.0 mmol/l and with no previously known diabetes, using a 75-g anhydric glucose load and measuring plasma glucose after 2 h in capillary plasma (11). Analysis of glucose was performed with the use of Reflotron benchtop analyzers (Boehringer Mannheim, Mannheim, Germany) on fresh samples. Information on cancer diagnosis was obtained by linkage to the national and regional cancer registers, and vital status was obtained from the Swedish population register with the use of a unique personal identification number. In October 2003, 74,207 subjects had been recruited. Participants were excluded if they had missing values for height, weight

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Abbreviations: IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Baseline characteristics of participants in the Västerbotten Intervention Project, northern Sweden*

	Women	Men
n	35,362	33,424
Age at entry (years) (distribution %)	46.1 ± 9.7	46.0 ± 9.8
29–35	13	14
36–45	32	32
46–55	31	31
56–61	24	23
Years of follow-up	8.3 ± 3.5	8.2 ± 3.6
Cancer cases (*n*)	1,440	1,251
Person-years at risk	292,652	273,715
BMI (kg/m^2)*	25.3 ± 4.2	26.0 ± 3.5
Normal (18.5–25)	56	43
Overweight (25–30)	31	46
Obese (>30)	13	11
Smoking status		
Current	21	18
Former	19	25
Never	60	57
Fasting glucose (*n*)	35,128	33,173
Fasting glucose (mmol/l)*	5.3 ± 0.9	5.5 ± 1.1
Normal (<6.1)	89	85
IFG (6.1–6.9)	9	12
Diabetic range (>6.9)	2	3
Cohort participants with OGTT† (*n*)	33,293	31,304
Postload glucose (mmol/l)	6.9 ± 1.6	6.3 ± 1.8
Normal (<8.9)	92	94
IGT (8.9–12.1)	7	5
Diabetic range (>12.1)	1	1

Data are means ± SD, percent, or *n*, unless otherwise indicated. *Fasting glucose levels in venous plasma. †Postload glucose levels in capillary plasma 2 h after an oral glucose tolerance test (OGTT) of 75 g glucose according to the World Health Organization (21).

(*n* = 1,180), or smoking status (*n* = 2,896), had a previous history of cancer except nonmelanoma skin cancer (*n* = 1,435), or had a BMI <18.5 kg/m^2 (*n* = 562).

Statistical methods

Directly standardized cancer rates based on 5-year age classes were calculated for each exposure category using the age distribution of the entire male or female study population. Relative risks (RRs) and 95% CIs were estimated with the use of standard Poisson models, as previously extensively described (12). Quartile cut points for the main factors (fasting and postload glucose levels) were determined in the full cohort. RRs by plasma glucose levels were adjusted for age as a time-dependent variable (5-year groups), year of recruitment (5-year intervals), fasting time (as 0, <8 h, or ≥8 h), and smoking status (never, former, or current smoker). All statistical models systematically included BMI as an adjustment variable and classified it into three groups (18.5–24.9, 25–29.9, and ≥30 kg/m^2). The breast cancer analysis was stratified into two groups (aged <49 years and aged ≥49 years at recruitment) as a surrogate for menopausal status at baseline, which was not available as a more detailed variable. Tests for linear trend were performed by computing likelihood ratio statistics and the associated *P* value for a variable with values equal to the median of each quartile of exposure. In addition, levels of glucose were analyzed according to current clinical definitions by the World Health Organization (13). Assuming that glucose levels would equally be related to risk for cancers that can affect both women and men, we calculated risk for all subjects combined for these sites.

The appropriateness of the assumption of a Poisson distribution of our data were examined by computing a dispersion parameter as the ratio of the Pearson's χ^2 statistics over the degrees of freedom of the model (14). This examination showed only a very minor degree of overdispersion, indicating that the Poisson assumption was acceptable. Repeated measurements of fasting and postload glucose at a resurvey performed 10 years later were available for 9,796 and 8,818 subjects, respectively. On the basis of these repeat measurements, RR estimates were corrected for attenuation due to random variations over time in plasma glucose levels (15,16), as described in detail in the online appendix (available at http://dx.doi.org/10.2337/dc06-0922).

Absolute risks of developing cancer within 20 years from age 40 were calculated as described by Gail et al. (17). Calculations were performed for two age categories, 40–49 and 50–59 years. Age-specific hazards of dying from competing risks were calculated from the same cohort. Absolute risk calculations were based on both uncorrected and corrected RR estimates. The attributable fraction, based on an exponential relationship between exposure and cancer, was calculated using both uncorrected and adjusted RR estimates. The attributable fraction expresses the expected reduction in disease occurrence that could be achieved if study subjects in the top quartile were shifted to any of the three lower quartiles. Estimates of the attributable fraction were obtained using both the uncorrected RR estimates and using RR estimates that had been corrected for attenuation due to random measurement error. The 95% CIs for the attributable fractions were estimated using a bootstrap method, based on 1,000 iterations (18). All statistical analyses were performed using SAS, version 9.1.3 (SAS, Cary, NC).

RESULTS — The distribution of baseline characteristics in the Västerbotten Intervention Project is presented in Table 1. Even though the proportions of subjects with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and glucose levels in the diabetic range were significantly higher among obese subjects, the absolute numbers of subjects affected by IFG or IGT were highest among normal-weight and overweight subjects (Fig. 1).

We observed statistically significant increases in mean glucose levels with calendar time. From 1989 to 2002, mean levels of fasting and postload glucose increased annually (1.3 and 0.6%, respectively; P_{trend} <0.0001), and age also was related positively to glucose levels (Pearson correlation r = 0.17 for fasting glucose and r = 0.20 for postload glucose; P < 0.0001). The Pearson correlation co-

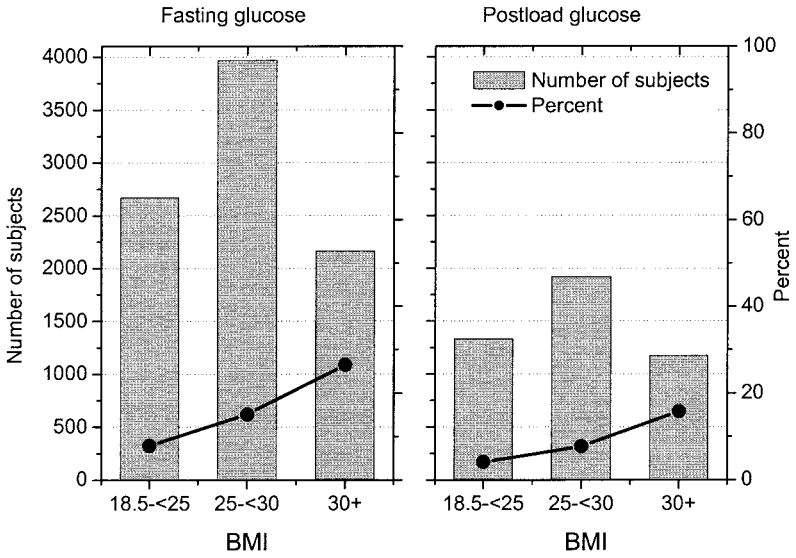

Figure 1—*Absolute number and proportion of women and men combined with IFG (fasting glucose ≥6.1 mmol/l) and IGT (postload glucose ≥8.9 mmol/l) according to BMI in the Västerbotten Intervention Project, northern Sweden.*

efficient between fasting and postload glucose was 0.34 ($P < 0.0001$), and the correlations between baseline and repeat measurement after 10 years of fasting glucose and postload glucose also were only modestly strong ($r = 0.37$ and $r = 0.34$, respectively; both $P < 0.0001$). In contrast, the correlation between two repeated measurements of BMI was much higher ($r = 0.81$; $P < 0.0001$).

Among women, RRs of developing cancer were statistically significantly increased with elevated plasma glucose concentrations (RR 1.26 [95% CI 1.09–1.47] [P_{trend} <0.001] and 1.31 [1.12–1.52] [P_{trend} <0.001], for the top versus bottom quartile of fasting and postload glucose, respectively [Table 2]). After correction for attenuation, these RR estimates increased to 1.75 (1.32–2.36) and 1.63 (1.26–2.18), respectively. Using the World Health Organization cut points, women with IFG, IGT, or glucose in the diabetic range risk also had an increased risk of cancer (all sites combined) compared with women with normal fasting glucose levels (Fig. 2). For separate female organ sites, we observed statistically significant increases for endometrial cancer with rising fasting and postload glucose up to an RR for the top versus bottom quartile of 1.86 (1.09–3.31) (P_{trend} = 0.019) and 1.82 (1.07–3.23) (P_{trend} = 0.028), respectively (Fig. 2).

In men, overall, no statistically significant associations were observed between glucose levels and cancer risk, with RR estimates of 1.08 (95% CI 0.92–1.27) (P_{trend} = 0.26) and 0.98 (0.84–1.16) (P_{trend} = 0.99), for top versus bottom quartiles of fasting and postload glucose, respectively (Table 2). Men with IFG, IGT, and glucose in the diabetic range also had no statistically significant increase in risk compared with men with glucose levels in the normal range (Fig. 2). After exclusion of prostate cancer, which was weakly and inversely associated with hyperglycemia, the risk of cancer became slightly higher than among all men, with an RR for the top versus bottom quartile of fasting and postload glucose of 1.12 (0.92–1.36) (P_{trend} = 0.16) and 1.17 (0.95–1.45) (P_{trend} = 0.095), respectively. Analyses of data for women and men combined showed statistically significant increases in risk of pancreas cancer, malignant melanoma, and urinary tract cancers among subjects who had elevated levels of fasting glucose (Table 2).

BMI was then systematically included in the Poisson models for the estimation of RRs with respect to plasma glucose levels. Globally, the changes in estimates after adjusting for BMI were only minor. After adjustment for BMI, the RR for the top versus bottom quartile for total cancer in women for fasting glucose decreased from 1.26 (95% CI 1.09–1.47) (P_{trend} < 0.001) to 1.22 (1.05–1.43) (P_{trend} < 0.001) and for postload glucose from 1.31 (1.12–1.52) (P_{trend} < 0.001) to 1.27 (1.09–1.48) (P_{trend} = 0.002). We also observed no significant difference in overall cancer risks associated with plasma glucose levels among smokers compared with nonsmokers (data not shown).

The absolute risks of cancer development during a 20-year period for a 40-year-old woman in the bottom and top quartiles of fasting glucose were 7 and 9%, respectively, and corresponding estimates corrected for attenuation effects due to within-subject variations in glucose level over time were 7 and 11%, respectively. The fractions of total cancer attributable to a level of glucose represented by the top quartile in women were calculated to be 5% (95% CI 2–8) and 4% (1–8), respectively, which rose to 10% (7–15) and 9% (6–15), respectively, after measurement error correction.

CONCLUSIONS — In this prospective cohort study, abnormal glucose metabolism was associated with a statistically significantly increased risk of cancer overall in women but not in men. High levels of fasting glucose in women and men were associated with statistically significantly increased risk of pancreatic cancer, malignant melanoma, and urinary tract cancers among subjects who had elevated levels of fasting glucose. These associations were independent of BMI, which showed only a very modest correlation with glucose levels.

For women, our RR estimates for cancer, all organ sites combined, were very similar to those in two recent reports. In the large Korean cohort study with 53,833 incident cases of cancer, Jee et al. (3) reported an RR of 1.15 for the top versus bottom quintile of fasting plasma glucose (and 1.22 for men), and Rapp et al. (8) reported very similar risk estimates, with RRs of 1.28 and 1.20 for the top versus bottom category of fasting glucose for women and men, respectively, from a recent large Austrian cohort study including a total of 5,212 cases of cancer.

A number of our findings concurred with those in previous prospective studies, including the rather strong and statistically significant association of fasting glucose levels with risk of pancreatic cancer (3,5,19), as well of endometrial cancer (20). We also observed a twofold increase of risk of malignant melanoma for study subjects with high fasting glucose. This latter finding has not been reported previously, although in our cohort (21) as well as in some other studies (22,23) excess body weight was found to be related to increased melanoma risk. Among women aged <49 years, who presumably were premenopausal, we observed an in-

Table 2—*RR of cancer according to fasting and postload glucose in quartiles in the Västerbotten Intervention Project, northern Sweden*

	1 (referent)	2	3	4	P_{trend}*
Women					
All sites					
Fasting glucose (n = 1,428)					
No cases	270	290	354	514	
Rate†	458	430	473	587	
RR (95% CI)‡	1	0.94 (0.79–1.11)	1.03 (0.87–1.21)	1.26 (1.09–1.47)	<0.001
Postload glucose (n = 1,328)					
No cases	261	267	345	455	
Rate	430	460	474	549	
RR (95% CI)	1	1.09 (0.92–1.29)	1.11 (0.95–1.31)	1.31 (1.12–1.52)	<0.001
Breast					
Fasting (n = 510)					
RR (95% CI)	1	0.92 (0.70–1.21)	1.03 (0.79–1.34)	1.06 (0.82–1.37)	0.454
Postload (n = 479)					
RR (95% CI)	1	0.93 (0.70–1.24)	1.22 (0.95–1.59)	1.20 (0.93–1.55)	0.069
Breast (aged <49 years)					
Fasting (n = 92)					
RR (95% CI)	1	0.65 (0.26–1.5)	1.88 (1.0–3.6)	2.13 (1.2–4.1)	0.002
Postload (n = 88)					
RR (95% CI)	1	1.02 (0.50–2.1)	1.86 (1.1–3.5)	1.37 (0.73–2.6)	0.213
Breast (aged ≥49 years)					
Fasting (n = 418)					
RR (95% CI)	1	0.91 (0.69–1.2)	0.94 (0.72–1.2)	0.90 (0.68–1.2)	0.492
Postload (n = 391)					
RR (95% CI)	1	1.01 (0.75–1.4)	1.08 (0.81–1.4)	1.23 (0.93–1.6)	0.113
Ovarian					
Fasting (n = 90)					
RR (95% CI)	1	0.39 (0.19–0.78)	0.76 (0.42–1.35)	0.89 (0.52–1.54)	0.824
Postload (n = 84)					
RR (95% CI)	1	0.64 (0.32–1.23)	0.71 (0.38–1.30)	0.94 (0.53–1.65)	0.955
Endometrium					
Fasting (n = 117)					
RR (95% CI)	1	1.32 (0.73–2.46)	1.16 (0.63–2.17)	1.86 (1.09–3.31)	0.019
Postload (n = 109)					
RR (95% CI)	1	1.37 (0.75–2.57)	0.84 (0.44–1.61)	1.82 (1.07–3.23)	0.028
Men					
All sites					
Fasting glucose (n = 1,241)					
No cases	257	265	289	430	
Rate	454	436	452	475	
RR (95% CI)	1	0.99 (0.83–1.17)	1.02 (0.86–1.21)	1.08 (0.92–1.27)	0.259
Postload glucose (n = 1,150)					
No cases	248	246	281	375	
Rate	477	437	446	458	
RR (95% CI)	1	0.93 (0.78–1.11)	0.97 (0.82–1.16)	0.98 (0.84–1.16)	0.992
Prostate					
Fasting (n = 458)					
RR (95% CI)	1	1.02 (0.77–1.35)	0.97 (0.73–1.29)	0.96 (0.74–1.26)	0.713
Postload (n = 425)					
RR (95% CI)	1	0.83 (0.62–1.10)	0.71 (0.53–0.95)	0.79 (0.61–1.02)	0.074
Women and men combined					
Stomach					
Fasting (n = 71)					
RR (95% CI)	1	0.99 (0.42–2.21)	1.36 (0.70–2.73)	1.46 (0.75–2.94)	0.205
Postload (n = 63)					
RR (95% CI)	1	1.53 (0.74–3.22)	1.35 (0.64–2.88)	1.23 (0.59–2.63)	0.717

Continued on following page

Table 2—*Continued*

	1 (referent)	2	3	4	P_{trend}*
Colon					
Fasting (n = 147)					
RR (95% CI)	1	0.95 (0.55–1.62)	0.90 (0.56–1.46)	1.16 (0.74–1.85)	0.470
Postload (n = 138)					
RR (95% CI)	1	1.13 (0.66–1.94)	1.17 (0.70–1.97)	1.23 (0.76–2.03)	0.422
Rectum					
Fasting (n = 87)					
RR (95% CI)	1	1.18 (0.59–2.32)	0.99 (0.53–1.87)	1.13 (0.62–2.12)	0.782
Postload (n = 82)					
RR (95% CI)	1	0.63 (0.30–1.27)	1.10 (0.61–2.01)	0.90 (0.49–1.66)	0.978
Pancreas					
Fasting (n = 62)					
RR (95% CI)	1	1.19 (0.47–2.97)	1.11 (0.49–2.59)	2.49 (1.23–5.45)	0.006
Postload (n = 56)					
RR (95% CI)	1	0.42 (0.16–0.97)	0.57 (0.26–1.23)	0.91 (0.47–1.78)	0.910
Kidney					
Fasting (n = 44)					
RR (95% CI)	1	1.35 (0.46–3.97)	1.49 (0.60–4.02)	2.08 (0.88–5.50)	0.092
Postload (n = 41)					
RR (95% CI)	1	1.40 (0.49–4.27)	1.97 (0.77–5.68)	1.76 (0.69–5.06)	0.247
Urinary tract					
Fasting (n = 97)					
RR (95% CI)	1	1.05 (0.50–2.20)	1.38 (0.75–2.61)	1.69 (0.95–3.16)	0.049
Postload (n = 83)					
RR (95% CI)	1	1.31 (0.72–2.40)	0.85 (0.43–1.65)	1.18 (0.65–2.17)	0.781
Respiratory tract					
Fasting (n = 114)					
RR (95% CI)	1	1.08 (0.58–1.98)	0.83 (0.47–1.48)	1.40 (0.85–2.38)	0.178
Postload (n = 104)					
RR (95% CI)	1	0.88 (0.48–1.59)	1.19 (0.68–2.06)	1.13 (0.67–1.94)	0.510
Melanoma					
Fasting (n = 92)					
RR (95% CI)	1	1.41 (0.66–3.04)	2.14 (1.15–4.24)	2.16 (1.14–4.35)	0.013
Postload (n = 88)					
RR (95% CI)	1	1.16 (0.59–2.30)	1.50 (0.80–2.89)	1.65 (0.89–3.17)	0.086
Non-Hodgkin lymphoma					
Fasting (n = 89)					
RR (95% CI)	1	0.84 (0.42–1.64)	0.99 (0.56–1.77)	0.89 (0.49–1.62)	0.786
Postload (n = 77)					
RR (95% CI)	1	3.06 (1.42–7.35)	3.05 (1.42–7.30)	2.53 (1.16–6.11)	0.081

*Test for trend was performed using class medians as scores. †Directly standardized rate per 100,000 person-years. ‡Risk ratio estimated from Poisson model with likelihood ratio CIs. Risk was adjusted for age, calendar year, and smoking, by including these covariates into the statistical model.

crease in breast cancer risk for elevated fasting glucose levels in accordance with an earlier observation (24).

For men, we found no statistically significant association between hyperglycemia and overall cancer risk. However, for prostate cancer, which accounted for more than two-thirds of all male cancers in the Northern Sweden Health and Disease Cohort, risk was nonsignificantly inversely related to glucose levels. In agreement with our findings, a modest decrease in prostate cancer risk has been consistently observed in men with diabetes (25,26). After exclusion of prostate cancer, the association between glucose levels and overall cancer risk became weakly positive in our cohort.

The true risk associated with long-term hyperglycemia may have been underestimated in our study as well as in other studies with a similar design (3–7), as there is substantial intraindividual variation over time in fasting and postload plasma glucose levels (27,28). Random variations over time will tend to bias estimates of relative and absolute risk toward the null (regression dilution bias) if the true determinant of the disease outcome is the long-term, usual level of glucose (28,29). We calculated relative and absolute risk estimates corrected for attenuation due to random fluctuations over time, using information from a second set of glucose measurements. After correction, the increase in RR associated with the highest levels of fasting and postload glucose in women for cancer at all sites combined increased substantially from 26 to 75% and from 31 to 63%, respectively.

In the 13 years for which there was sufficient number of observations, mean

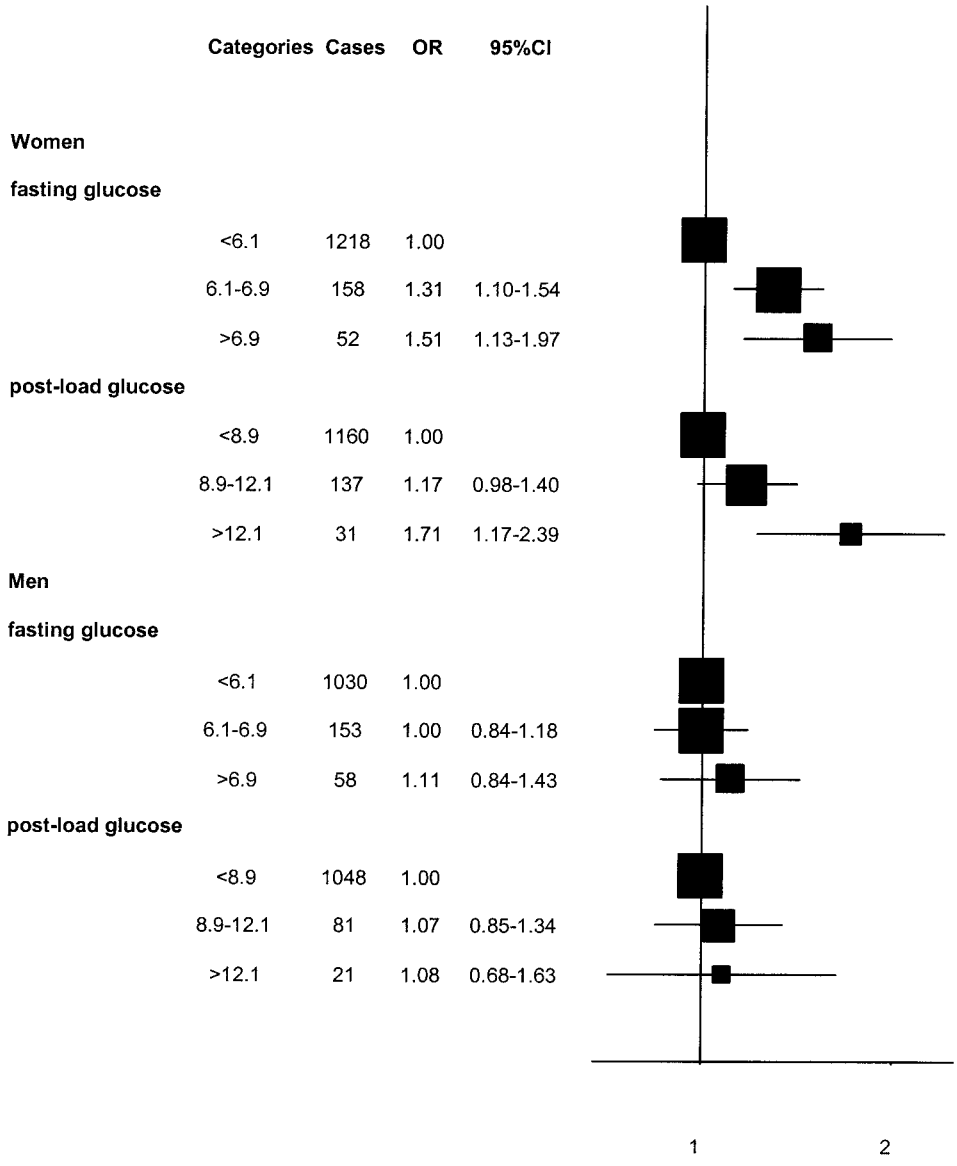

Figure 2—*RR of overall cancer according to World Health Organization categories of fasing and postload glucose plasma levels (mmol/l) in women and men in the Västerbotten Intervention Project, northern Sweden.*

levels of fasting and postload glucose rose ~17 and 8%, respectively, and with increasing age there was a clear increase in the prevalence of hyperglycemia in our cohort, in accordance with what has been reported for other populations (30,31). Thus, the fraction of total cancer incidence related to abnormal glucose metabolism is likely to increase in the near future in our population as well as in other populations.

In conclusion, our finding of a statistically significant association of hyperglycemia with overall cancer risk in women and an increase in risk of cancer at many sites in women and men is essentially in accordance with the observations in some other large cohort studies, suggesting that abnormal glucose metabolism is a general risk factor for cancer development. Although the proportion of subjects with hyperglycemia was highest among obese subjects, the absolute numbers of subjects with hyperglycemia were larger among women and men who were overweight or had normal body weight, and plasma glucose levels remained associated with cancer risk after adjustment for BMI. This observation may have considerable implications for public health strategies, as key determinants of hyperglycemia are known and modifiable. A lifestyle that decreases plasma glucose levels may reduce overall cancer risk not only among overweight or obese subjects but most likely also among subjects with normal body weight. At the same time, current evidence suggests that such a strategy also would contribute to the prevention of diabetes and cardiovascular disease.

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