Blood glucose and risk of incident and fatal cancer in the Metabolic syndrome and Cancer project (Me-Can)

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Background

Prospective studies have indicated that elevated blood glucose levels may increase the risk of cancer, but the strength of the association is unclear. We examined the association between blood glucose and cancer risk in a prospective study of six European cohorts.

Methods and Findings

The Metabolic syndrome and Cancer project (Me-Can) includes cohorts from Norway, Austria, and Sweden; the current study included 274,126 men and 275,818 women. Mean age at baseline was 44.8 years and mean follow-up time was 10.4 years. Excluding the first year of follow-up, 18,621 men and 11,664 women were diagnosed with cancer, and 6,973 men and 3,088 women died of cancer. We used Cox regression models to calculate relative risk (RR) for glucose levels, and included adjustment for body mass index (BMI) and smoking status in the analyses. RRs were corrected for regression dilution ratio of glucose. RR (95% confidence interval) per 1 mmol/l increment of glucose for overall incident cancer was 1.05 (1.01-1.10) in men and 1.11 (1.05-1.16) in women, and corresponding RRs for fatal cancer were 1.15 (1.07-1.22) and 1.21 (1.11-1.33), respectively. Significant increases in risk among men were found for incident and fatal cancer of the liver, gallbladder and respiratory tract, for incident thyroid cancer and multiple myeloma, and for fatal rectal cancer. In women, significant associations were found for incident and fatal cancer of the pancreas, for incident urinary bladder cancer, and for fatal cancer of the uterine corpus, cervix uteri, and stomach.

Conclusions

Data from our study indicate that abnormal glucose metabolism, independently of BMI, is associated with an increased risk of cancer overall and at several cancer sites. Our data showed stronger associations among women than among men, and for fatal cancer compared to incident cancer.

Key words: cohort studies, neoplasms, blood glucose

Introduction

Elevated blood glucose has been associated with an increased risk of cancer overall in several prospective studies [1,2,3,4,5,6]. The strongest evidence comes from a Korean cohort study of 1.3 million men and women that reported an increased risk of incident as well as of fatal cancer in subjects with high glucose levels [1]. Prospective studies of glucose and cancer risk in cohorts of European and US populations have been much smaller, and these studies did not concurrently report on risk of incident and fatal cancer [2,3,4,5,6,7]. Previous results from cohorts in Austria [2] and Sweden [3] included in the current study, also indicated that elevated fasting glucose is related to an increased risk of overall incident cancer. However, the relatively modest sample size in these studies resulted in limited power to estimate risks for individual cancer sites. Furthermore, exposure assessment by glucose measurement at a single occasion carries a substantial random error due to technical measurement error and within-person variation of blood glucose level [8,9]. Such inaccuracy of exposure assessment will dilute the association with outcome, i.e. regression dilution bias [8,10,11]. In several prospective studies of metabolic factors and risk of cardiovascular disease, data from multiple examinations have been used to correct risk estimates for random error in exposure classification, which resulted in substantially stronger associations than estimates based on uncorrected exposures [12,13,14]. To date, correction for random error has only been performed in one study on glucose and cancer risk [3].

The aim of this study was to investigate the association between blood glucose and risk of incident and fatal cancer overall and at specific sites, as well as all cause mortality, in a large study of six European cohorts including correction for random error in glucose level.

Material and Methods

Me-Can

The Metabolic syndrome and Cancer project (Me-Can) includes data from population-based cohorts in Norway, Austria, and Sweden. A detailed description of Me-Can has recently been published [15]. In brief, the Norwegian cohorts includes the Oslo study I cohort (Oslo) [16,17], the Norwegian Counties Study (NCS) [18,19], the Cohort of Norway (CONOR) [20], and the Age 40-programme (40-y) [21]. The Austrian cohort consists of the Vorarlberg Health Monitoring and Prevention Programme (VHM&PP) [2], and the Swedish cohorts are the Västerbotten Intervention Project (VIP) [22], and the Malmö Preventive Project (MPP) [23,24]. Written informed consent was obtained from all participants included in this study, and the study was approved by research ethical committees in the respective countries.

Data on height, weight, blood pressure, and blood, plasma or serum levels of glucose, total cholesterol, and triglycerides had been collected at health examinations in all cohorts. Height and weight were measured in a similar way in all cohorts; without shoes and with light indoor clothing. In the Norwegian cohorts, fasting was not required before the examination, and fasting time was recorded as less than 1 hour, 1-2, 2-4, 4-8, or more than 8 hours. Fasting time in the VIP was recorded as less than 4 hours, 4-8, or more than 8 hours, and from 1992, participants were asked to fast for at least eight hours before the examination. In the MPP and after the initial three years in the VHM&PP, a minimum of eight hours fasting time was implemented. Glucose levels were measured in the Oslo and the NCS in serum glucose with a non-enzymatic method; in CONOR and the 40-y cohort - serum/enzymatic; in the VHM&PP and the VIP - plasma/enzymatic; and in the MPP – whole blood/enzymatic. In the Norwegian cohorts, the non-enzymatic method used during the first study period yielded 0.8-1.1 mmol/l higher levels than the true concentration defined as the value found with a specific enzymatic method [25].

Follow-up and selection of subjects

Each of the cohorts was linked to the respective National registers for identification of a) cancer diagnosis, b) migration, c) vital status, and d) cause of death, with death attributed to cancer if the underlying cause of death was cancer. Follow-up for each of the cohorts includes the year as follows: Norwegian cohorts, a-c) 2005, d) 2004; the VHM&PP, a) 2003, b) no information available, c-d) 2003; the VIP and the MPP a-c) 2006, d) 2004.

Selection of subjects for the study is described in Figure 1. From the original data with 904,060 subjects and 1,600,296 observations, we excluded observations with: non-matching data, a cancer diagnosis at or before the date of health examination, extreme values of metabolic factors [15] (<1 mmol/l for glucose and <15 or >60 kg/m^2 for body mass index, BMI), missing data for BMI, glucose or fasting time, a shorter time than one year between the date of examination and end of follow-up for cancer incidence, and observations in the VHM&PP that included data on post-load glucose instead of fasting glucose. From the remaining 611,459 subjects with 1,025,940 observations, we selected the first observation for each subject, and if data from a fasting state and data on smoking status was available, the first of these observations was selected. Due to policy restrictions imposed by the Norwegian Institute of Public Health that the proportion of Norwegian subjects in Me-Can studies should not exceed approximately 50% (56% after the above selection), we further excluded 1,868 subjects in Norway without data on smoking status, and also the entire NCS cohort (n = 59,647). The final data set included 549,944 subjects, 274,126 men and 275,818 women.

Categorisation of cancers

Incident and fatal cancers, categorised according to the International Classification of Diseases, seventh revision (ICD-7) codes, were grouped into cancer sites as grouped in the Eurostat European shortlist for cause of death [26], which was used for cause of death classification in the Norwegian cohorts. Incident cancers were further divided into relevant subgroups. Relative risks (RR) for incident and fatal cancer at specific sites are presented separately for men and women if the number of cases in each group was higher than 50, and risks are presented for men and women combined if the number of cases in each group was less than or equal to 50 and if the total number of cases was more than 80.

Statistical analysis

In order to reduce the probability of reverse causation, rates, RRs and absolute risks were calculated with follow-up starting one year after the baseline examination. Subjects were followed until the date of event, i.e. cancer diagnosis or cancer death, or until the date of death from any cause, emigration, or end of follow-up, whichever occurred first. Rates were directly age-standardized in 5-year

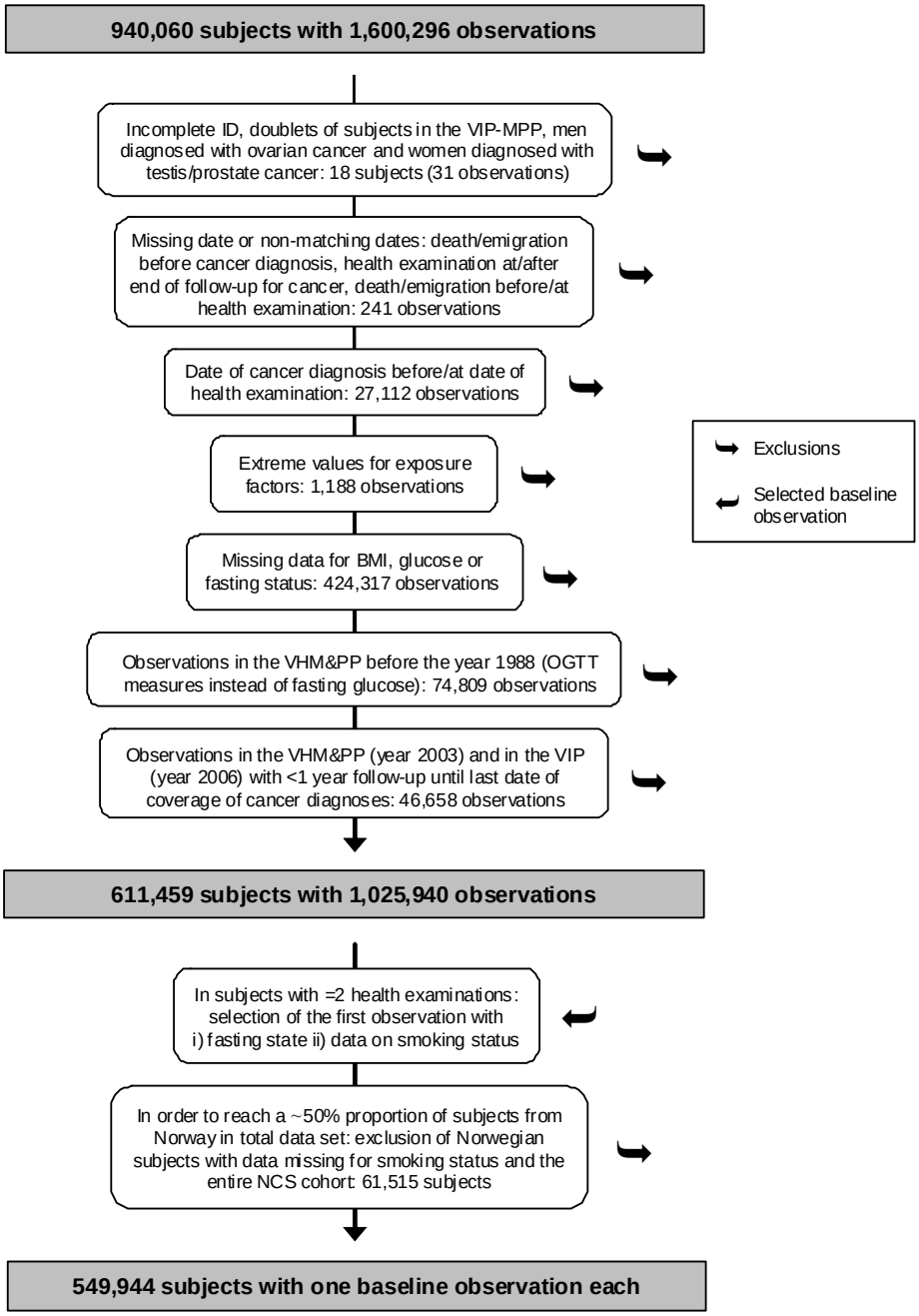


Figure 1. Flowchart of data cleaning and selection of subjects/observations. OGTT, oral glucose tolerance test. NCS, Norwegian Counties Study

categories, using the European standard population as the reference [27]. We used Cox proportional hazards regression to calculate hazard ratios, denoted as relative risks, for glucose levels with risk of incident and fatal cancer, and of death from all causes. Age was used as time variable and all estimates were stratified by subcohort, sex, and by categories of birth date: before 1923, 1923-1930, 1931-1938, 1939-1946, 1947-1954, 1955 and later. We estimated RR for glucose levels in quintiles and deciles, for which cut-off levels were calculated within each subcohort, sex, and category of fasting time. *P* for trend over quintiles and deciles refers to the *p*-value for the Wald test of a linear risk estimate, assigning subjects included in each analysis the mean sex- and cohort specific glucose level within the corresponding quantile. RR was also assessed for glucose as a continuous variable, i.e. per 1 mmol/l increment. In order to exclude outliers, these analyses were restricted to subjects with glucose levels lower than 10 mmol/l (99% of subjects). All analyses included adjustment for age at measurement

(continuous), BMI (categories: <22.5, 22.5-, 25.0-, 27.5-, 30.0-, 32.5- kg/m^2) and smoking status (categories: never smoker, ex-smoker, current smoker, and unknown), and analyses of glucose as a continuous variable were also adjusted for fasting time.

We calculated regression dilution ratio (RDR) of glucose in order to adjust RRs for random error in glucose level [8,10,11]. RDR was calculated based on data from repeated health examinations in 133,820 subjects, including 406,364 observations, in the full Me-Can cohort. Only repeated measurements with the same fasting time and in the same cohort as at baseline, and with data on smoking status, were used. However, as the same method for glucose measurement had been used in the Oslo and the NCS cohorts, and in the CONOR and 40-y cohorts, respectively, subjects with measurements in the Oslo and in the NCS, or in CONOR and in the 40-y cohort, were included in analyses. Mean time between the baseline measurement and repeated measurements was 6.9 (standard deviation, SD = 3.9) years. We used a linear mixed effects model, similar to that described by Wood *et al.* [11], that included age at baseline, fasting time, smoking status, sex, and time from baseline as fixed effects, and cohort as random effect. RDR was estimated separately for men and women, and combined, in models for i) glucose standardised within cohort, sex and fasting time, and ii) for glucose only including subjects with a baseline glucose level lower than 10 mmol/l. Model i) was used to predict RDR among subjects in the current study with data on smoking status, for correction of RRs in quantiles, and model ii) was used to predict RDR among subjects with data on smoking status and with a glucose level lower than 10 mmol/l, for correction of RRs of per 1 mmol/l increment. RDR was predicted for the time point at five years after baseline measurement, i.e. half the follow-up time [8,10,11]. We used the mean of predicted RDRs for correction of RR, which resulted in RDRs for quantile analyses of: 0.30 among men, 0.30 among women, and 0.31 overall, and in analyses of per 1 mmol/l increment: 0.40 among men, 0.43 among women, and 0.41 overall. Correction of RRs for RDR was obtained by exp(log(RR)/RDR), using the sex-specific RDR in analyses that included men or women only, and using the combined RDR in analyses that included both sexes.

Cox proportional hazards assumption was checked for glucose and covariates by the statistical test of Schoenfeld residuals. For some cancers, there was an indication of violation of proportionality for BMI or smoking status, but as RRs with and without stratification of the variable within the model were very similar, BMI and smoking status were not kept as stratum in the final model. For a few cancers, there was indication of violation of the proportionality over age for glucose; however, we report RRs only in the full study group and not in subgroups of age. Absolute risks of incident and fatal cancer between 50 and 70 years of age were calculated

Table 1. Baseline characteristics of study subjects in Me-Can

	Men	Women
Baseline measurement, year	1972-2005	1977-2005
Subjects, *n*	274,126	275,818
Baseline age, years		
Mean (SD)	44.7 (11.6)	45.0 (12.8)
Categories, *n* (%)		
<30	24,756 (9)	30,461 (11)
30- <45	143,291 (52)	141,638 (51)
45- <60	73,567 (27)	65,793 (24)
60-	32,512 (12)	37,926 (14)
Smoking status, *n* (%)		
Never smoker	110,154 (40)	137,767 (50)
Ex-smoker	85,094 (31)	73,263 (27)
Current smoker	77,995 (29)	64,097 (23)
Missing	883 (0)	691 (0)
BMI, kg/m^2		
Mean (SD)	25.8 (3.5)	25.0 (4.5)
Categories, *n* (%)		
<25	120,026 (44)	159,700 (58)
25- <30	123,132 (45)	80,836 (29)
30-	30,968 (11)	35,282 (13)
Follow-up, years		
Mean (SD)	11.3 (7.4)	9.6 (4.4)
Categories, *n* (%)		
<5	39,411 (14)	39,017 (14)
5 - <15	184,479 (67)	206,769 (75)
15 - <25	21,583 (8)	27,687 (10)
25-	28,653 (11)	2,345 (1)

SD, standard deviation; BMI, body mass index.

Table 2. Characteristics of subjects within quintile levels of glucose

		Quintile 1-5 (mean glucose level, mmol/l)				
		1 (4.1)	**2 (4.7)**	**3 (5.0)**	**4 (5.4)**	**5 (6.7)**
Baseline age, years, mean (SD)	Men	42.5 (11.1)	43.3 (11.1)	44.1 (11.4)	45.1 (11.6)	48.1 (12.1)
	Women	41.9 (11.7)	43.0 (11.9)	44.3 (12.5)	45.7 (12.8)	49.5 (13.5)
BMI, kg/m^2, mean (SD)	Men	25.2 (3.3)	25.5 (3.3)	25.7 (3.4)	26.0 (3.5)	26.7 (3.9)
	Women	24.0 (3.9)	24.5 (4.1)	24.8 (4.2)	25.2 (4.4)	26.4 (5.1)
Current smoker, %	Men	29	29	28	29	29
	Women	24	24	23	23	22

SD, standard deviation; BMI, body mass index.

as described by Gail *et al.* [28]. For this method, risk of cancer and of dying from other causes than cancer was derived from the cohort for ages 50 to 60 years and 60 to 70 years, respectively. Statistical analyses were performed in Stata (version 9.2, StataCorp LP, College Station, Texas), and R (version 2.7.2, used for RDR calculation).

Results

Baseline characteristics and follow-up

Mean age at baseline was 44.7 (SD = 11.6) years in men and 45.0 (SD = 12.8) years in women (Table 1). The prevalence of overweight or obesity, i.e. BMI 25 kg/m^2 or higher, was 56% among men and 42% among women. All participants in the VHM&PP and the MPP and 90% of participants in the VIP had fasted more than eight hours before the health examination, whereas 95% of subjects in the Norwegian cohorts had fasted less than eight hours. Among subjects that had fasted more than eight hours, 8% of men and 6% of women had impaired glucose levels according to the World Health Organization definition [29] (6.1-6.9 mmol/l in serum/plasma or 5.6-6.0 mmol/l in whole blood) and 4% of men and 3% of women had diabetic glucose levels (≥7.0 mmol/l in serum/plasma or ≥6.0 mmol/l in whole blood). Baseline age and BMI increased for each increment of glucose quintile (Table 2).

The mean follow-up time was 11.3 (SD = 7.4) years in men and 9.6 (SD = 4.4) years in women. Excluding the first year of observation, 18,621 men and 11,664 women were diagnosed with cancer during follow-up and 6,973 men and 3,088 women died of cancer.

Glucose and relative risk of cancer

Glucose was significantly positively associated with risk of overall incident and fatal cancer in men, the RR (95% confidence interval) per 1 mmol/l increment was for incident cancer 1.05 (1.01-1.10), and for fatal cancer 1.15 (1.07-1.22) (Table 3 and 4). In analysis of glucose in quintiles, the RR for the top versus bottom quintile was for incident cancer 1.18 (1.00-1.37, p for trend = 0.06), and for fatal cancer 1.50 (1.18-1.94, p for trend < 0.001). Significant increases in risk of incident and fatal cancer at specific sites per 1 mmol/l increment in glucose among men were observed for cancer of the liver, gallbladder, and the respiratory tract. Significant linear associations were also found for incident thyroid cancer, multiple myeloma, and for fatal rectal cancer, and glucose in the top quintile was associated with a significant increased risk of fatal colon cancer.

In women, the association between a 1 mmol/l increase in glucose level and overall cancer was somewhat stronger than in men; the RR among women was for incident cancer 1.11 (1.05-1.16), and for fatal cancer 1.21 (1.11-1.33) (Table 3 and 4). Significant positive associations among women were observed for incident and fatal cancer of the stomach (borderline significant for incidence) and pancreas. A significant linear association was also observed for incident urinary bladder cancer and for fatal cancer of the cervix uteri and uterine corpus cancer. Furthermore, top quintile level of glucose was significantly associated with an increased risk of incident endometrial cancer, and a decreased risk of incident thyroid cancer.

In men and women combined, a 1 mmol/l increment in glucose level was associated with an increased risk of death from cancer of the oropharynx and oesophagus. We observed no differences in the association between glucose and risk of cancer between subgroups of fasting time in men or women (data not shown).

Decile levels of glucose and risk

We further explored risk of incident and fatal cancer, and of death from all causes, by deciles of glucose levels. In order to use a broad referent category that includes healthy normal glucose levels, we used the lowest 40% of glucose levels as referent group (Figure 2). Among fasting subjects, the cut-off for impaired fasting glucose was within decile nine to ten. RR of incident and fatal cancer, and of overall death, increased with increasing deciles, and in men, the strongest risk increase of cancer death and of death overall was observed between decile nine and ten. In men, the RR for top decile versus decile 1-4

Table 3. Relative risk of incident cancer by glucose in quintiles and per 1 mmol/l increment

Site (ICD-7)	Sex[b]	*n* cases[c]	Quintile 1-5, relative risk (95% CI)[a]					*p* for trend	Relative risk (95% CI) per 1 mmol/l increment[a,c]
			1 (ref)	2	3	4	5		
Total cancer	Men								
	Person-years		550,091	545,386	517,011	588,557	537,656		
	n cases	18,621	3,346	3,437	3,265	4,234	4,339		
	Rate[d]		529	535	531	564	549		
	Relative risk		1.00	1.07 (0.90-1.25)	1.10 (0.93-1.29)	1.18 (1.03-1.37)	1.18 (1.00-1.37)	0.06	1.05 (1.01-1.10)
	Women								
	Person-years		460,543	435,465	497,999	447,399	467,908		
	n cases	11,664	1,946	1,842	2,329	2,441	3,106		
	Rate[d]		383	367	376	409	424		
	Relative risk		1.00	0.87 (0.70-1.07)	0.90 (0.73-1.10)	1.18 (0.97-1.42)	1.29 (1.07-1.59)	<0.001	1.11 (1.05-1.16)
Lip, oral cavity, pharynx (140-149)	Men	453	1.00	0.81 (0.29-2.34)	1.37 (0.48-3.86)	1.99 (0.76-5.31)	1.89 (0.70-5.10)	0.2	1.27 (0.97-1.66)
	Women	128	1.00	0.73 (0.08-6.46)	2.93 (0.44-19.6)	1.14 (0.15-8.65)	1.89 (0.28-13.0)	0.4	1.37 (0.87-2.14)
Oesophagus (150)	All	246	1.00	0.71 (0.18-2.89)	0.66 (0.16-2.70)	1.24 (0.35-4.55)	1.48 (0.41-5.33)	0.3	1.29 (0.92-1.80)
Stomach (151)	Men	628	1.00	0.68 (0.28-1.64)	1.07 (0.44-2.46)	0.76 (0.33-1.74)	0.81 (0.35-1.84)	0.5	0.93 (0.75-1.17)
	Women	297	1.00	0.84 (0.18-3.78)	2.34 (0.63-8.80)	1.84 (0.48-7.09)	2.65 (0.73-9.42)	0.2	1.31 (1.00-1.73)
Colon (153)	Men	1,455	1.00	0.93 (0.52-1.64)	0.97 (0.54-1.74)	0.73 (0.42-1.29)	1.33 (0.79-2.28)	0.2	1.02 (0.88-1.18)
	Women	979	1.00	0.97 (0.44-2.05)	1.03 (0.50-2.10)	1.03 (0.52-2.16)	1.33 (0.65-2.59)	0.5	0.99 (0.84-1.16)
Rectum, anus (154)	Men	899	1.00	1.74 (0.81-3.69)	1.94 (0.90-4.22)	2.52 (1.21-5.10)	1.69 (0.81-3.53)	0.5	1.14 (0.94-1.37)
	Women	446	1.00	0.84 (0.28-2.52)	0.79 (0.28-2.28)	1.18 (0.44-3.29)	1.00 (0.37-2.79)	0.7	1.09 (0.85-1.40)
Liver, intrahepatic bile ducts (155.0)	Men	176	1.00	0.84 (0.14-4.69)	1.74 (0.32-9.42)	0.37 (0.06-2.16)	3.45 (0.73-16.1)	0.02	1.76 (1.21-2.56)
	Women	60	1.00	0.02 (0.00-0.93)	0.35 (0.02-4.89)	0.73 (0.06-9.11)	0.52 (0.04-6.22)	0.7	1.70 (0.94-3.08)
Gallbladder, biliary tract (155.1-155.3)	Men	79	1.00	5.10 (0.37-70.2)	1.25 (0.06-23.6)	5.10 (0.38-67.0)	6.71 (0.52-86.4)	0.2	2.01 (1.14-3.53)
	Women	77	1.00	7.36 (0.40-133)	1.99 (0.11-38.1)	2.72 (0.14-49.8)	7.50 (0.52-110)	0.1	1.58 (0.96-2.61)
Pancreas (157)	Men	418	1.00	0.50 (0.16-1.55)	1.25 (0.42-3.78)	1.50 (0.54-4.22)	1.99 (0.73-5.53)	0.07	1.28 (0.97-1.68)
	Women	230	1.00	2.34 (0.40-13.6)	2.72 (0.52-14.1)	5.64 (1.14-28.4)	12.1 (2.65-55.1)	0.001	1.55 (1.12-2.13)
Larynx, trachea/bronchus/lung (161, 162)	Men	2,294	1.00	1.07 (0.68-1.69)	0.84 (0.52-1.33)	1.33 (0.87-2.10)	1.42 (0.90-2.16)	0.09	1.15 (1.02-1.29)
	Women	659	1.00	1.94 (0.81-4.69)	0.97 (0.40-2.28)	1.84 (0.79-4.22)	1.25 (0.54-2.93)	1.0	1.11 (0.89-1.38)
Breast (170)	Women	4,094	1.00	0.90 (0.65-1.29)	0.90 (0.65-1.25)	1.29 (0.93-1.79)	1.03 (0.73-1.42)	0.6	1.06 (0.98-1.16)
Cervix uteri (171)	Women	280	1.00	0.76 (0.21-2.65)	0.56 (0.16-1.89)	1.42 (0.42-4.59)	0.38 (0.11-1.42)	0.3	0.85 (0.59-1.21)
Other parts of uterus (172, 174)	Women	762	1.00	0.97 (0.40-2.40)	0.93 (0.40-2.22)	1.84 (0.79-4.13)	2.65 (1.21-5.86)	0.001	1.14 (0.95-1.38)[e]
Endometrium (172)	Women	727	1.00	1.03 (0.40-2.59)	0.90 (0.37-2.16)	1.89 (0.81-4.40)	2.59 (1.14-5.75)	0.003	1.14 (0.95-1.38)[e]
Ovary (175.0)	Women	504	1.00	0.52 (0.19-1.37)	0.76 (0.30-1.89)	0.50 (0.19-1.25)	0.58 (0.23-1.46)	0.3	0.85 (0.66-1.10)
Prostate (177)	Men	5,713	1.00	1.18 (0.87-1.59)	1.14 (0.84-1.55)	1.10 (0.84-1.46)	0.93 (0.70-1.21)	0.2	0.97 (0.90-1.04)
Testis (178)	Men	220	1.00	1.18 (0.32-4.31)	1.03 (0.28-3.95)	0.58 (0.14-2.40)	1.07 (0.25-4.59)	1.0	0.89 (0.59-1.34)
Kidney, renal cell (180.0, 180.9)	Men	505	1.00	3.07 (1.10-8.65)	3.45 (1.25-9.75)	2.28 (0.81-6.34)	2.65 (0.97-7.36)	0.4	1.14 (0.89-1.46)
	Women	210	1.00	0.37 (0.07-1.89)	0.60 (0.14-2.65)	0.52 (0.11-2.34)	0.81 (0.20-3.29)	0.8	1.02 (0.72-1.46)

Bladder (181)	Men	1,280	1.00	0.90 (0.48-1.64)	0.81 (0.42-1.50)	1.25 (0.70-2.22)	1.18 (0.65-2.16)	0.3	1.17 (1.00-1.37)
	Women	227	1.00	0.76 (0.14-4.31)	1.64 (0.35-7.63)	1.64 (0.35-7.77)	3.61 (0.87-15.4)	0.04	1.45 (1.05-2.01)
Melanoma of skin (190)	Men	863	1.00	1.37 (0.68-2.72)	1.00 (0.48-2.05)	0.90 (0.44-1.84)	0.87 (0.42-1.84)	0.7	0.92 (0.75-1.13)
	Women	592	1.00	0.73 (0.30-1.79)	0.60 (0.25-1.42)	0.63 (0.26-1.50)	1.14 (0.50-2.59)	0.5	1.04 (0.83-1.31)
Non-melanoma of skin (191)	Men	684	1.00	0.35 (0.15-0.84)	0.97 (0.44-2.16)	0.65 (0.29-1.42)	0.56 (0.25-1.25)	0.6	0.96 (0.77-1.19)
	Women	337	1.00	1.21 (0.30-4.89)	1.89 (0.54-6.71)	1.55 (0.42-5.64)	3.07 (0.93-10.3)	0.05	1.17 (0.89-1.53)
Brain, nervous tissue (193)	Men	331	1.00	1.84 (0.60-5.64)	0.90 (0.28-2.93)	1.21 (0.40-3.78)	0.44 (0.13-1.50)	0.07	0.59 (0.42-0.84)
	Women	201	1.00	0.76 (0.14-3.95)	1.14 (0.24-5.20)	1.69 (0.37-7.63)	1.89 (0.42-8.35)	0.4	1.34 (0.92-1.94)
Thyroid gland (194)	Men	97	1.00	2.40 (0.24-25.1)	2.34 (0.21-25.4)	1.46 (0.14-16.1)	11.3 (1.29-98.3)	0.02	1.88 (1.16-3.07)
	Women	180	1.00	0.46 (0.10-2.10)	0.50 (0.12-2.10)	0.28 (0.06-1.29)	0.18 (0.04-0.87)	0.05	0.72 (0.47-1.10)
Lymph/hematopoietic tissue (200-209)	Men	1,426	1.00	1.07 (0.60-1.94)	0.68 (0.37-1.21)	1.50 (0.87-2.65)	1.25 (0.70-2.16)	0.3	1.10 (0.95-1.28)
	Women	793	1.00	0.70 (0.32-1.59)	0.76 (0.35-1.64)	0.73 (0.33-1.59)	1.18 (0.56-2.46)	0.3	1.19 (0.99-1.43)
Non-Hodgkin's lymphoma (200, 202)	Men	634	1.00	0.79 (0.33-1.79)	0.42 (0.17-1.00)	1.07 (0.50-2.40)	0.65 (0.28-1.50)	0.5	0.89 (0.71-1.13)
	Women	378	1.00	0.73 (0.23-2.40)	0.81 (0.28-2.52)	0.97 (0.32-3.00)	1.29 (0.44-3.78)	0.4	1.24 (0.95-1.61)
Hodgkin's lymphoma (201)	All	113	1.00	0.79 (0.11-5.64)	0.76 (0.11-5.54)	1.44 (0.23-9.36)	1.13 (0.16-7.93)	0.8	1.23 (0.73-2.06)
Multiple myeloma (203)	Men	252	1.00	1.14 (0.26-4.69)	0.87 (0.19-3.78)	1.79 (0.48-6.96)	2.93 (0.79-11.1)	0.04	1.59 (1.13-2.23)
	Women	148	1.00	0.32 (0.05-2.05)	0.48 (0.09-2.59)	0.12 (0.02-0.81)	0.84 (0.17-4.13)	0.7	0.92 (0.58-1.45)
Leukemia (204-207)	Men	398	1.00	2.34 (0.76-7.23)	1.37 (0.42-4.59)	2.93 (0.97-8.65)	2.22 (0.73-6.71)	0.2	1.17 (0.89-1.54)
	Women	192	1.00	0.42 (0.08-2.28)	0.81 (0.17-3.78)	0.56 (0.11-2.72)	0.84 (0.19-3.78)	0.8	1.29 (0.90-1.86)
Other cancer[f]	Men	909	1.00	0.87 (0.42-1.79)	1.50 (0.73-3.14)	1.59 (0.79-3.22)	1.46 (0.70-3.00)	0.4	1.12 (0.92-1.36)
	Women	583	1.00	1.03 (0.38-2.79)	0.60 (0.23-1.55)	1.99 (0.81-4.99)	2.52 (1.03-6.10)	0.006	1.33 (1.07-1.65)

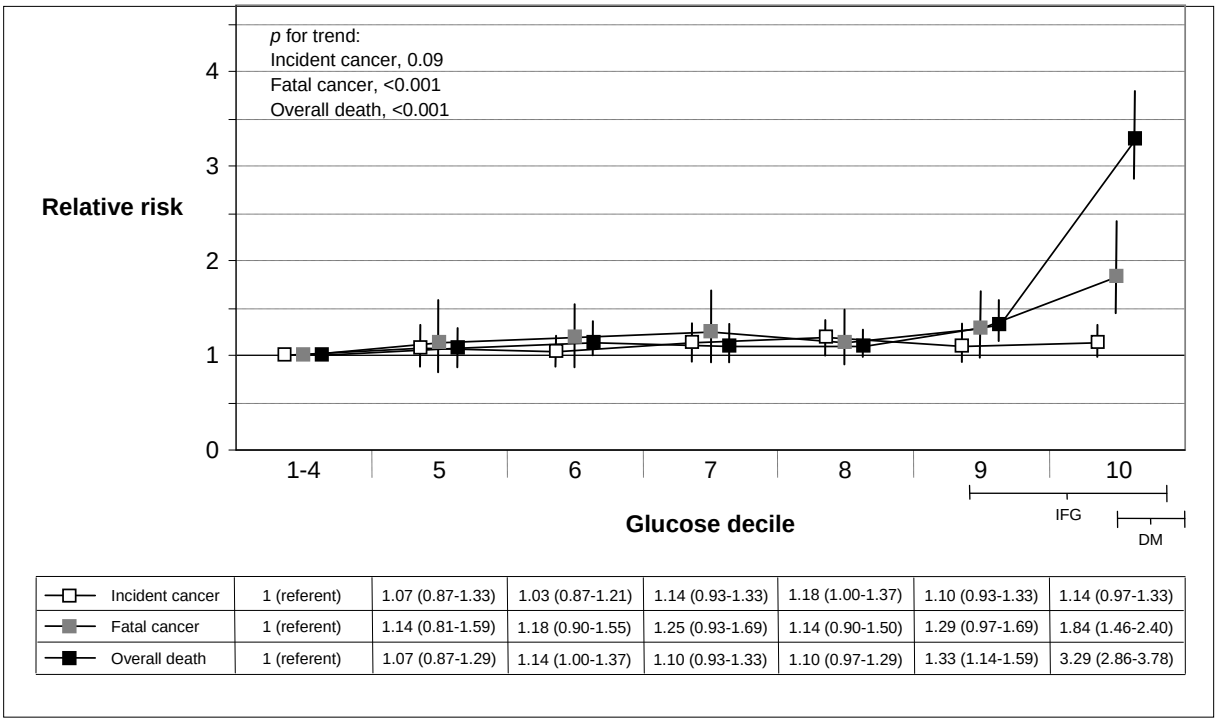
[a]Relative risks (RR) reported with three significant figures, estimated from Cox models with attained age as time scale, stratified by cohort, and adjusted for baseline age, birth year, body mass index, and smoking status, and RRs per 1 mmol/l were additionally adjusted for fasting time. RRs are corrected for regression dilution ratio (RDR); conversion into uncorrected RR = exp(log(RR)*RDR). RDR quintiles: men, 0.30; women, 0.30; all, 0.31. RDR per 1 mmol/l: men, 0.40; women, 0.43; all, 0.41.
[b]Relative risks are presented separately for men and women if the number of cases in each group was more than 50, and combined if the number of cases in each group was less than or equal to 50 and if the total number of cases was more than 80.
[c]Relative risks per 1 mmol/l increment included subjects with glucose levels lower than 10 mmol/l (99% of subjects). Number of cases corresponds to quintile analyses which included all subjects.
[d]Per 100,000 person-years, age-standardized to the European standard population.
[e]Relative risks were significant in analyses that also included subjects with glucose levels equal to or higher than 10 mmol/l.
[f]Other cancer than the separately presented sites.
CI, confidence interval; ICD-7, International Classification of Diseases, seventh revision; ref, referent group.

Table 4. Relative risk of overall death and of fatal cancer by glucose in quintiles and per 1 mmol/l increment

Site (ICD-7)	Sex[b]	*n* cases[c]	Quintile 1-5, relative risk (95% CI)[a] 1 (ref)	2	3	4	5	*p* for trend	Relative risk (95% CI) per 1 mmol/l increment[a,c]
Overall death	Men								
	Person-years[d]		510,654	508,473	477,979	545,596	496,955		
	n cases	21,445	3,721	3,644	3,523	4,552	6,005		
	Rate[e]		766	752	745	780	932		
	Relative risk		1.00	0.90 (0.79-1.07)	1.07 (0.90-1.25)	1.07 (0.90-1.21)	2.22 (1.94-2.52)	<0.001	1.29 (1.24-1.33)
	Women								
	Person-years[d]		423,829	398,725	458,898	409,746	428,549		
	n cases	8,424	1,142	1,074	1,455	1,644	3,109		
	Rate[e]		355	320	338	366	463		
	Relative risk		1.00	0.73 (0.54-0.97)	0.76 (0.58-0.97)	1.03 (0.81-1.33)	2.34 (1.84-2.93)	<0.001	1.36 (1.29-1.43)
Total cancer	Men								
	n cases	6,973	1,271	1,223	1,191	1,549	1,739		
	Rate[e]		238	221	228	236	246		
	Relative risk		1.00	0.90 (0.68-1.18)	1.10 (0.84-1.42)	1.14 (0.87-1.46)	1.50 (1.18-1.94)	<0.001	1.15 (1.07-1.22)
	Women								
	n cases	3,088	472	430	581	653	952		
	Rate[e]		118	108	119	128	139		
	Relative risk		1.00	0.79 (0.50-1.21)	0.84 (0.56-1.25)	1.29 (0.87-1.94)	1.69 (1.18-2.52)	<0.001	1.21 (1.11-1.33)
Lip, oral cavity, pharynx (140-149)	All	180	1.00	1.57 (0.30-8.34)	1.07 (0.18-6.08)	3.32 (0.69-16.0)	5.33 (1.13-24.9)	0.01	1.50 (1.00-2.25)
Oesophagus (150)	All	187	1.00	0.61 (0.11-3.39)	0.69 (0.12-3.86)	2.45 (0.55-10.8)	4.65 (1.10-20.2)	0.005	1.73 (1.19-2.53)
Stomach (151)	Men	438	1.00	0.63 (0.23-1.74)	0.68 (0.24-1.89)	0.65 (0.25-1.79)	0.60 (0.23-1.59)	0.3	0.94 (0.72-1.23)
	Women	198	1.00	1.07 (0.16-6.71)	1.84 (0.35-9.91)	1.50 (0.26-8.35)	5.31 (1.10-25.4)	0.01	1.56 (1.13-2.14)
Colon (153)	Men	567	1.00	0.81 (0.30-2.16)	1.18 (0.46-3.07)	1.07 (0.42-2.65)	2.72 (1.14-6.46)	0.004	1.09 (0.87-1.37)[f]
	Women	306	1.00	0.38 (0.10-1.55)	0.38 (0.11-1.37)	0.40 (0.11-1.42)	0.97 (0.30-3.07)	0.4	1.15 (0.87-1.52)
Rectum, anus (154)	Men	332	1.00	0.84 (0.23-3.14)	1.21 (0.33-4.50)	2.86 (0.90-9.26)	2.93 (0.90-9.58)	0.02	1.44 (1.08-1.92)
	Women	125	1.00	0.20 (0.02-2.22)	1.33 (0.19-9.42)	1.79 (0.26-12.2)	1.03 (0.15-6.96)	0.6	1.11 (0.71-1.74)
Liver, intrahepatic bile ducts (155.0)	All	134	1.00	0.36 (0.05-2.63)	0.64 (0.10-4.28)	0.38 (0.06-2.45)	2.22 (0.43-11.5)	0.05	1.77 (1.19-2.62)
Pancreas (157)	Men	450	1.00	0.65 (0.23-1.89)	1.00 (0.33-2.86)	0.84 (0.30-2.34)	2.34 (0.90-6.22)	0.02	1.24 (0.95-1.61)[f]
	Women	262	1.00	2.34 (0.42-12.8)	2.22 (0.44-10.9)	4.79 (1.00-22.4)	12.8 (3.00-54.6)	<0.001	1.70 (1.29-2.24)
Larynx, trachea/bronchus/lung (161, 162)	Men	1,846	1.00	0.93 (0.56-1.55)	1.03 (0.60-1.74)	1.59 (0.97-2.59)	1.59 (0.97-2.59)	0.03	1.21 (1.06-1.37)
	Women	433	1.00	1.37 (0.44-4.22)	0.76 (0.25-2.28)	2.52 (0.90-7.23)	1.89 (0.68-5.31)	0.2	1.29 (1.00-1.65)
Breast (170)	Women	387	1.00	0.87 (0.28-2.79)	1.14 (0.40-3.37)	1.25 (0.42-3.69)	0.87 (0.30-2.59)	0.7	0.97 (0.74-1.28)
Cervix uteri (171)	Women	51	1.00	6.10 (0.14-253)	3.00 (0.07-125)	32.8 (1.10-994)	21.2 (0.68-662)	0.04	2.26 (1.20-4.28)
Other parts of uterus (172, 174)	Women	81	1.00	0.33 (0.01-9.11)	0.70 (0.04-12.8)	0.84 (0.05-14.7)	9.26 (0.79-109)	0.003	1.69 (1.05-2.73)
Ovary (175.0)	Women	249	1.00	0.14 (0.03-0.63)	0.44 (0.12-1.59)	0.30 (0.08-1.18)	0.50 (0.14-1.74)	0.9	0.94 (0.67-1.32)
Prostate (177)	Men	817	1.00	1.29 (0.63-2.79)	1.29 (0.60-2.79)	0.65 (0.30-1.42)	0.81 (0.38-1.69)	0.4	0.97 (0.80-1.18)

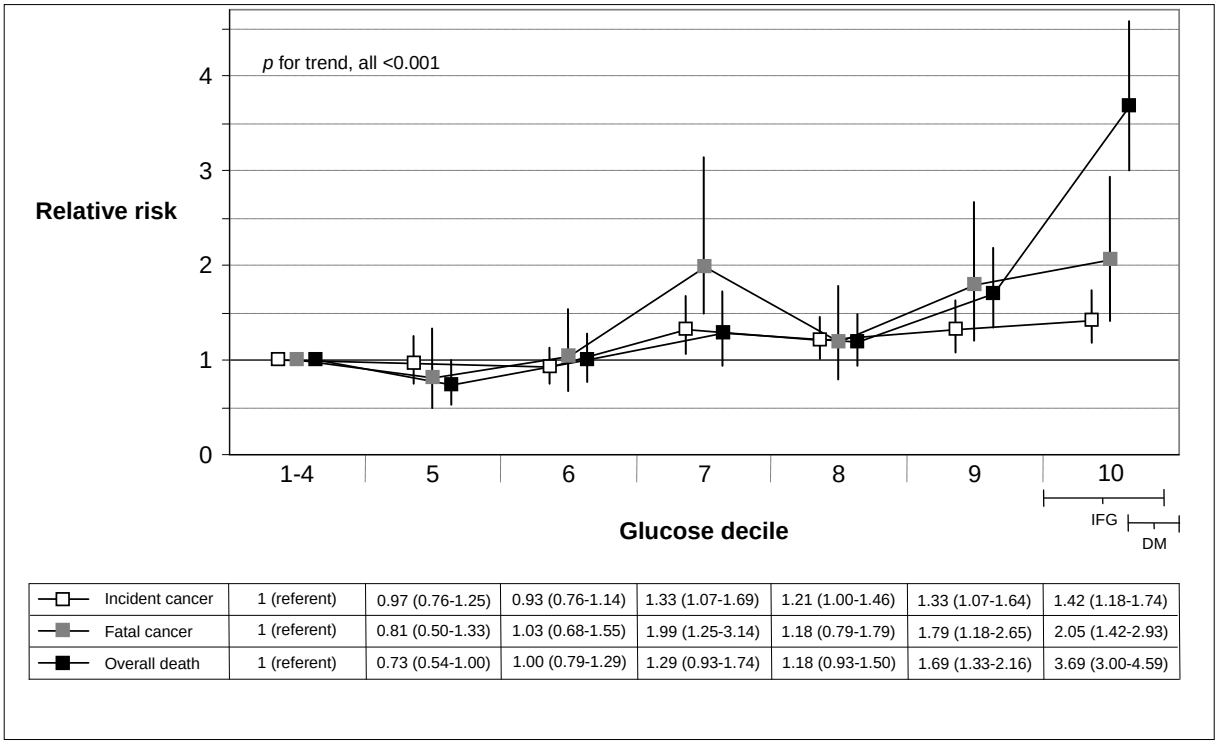
Kidney, renal cell (180.0, 180.9)	Men	197	1.00	1.50 (0.30-7.50)	2.46 (0.52-11.9)	0.76 (0.15-3.86)	1.79 (0.38-8.20)	0.8	1.25 (0.84-1.87)
	Women	59	1.00	0.73 (0.04-13.9)	0.25 (0.01-4.69)	0.02 (0.00-0.73)	0.87 (0.07-11.1)	0.6	0.94 (0.48-1.85)
Bladder (181)	All	250	1.00	0.26 (0.07-1.00)	0.59 (0.16-2.22)	0.43 (0.12-1.57)	0.82 (0.24-2.76)	0.6	1.10 (0.77-1.55)
Melanoma of skin (190)	All	220	1.00	3.32 (0.71-15.3)	3.54 (0.76-16.6)	4.28 (0.97-19.0)	4.20 (0.94-18.7)	0.2	1.10 (0.74-1.63)
Lymph/hematopoietic tissue (200-209)	Men	611	1.00	0.60 (0.26-1.46)	0.44 (0.17-1.07)	1.00 (0.44-2.22)	0.81 (0.35-1.84)	0.9	1.06 (0.84-1.34)
	Women	237	1.00	1.29 (0.30-5.53)	0.48 (0.11-1.99)	0.56 (0.14-2.34)	0.65 (0.17-2.52)	0.6	0.90 (0.64-1.26)
Other cancer[g]	Men	929	1.00	1.10 (0.54-2.28)	1.84 (0.90-3.78)	0.90 (0.46-1.84)	1.18 (0.58-2.40)	0.9	1.01 (0.83-1.22)
	Women	513	1.00	0.93 (0.30-2.79)	1.14 (0.42-3.22)	2.59 (0.97-6.96)	1.94 (0.73-5.10)	0.1	1.24 (0.99-1.54)

[a]Relative risks (RR) reported with three significant figures, estimated from Cox models with attained age as time scale, stratified by cohort, and adjusted for baseline age, birth year, body mass index, and smoking status, and RRs per 1 mmol/l were additionally adjusted for fasting time. RRs are corrected for regression dilution ratio (RDR); conversion into uncorrected RR = exp(log(RR)*RDR). RDR quintiles: men, 0.30; women, 0.30; all, 0.31. RDR per 1 mmol/l: men, 0.40; women, 0.43; all, 0.41.
[b]Relative risks are presented separately for men and women if the number of cases in each group was more than 50, and combined if the number of cases in each group was less than or equal to 50 and if the total number of cases was more than 80.
[c]Relative risks per 1 mmol/l increment included subjects with glucose levels lower than 10 mmol/l (99% of subjects). Number of cases corresponds to quintile analyses which included all subjects.
[d]Person-years for cancer death corresponds to those for overall death.
[e]Per 100,000 person-years, age-standardized to the European standard population.
[f]Relative risks were significant in analyses that also included subjects with glucose levels equal to or higher than 10 mmol/l.
[g]Other cancer than the separately presented sites.
CI, confidence interval; ICD-7, International Classification of Diseases, seventh revision; ref, referent group.



Incident cancer	1 (referent)	1.07 (0.87-1.33)	1.03 (0.87-1.21)	1.14 (0.93-1.33)	1.18 (1.00-1.37)	1.10 (0.93-1.33)	1.14 (0.97-1.33)
Fatal cancer	1 (referent)	1.14 (0.81-1.59)	1.18 (0.90-1.55)	1.25 (0.93-1.69)	1.14 (0.90-1.50)	1.29 (0.97-1.69)	1.84 (1.46-2.40)
Overall death	1 (referent)	1.07 (0.87-1.29)	1.14 (1.00-1.37)	1.10 (0.93-1.33)	1.10 (0.97-1.29)	1.33 (1.14-1.59)	3.29 (2.86-3.78)

Figure 2a. Relative risk (95% CI) in men, of incident cancer (*n* = 18,621), fatal cancer (*n* = 6,973), and of death from all causes (*n* = 21,445) by deciles of glucose. IFG indicates the range of impaired fasting glucose in the cohorts among subjects that had fasted more than eight hours before the blood draw, and DM indicates the range of diabetic glucose levels. Glucose levels in the Oslo study I were recalculated (level-0.95) to correspond with enzymatic levels.



Incident cancer	1 (referent)	0.97 (0.76-1.25)	0.93 (0.76-1.14)	1.33 (1.07-1.69)	1.21 (1.00-1.46)	1.33 (1.07-1.64)	1.42 (1.18-1.74)
Fatal cancer	1 (referent)	0.81 (0.50-1.33)	1.03 (0.68-1.55)	1.99 (1.25-3.14)	1.18 (0.79-1.79)	1.79 (1.18-2.65)	2.05 (1.42-2.93)
Overall death	1 (referent)	0.73 (0.54-1.00)	1.00 (0.79-1.29)	1.29 (0.93-1.74)	1.18 (0.93-1.50)	1.69 (1.33-2.16)	3.69 (3.00-4.59)

Figure 2b. Relative risk (95% CI) in women, of incident cancer (*n* = 11,664), fatal cancer (*n* = 3,088), and of death from all causes (*n* = 8,424) by deciles of glucose. IFG indicates the range of impaired fasting glucose in the cohorts among subjects that had fasted more than eight hours before the blood draw, and DM indicates the range of diabetic glucose levels.

for incident cancer was 1.14 (0.97-1.33, p for trend = 0.09), for fatal cancer 1.84 (1.46-2.40, p for trend < 0.001), and for overall death 3.29 (2.86-3.78, p for trend < 0.001). RRs of total cancer, excluding prostate cancer, were for incident cancer 1.37 (1.14-1.64, p for trend = 0.002), and for fatal cancer 2.10 (1.59-2.72, p for trend < 0.001). In women, the RR for top decile versus decile 1-4 for overall incident cancer was 1.42 (1.18-1.74, p for trend < 0.001), for fatal cancer 2.05 (1.42-2.93, p for trend < 0.001), and for overall death 3.69 (3.00-4.59, p for trend < 0.001).

The absolute risk of incident cancer over a 20-year period for a 50-year old man in decile 1-4 and decile ten of glucose was 14.0% and 15.7%, respectively, and the corresponding risk of fatal cancer was 5.0% and 8.8%. In women, the corresponding absolute risks of developing cancer were 12.2% and 16.7%, and for cancer death, 3.0% and 6.0%, respectively.

Discussion

In this large prospective cohort study, elevated blood glucose was significantly associated with an increased risk of incident and fatal cancer at all sites combined, and of several specific cancers. In women, a linear association between glucose and risk of overall incident and fatal cancer was observed, and levels within the upper normal range were also related to increases in risk. In men, the association between glucose and total incident cancer was somewhat weaker, and risk of fatal cancer increased only at levels approximately equivalent to impaired glucose levels. Women in the top glucose decile had twice the risk of fatal cancer compared to women with glucose levels below the 40th percentile and the risk increase among men in the top decile was almost the same. Risk estimates were obtained after correction for random error in glucose levels, which was high in our study in accordance with previous observations [3,8,9]. The estimates of excess risk of fatal cancer in the top decile corrected for regression dilution were four-fold higher than the uncorrected estimates. These data indicate that in previous analyses without such correction, risk estimates for increasing glucose may have been underestimated [1,2,3,4,5,6,7].

Results from our study and those from the largest study reported to date, on men and women in Korea [1], were largely congruent and together these studies strongly support high blood glucose as a risk factor for cancer. In our study, associations between glucose and overall incident and fatal cancer were stronger in women than in men, whereas in the Korean study, stronger associations were reported for men, for whom a significant increased risk of fatal cancer was observed already at levels below impaired fasting glucose. These differences between studies may be explained by different proportions of specific cancers in the populations. For example, prostate cancer is much more common in Europe than in Asia [30], and as glucose was not related to prostate cancer in either study, exclusion of prostate cancer in analyses of total cancer in our study strengthened the association with cancer. Type 2 diabetes has consistently been related to an increased risk of cancer at many sites [1,31,32,33], and the findings in our and the Korean study suggest that also impaired fasting glucose levels, and to a lesser extent also glucose levels within the upper normal range are associated with an increased risk of cancer.

Specific cancers for which there were strong associations between glucose and risk of incident and fatal cancer in the Korean study [1] and in our study, were pancreas cancer, particularly in women, and liver cancer in men. Moreover, both studies showed strong associations between elevated glucose and risk of fatal cancer of the oesophagus and cervix uteri, and of fatal colorectal cancer in men. In our study, elevated glucose was also associated with an increased risk of cancer of the respiratory tract in men, and of gastric cancer in women, whereas no such associations were found in the Korean study. Smoking is strongly related to lung cancer and gastric cancer [34], and confounding or interaction between glucose and smoking may possibly explain the divergent findings. The proportion of current smokers in men was 29% in our study and 59% in the Korean study, and corresponding proportions were 23% and 4% in women. We observed no confounding or effect modification by smoking status in analyses of these cancers, but residual confounding may be present due to an imprecise or incorrect categorisation of smoking status.

Our study is the first to report data on glucose and risk of oropharyngeal cancer (limited data in Jee *et al.* [1]), and suggests an increased risk of death from these cancers in subjects with elevated glucose. Furthermore, data on prediagnostic glucose levels and risk of multiple myeloma and thyroid cancer have previously only been reported from the VHM&PP cohort [2]. We found a significant increase in risk of these cancers in men with high glucose, whereas intriguingly, risk of thyroid cancer was markedly decreased in women with high glucose. Incidence rates of thyroid cancer are 2-3 times higher in women than in men, possibly influenced by female sex hormones [35,36,37], and we speculate that an interaction between sex hormones and glucose may underlie our findings, alternatively the results may be a chance finding.

Insulin and bioavailable insulin-like growth factor-I (IGF-I) are possible links between glucose and cancer; hyperglycaemia induces elevation of these hormones which stimulate tumour growth [38].

Glucose may also have a direct tumour promoting effect as glucose is used as energy substrate in tumour cells, particularly in fast-growing, highly proliferative tumour cells [39,40,41]. However, the importance of extracellular glucose concentration for tumour growth - and thereby a direct link between glucose itself and cancer risk - is unclear.

Although the link between glucose and cancer may be causal, confounding may also be involved. We controlled for two major expected confounders, BMI and smoking, and found that the association between glucose and cancer risk remained after adjustment for these factors. However, other putative confounding factors may be relevant. For example, a genetic variant with opposite effects on risk of type 2 diabetes and prostate cancer has recently been reported [42], and this could partly explain the null association between glucose and prostate cancer in our study as well as the consistently reported reduced risk of prostate cancer in men with type 2 diabetes [43]. Various lifestyle factors, related to glucose but with other pathways to cancer, are also potential confounders, e.g. alcohol for cancer of the oropharynx, oesophagus, liver, and colorectum, salt for gastric cancer, and physical activity and fruit and vegetable consumption for a number of cancers [44].

The association between glucose and cancer risk was stronger for fatal cancer overall and at several sites, than for incident cancer. The explanation for this difference may vary between cancer types. Possibly, high glucose and related factors are more important for tumour progression than for tumour initiation. Alternatively, persons with high glucose may be diagnosed with cancer at a later stage, e.g. due to different health care seeking behaviour, or the results may be caused by inconsistencies in classification of cancer diagnosis versus cause of death [45,46].

Previous studies have consistently shown an association between elevated glucose levels and risk of cardiovascular disease and also to all cause mortality [1,47,48,49]. Accordingly, we found that elevated glucose was strongly related to an increased risk of all cause mortality; glucose levels in the top decile were related to a more than three-fold increased risk. Our data indicate that glucose control by a healthy diet and physical activity may decrease risk of cancer at many sites in addition to a decreased risk of cardiovascular disease.

Strengths of our study include the large sample size from six European population-based cohorts with virtually complete capture of cancer cases [2,50,51], the use of incident as well as fatal cancer as endpoints, and the correction of risk estimates for intra-individual variation of glucose levels by the use of a large number of repeated measurements. In all cohorts, data were available for BMI and smoking status, and these factors were used as adjustment in analyses. Limitations of our study include the lack of data on other covariates that may have influenced risk estimates, and the different protocols for measurement of glucose applied in subcohorts, which resulted in a limited application of absolute levels to our data.

In conclusion, abnormal glucose metabolism is, independently of BMI, associated with increases in risk of cancer incidence and cancer death overall and at many specific sites. Furthermore, our data showed a linear and somewhat stronger association among women than among men, and the association was stronger for fatal compared to incident cancer.

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