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ARTICLE

Diabetes, prediabetes and cancer mortality

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Abstract
Aims/hypothesis We aimed to investigate the risk of cancer mortality in relation to the glucose tolerance status classified according to the 2 h OGTT.
Methods Data from 17 European population-based or occupational cohorts involved in the DECODE study comprising 26,460 men and 18,195 women aged 25–90 years were collaboratively analysed. The cohorts were recruited between 1966 and 2004 and followed for 5.9 to 36.8 years. Cox proportional hazards analysis with adjustment for cohort, age, BMI, total cholesterol, blood pressure and smoking status was used to estimate HRs for cancer mortality.
Results Compared with people in the normal glucose category, multivariable adjusted HRs (95% CI) for cancer mortality were 1.13 (1.00, 1.28), 1.27 (1.02, 1.57) and 1.71 (1.35, 2.17) in men with prediabetes, previously undiagnosed diabetes and known diabetes, respectively; in women they were 1.11 (0.94, 1.30), 1.31 (1.00, 1.70) and 1.43 (1.01, 2.02), respectively. Significant

Electronic supplementary material The online version of this article (doi:10.1007/s00125-010-1796-7) contains details of the DECODE Study Group which are available to authorised users.

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increases in deaths from cancer of the stomach, colon–rectum and liver in men with prediabetes and diabetes, and deaths from cancers of the liver and pancreas in women with diabetes were also observed. In individuals without known diabetes, the HR (95% CI) for cancer mortality corresponding to a one standard deviation increase in fasting plasma glucose was 1.06 (1.02, 1.09) and in 2 h plasma glucose was 1.07 (1.03, 1.11).
Conclusions/interpretation Diabetes and prediabetes were associated with an increased risk of cancer death, particularly death from liver cancer. Mortality from all cancers rose linearly with increasing glucose concentrations.

Keywords Cancer · Diabetes · Mortality

Abbreviations

2-hPG	2 h Plasma glucose
DECODE	Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe
FPG	Fasting plasma glucose
MPP	Malmö Preventive Project
NGT	Normal glucose tolerance
NHANES	National Health and Nutrition Examination Survey

Introduction

Epidemiological studies have shown that diabetes [1–7] or certain treatments for diabetes may increase the risk [8–10] of developing cancer. Diabetes may also affect the treatment of cancer; some types of cancer are treated less aggressively in patients with diabetes than in patients without diabetes [11]. Evidence for the association between diabetes and cancer-related mortality is, however, still limited and results from different studies are controversial. It was reported that diabetic patients suffered from higher mortality rates from all cancers [12] or some types of cancers [13, 14] than the general population. Pre-existing diabetes was a risk factor for all-cancer death in Japanese women [15] and for death from some types of cancers in a US population [16]. No association between diabetes and all-cancer mortality was found in an occupational male group (Whitehall study) in the UK [17] or in the Second National Health and Nutrition Examination Survey (NHANES II) Mortality Study in the USA [18]. The NHANES II has, however, found IGT to be associated with a higher risk of cancer mortality. Cancer mortality may also increase with increasing fasting [19, 20], non-fasting [20] or postload [21] glucose levels.

The aim of this study was to investigate the risk of cancer mortality in relation to the glucose tolerance status based on data from the Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe (DECODE) Study.

Methods

The study populations and the methods used to recruit participants for the DECODE study have been reported previously [22, 23]. In brief, researchers in Europe who had performed population-based studies or large studies in occupational groups using the standard 2 h 75 g OGTT were invited to participate in the DECODE study. In the current study, 15,631 participants (12,999 men and 2,632 women) from the Malmö Preventive Project (MPP, Sweden) who underwent 2 h OGTT using 30 g oral glucose load per body surface area (m^2) [24] were also included. Individual data from each study cohort were sent to the Diabetes Prevention Unit of the National Institute for Health and Welfare in Helsinki, Finland, for data analyses. Each study was approved by the local ethics committees and the analysis plan was approved by the ethics committee of the National Institute for Health and Welfare.

A total of 44,655 participants from 17 study cohorts with prospective data on cause-specific mortality and all other required variables of fasting plasma glucose (FPG), 2 h plasma glucose (2-hPG) after a glucose load, BMI, total serum cholesterol, blood pressure and smoking status were included in the current data analyses. All 17 study cohorts included men (n=26,460) and 14 also included women (n=18,195). The baseline age of the participants ranged from 25 to 90 years with mean ages varying from 45 to 76 years in different study cohorts. The study cohorts were recruited between 1966 and 2004 and followed up for 5.9 to 36.8 years, with median

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(25th, 75th percentile) follow up of 15.8 years (9.1, 23.2 years) in all cohorts combined (Table 1). Men contributed 467,872 person-years and women contributed 252,503 person-years of follow up. Informed consent was obtained from all participants in each study.

In the current study population, participants who had a prior history of diabetes or who were on antihyperglycaemic treatment before the baseline survey were considered as having known diabetes. Participants without known diabetes at the baseline survey were classified according to the World Health Organization definition [25]. Undiagnosed diabetes is defined as having either FPG ≥ 7.0 mmol/l and/or 2-hPG ≥ 11.1 mmol/l. IGT is defined as having FPG < 7.0 mmol/l and 2-hPG ≥ 7.8 mmol/l but <11.1 mmol/l. IFG is defined as having FPG ≥ 6.1 mmol/l but <7.0 mmol/l and 2-hPG < 7.8 mmol/l. NGT is defined as FPG < 6.1 mmol/l and 2-hPG < 7.8 mmol/l. People with IGT and/or IFG were labelled as having 'prediabetes'.

Vital status and the cause of death were obtained from national cause-of-death registers or from medical records if the register was not available in some countries for each participant in all studies. Participants who emigrated, for whom the vital status could not be confirmed, were considered as censored cases. Cancer death was defined by the International Classification of Disease codes 140-207 and 209 (8th revision), codes 140-208 (9th revision) and codes C00-C97 (10th revision). No data on autopsy was provided.

Statistical methods Statistical analysis was performed using the SPSS for Windows version 15.0 (SPSS Inc, Chicago, IL, USA) and STATA version 9.2 (StataCorp, College Station, TX, USA). Means and differences in means between groups were estimated using univariate general linear models with adjustments for age and study for continuous variables. χ^2 test was used to test differences in proportions between groups. Crude mortality rates per 1,000 person-years were calculated for each glucose tolerance category. HRs and their 95% CIs for cancer death were estimated using a Cox proportional hazards model for different glucose intolerance groups at the presence of

Table 1 Mean (±SD) age at baseline and number (%) of cancer deaths during the follow-up in each study cohort

Study cohort	Men (*n*)	Women (*n*)	Age (years)	Cancer deaths (*n*)		Maximum follow-up (years)
				Men	Women	
Denmark						
Glostrup [35]	1,050	1,029	52.1±12.2	109 (10.4)	88 (8.6)	27.0
Finland						
East–West Finland[a] [36]	405	–	76.2±4.5	70 (17.3)	–	17.1
FINRISK-1987 [37]	1,261	1,440	54.0±5.7	119 (9.4)	90 (6.3)	20.9
FINRISK-1992 [37]	877	1,041	54.1±6.0	44 (5.0)	53 (5.1)	16.0
FINRISK-2002 [38]	1,786	2,055	57.9±7.8	35 (2.0)	18 (0.9)	5.9
Helsinki policemen[a] [39]	1,136	–	44.7±8.0	175 (15.4)	–	36.8
Oulu [40]	418	603	60.9±9.7	21 (5.0)	12 (2.0)	15.0
Vantaa [41]	271	335	65.1±0.4	22 (8.1)	19 (5.7)	17.9
Italy						
Cremona [42]	800	999	58.4±10.8	102 (12.8)	63 (6.3)	15.7
The Netherlands						
Hoorn [43]	1,116	1,317	61.6±7.3	62 (5.6)	52 (3.9)	10.2
Poland						
Krakow [44]	163	186	57.8±8.3	3 (1.8)	3 (1.6)	6.6
Sweden						
Northern Sweden MONICA Survey [45]	1,733	1,760	48.9±13.4	42 (2.4)	33 (1.9)	20.6
Malmö (MPP) [24]	12,999	5,881	49.6±4.9	1,381 (10.6)	367 (6.2)	30.3
Uppsala[a] [46]	1,164	–	71.0±0.6	123 (10.6)	–	12.4
UK						
Cambridge (Ely) [47]	435	607	54.0±7.8	19 (4.4)	30 (4.9)	15.7
Goodinge [48]	448	566	54.6±10.3	19 (4.2)	27 (4.8)	9.7
Newcastle [49]	398	376	54.8±12.5	19 (4.8)	15 (4.0)	10.6
Total	26,460	18,195	53.4±9.5	2,365 (8.9)	870 (4.8)	36.8

[a] The cohort includes only men

covariates of study cohort, age at baseline (years), BMI (kg/m^2), systolic blood pressure (mmHg), serum cholesterol (mmol/l) and smoking status. Stratified analysis by the BMI tertiles was also made for different glucose intolerance groups adjusting for study cohort, age, sex, systolic blood pressure, serum cholesterol and smoking status. Fasting insulin was analysed in only a subgroup of men (n=15,227) and women (n=9,221) who had fasting insulin measured at baseline survey. Time since baseline was used as the time-scale in the Cox proportional hazards model. Interaction between the glucose intolerance and smoking status was examined to evaluate whether the effect of glucose intolerance on cancer mortality differed in smokers from that in non-smokers.

The HRs (95% CIs) for cancer death corresponding to a study-specific one standard deviation (SD) increase in linear form of the FPG and 2-hPG in individuals without a prior history of diabetes were also estimated for each study adjusting for age, sex, BMI, systolic blood pressure, cholesterol and smoking status. Heterogeneity between studies was assessed using Cochran's Q statistics and I^2 statistics, a transformation of Q that estimates the percentage of total variation across studies that is due to heterogeneity [26]. An overall HR for all studies combined was then calculated using the Mantel–Haenszel method for a fixed-effect model. The influence of individual studies on the overall estimate was assessed by calculating pooled HRs while omitting one study at a time.

Results

Individuals who died from cancer were older, less obese and comprised a higher proportion of current smokers than others (Table 2). A total of 2,365 cancer deaths were documented in men during a median follow-up of 18.0 years and 870 cancer deaths were recorded in women during 14.9 years. Age-standardised all-cancer mortality rate was higher in individuals with diabetes than in those without in both sexes (Table 3).

Compared with NGT, the multivariable-adjusted HRs (95% CI) for all-cancer death increased with worsening glucose intolerance status; they were 1.13 (1.00, 1.28) for prediabetes, 1.27 (1.02, 1.57) for previously undiagnosed diabetes and 1.71 (1.35, 2.17) for known diabetes in men. The results were similar in women (Table 3). The multivariable-adjusted HR for site-specific cancer death was estimated when more than 90 events accumulated in a cancer subgroup. Certain types of site-specific cancers were combined in the final data analyses because of the low numbers in each group. Compared with individuals with NGT, the HR was higher for death from cancers in stomach, colon–rectum and liver in men with prediabetes and diabetes, and for deaths from cancers in liver and pancreas in women; however, this increase was only of borderline significance in women with prediabetes and undiagnosed diabetes (Table 3). The interaction term between glucose intolerance and smoking was not statistically significant, i.e. smoking did not modify the effect of glucose intolerance on cancer.

The multivariable-adjusted HRs for all-cancer death was also estimated within each BMI tertile. Compared with NGT, the HRs (95% CIs) were 1.14 (0.96, 1.36) for prediabetes, 1.15 (0.76, 1.73) for previously undiagnosed diabetes and 1.58 (1.06, 2.35) for known diabetes in individuals in the lowest tertile of BMI (<24.0 kg/m^2); they were 1.27 (1.08, 1.50), 1.12 (0.79, 1.59) and 1.69 (1.16, 2.46) in the middle

Table 2 Baseline characteristics of men and women by all-cancer death

Variable	Cancer death in men		Cancer death in women	
	No	Yes	No	Yes
n (%)	24,095 (91.1)	2,365 (8.9)	17,325 (95.2)	870 (4.8)
Age (years)	52.0±0.1	54.2±0.2 [a]	54.9±0.1	57.4±0.3 [a]
BMI (kg/m^2)	25.9±0.02	25.5±0.1 [a]	26.3±0.04	25.9±0.2 [b]
Blood pressure (mmHg)				
Systolic	135±0.1	135±0.4	134±0.1	133±0.7 [b]
Diastolic	85±0.1	86±0.2	81±0.1	81±0.4
Cholesterol (mmol/l)	5.9±0.01	5.9±0.02	6.2±0.01	6.3±0.04[a]
Glucose tolerance status, n (%)				
Normal glucose tolerance	18,169 (75.4)	1,817 (76.8)	10,879 (62.8)	518 (59.5)
Prediabetes	4,149 (17.2)	372 (15.7)	4,746 (27.4)	246 (28.3)
Undiagnosed diabetes	1,075 (4.5)	95 (4.0)	1,129 (6.5)	67 (7.7)
Known diabetes	702 (2.9)	81 (3.4)	571 (3.3)	39 (4.5)
Smoking status, n (%)				
Current smoker	9,386 (39.0)	1,310 (55.4)[a]	4,208 (24.3)	314 (36.1)[a]
Ex-smoker	4,586 (19.0)	327 (13.8)	2,730 (15.8)	108 (12.4)

Data are cohort-adjusted and age-adjusted mean ± SE or n (%)

Prediabetes included impaired fasting glucose and/or impaired glucose tolerance

[a] p<0.001, [b] p<0.05 for the difference between groups with and without cancer death

Table 3 Crude cancer mortality (per 1,000 person-years) and multivariable-adjusted HR in relation to glucose tolerance status in men and women

Type of cancer	NGT	Prediabetes	Undiagnosed diabetes	Known diabetes	All diabetes
Men					
All cancers					
No. of deaths	1,817	372	95	81	176
Mortality	4.76	5.69	6.92	11.67	8.52
HR (95% CI)[a]	1.0	1.13 (1.00, 1.28)	1.27 (1.02, 1.57)	1.71 (1.35, 2.17)	1.44 (1.21, 1.70)
Stomach or colon–rectum					
No. of deaths	258	70	19	17	36
Mortality	0.68	1.07	1.38	2.45	1.74
HR (95% CI)[a]	1.0	1.46 (1.09, 1.94)	1.69 (1.03, 2.76)	2.07 (1.21, 3.51)	1.84 (1.25, 2.71)
Liver					
No. of deaths	42	17	6	9	15
Mortality	0.11	0.26	0.44	1.30	0.73
HR (95% CI) [a]	1.0	2.32 (1.25, 4.33)	3.61 (1.42, 9.19)	7.50 (3.21, 17.54)	5.16 (2.56, 10.41)
Pancreas					
No. of deaths	138	24	9	7	16
Mortality	0.36	0.37	0.66	1.01	0.77
HR (95% CI) [a]	1.0	0.88 (0.56, 1.41)	1.52 (0.74, 3.12)	1.92 (0.85, 4.33)	1.67 (0.94, 2.97)
Bronchus and lung					
No. of deaths	497	88	15	10	25
Mortality	1.30	1.35	1.09	1.44	1.21
HR (95% CI) [a]	1.0	1.14 (0.89, 1.46)	0.85 (0.50, 1.45)	0.93 (0.49, 1.78)	0.88 (0.58, 1.35)
Prostate					
No. of deaths	209	52	14	13	27
Mortality	0.55	0.79	1.02	1.87	1.31
HR (95% CI) [a]	1.0	1.01 (0.73, 1.40)	1.09 (0.62, 1.93)	1.64 (0.90, 2.99)	1.30 (0.84, 2.01)
Kidney or bladder					
No. of deaths	119	14	5	6	11
Mortality	0.31	0.21	0.36	0.86	0.53
HR (95% CI) [a]	1.0	0.59 (0.33, 1.05)	0.84 (0.33, 2.13)	1.93 (0.79, 4.71)	1.20 (0.61, 2.37)
Women					
All cancers					
No. of deaths	518	246	67	39	106
Mortality	3.17	3.63	4.42	6.60	5.04
HR (95% CI) [a]	1.0	1.11 (0.94, 1.30)	1.31 (1.00, 1.70)	1.43 (1.01, 2.02)	1.35 (1.08, 1.68)
Stomach or colon–rectum					
No. of deaths	66	40	3	2	5
Mortality	0.40	0.59	0.20	0.34	0.24
HR (95% CI) [a]	1.0	1.52 (1.00, 2.31)	0.49 (0.15, 1.59)	0.46 (0.11, 1.93)	0.48 (0.19, 1.21)
Liver					
No. of deaths	8	5	3	6	9
Mortality	0.05	0.07	0.20	1.02	0.43
HR (95% CI) [a]	1.0	1.58 (0.49, 5.09)	3.67 (0.89, 15.12)	10.87 (3.16, 37.39)	6.37 (2.18, 18.62)
Pancreas					
No. of deaths	47	21	7	6	13
Mortality	0.29	0.31	0.46	1.02	0.62
HR (95% CI) [a]	1.0	1.08 (0.63, 1.85)	1.71 (0.74, 3.94)	3.13 (1.21, 8.08)	2.13 (1.09, 4.16)
Bronchus and lung					
No. of deaths	81	38	8	3	11
Mortality	0.50	0.56	0.53	0.51	0.52

Table 3 (continued)

Type of cancer	NGT	Prediabetes	Undiagnosed diabetes	Known diabetes	All diabetes
HR (95% CI) [a]	1.0	1.12 (0.75, 1.69)	1.03 (0.49, 2.19)	0.72 (0.21, 2.43)	0.93 (0.48, 1.81)
Breast					
No. of deaths	68	42	12	5	17
Mortality	0.42	0.62	0.79	0.85	0.81
HR (95% CI) [a]	1.0	1.47 (0.97, 2.22)	1.76 (0.92, 3.35)	1.44 (0.55, 3.76)	1.65 (0.93, 2.93)
Kidney or bladder					
No. of deaths	17	12	2	5	7
Mortality	0.10	0.18	0.13	0.85	0.33
HR (95% CI) [a]	1.0	1.46 (0.67, 3.21)	1.03 (0.23, 4.61)	3.62 (1.09, 11.97)	1.97 (0.75, 5.15)
Total					
No. of deaths	2,335	618	162	120	282
Mortality	4.28	4.64	5.61	9.34	6.76
HR (95% CI) [a]	1.0	1.12 (1.02, 1.23)	1.28 (1.08, 1.51)	1.57 (1.29, 1.91)	1.38 (1.21, 1.58)
Stomach or colon–rectum					
No. of deaths	324	110	22	19	41
Mortality	0.59	0.83	0.76	1.48	0.98
HR (95% CI) [a]	1.0	1.46 (1.15, 1.84)	1.24 (0.79, 1.94)	1.46 (0.89, 2.39)	1.33 (0.94, 1.89)
Liver					
No. of deaths	50	22	9	15	24
Mortality	0.09	0.17	0.31	1.17	0.58
HR (95% CI) [a]	1.0	2.01 (1.17, 3.44)	3.51 (1.63, 7.55)	8.47 (4.25, 16.86)	5.38 (3.03, 9.53)
Pancreas					
No. of deaths	185	45	16	13	29
Mortality	0.34	0.34	0.55	1.01	0.70
HR (95% CI) [a]	1.0	1.02 (0.72, 1.44)	1.67 (0.97, 2.85)	2.34 (1.27, 4.32)	1.90 (1.24, 2.93)
Bronchus and lung					
No. of deaths	578	126	23	13	36
Mortality	1.06	0.95	0.80	1.01	0.86
HR (95% CI) [a]	1.0	1.11 (0.90, 1.37)	0.90 (0.58, 1.38)	0.87 (0.49, 1.54)	0.89 (0.62, 1.27)
Kidney or bladder					
No. of deaths	136	26	7	11	18
Mortality	0.25	0.20	0.24	0.86	0.43
HR (95% CI)[a]	1.0	0.82 (0.52, 1.27)	0.90 (0.41, 1.98)	2.45 (1.23, 4.88)	1.44 (0.83, 2.47)

Prediabetes included impaired fasting glucose and/or impaired glucose tolerance

[a] Adjusted for study cohort, age, sex (when men and women are combined), BMI, systolic blood pressure, cholesterol and smoking status

NGT, normal glucose tolerance

tertile (BMI 24.0–27.1 kg/m^2) and 0.99 (0.85, 1.16), 1.36 (1.09, 1.69) and 1.51 (1.14, 2.00) in the upper tertile of the BMI distribution (BMI ≥ 27.2 kg/m^2). The risk of all-cancer deaths therefore increased in individuals with diabetes irrespective of their BMI levels.

After adding fasting insulin into the multivariable model in a subgroup of individuals, we obtained HRs (95% CIs) of 1.18 (1.02, 1.38), 1.34 (1.04, 1.74) and 1.52 (1.09, 2.12) in men with prediabetes, undiagnosed and diagnosed diabetes for all-cancer deaths; while these were 1.19 (1.03, 1.38), 1.36 (1.05, 1.76) and 1.58 (1.14, 2.18), respectively, when fasting insulin was not fitted in the model. In women, these values were 1.20 (0.92, 1.56), 1.23 (0.79, 1.91) and 1.71 (1.00, 2.93) after addition of fasting insulin and 1.21 (0.92, 1.58), 1.26 (0.81, 1.95) and 1.91 (1.13, 3.21) before adjusting for fasting insulin. The results therefore did not change substantially after adding fasting insulin into the multivariable model.

After excluding the cancer deaths that occurred within 5 years after the baseline examination, the HRs (95% CIs) for all-cancer death were 1.10 (0.96, 1.26) for prediabetes, 1.27 (0.99, 1.62) for previously undiagnosed diabetes and 1.62 (1.21, 2.18) for known diabetes in men; they were 1.03 (0.86, 1.24), 1.25 (0.92, 1.69) and

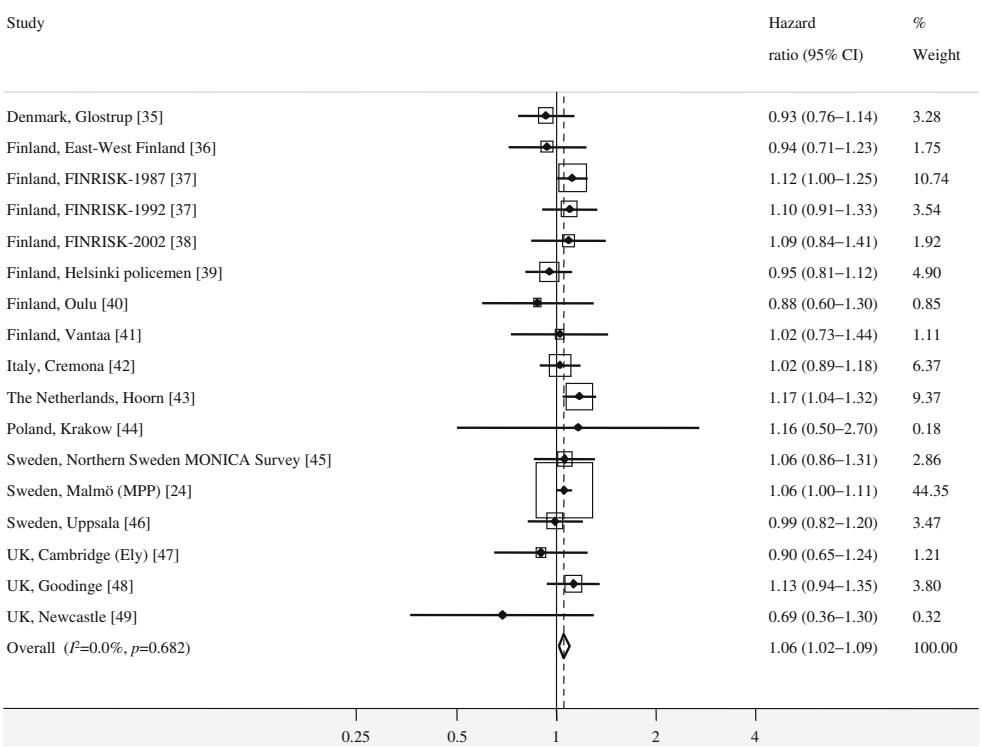

Fig. 1 HR (black circle) and 95% CI (horizontal line) of all-cancer death corresponding to a study-specific one SD increase in fasting plasma glucose for each study cohort and for all cohorts pooled together. The size of the square is proportional to the percentage weight of each study cohort

1.14 (0.73, 1.77) in women and 1.07 (0.96, 1.19), 1.25 (1.03, 1.51) and 1.39 (1.09, 1.77) when men and women were combined.

The 17 studies were homogeneous with respect to the effect of FPG and 2-hPG on all-cancer death in individuals without known diabetes (Q=12.9 on 16 *df*, I^2=0.0%, p=0.68 for FPG and Q=17.0 on 16 *df*, I^2=5.9%, p=0.38 for 2-hPG). Multivariate-adjusted overall HRs (95% CIs) for all-cancer death were 1.06 (1.02, 1.09) and 1.07 (1.03, 1.11) corresponding to a one SD increase in FPG and 2-hPG, respectively (Figs 1 and 2). Leaving any one study out from the data analyses did not substantially

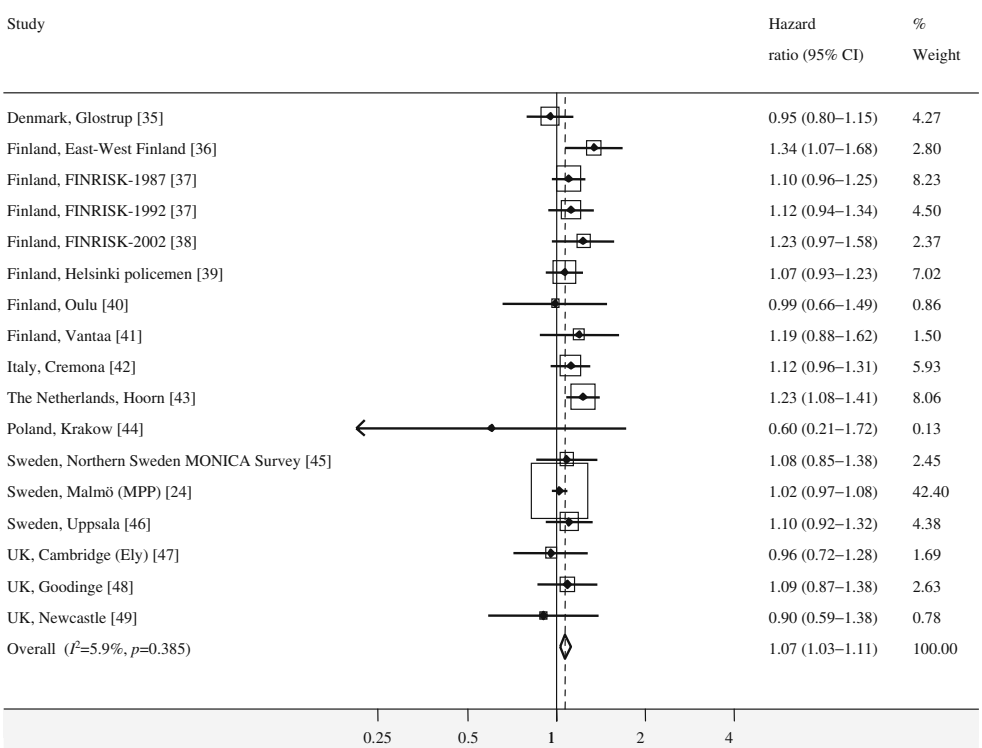

Fig. 2 HR (black circle) and 95% CI (horizontal line) of all-cancer death corresponding to a study-specific one SD increase in 2 h plasma glucose for each study cohort and for all cohorts pooled together. The size of the square is proportional to the percentage weight of each study cohort

change the pooled HR for either FPG or 2-hPG. Removing the MPP study, which contributed to more than 40% weight of the overall estimate, only slightly increased the pooled HR for 2-hPG (from 1.07 [95% CI 1.03, 1.11] to 1.11 [1.06, 1.17]).

Discussion

In this collaborative study, we found that mortality from certain types of cancers, particularly from liver cancer, was significantly increased not only in diabetic but also in prediabetic populations compared with people with NGT. The risk increased with deterioration in glucose intolerance status and was highest in people with known diabetes. Cancer mortality also increased with increasing FPG and 2-hPG concentrations.

It was reported that diabetes independently predicted all-cancer mortality in women in a Japanese population [15]; and mortality from cancers of colon, liver, pancreas and bladder in men and from cancers of colon, pancreas and breast in women in a US population [16]. Notably, the diagnosis of diabetes was based on self-report in these studies, those without symptoms of diabetes were not identified. The impact of previously undiagnosed diabetes and prediabetes on cancer death was therefore not determined. OGTTs were performed in the Whitehall study in the UK [17] and in the NHANES II Mortality Study in the USA [18]; neither previously diagnosed nor undiagnosed diabetes predicted cancer death in these studies, whereas IGT did so in the NHANES II Study. The number of patients with diabetes was, however, much lower in the both studies compared with our study.

Several mechanisms may be involved in the relationship between glucose intolerance and the risk of cancer mortality. Oxidative stress and accumulated advanced glycation end-products induced by hyperglycaemia at the cellular level may play important roles in cancer development and progression [27]. Hyperinsulinaemia and increased level of bioavailable insulin-like growth factor I related to insulin resistance [28] may promote cancer cell proliferation [29] and may also relate to worse cancer outcome [29]. In our study, adjustment for fasting insulin did not alter the relationship between glucose intolerance and all-cancer death. Treatment choices for cancer patients with diabetes may be limited by the presence of hyperglycaemia and co-existing diabetes complications [30] and certain types of cancer may be treated less aggressively in patients with diabetes as a co-morbidity than in patients without diabetes [11], which may also lead to the worse cancer survival in patients with diabetes. Although certain glucose-lowering agents have been reported to increase the risk of cancer incidence [10] and cancer mortality [31], the overall effect of glucose-lowering treatments on cancer mortality in our study population is unclear because the information on treatment was not available in detail.

The collaborative data analysis with a relatively large number of all-cancer death events accumulated increased statistical power, and enabled data analysis for site-specific cancers in subgroups. The effect of glucose intolerance on cancer mortality was homogeneous across studies. Diabetes was classified based on a standard 2 h 75 g OGTT, which was not available in similar studies previously reported. There were, however, several limitations with the data. First, the date of cancer diagnosis was not documented; the actual onset of prediabetes and undiagnosed diabetes was also not known in one cross-sectional survey; as a result, the direction of a causative relationship, if any, between glucose intolerance and certain types of cancer such as cancer of the pancreas cannot be determined. Second, the duration of known diabetes, data on detailed treatments for diabetic patients at baseline and during follow-up were not available; the effect of glucose-lowering agents on the risk of cancer death cannot be estimated. Third, alcohol consumption and history of hepatitis and cirrhosis were not recorded in the present study, which might confound the effect of glucose intolerance on risk of death from liver cancer. Dietary factors and physical activity were also potential confounders but not available in this study. Fourth, HbA_{1c} was not determined and individuals who met only HbA_{1c} criteria for diabetes [32] might have been misclassified as prediabetes or NGT [33, 34], which might have obscured the relationship between diabetes and cancer mortality. This needs to be further investigated.

In conclusion, the present study confirmed that diabetes and prediabetes are independent risk predictors for all-cancer death, particularly death from liver cancer. In individuals without known diabetes, FPG and 2-hPG concentrations are positively related to the risk of all-cancer death.

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Duality of interest R. Heine is an employee and stock holder of Eli Lilly and company. The other authors declare that there is no duality of interest associated with this manuscript.

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