Diabetes status and post-load plasma glucose concentration in relation to site-specific cancer mortality: findings from the original Whitehall study

Abbreviated title: Diabetes, blood glucose and cancer mortality

G. David Batty[a] PhD
Senior Research Fellow in Epidemiology

Martin J Shipley[b] MSc
Senior Lecturer in Medical Statistics

Michael Marmot[b] FFPHM
Professor of Epidemiology

George Davey Smith[c] MD
Professor of Clinical Epidemiology

[a]Department of Social Medicine
Institute of Public Health
University of Copenhagen
Blegdamsvej 3, 2200 N
DENMARK
E. david.batty@pubhealth.ku.dk

[b]Department of Epidemiology and Public Health
University College London
1-19 Torrington Place
LONDON, WC1E 6BT

[c]Division of Epidemiology
Department of Social Medicine
University of Bristol
Canynge Hall
Whiteladies Road
BRISTOL, BS8 2PR

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Correspondence to David Batty

Abstract

Objective: While several studies have reported on the relation of diabetes status with pancreatic cancer risk, the predictive value of this disorder for other malignancies is unclear.

Methods: The Whitehall study, a 25 year follow-up for mortality experience of 18,006 men with data on post-challenge blood glucose and self-reported diabetes, allowed us to address these issues.

Results: There were 2158 cancer deaths at follow-up. Of the fifteen cancer outcomes, diabetes status was positively associated with mortality from carcinoma of the pancreas and liver, while the relationship with lung cancer was inverse, after controlling for a range of potential covariates and mediators which included obesity and socioeconomic position. After excluding deaths occurring in the first 10 years of follow-up to examine the effect of reverse causality, the magnitude of the relationships for carcinoma of the pancreas and lung was little altered, while for liver cancer it was markedly attenuated.

Conclusions: In the present study, diabetes status was related to pancreatic, liver and lung cancer risk. Cohorts with serially collected data on blood glucose and covariates are required to further examine this area.

Keywords: blood glucose, cancer, diabetes, cohort study

Introduction

An unexpectedly high prevalence of hyperglycaemia in cancer patients was first described over a century ago.[1;2] However, it is only in the last two decades that population-based cohort studies – largely established to identify risk factors for cardiovascular disease – have accumulated sufficient cancer cases to allow an examination of the role of diabetes, assessed prior to cancer presentation, in the development of this condition. While an excess of total cancer cases is seen in some,[3-6] but not all,[7-9] diabetes groups, the pattern of association is most consistent for pancreatic cancer.[10-13] Mechanisms advanced to explain the diabetes-pancreatic cancer relationship include the carcinogenesis-stimulating effects of insulin – the so called 'insulin hypothesis' – and the activation of insulin-like-growth-factor 1 (IGF-1) receptor which enhances pancreatic cell proliferation.[14] Although IGF-1 has also been implicated in the aetiology of colorectal and prostate malignancies,[15] the association of diabetes with these malignancies, amongst others, has not been extensively examined.

In addition to this limited evidence base, interpretation of results from many existing studies is hampered by one or more of the following methodological limitations. Firstly, that diabetes status is poorly characterised, with most investigators relying on self-reports of physician diagnoses rather than direct blood glucose measurement, leads to misclassification of this exposure. Secondly, for some cancers (e.g., pancreatic), it has been postulated that diabetes is a clinical manifestation of occult malignancy,[16] raising concerns

about reverse causality.[10] Thirdly, confounding by characteristics such as obesity and socioeconomic position – predictors of both diabetes and cancer risk – may be an alternative explanation for some of the associations seen. Finally, a focus in many reports on a single malignant neoplasm as the endpoint of interest, rather than a range, limits insights into specificity of association – an important criteria in the assessment of causation in observational studies.[17]

In the present study, we report on the relation of diabetes status and post-load plasma glucose with cancer mortality in a follow-up of 18,403 male British government employees. In this cohort, the measurement of fasting post-challenge blood glucose in addition to self-reported diabetes status; the assessment of potential confounding variables including overweight and socioeconomic position; the high number of cases – the cohort has accumulated in excess of two thousand cancer deaths over 25 years of surveillance; and analyses across a number of cancer sites, allows us to address the aforementioned shortcomings. This report extends considerably earlier findings from the Whitehall study[7] by reporting on a later follow-up with many more cancer deaths and therefore a greater range of site-specific outcomes.

Materials and Methods

Study participants

In the Whitehall study, data were collected on 18,403 non-industrial London-based male government employees aged from 40 to 64 yr. when examined

between September 1967 and January 1970, representing a 74% response proportion. Data collection involved the completion of a study questionnaire and participation in a medical examination, both of which have been described in detail elsewhere.[18] In brief, the questionnaire included enquiries regarding civil service employment grade (an indicator of socio-economic position),[19;20] smoking habits,[21] intermittent claudication,[22;23] angina,[22;24] chronic bronchitis,[25] and physical activity while travelling to work[26] and during leisure time.[27;28] Forced expiratory volume in one second (FEV_1) (adjusted for height[27]), ischaemia,[29] fasting plasma cholesterol,[30] two-hour blood glucose,[31] blood pressure,[32] height,[33] and weight[34] were determined using standardised protocols.

Assessment of diabetes status and plasma glucose level

Each man was requested to fast from the night before the medical examination which was held in the morning. Capillary blood samples were drawn from the ear lobe two hours after participants drank a glucose preparation equivalent to 50g of anhydrous dextrose ('Lucozade' drink). From these samples, blood sugar concentration was estimated using the ferricyanide reduction micromethod on an autoanalyser (Technicon method N-9a). Study participants were categorised into three groups based on data from the questionnaire and the post-load blood glucose test:[7;27 35] (1) *Men with diabetes:* a positive response to the questionnaire enquiry "are you, or have you been, diabetic?" or, blood glucose level two hours after the glucose load of ≥11.1 mmol/l (≥200

mg/100ml); (2) *Men with impaired glucose tolerance:* blood glucose of 5.4 to 11.0 mmol/l (96 to 199 mg/100ml); (3) *Normoglycaemic men:* all remaining subjects. Furthermore, blood glucose results in the normoglycaemic group were sub-divided into quartiles: ≤ 66; 67-73; 74-79; 80-95 mg/100ml.[7]

Mortality ascertainment

Records from 18,260 men (99.2% of the 18,403 eligible) were traced and flagged at the National Health Service Central Registry, representing an almost complete 25 years follow-up until 31st January 1995. Death certificates were coded according to the eighth revision of the International Classification of Diseases (ICD).[36] Mortality was classified as being due to all malignant neoplasms (ICD 140-208) – referred to here as 'all-cancers'. This group was sub-divided into thirteen individual sites: oesophagus (ICD 150); stomach (ICD 151); colon (ICD 153); rectum (ICD 154); liver (ICD 155-156); pancreas (ICD 157); trachea, bronchus and lung (ICD 162 – referred to as 'lung cancer'); prostate (ICD 185); bladder (ICD 188); kidney (ICD 189); brain (ICD 191); lymphoma (ICD 200-203); and leukaemia (ICD 204-207). 'Other' cancer comprised deaths due to malignancies occurring at sites other than the aforementioned.

Statistical analyses

Employment grade was categorised as administrative, professional or executive, clerical, and "other grades" (men in messenger and other unskilled

manual jobs). For 873 men from the Diplomatic Service and the British Council, employment grade was not comparable to the rest of the sample and they have been classified as a separate group. Smoking was classified according to cigarette use as 'current smoker', 'ex-smoker' and 'never smoker'. The 378 men who smoked pipes or cigars only have been included as a separate group in the analyses that involve smoking status. During the baseline study, the physical activity enquiries on the questionnaire were modified. Levels of this behaviour were therefore determined from either an item about travel activity[26] (administered to approximately two-thirds of men) or from leisure activities[28] (administered to the remainder). Existing disease at entry to the study was defined as a positive response to enquiries regarding intermittent claudication, physician-diagnosed heart problems or high blood pressure (one question), dyspnoea, and bronchitis. The existence of ischaemia was determined from ischaemic signs on an ECG trace, or positive responses to either the Rose angina questionnaire, or a report of severe pain across the front of the chest lasting half and hour or more.[24]

Among the 18,260 men who were successfully traced, 870 men had some missing data for one or more of the following variables: self-reported diabetes or plasma blood glucose (128 men), physical activity (38), blood pressure-lowering medication (10), marital status (4), systolic blood pressure (6), cholesterol (679), body mass index (3), height (3), FEV_1 (12), triceps skinfold thickness (24), and smoking status (4). To clarify data interpretation, the 46

men who reported that their diabetes was controlled by insulin medication were excluded to ensure that only men with type 2 diabetes were present in the analyses. We also excluded 26 men because of missing information as to their cause of death. In order to maximise the number of men in the analysis, the few with missing data values for continuous measures only (listed below) were retained in the mortality analyses and multiple imputation used to produce values for these missing measures. Thus, five datasets with imputed measures were generated and the regression estimates from the analysis of these were averaged.[37] The final number of men upon which all the cancer mortality analyses were based was 18,006.

In analyses of baseline characteristics according to diabetes status, their prevalence was adjusted for age (5 year age groups) by the direct standardisation method. Trends in these proportions were tested for statistical significance using the Mantel-Haenszel test. For baseline characteristics expressed as continuous variables, least squares means were used to present the age-adjusted means and tests for trend across diabetes groups were computed by fitting a linear trend term.

Models fitted with a plasma blood glucose by follow-up time interaction term confirmed that the proportional hazards assumption was not violated. Thus, hazard ratios and accompanying confidence intervals were computed for the

relation of diabetes and blood glucose level with each mortality outcome using Cox's proportional hazards regression model[38] with follow-up period as the time scale. Using this technique we conducted three separate analyses. First, the relation of diabetes and impaired glucose tolerance with cancer mortality was examined using the normoglycaemic group as the referent category. Second, in the sub-group of men who were designated normoglycaemic, we explored the association across quartiles of blood glucose with cancer mortality using the lowest quartile as the referent category. Third, in the normoglycaemic group, the association of a one standard deviation (9.57 mg/100ml) increase in blood glucose with cancer mortality was assessed.

These models were initially adjusted for age and then for other potential confounding (employment grade, smoking status, physical activity, systolic blood pressure, blood pressure-lowering medication, marital status, disease at study entry, unexplained weight loss) and mediating (body mass index, triceps skinfold thickness, height-adjusted FEV_1, plasma cholesterol) variables. Of these, age, plasma cholesterol, systolic blood pressure, body mass index, triceps skinfold thickness, and height-adjusted FEV_1 were fitted as continuous variables, whereas employment grade (5 levels), marital status (4), physical activity (6), blood pressure lowering medication (2), smoking status (4) (with additional adjustment for the number of cigarettes smoked per day in current smokers), unexplained weight loss in the past year (2) and disease at entry (2) were fitted as categorical variables. Tests for trend in mortality rates across

diabetes groups were again computed by fitting a linear trend term.

To address the issue of reverse causality – as discussed, for some cancers tumour presence may increase elevate blood glucose levels so generating a positive blood glucose–cancer association[10] – we excluded deaths in the first 10 years of mortality surveillance and repeated our analyses. In so doing, we reasoned that a large proportion of deaths attributable to cancer, if present at study induction, would have occurred within this time frame.[39] All statistical analyses were computed using SAS computer software.[40]

Results

In table 1 the relationship of each study covariate with diabetes status in all study participants and with blood glucose in the sub-group who were normoglycaemic are presented. In the former analysis, the most favourable levels of each baseline characteristic were generally seen in persons who had normal levels of blood sugar: these men were younger, taller, leaner, had lower systolic blood pressure and higher pulmonary function than those with diabetes or IGT. They were also less likely to be of low employment grade, be without a partner, and report recent weight loss or carry a morbid load. In contrast, the prevalence of cigarette smoking was lowest in the IGT and diabetes groups. In men classified as normoglycaemic, the relationship between blood glucose and

covariate data was similar to some of those seen in the afore mentioned analysis.

After 25 years follow-up there were 2158 cancer deaths in this cohort. In Table 2 the relation between diabetic status and fifteen cancer mortality outcomes is depicted. Most of the cancer mortality endpoints were unrelated to diabetes status. Three associations at conventional levels of statistical significance emerged in multiply-adjusted analyses: both cancer of the pancreas ($HR_{\text{diabetes vs normoglycaemic}}$; 95% confidence interval: 3.99; 1.44, 11.0; P_{trend}=0.02) and liver (9.22; 2.66, 31.9; P_{trend}=0.001) were positively and incrementally associated with diabetes status, while the relation with lung cancer was inverse (0.31; 0.08, 1.24; P_{trend}=0.06). Bladder cancer rates were also raised in the IGT group ($HR_{\text{IGT vs normoglycaemic}}$; 95% confidence interval: 2.19; 1.16, 4.16; $P_{difference}$=0.02); but the trend across the three diabetes status groups was non-significant (P=0.15).

When we excluded deaths in the first ten years of follow-up to explore the issue of reverse causality (table 3) the attenuation of risk for liver cancer was marked (4.74; 0.59, 37.9) but less pronounced for carcinoma of the pancreas (3.34; 0.81, 13.8) and lung (0.54; 0.13, 2.16). Given the low number of cases on which these analyses are based – there was only one liver cancer case in the diabetes group, for instance – and the accompanying statistical imprecision, some of these results should be viewed with caution.

When we examined the relation of blood glucose to cancer mortality experience in men who were classified as normoglycaemic there was a suggestion of a positive association between liver cancer and blood glucose, however, statistical significance was not attained when this or any other cancer sub-types were the outcomes of interest (data not shown). Essentially the same null associations were apparent when we excluded deaths occurring in the first 10 years of follow-up (data not shown).

Discussion

In this study we related diabetes status and blood glucose level to fifteen cancer mortality endpoints in a large cohort of British male government employees. The main findings were that mortality from cancer of the pancreas and liver were positively and incrementally related to diabetes status, while the association with lung cancer was in the opposite direction. On excluding deaths in the first 10 years of mortality surveillance, there was some attenuation of risk for liver cancer, although the number of deaths was small and confidence intervals wide. In the subgroup of men who were classified as normoglycaemic, blood glucose was essentially unrelated to any of the cancer endpoints featured in our analyses.

A decade ago some of us reported on findings from an earlier (19 yr.) follow-up of Whitehall study participants[7] to respond the suggestion in one of the few

other cohort studies with measured blood glucose levels[3] that diabetes and impaired glucose tolerance were related to cancer risk. Although there was no evidence of an effect of diabetes status on most of the ten cancer endpoints featured in that analyses, diabetes status was weakly related to rates of lung cancer and, more strongly, pancreatic cancer, in the same directions as in the present analysis. At this earlier stage of follow-up there were insufficient liver cancer deaths to examine the predictive capacity of diabetes status for this condition as we have herein.

Alternative explanations

Pancreatic cancer is the malignancy most commonly linked with diabetes. The finding in several studies[11-13;41] of an elevated risk of this malignancy in diabetic groups has been attributed to reverse causality,[42] such that existing but clinically undetected carcinoma at study induction leads to elevated blood glucose levels. That a high proportion of pancreatic cancer patients reportedly present with diabetes or IGT,[16;43] and partial pancreatectomy in a small group of cancer patients had a normalising effect on blood glucose levels,[44] provides some support for this assertion. To examine the role of reverse causality in the diabetes–pancreatic cancer relation, we excluded those deaths occurring in the first 10 years of mortality surveillance (table 3), following which the positive relationship was of similar magnitude. In a comprehensive meta-analysis,[10] all of the eight cohort studies reviewed (we exclude an earlier follow-up[7] of the present investigation) reported a positive diabetes–pancreatic cancer relation,

although statistical significance was not seen in three of these. Additionally, with few exceptions,[45] reports appearing subsequently show statistically elevated rates of pancreatic carcinoma in the high blood glucose or diabetes groups[4;45-49]

In comparison with the evidence base for pancreatic cancer, reports of the relationship between diabetes and liver cancer are more sparse. In those conducted, an elevated risk of liver cancer has been reported in populations drawn from Italy,[50] Sweden,[51] Denmark,[4] the US,[52] and Japan.[53] In the present UK-based study population we made the same observation. Although the magnitude of this relationship was noticeably weaker after we excluded deaths in the first decade of mortality surveillance, this analysis was based on few events.

In all our analyses, effect estimates were adjusted for several important confounding or mediating variables, including overweight and socioeconomic position. Another important covariate may be alcohol consumption.[54] In a randomly selected subgroup of study participants in the Whitehall study we have information on diet, including patterns of alcohol use.[55] Although there were too few cancers in this group (176 cancer deaths in 1,658 men) to facilitate site-specific analyses by alcohol use, that there was no difference in alcohol consumption levels across the diabetes categories suggests that this behaviour does not have a confounding role at least in the present study.

Rates of lung cancer were lower in persons with diabetes and IGT. The same observation has been made elsewhere,[56-58] although this is not a universal finding.[4;6;8] The apparent protective effect of diabetes has been most commonly ascribed to the generally lower prevalence of smoking – a powerful predictor of lung cancer risk – in people with diabetes in comparison to individuals without this condition. However, there was a modest difference (3.5%) in cigarette smoking prevalence between the diabetes and normoglycaemics groups at baseline (table 1), probably too small to completely account for the marked disparity in lung cancer death rates 25 years later. Over the period of mortality surveillance, it may be that these differences in smoking patterns between the diabetes and non-diabetes groups were further accentuated due the more intense scrutinisation of lifestyle that persons with this condition – presumably some following diagnosis in the present study – would have received from their diabetologists. Survivors from the original Whitehall study have recently been mailed a follow-up questionnaire with enquiries about current smoking habits.[59] However, when smoking status at baseline and follow-up were stratified by diabetes status (diabetes, IGT and normoglycaemia), there were too few observations to test this hypothesis (Elizabeth Breeze, 2004 – personal communication).

Plausible mechanisms of effect

The most frequently advanced mechanism linking blood glucose with cancer of the pancreas and liver is the so called 'insulin hypothesis'. Thus, in vitro, insulin seems to stimulate carcinogenesis in these organs.[60 61] In addition, high concentrations of insulin activate insulin-like-growth-factor 1 (IGF-1) receptors, which in turn have been demonstrated to enhance pancreatic cell proliferation.[14] However, although IGF-1 has also been implicated in the aetiology of colorectal and prostate malignancies,[15] there was no relationship between these cancers and diabetes in the present investigation. It is also plausible that the medication used to treat diabetes may precipitate some cancers. Such an explanation requires investigation.

Study strengths and limitations

The strengths of the present study include its almost complete follow-up for mortality experience, so minimising any potential bias due to selection; the availability of data on a range of potential covariates and mediators, including socioeconomic position and adiposity; extended follow-up, so facilitating examination of reverse causality; and a cohort well characterised for diabetes owing to the assessment of both self-reported diabetes and blood glucose levels. However, while blood glucose was assessed objectively, in having only a single baseline measurement there will have been some misclassification of measurement at baseline. Further misclassification will occur as the population ages and participants go on to develop IGT and diabetes. Both these factors are

likely to lead to a conservative estimation of cancer risk. In the present investigation, as in earlier reports from the Whitehall study,[35;62;63] there was clear evidence of an association of blood glucose with total and cardiovascular disease mortality ($HR_{\text{diabetics vs. normoglycaemics}}$; 95% CI: 2.00; 1.54, 2.60). Because this has been demonstrated in several other populations,[64;65] it appears that the predictive validity of the blood glucose data is high. Additionally, diabetes status was associated with some covariates in the expected directions suggesting some concurrent validity. Finally, given that the relation of diabetes status with fifteen cancer outcomes was examined – necessarily conducting multiple tests – it is highly plausible that some the associations found herein could have been identified by chance.

In conclusion, in this large scale prospective study offering in excess of two thousand cancer deaths, measured blood glucose levels and self-reported diabetes were unrelated to most of the fifteen cancer endpoints we examined. There was evidence of a positive relation of diabetes status with carcinoma of liver and pancreas, and the association with lung cancer was inverse. Further studies which hold data on serially administered blood glucose measurements and cancer outcomes are required.

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Table 1. Association between diabetes status, blood glucose and baseline characteristics[a] in the Whitehall study

	Diabetes status			P-value for trend	Quartiles of blood glucose (normoglycaemics)				P-value for trend
	Normo-glycaemic	IGT	NIDDM		Quartile 1 (lowest)	Quartile 2	Quartile 3	Quartile 4	
Number[b]	16,843	975	188		4299	4231	3813	4500	
				Mean (standard error)					
Age	51.4 (0.1)	53.1 (0.2)	55.8 (0.4)	0.001	51.8 (0.1)	51.4 (0.1)	51.2 (0.1)	51.2 (0.1)	0.001
Tricep skinfold thickness (mm)	44.6 (0.1)	45.1 (0.5)	43.1 (1.2)	0.87	45.0 (0.2)	44.8 (0.2)	44.3 (0.3)	44.4 (0.2)	0.04
Body mass index (kg/m^2)	24.7 (0.02)	25.2 (0.1)	25.7 (0.2)	0.001	24.6 (0.4)	24.7 (0.4)	24.7 (0.5)	24.8 (0.4)	0.003
Plasma cholesterol (mmol/l)	5.11 (0.01)	5.06 (0.04)	5.15 (0.09)	0.44	5.06 (0.2)	5.10 (0.2)	5.13 (0.2)	5.15 (0.2)	0.001
FEV_1[c] (l/sec)	3.13 (0.01)	3.05 (0.02)	2.98 (0.04)	0.001	3.12 (0.01)	3.15 (0.01)	3.15 (0.01)	3.14 (0.01)	0.11
Systolic BP (mmHg)	135.6 (0.2)	141.5 (0.7)	138.7 (1.5)	0.001	133.8 (0.3)	135.0 (0.3)	135.8 (0.3)	137.3 (0.3)	0.001
Height (cm)	176.0 (0.1)	174.8 (0.2)	173.8 (0.5)	0.001	175.4 (0.1)	176.2 (0.1)	176.3 (0.1)	176.1 (0.1)	0.001
				Percent (standard error)					
Inactive / zero travel time	16.0 (0.3)	15.1 (1.2)	21.6 (3.6)	0.53	19.3 (0.6)	16.2 (0.6)	14.4 (0.6)	14.1 (0.5)	0.001
Weight loss in last yr	2.1 (0.1)	1.6 (0.4)	8.6 (2.6)	0.08	2.5 (0.2)	2.2 (0.2)	1.7 (0.2)	2.2 (0.2)	0.25
Current cigarette smoker	41.5 (0.4)	40.5 (1.6)	37.9 (4.3)	0.06	45.0 (0.8)	41.2 (0.8)	40.3 (0.8)	39.4 (0.7)	0.001
Low work grade	23.3 (0.3)	28.4 (1.4)	39.9 (4.0)	0.001	22.9 (0.6)	23.0 (0.6)	22.9 (0.7)	24.2 (0.6)	0.18
No partner	11.5 (0.3)	14.5 (1.2)	19.6 (3.5)	0.001	11.7 (0.5)	11.1 (0.5)	10.9 (0.5)	12.2 (0.5)	0.52
Disease at study entry[d]	20.2 (0.3)	27.9 (1.4)	23.1 (3.4)	0.001	20.2 (0.6)	20.7 (0.6)	20.7 (0.7)	19.4 (0.6)	0.32
Blood pressure-lowering medication	1.5 (0.1)	2.4 (0.5)	1.2 (0.6)	0.06	1.4 (0.2)	1.3 (0.2)	1.6 (0.2)	1.6 (0.2)	0.30

[a]Adjusted for age (age is unadjusted)
[b]Numbers in the analysis for each variable differ slightly owing to missing values
[c]FEV_1 = Forced expiratory volume in one second (adjusted for height)
[d]see methods section for definition

Table 2. Hazard ratios (95% confidence intervals) for diabetes status in relation to cancer mortality in the Whitehall study

Cancer outcome[d]	Adjustment	Number of deaths			Hazard ratio (95% CI)			P-value for trend
		Normo-glycaemic (N=16,843)	IGT (N=975)	NIDDM (N=188)	Normo-glycaemic	IGT	NIDDM	
All Cancers	Age	2158	130	16	1.0 (ref)	1.03 (0.87, 1.23)	0.73 (0.44, 1.19)	0.58
	Multiple[a]	-	-	-	1.0	1.01 (0.84, 1.20)	0.74 (0.45, 1.20)	0.47
Oesophagus	Age	73	4	2	1.0	0.98 (0.36, 2.70)	3.00 (0.73, 12.3)	0.41
	Multiple	-	-	-	1.0	0.89 (0.32, 2.44)	3.02 (0.72, 12.6)	0.43
Stomach	Age	149	11	2	1.0	1.25 (0.68, 2.31)	1.26 (0.31, 5.09)	0.46
	Multiple	-	-	-	1.0	1.24 (0.67, 2.29)	1.24 (0.30, 5.03)	0.49
Colon	Age	193	11	1	1.0	0.97 (0.53, 1.79)	0.50 (0.07, 3.60)	0.61
	Multiple	-	-	-	1.0	0.95 (0.52, 1.76)	0.45 (0.06, 3.26)	0.52
Rectum	Age	73	2	0	1.0	0.43 (0.12,1.93)	0.0[c]	0.19
	Multiple	-	-	-	1.0	0.46 (0.11, 1.90)	0.0[c]	0.18
Liver	Age	31	4	3	1.0	2.47 (0.87, 7.03)	12.24 (3.68, 40.7)	<0.001
	Multiple	-	-	-	1.0	1.91 (0.66, 5.49)	9.22 (2.66, 31.9)	0.001
Pancreas	Age	102	8	4	1.0	1.35 (0.66, 2.78)	3.88 (1.42, 10.7)	0.02
	Multiple	-	-	-	1.0	1.35 (0.66, 2.80)	3.99 (1.44, 11.0)	0.02
Lung	Age	647	34	2	1.0	0.86 (0.61, 1.21)	0.27 (0.07, 1.07)	0.05
	Multiple	-	-	-	1.0	0.83 (0.59, 1.18)	0.31 (0.08, 1.24)	0.06
Prostate	Age	240	14	0	1.0	1.00 (0.58, 1.72)	0.0[c]	0.34
	Multiple	-	-	-	1.0	1.05 (0.61, 1.81)	0.0[c]	0.47
Bladder	Age	84	11	0	1.0	2.25 (1.20, 4.23)	0.0[c]	0.16
	Multiple	-	-	-	1.0	2.19 (1.16, 4.16)	0.0[c]	0.15
Kidney	Age	46	3	0	1.0	1.17 (0.36, 3.76)	0.0[c]	0.83
	Multiple	-	-	-	1.0	1.10 (0.34, 3.56)	0.0[c]	0.80
Brain	Age	47	3	0	1.0	1.16 (0.36, 3.72)	0.0[c]	0.99
	Multiple	-	-	-	1.0	1.22 (0.38, 3.96)	0.0[c]	0.87
Lymphoma	Age	106	8	0	1.0	1.39 (0.68, 2.85)	0.0[c]	0.92
	Multiple	-	-	-	1.0	1.31 (0.63, 2.70)	0.0[c]	0.98
Leukaemia	Age	74	3	1	1.0	0.70 (0.22, 2.21)	1.32 (0.18, 9.55)	0.78
	Multiple	-	-	-	1.0	0.69 (0.22, 2.21)	1.28 (0.18, 9.37)	0.76
Other cancers	Age	293	14	1	1.0	0.86 (0.50, 1.47)	0.38 (0.05, 2.71)	0.30
	Multiple	-	-	-	1.0	0.82 (0.48, 1.40)	0.37 (0.05, 2.62)	0.23

[a]Adjustment for confounding (age, employment grade, smoking status, physical activity, systolic blood pressure, blood pressure-lowering medication, marital status, disease at study entry, unexplained weight loss) and mediating (body mass index, triceps skinfold thickness, height adjusted FEV_1, plasma cholesterol) variables.
[b]see methods section for definition
[c]95% confidence interval could not be computed since the number of deaths was zero
[d]cancer sub-types are ordered according to ascending ICD 8 code

Table 3. Hazard ratios (95% confidence intervals) for diabetes status in relation to cancer mortality in the Whitehall study – excluding deaths occurring in the first 10 years of follow-up

Cancer outcome[d]	Adjustment	Number of deaths			Hazard ratio (95% CI)			P-value for trend
		Normo-glycaemic (N=15, 231)	IGT (N=815)	NIDDM (N=132)	Normo-glycaemic	IGT	NIDDM	
All Cancers	Age	1670	94	9	1.0 (ref)	1.01 (0.82, 1.24)	0.61 (0.32, 1.18)	0.38
	Multiple[a]	-	-	-	1.0	0.99 (0.80, 1.22)	0.63 (0.33, 1.22)	0.36
Oesophagus	Age	63	4	2	1.0	1.18 (0.43, 3.24)	3.86 (0.94, 15.9)	0.14
	Multiple	-	-	-	1.0	1.05 (0.38, 2.91)	4.00 (0.96, 16.7)	0.20
Stomach	Age	108	7	0	1.0	1.16 (0.54, 2.48)	0.0[c]	0.75
	Multiple	-	-	-	1.0	1.14 (0.53, 2.47)	0.0[c]	0.71
Colon	Age	148	6	1	1.0	0.73 (0.32, 1.64)	0.78 (0.11, 5.55)	0.45
	Multiple	-	-	-	1.0	0.70 (0.31, 1.60)	0.72 (0.10, 5.19)	0.40
Rectum	Age	55	2	0	1.0	0.64 (0.16, 2.64)	0.0[c]	0.37
	Multiple	-	-	-	1.0	0.61 (0.15, 2.53)	0.0[c]	0.33
Liver	Age	22	3	1	1.0	2.62 (0.78, 8.77)	6.17 (0.83, 46.1)	0.02
	Multiple	-	-	-	1.0	2.31 (0.68, 7.83)	4.74 (0.59, 37.9)	0.06
Pancreas	Age	78	6	2	1.0	1.38 (0.60, 3.17)	2.93 (0.72, 12.0)	0.13
	Multiple	-	-	-	1.0	1.41 (0.61, 3.25)	3.34 (0.81, 13.8)	0.10
Lung	Age	463	21	2	1.0	0.78 (0.50, 1.21)	0.45 (0.11, 1.81)	0.12
	Multiple	-	-	-	1.0	0.78 (0.50, 1.21)	0.54 (0.13, 2.16)	0.16
Prostate	Age	225	14	0	1.0	1.09 (0.63, 1.86)	0.0[c]	0.51
	Multiple	-	-	-	1.0	1.16 (0.67, 1.99)	0.0[c]	0.70
Bladder	Age	66	9	0	1.0	2.48 (1.24, 4.99)	0.0[c]	0.11
	Multiple	-	-	-	1.0	2.36 (1.16, 4.80)	0.0[c]	0.11
Kidney	Age	35	1	0	1.0	0.55 (0.08, 4.01)	0.0[c]	0.45
	Multiple	-	-	-	1.0	0.57 (0.08, 4.18)	0.0[c]	0.48
Brain	Age	19	2	0	1.0	2.01 (0.47, 8.66)	0.0[c]	0.60
	Multiple	-	-	-	1.0	2.09 (0.48, 9.16)	0.0[c]	0.54
Lymphoma	Age	89	6	0	1.0	1.25 (0.55, 2.87)	0.0[c]	0.93
	Multiple	-	-	-	1.0	1.20 (0.52, 2.77)	0.0[c]	0.87
Leukaemia	Age	56	2	0	1.0	0.62 (0.15, 2.56)	0.0[c]	0.35
	Multiple	-	-	-	1.0	0.60 (0.15, 2.48)	0.0[c]	0.32
Other cancers	Age	240	11	1	1.0	0.85 (0.46, 1.55)	0.52 (0.07, 3.67)	0.41
	Multiple	-	-	-	1.0	0.80 (0.43, 1.46)	0.50 (0.07, 3.59)	0.32

[a]Adjustment for confounding (age, employment grade, smoking status, physical activity, systolic blood pressure, blood pressure-lowering medication, marital status, disease at study entry, unexplained weight loss) and mediating (body mass index, triceps skinfold thickness, height adjusted FEV_1, plasma cholesterol) variables.
[b]see methods section for definition
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