CLINICAL STUDY

Incidence and predictors of all-cause and site-specific cancer in type 2 diabetes: the Fremantle Diabetes Study

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Abstract

Objective: To explore the relationship between diabetes and cancer.

Design: The Fremantle Diabetes Study (FDS) was a community-based longitudinal observational study of 1426 subjects, 1294 of which had type 2 diabetes.

Methods: The FDS type 2 cohort and four age-, sex- and postcode-matched controls per case were followed for cancer events from 1993 until mid-2010 and incidence rate ratios (IRRs) were calculated. Competing risks proportional hazards models generated risk factors for incident cancers in the diabetic group.

Results: There were 309 first cancers over 13 051 patient-years, or 2368 (95% confidence interval (95% CI) 2111–2647)/100 000 patient-years in the diabetes patients vs 1131 over 60 324 patient-years (1875 (1769–1987)/100 000 patient-years) in the controls. For those aged ≥ 45 years, the risk of all-cause cancer was elevated in type 2 diabetic men (IRRs 1.23, 95% CI 1.04–1.45) and women (1.30, 1.06–1.59). The incidence of colorectal cancer was increased (1.36, 1.01–1.82), especially in diabetic men aged 75–84 years (2.14, 1.22–3.64). Age at diabetes diagnosis (sub-hazard ratio 1.05, 1.02–1.09), calcium channel blocker therapy (2.37, 1.39–4.06), recent exercise (2.11, 1.06–4.20) and serum total cholesterol (0.68, 0.52–0.88) increased colorectal cancer risk. Pancreatic cancer was also more frequent in the diabetic patients (IRR 2.26, 1.20–4.10). Diabetic men and women had similar risks of prostate and breast cancer to those of controls (0.83, 0.59–1.14 and 0.86, 0.52–1.36).

Conclusions: Type 2 diabetes is associated with a moderately increased cancer risk in well-characterised community-based patients, especially pancreatic cancer and colorectal cancer in older men. Recommended cancer screening should be considered as part of routine diabetes management.

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Introduction

The weight of evidence, derived largely from pooled cohort studies, administrative databases and meta-analyses, suggests that type 2 diabetes is associated with an increased risk of a number of cancers including those of liver (1), pancreas (2), colon and rectum (3), breast (4), endometrium (5) and bladder (6), while there may be a decreased risk in the case of prostate cancer (7). Associations between diabetes and cancer may, however, be confounded by co-incident risk factors including ageing, obesity and insulin resistance, an imprudent diet and lack of physical activity (8). In addition, some diabetes treatments may increase (9, 10, 11) or decrease (12) cancer risk. A further issue that can confound interpretation of cancer rates in diabetes is the occurrence of non-cancer-related deaths such as those from cardiovascular disease. Without consideration of such competing risks, estimation of predictors of incident cancer might be confounded (13).

There are few prospective studies that have explored cancer incidence, risk factors and competing risks in detail in community-based type 2 diabetic patients. Such studies would facilitate a more accurate assessment of the independent contribution of diabetes and diabetes-related variables to the development of cancer, which, even if small, would have important consequences at a population level. We have, therefore, examined the relationship between diabetes and total and major site-specific cancer in a well-characterised prospectively studied cohort of Australian adults with diabetes and in age-, sex- and postcode-matched non-diabetic controls.

Materials and methods

Patients

The Fremantle Diabetes Study (FDS) Phase I was a longitudinal observational cohort study of patients

from a postcode-defined urban community of 120 097 people. Descriptions of recruitment, sample characteristics including classification of diabetes type, and details of non-recruited patients have been published elsewhere (14). Of 2258 diabetic patients identified between 1993 and 1996, 1426 (63%) were recruited to the FDS and 1294 had clinically diagnosed type 2 diabetes. Eligible patients who declined participation were a mean of 1.4 years older than participants, but their sex distribution, the proportion with type 2 diabetes and their use of blood glucose-lowering therapies were similar (15). The FDS protocol was approved by the Human Rights Committee at Fremantle Hospital and all subjects gave informed consent before participation.

Selection of controls

It is compulsory for all Australians aged 18 years and over to vote in Federal and State elections and thus all adults resident in the FDS catchment area are listed on the electoral roll. Four age-, sex- and postcode-matched non-diabetic controls were randomly selected from this source for each FDS participant at the time of FDS study entry. The requirement for postcode matching was based on the fact that there are substantial socio-economic and environmental differences between residential districts within the FDS catchment area. Some of the lowest socio-economic districts are located adjacent to heavy industry and thus exposed to potential carcinogens (16, 17). Non-diabetic status was defined as diabetes not being coded at any time on any Western Australia health database. Matches could not be made for five children and four elderly participants, and these patients were excluded from estimation of incident rate ratios, leaving 1289 (99.6%) diabetic participants who were matched with 5156 non-diabetic controls. Five controls died just before entry into FDS by their matched case and were therefore excluded. Because the range of data available for the control subjects was limited to date of birth, sex and postcode, they were used only for estimation of incidence rate ratios (IRRs; see below).

To provide additional comparative control data, we used published data from the Australian Cancer Database 2007 (18). This source did not allow analysis by diabetes status. The overall national cancer incidence remained relatively stable over the period of follow-up in this study, being an average 1192/100 000 and ranging from 1149/100 000 in 1999 to 1236/100 000 in 2007 for those 45 years and older.

Cancer registration, hospitalisation and mortality ascertainment

All deaths, hospitalisations and cancer registrations in the state of Western Australia are recorded in the Western Australia Data Linkage System (19), which was used to provide FDS patient and control outcomes

from 1982 until end-June 2010. Incident hospitalisation/registration for cancer events was defined as a hospital admission/cancer registration with principal or secondary diagnosis of malignant cancer but excluding non-melanocytic skin cancer (NMSC), equivalent to an International Classification of Disease (ICD)-9 code 140–208 (excluding 173), 238.4, 238.71, 238.72, 238.75, 238.76, 238.79 or 273.3, or an ICD-10 code of C00–C96 (excluding C44), D45, D46, D47.1 or D47.3. The documentation of cancer in death certificates was also used to define incident cancer, even if the cause of death was not cancer. As has been done in similar analyses (20), the development of a cancer at one site did not exclude subjects from analyses of a first cancer at another site.

Statistical analysis

The computer packages Stata IC 10.0 (StataCorp LP, College Station, TX, USA) and SPSS for Windows (version 17.0; SPSS Inc., Chicago, IL, USA) were used for statistical analysis. Data are presented as proportions, mean $\pm$ s.d., geometric mean (s.d. range), or, in the case of variables that did not conform to a normal or log-normal distribution, median and inter-quartile range (IQR). For independent samples, two-way comparisons for proportions were by Fisher's exact test, for normally distributed variables by Student's *t*-test, and for non-normally distributed variables by Mann–Whitney *U* test. A two-tailed significance level of $P < 0.05$ was used throughout. Ten-year age- and sex-specific incident rates of any (excluding NMSC) and site-specific cancers for the FDS cohort were compared with those derived for the non-diabetic controls, and IRRs were derived. Ten-year age groups starting at 45 years of age were selected due to the middle to older age of people with type 2 diabetes. In addition, Cox proportional hazards modelling was used to generate hazard ratios (HRs) for cancer in those with type 2 diabetes adjusting for gender. Owing to the presence of covariates strongly associated with age, age was used as the timescale with left truncation of age at study entry (21).

Associations between potential predictors and incident cancer were explored with competing risk models. The predictors of the cumulative incidence of cancer in FDS participants, accounting for the competing event of non-cancer death, were ascertained using the Fine and Gray model (13), which extends the Cox proportional hazards model to competing risk data by considering the sub-distribution hazard. This method was used because traditional Cox models are limited by the assumption that the event of interest will eventually occur. In a study of cancer, for example, a subject dying from a stroke (a competing risk) before any cancer was diagnosed is treated as if they were right censored and could later develop cancer. The Fine and Gray model controls for this bias and yields a sub-HR (sHR), which is the ratio of hazards associated with the cumulative

incidence function (or absolute cause-specific risk) under varying values of a given covariate. The SHR may be interpreted as a HR. Competing risk was defined separately for each cancer site as mortality from causes other than that of interest (e.g. death from a non-cancer cause or from a cancer at another site).

Age was used as the timescale with left truncation of age at study entry (21). The most parsimonious model of predictors of incident cancer was determined. All clinically plausible baseline variables at $P \leq 0.20$ in bivariate analyses were considered for entry, including demographic and diabetes-related factors, the presence of other complications and risk factors for cancer. As serum LDL-cholesterol was calculated and therefore missing for values of serum triglycerides ≥ 4.5 mmol/l, it was not considered for entry into the models. A formal check of proportionality was undertaken by the use of time-varying covariate effects. The observed non-proportional hazards for age at diagnosis of diabetes for all-cause cancer was accounted for by stratifying the analyses by age of diagnosis (< 60 and ≥ 60 years).

Results

Baseline patient characteristics

At study entry, the 1294 FDS type 2 participants had a mean $\pm$ s.d. age of 64.1 ± 11.3 years, 48.8% were male and their median (IQR) diabetes duration was 4.0 (1.0–9.0) years.

Cancer incidence

A previous cancer history was recorded for 110 (8.5%). Of the remaining 1184 participants, over one quarter (309 or 26.1%) were hospitalised for, were registered with or died from/with malignant cancer during 13 051 patient-years (mean $\pm$ s.d. 11.0 ± 5.5 years) of follow-up to the first diagnosis of cancer after baseline, death or end-June 2010, whichever came first. This represented a crude incidence of 2368 (95% confidence interval (95% CI) 2111–2647) events/100 000 patient-years. There were 1131 database-identified cancer events in the controls (23.3%) over 60 324 patient-years, representing a crude incidence of 1875 (1769–1987)/100 000 patient-years.

Among 1282 without a history of colorectal cancer at entry, 63 (4.9%) developed colorectal cancer. The crude incidence of colorectal cancer was 416 (95% CI 320–533)/100 000 patient-years. Men had a significantly higher incidence of colorectal cancer than women with an IRR of 1.88 (95% CI 1.10–3.26, $P=0.015$). Among 615 men free of prostate cancer at entry, 45 (7.3%) developed prostate cancer, a crude incidence of 661 (95% CI 482–884)/100 000 patient-years. Among 644 women free of breast cancer at baseline, 22 (3.4%) developed breast cancer with a

crude incidence of 278 (95% CI 174–420)/100 000 patient-years. Excluding two cases of pancreatic cancer that were diagnosed before diabetes diagnosis, 18 (1.4%) developed pancreatic cancer during follow-up, a crude incidence of 117 (95% CI 69–185)/100 000 patient-years.

Incidence rate and HRs of cancer in patients vs controls

Table 1 summarises IRRs for any malignancy, and colorectal, breast, prostate and pancreatic cancer for the FDS type 2 diabetic cohort in comparison with the age-, sex- and postcode-matched controls. All-cause, colorectal and pancreatic cancers were increased in type 2 diabetes, and the incidence of all-cause cancer was significantly elevated in both men and women with diabetes. The incidence of colorectal cancer for 75- to 84-year-old men with type 2 diabetes was 2.14 times higher than controls, while the corresponding incidence for women was increased by 47%, but this was not statistically significant. Unadjusted and sex-adjusted HRs for first cancer at any and each site in the prevalent type 2 diabetes cohort compared with the matched non-diabetic cohort following entry into the FDS are presented in [Supplementary Table 1](#), see section on [supplementary data](#) given at the end of this article. The HRs for diabetes were consistent with the IRRs in [Table 1](#), while all cancers except breast were associated with increasing age.

The IRRs for cancer in patients in the FDS cohort ≥ 45 years relative to national notifications in the same age group were 2.04 (1.82–2.29) for all-cause cancer (1.81 (1.50–2.15) for women and 2.08 (1.79–2.40) for men), 2.44 (1.88–3.12) for colorectal cancer (2.06 (1.32–3.07) for women and 2.71 (1.93–3.71) for men), 1.70 (1.24–2.28) for prostate cancer, 1.05 (0.66–1.59) for breast cancer and 4.11 (2.43–6.49) for pancreatic cancer.

Bivariate predictors of incident cancer

Two patients who were lost to follow-up were excluded from analyses of risk factors for incident cancer. This left 1182 participants without a previous history of cancer at study entry who did or did not go on to develop a malignant cancer during follow-up. In bivariate analysis of baseline variables (see [Table 2](#)), older age at study entry and at diabetes diagnosis, male sex and current or former smoking were significantly associated with any incident cancer. A lower prevalence of retinopathy, lower HbA1c, lower total serum cholesterol and lower serum LDL-cholesterol were associated with the development of cancer during follow-up.

For site-specific cancer (see [Supplementary Table 2](#), see section on [supplementary data](#) given at the end of this article), older age at study entry and diabetes diagnosis, male sex, recent exercise, total serum

Table 1 Age-specific incidence rate per 100 000 patient-years and incidence rate ratio (IRR) vs age-, sex- and postcode-matched non-diabetic controls of first record (hospitalisation, cancer register and death) of all (excluding NMSC) and site-specific cancer for persons aged ≥ 45 years.

Cancer type	Age group (years)					Total
	45–54	55–64	65–74	75–84	85+	
All (both genders)						
FDS: no. of cancers	12	36	130	109	20	307
FDS: years	1271.9	2986.8	4724.8	3003.4	613.2	12 600.1
FDS: IR	943.5	1205.3	2751.5	3629.2	3261.6	2436.5
Control: no. of cancers	27	120	413	450	117	1127
Control: years	5338.5	12 814.3	20 956.0	15 534.1	3772.9	58 415.7
Control: IR	505.8	936.5	1970.8	2896.9	3101.1	1929.3
IRR	1.87	1.29	1.40	1.25	1.69	1.26
95% CI	0.86–3.81	0.86–1.88	1.14–1.71	1.01–1.55	0.12–1.70	1.11–1.43
All (women)						
FDS1: no. of cancers	7	15	38	50	13	123
FDS1: years	677.2	1511.1	2462.9	1725.5	441.1	6817.8
FDS1: IR	1033.7	992.6	1542.9	2897.7	2947.0	1804.1
Control: no. of cancers	19	50	143	161	70	443
Control: years	2845.5	6634.3	108 230.0	8924.7	2676.5	31 911.0
Control: IR	667.7	753.7	1320.4	1804.0	2615.3	1388.2
IRR	1.55	1.32	1.17	1.61	1.13	1.30
95% CI	0.55–3.85	0.69–2.38	0.79–1.68	1.15–2.22	0.57–2.05	1.06–1.59
All (men)						
FDS1: no. of cancers	5	21	92	59	7	184
FDS1: years	594.7	1475.7	2261.9	1277.9	172.1	5782.3
FDS1: IR	840.7	1423.1	4067.4	4616.9	4068.1	3182.1
Control: no. of cancers	8	70	270	289	47	684
Control: years	2493.1	6180.0	10 126.0	6609.3	1096.3	26 504.7
Control: IR	320.9	1132.7	2666.4	4372.6	4287.1	2580.7
IRR	2.62	1.30	1.53	1.06	0.95	1.23
95% CI	0.67–9.08	0.76–2.15	1.19–1.94	0.78–1.40	0.36–2.11	1.04–1.45
Colorectal (both genders)						
FDS1: no. of cancers	1	3	21	31	7	63
FDS1: years	1336.8	3299.5	5531.1	3733.5	751.9	14 652.8
FDS1: IR	74.8	90.9	379.7	830.3	931.0	430.0
Control: no. of cancers	3	17	73	80	30	203
Control: years	5477.0	13 509.2	23 058.5	17 898.7	4450.1	64 393.55
Control: IR	54.8	125.8	316.6	447.0	674.1	315.2
IRR	1.37	0.72	1.20	1.86	1.38	1.36
95% CI	0.03–17.01	0.14–2.50	0.70–1.97	1.19–2.84	0.51–3.12	1.01–1.82
Colorectal (women)						
FDS1: no. of cancers	1	1	8	10	4	24
FDS1: years	729.5	1714.4	2811.0	2083.8	513.8	7852.6
FDS1: IR	137.1	58.3	284.6	479.9	778.5	305.6
Control: no. of cancers	2	4	22	32	15	75
Control: years	2938.6	7027.5	11 664.9	9826.7	3030.4	34 488.1
Control: IR	68.1	56.9	188.6	325.6	495.0	217.5
IRR	2.01	1.02	1.51	1.47	1.57	1.41
95% CI	0.03–38.69	0.02–10.36	0.58–3.52	0.65–3.07	0.38–4.94	0.85–2.25
Colorectal (men)						
FDS1: no. of cancers	0	2	13	21	3	39
FDS1: years	607.3	1585.1	2720.0	1649.7	238.1	6800.2
FDS1: IR	0	126.2	477.9	12 723.0	1260.1	573.5
Control: no. of cancers	1	13	51	48	15	128
Control: years	2538.4	6481.6	11 393.7	8072.0	1419.7	29 905.4
Control: IR	39.4	200.6	447.6	594.7	1056.6	428.0
IRR	0	0.63	1.07	2.14	1.19	1.34
95% CI	–	0.07–2.78	0.53–1.99	1.22–3.64	0.22–4.22	0.91–1.93
Prostate						
FDS1: no. of cancers	1	5	25	14	0	45
FDS1: years	607.2	1573.0	2582.5	1585.8	254.1	6602.7
FDS1: IR	164.7	317.9	968.0	882.8	0	681.5
Control: no. of cancers	1	25	94	106	13	239
Control: years	2538.9	6399.9	11 009.3	7664.2	1322.2	28 934.6
Control: IR	39.4	390.6	853.8	1383.0	983.2	826.0
IRR	4.18	0.81	1.13	0.64	0	0.83
95% CI	0.05–328.2	0.24–2.16	0.70–1.78	0.34–1.12	–	0.59–1.14

Table 1 Continued

Cancer type	Age group (years)					Total
	45–54	55–64	65–74	75–84	85+	
Breast						
FDS1: no. of cancers	2	6	6	7	1	22
FDS1: years	724.0	1651.3	2726.7	2040.2	516.5	7658.8
FDS1: IR	276.2	363.3	220.0	343.1	193.6	287.3
Control: no. of cancers	20	34	38	19	0	111
Control: years	2804.4	6652.1	11 210.6	9519.4	2925.7	33 112.2
Control: IR	713.2	511.1	339.0	199.6	0	335.2
IRR	0.39	0.71	0.65	1.72	–	0.86
95% CI	0.04–1.59	0.24–1.71	0.22–1.55	0.61–4.27	–	0.52–1.36
Pancreas (both genders)						
FDS1: no. of cancers	1	1	5	8	3	18
FDS1: years	1340.8	3312.0	5590.4	3925.9	808.3	14 977.4
FDS1: IR	74.6	30.2	89.4	203.8	371.2	120.2
Control: no. of cancers	2	4	11	10	8	35
Control: years	5486.569	13 606.0	23 507.4	18 494.5	4677.4	65 771.8
Control: IR	36.5	29.4	46.8	54.1	171.0	53.2
IRR	2.05	1.03	1.91	3.77	2.17	2.26
95% CI	0.03–39.30	0.02–10.38	0.52–5.97	1.29–10.61	0.37–9.04	1.20–4.10

IR, incidence rate.

cholesterol, LDL-cholesterol, systolic blood pressure and antihypertensive therapy were associated with future colorectal cancer. Incident breast cancer in women was associated with higher alcohol consumption. Incident prostate cancer was associated with lower levels of albuminuria. Pancreatic cancer was associated with significantly higher fasting plasma glucose and a trend to a male predominance.

Independent predictors of incident cancer in patients with type 2 diabetes

Table 3 shows the predictors of all-cause cancer among the cohort for all patients with type 2 diabetes. Male sex and age at diagnosis of diabetes predicted incident cancer for those aged ≥ 60 years at diabetes diagnosis. For those younger than 60 years of age at diabetes diagnosis, smoking (current and ex-) independently predicted risk while an elevated urinary albumin:creatinine ratio was inversely associated. Older age at diabetes diagnosis independently predicted colorectal cancer and the use of calcium channel blockers and exercising both more than doubled the risk of colorectal cancer. Elevated total serum cholesterol was inversely associated with colorectal cancer. Metformin use independently predicted prostate cancer incidence while elevated fasting serum glucose and albuminuria appeared protective against prostate cancer. No competing risk analyses were performed for incident breast and prostatic cancer because the number of cases was small ($n \leq 22$).

Discussion

The present data confirm that cancer is a common co-morbidity of type 2 diabetes. Nearly one-third of our

community-based cohort developed cancer before or during an average 11 years of observation. Compared with age-, sex- and postcode-matched non-diabetic controls, the FDS type 2 patients had a significantly increased risk of incident all-cause cancer that was present for both genders and consistent across age groups. Among site-specific cancers, there was an excess risk of both colorectal and pancreatic cancers. For colorectal cancer, the risk was greatest (more than double that of controls) in men aged 75–84 years. Men and women with type 2 diabetes in our cohort had incidence rates of prostate and breast cancer, respectively, that were not significantly different to those of matched controls. A variety of diabetes-related and non-diabetes-related variables were associated with incident cancer in competing risk models that have potential implications for management.

Our estimated all-cause cancer IRRs for type 2 men (1.23) and women (1.30) are very close to those for people with diabetes in large population-based studies from Korea (1.24 and 1.33 respectively) (22) and Japan (1.27 and 1.21 respectively) (23). There are few similar data for predominantly Europid cohorts (24). A relatively small recent US study involving 599 diabetic patients found a HR of 1.22 relative non-diabetic controls (25). A Danish study utilising a population-based register (26) found that men and women with diabetes were at 10% increased risk but only hospitalised patients were included and diabetes status was ascertained using inpatient coding alone. Because of differences in apparent relationships between diabetes and the various types of malignancy, analyses of associations with all-cause cancers have been discouraged (8). However, the consistency of the results of this and other studies (22, 23, 24, 26, 27) suggests that there is a moderate diabetes-specific increase in overall

cancer risk. Possible unifying underlying mechanisms include direct promotion of cell growth and an increase in the likelihood of metastasis through altered endothelial permeability by hyperglycaemia (28), while hyperinsulinaemia and elevated circulating insulin-like

growth factor concentrations may also promote tumour growth (29). Our data suggest that the smoking-associated increased risk of many forms of cancer is greatest in diabetic patients who are < 60 years of age.

Table 2 Baseline characteristics of people with type 2 diabetes and no history of malignant cancer (excluding NMSC and those with diabetes duration ≤ 1 year at time of first cancer diagnosis) who did and did not develop cancer during follow-up. Data are percentage or mean $\pm$ s.d. or median (IQR) or geometric mean (s.d. range).

	No cancer	Incident cancer	P value
<i>n</i> (%)	873 (73.9%)	309 (26.1%)	
Age (years)	63.1 $\pm$ 12.0	65.2 $\pm$ 9.2	0.002
Sex (% male)	45.1	59.5	<0.001
Ethnic background (%)			
Anglo-Celt	61.2	67.6	0.13
Southern European	19.8	16.8	
Other	19.0	15.5	
Education beyond primary level (%)	74.7	74.3	0.88
Not fluent in English (%)	16.9	12.9	0.12
Smoking status (%)			
Never	48.4	36.4	0.001
Ex-smoker	37.9	44.5	
Current smoker	13.7	19.2	
Any exercise in past 2 weeks (%)	71.2	75.2	0.18
Alcohol consumption (standard drinks/day)	0 (0–0.4)	0 (0–0.8)	0.12
Age at diabetes diagnosis (years)	56.9 $\pm$ 12.2	59.7 $\pm$ 9.9	<0.001
Diabetes duration (years)	4.0 (1.0–9.0)	4.0 (1.0–9.0)	0.69
Fasting serum glucose (mmol/l)	8.6 (6.9–11.0)	8.1 (6.8–10.4)	0.05
HbA1c (%)	7.6 (6.4–8.9)	7.1 (6.4–8.5)	0.009
Fasting serum insulin (pmol/l) in non-insulin-treated patients	74.6 (38.3–145.5)	73.4 (39.1–137.8)	0.74
Diabetes treatment (%)			
Diet	31.3	33.7	0.33
Oral glucose-lowering medications (OAD)	55.9	56.6	
Insulin $\pm$ OAD	12.8	9.7	
Metformin (%)	33.8	31.2	0.44
Sulphonylureas (%)	42.8	42.2	0.89
Body mass index (kg/m ² ; %)	29.7 $\pm$ 5.7	29.4 $\pm$ 4.9	0.40
< 25.0	17.4	17.5	0.69
25.0–29.9	40.5	37.9	
≥ 30.0	42.1	44.7	
Waist circumference (cm)			
Men	103.0 $\pm$ 11.8	103.2 $\pm$ 11.2	0.81
Women	96.8 $\pm$ 13.4	97.3 $\pm$ 12.0	0.73
Waist:hip ratio			
Men	0.96 $\pm$ 0.06	0.95 $\pm$ 0.05	0.78
Women	0.87 $\pm$ 0.07	0.86 $\pm$ 0.06	0.79
Obese by waist circumference (%)			
Men	52.2	53.8	0.72
Women	74.5	77.6	0.56
Systolic blood pressure (mmHg)	150 $\pm$ 24	151 $\pm$ 23	0.43
Diastolic blood pressure (mmHg)	81 $\pm$ 11	80 $\pm$ 11	0.81
Taking antihypertensive medication (%)	49.0	53.7	0.17
ACE inhibitors	22.2	19.1	0.26
β -Blockers	14.8	19.1	0.09
Calcium channel blockers	18.2	20.4	0.40
Total serum cholesterol (mmol/l)	5.5 $\pm$ 1.1	5.3 $\pm$ 1.0	0.002
HDL-cholesterol (mmol/l)	1.06 $\pm$ 0.32	1.06 $\pm$ 0.33	0.79
LDL-cholesterol (mmol/l)	3.5 $\pm$ 0.9	3.3 $\pm$ 0.9	0.001
Serum triglycerides (mmol/l)	1.9 (1.1–3.3)	1.8 (1.1–3.1)	0.26
Taking lipid-lowering medication (%)	10.0	12.1	0.33
Urinary albumin:creatinine ratio (ACR; mg/mmol)	3.1 (0.7–13.8)	2.7 (0.7–10.0)	0.10
Peripheral neuropathy (%)	31.1	30.5	0.88
Any retinopathy (%)	17.9	12.3	0.024
Coronary heart disease (%)	27.5	27.5	1.00
Cerebrovascular disease (%)	10.0	8.7	0.58
Peripheral arterial disease (%)	28.2	28.5	0.94

Table 3 Competing risk proportional hazards models exploring associations with all (excluding NMSC), colorectal and prostate incident cancer with age as the timescale. Data are sub-hazard ratios and 95% confidence intervals.

	Any cancer		Colorectal cancer 63/1282	Prostate cancer 45/615
	Age at diabetes diagnosis <60 years 159/677	Age at diabetes diagnosis ≥60 years 147/503		
Male		1.94 (1.40–2.70)		
Age at diabetes diagnosis (per year) ^a		1.04 (1.003–1.08)	1.05 (1.02–1.09)	
Ex-smoker	1.65 (1.15–2.37)			
Current smoker	2.20 (1.44–3.36)			
Any exercise in past 2 weeks			2.11 (1.06–4.20)	
Metformin use				2.16 (1.19–3.90)
Calcium channel blocker use			2.37 (1.39–4.06)	
Fasting serum glucose (mmol/l)				0.88 (0.77–0.99)
Total serum cholesterol (per 1 mmol/l)			0.68 (0.52–0.88)	
Log _e (urinary albumin:creatinine; mg/mmol) ^b	0.86 (0.77–0.96)			0.75 (0.60–0.94)

^aAge at diagnosis of diabetes unavailable for two participants (one age <60 years, one aged ≥60 years).

^bA 2.72-fold increase in urinary albumin:creatinine ratio (ACR) corresponds to an increase of 1 in log_e(ACR).

In the case of the main solid organ cancers, our significantly increased IRR of 1.36 for colorectal cancer in type 2 diabetic patients is consistent with those from meta-analyses of case-control and cohort studies (between 1.15 and 1.42) (3, 20, 30). Meta-analyses have also shown that this association is stronger among males than females (3) and our data indicate that older men (aged ≥75 years) are at particular risk. In competing risk modelling, an older age at diagnosis, recent exercise and use of calcium channel blocking drugs were positively associated with colorectal cancer in the FDS cohort, while there was an inverse association with total serum cholesterol.

An effect of age at diagnosis on colorectal cancer incidence, which was probably the main contributor to the same association for all-cause cancer, has been reported previously. Consistent with the present data, one study showed that there was no association between diabetes and colorectal cancer if the diagnosis of diabetes was made before 60 years of age whereas a significant positive association was seen when diabetes was diagnosed later in life (31). This finding was attributed to dietary modification as part of the management of younger patients which might, in turn, attenuate subsequent colorectal cancer risk. Alternatively, there may be ascertainment bias in that older patients diagnosed with diabetes may be screened more intensively for age-related co-morbidities such as cancer. Although we employed a competing risk analysis, it is also possible that surviving relatively insulin-sensitive patients diagnosed at a younger age and at reduced risk of cardiovascular disease were over-represented in our cohort. Such a survivor bias may also explain the apparently paradoxical positive relationship between recent exercise and colorectal cancer in our cohort. Although exercise should be protective against colon cancer (32), there is no clear relationship in the case of rectal cancer (33). There is also some evidence that physical activity over a lifetime is more important

than recent exercise, such as assessed in the FDS, in gastrointestinal cancer prevention (34).

We found a positive association between use of calcium channel blockers and colorectal cancer that may also have reflected confounding. Those patients who were more aggressively treated for cardiovascular risk factors such as hypertension may have been less likely to die of cardiovascular disease and thus more likely to develop subsequent cancer. Alternatively, those requiring such medication were at inherently higher risk of colon cancer due to lifestyle factors common to cardiovascular risk and colorectal cancer. However, laboratory and clinical evidence that this group of drugs directly predisposes to cancer emerged in the 1990s (35). Most subsequent clinical studies have failed to confirm this link, including for colorectal cancer (36, 37), but the original positive reports were in older patients (38, 39, 40) and most of our colorectal cancer cases were in those aged ≥75 years. It is also possible that diabetes may act in concert with calcium channel blockers to increase cancer risk. It is reassuring, given recent controversies (41), that we did not find an association between renin-angiotensin blocking drugs and cancer in our cohort. The inverse association between total serum cholesterol and colorectal cancer risk observed in our cohort is not novel outside the context of diabetes (42, 43, 44) and may reflect preclinical effects of malignancies on cholesterol absorption, transport, metabolism and/or utilisation (44, 45).

We did not find that prostate cancer incidence was influenced by diabetes. An apparently protective effect of diabetes (20, 29) has not been a consistent finding and may depend on factors such as duration of glycaemic exposure (7). Fasting serum glucose and albuminuria were inversely associated with prostate cancer in our cohort, while metformin therapy proved a positive associate. The inverse association with glycaemia has been documented in a range of other studies (46),

including one that used a competing risk approach (47). As with cholesterol and colorectal cancer (44, 45), malignancies such as prostate cancer may have preclinical effects on glucose metabolism (46). In a study of non-diabetic individuals, baseline albuminuria was significantly correlated with the subsequent incidence of cancer (48), but the low plasma glucose concentrations in those men in our cohort who went on to be diagnosed with prostate cancer relative to those who did not may have confounded this association in this study. Alternatively, those with a low urinary albumin:creatinine ratio were those who were at low cardiovascular risk (49) and thus a survivor subset at risk of the later development of malignancy.

The positive association between prostate cancer and metformin therapy in our cohort runs contrary to accumulating data from both animal and human studies, suggesting that metformin has anti-cancer effects (12), a recent large Danish population-based study showing a reduced relative risk (RR) for metformin users for any cancer (50), and the suggestion of a protective effect against prostate cancer in an epidemiological survey (51). However, a nested case-control study from a UK general practice database showed that metformin did not decrease the risk of prostate cancer (52). In secondary analyses, prostate cancer risk was found to increase as a function of the number of metformin prescriptions dispensed (52). The authors suggested that one possible explanation may relate to metformin-specific effects on the hormonal profile of men with diabetes, with better glycaemic control associated with higher serum testosterone concentrations and thus a greater risk of prostate cancer. In a study of men who underwent radical prostatectomy for prostate cancer, diabetes was associated with an increased risk of recurrence regardless of whether they were treated with metformin (53). Consistent with the results of the large Danish study (50), we did not find that blood glucose-lowering therapies other than metformin were independently associated with cancer.

There was no association between type 2 diabetes and breast cancer in our cohort. This may have reflected the relatively small number of events, which also precluded an assessment of predictive variables. Data from a recent meta-analysis support a 20% increase in the risk of breast cancer in diabetic women (4). Hyperglycaemia and insulin resistance are strong associates (54) and metformin therapy may be protective (12). Interestingly and consistent with the present findings, a recent Canadian administrative database study found no association between type 2 diabetes and breast cancer after allowing for initial detection bias (20). The IRR for pancreatic cancer in our diabetic patients (2.26) is consistent with relative risks of between 1.82 and 2.17 in a variety of studies including pooled meta-analyses (55). This includes patients developing pancreatic cancer after many years of diabetes, especially in men (22), which addresses the issue of reverse causality.

Our matched controls were selected to have no documented evidence of diabetes during follow-up, mainly because we were concerned that there were patients with undiagnosed diabetes at the start of follow-up. This may, in turn, have influenced subsequent cancer risk and attenuated diabetes effects if these patients had been included. It is of interest that IRRs for the FDS cohort relative to national notifications were, by contrast, higher in all cases especially for pancreatic cancer. This provides some support for our approach of matching on postcode, a surrogate marker of socio-economic status and environmental exposures, as well as age and gender, as has been done by others (20).

Our study had limitations. First, the number of subjects and thus cancer events was low compared with those of most administrative database and intervention studies. This has been an issue for many similar detailed epidemiological studies (3, 4, 6, 7, 12, 25, 30, 31, 56), a number of which had smaller sample sizes than this study. Secondly, we may have recruited relatively healthy diabetic patients into the FDS, but the FDS cohort appears representative of diabetes in the local community (15) and this potential source of bias would be offset through diabetic patients being more likely to seek medical treatment including assessments that might detect malignancy. Thirdly, we had limited power to examine site-specific cancers and their relationship with diabetes and could not reliably determine age-specific IRRs or possible changes in IRR by calendar year. Lastly, despite evidence that diabetes worsens prognosis after diagnosis of malignancy (57), we did not have sufficient cancer-related deaths to meaningfully examine a relationship with diabetes. The strengths of the FDS include its well characterised community-dwelling patients who have a low rate of migration out of Western Australia (58), the availability of a comprehensive validated linkage system for ascertainment of cancer events (19), and use of statistical modelling that allowed examination of the risk of cancer while accounting for the occurrence of competing events.

The clinical implications of this study are various. The increased incidence of all-cause cancer is justification for adopting recommended cancer screening strategies as part of diabetes management if they are not being implemented as part of other aspects of clinical care. In some cases, such as for colorectal cancer in men aged ≥ 75 years, there is a strong argument for intensified screening practices. Although colonoscopic screening has been recommended for all type 2 patients about to start insulin therapy (56), our data do not provide support for this suggestion, especially in those patients diagnosed at a younger age. The positive association between metformin therapy and prostate cancer incidence found in this and other studies (52) needs to be further evaluated. The benefits of metformin for cardiovascular disease prevention (59) are likely to more than compensate for

any potential increase in prostatic cancer risk in older diabetic males, but there may be some specific clinical situations in which metformin should be avoided. As changes in cardiovascular disease management improve outcome in diabetic patients (60), diagnosis and treatment of cancer will become a more important part of diabetes care.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-12-0053>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

D J Magliano initiated the analyses and produced the first draft of the paper. W A Davis, senior biostatistician associated with the FDS, took responsibility for data linkage and the analysis and initial interpretation of the data. J E Shaw contributed to data interpretation and provided critical review of the paper. D G Bruce, co-investigator of the FDS, contributed to data interpretation and provided critical review of the paper. T M E Davis, the principal investigator of the FDS, assisted with analysis and interpretation and produced the final version of the paper.

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