Diabetes, Glycated Hemoglobin, and Risk of Cancer in the UK Biobank Study

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ABSTRACT

Background: Evidence suggest that diabetes and glycated hemoglobin (HbA1c) levels are associated with cancer risk. However, previous studies have been limited variably by failure to adjust for cancer-specific risk factors (e.g., body mass index), inattention to diabetes duration and use of antidiabetic medications, and failure to stratify by obesity.

Methods: We examined the association between diabetes, HbA1c, and cancer risk in the UK Biobank, using data from 476,517 participants (54% women), followed for an average period of 7.1 years. Diabetes was defined on the basis of baseline self-reported diagnosis of diabetes and/or use of diabetes medication, while HbA1c measured at baseline was categorized as low (<31 mmol/mol), normal (31–<39 mmol/mol), increased risk (39–<48 mmol/mol), and high risk for diabetes (≥48 mmol/mol). Multivariable Cox proportional hazards models were used to estimate the association of diabetes and cancer at different anatomical sites, with adjustment for cancer-specific risk factors.

Results: Diabetes was associated with increased risk of cancers of the stomach, liver, bladder, endometrium, and lung among smokers, and with decreased risk of prostate cancer. Compared with the normal HbA1c category, the increased risk category was positively associated with risk of cancers of the colon, liver, bladder, and lung among smokers, and the high-risk category was associated with increased risk of cancers of the esophagus, liver, pancreas, and bladder, and with decreased risk of prostate cancer.

Conclusions: These results suggest that both diabetes and/or elevated HbA1c are associated with risk of cancer at several anatomic sites.

Impact: The associations of diabetes and HbA1c levels with cancer suggest their importance in cancer prevention.

Introduction

Large-scale epidemiologic studies have shown that diabetes is associated with increased risk of cancer at several anatomic sites (1). However, only a few of the studies to date have provided results based on robust evidence (1). Indeed, an umbrella review of meta-analyses of observational studies of the association between diabetes and cancer at different anatomic sites concluded that significant, unbiased evidence of association was available only for cancers of the breast, endometrium, and colon (1).

Although the pathophysiologic mechanisms underlying the association of diabetes with cancer are still under investigation, experimental data suggest that hyperglycemia, hyperinsulinemia, insulin resistance, and chronic inflammation play pivotal roles (2). Several studies have suggested a positive association between insulin levels and risk of various cancers (3). Evidence for a role for elevated glucose levels comes from studies of fasting glucose levels (4) or of glycated hemoglobin (HbA1c) in relation to cancer risk (5). Glycated hemoglobin reflects the average glucose concentration over a period of 2–3 months (6), can be measured in a nonfasting state, has high repeatability, and is not affected by daily glucose fluctuation. Therefore, it is considered to be a more stable marker of glucose level than fasting glucose and a better predictor of vascular and cardiometabolic disease risk even among nondiabetic individuals (7). Data on the association of HbA1c with cancer are limited to the most frequently occurring malignancies and suggest positive associations between HbA1c and risk of colorectal, pancreatic, respiratory, and female genital tract cancers (5, 8–10).

Inconsistencies in the literature may have resulted from the limitations of some of the previous studies, including failure to adjust for obesity (11) and other cancer-specific risk factors, and failure to investigate possible effect modification by obesity, as well as inattention to diabetes duration and antiglycemic medication use. To address these limitations, we examined the association between diabetes and glycated hemoglobin levels with risk of cancer in the UK Biobank cohort, a large population-based prospective study.

Methods

Study population

A detailed description of the UK Biobank study design was published previously (12). Briefly, UK Biobank is a large, prospective, population-based cohort study of 502,536 individuals (54.4% women) who, at the time of recruitment, between 2006 and 2010, were aged 40–69 years and living in England, Wales, or Scotland within approximately 25 miles of one of the 22 study assessment centers. Information on demographic and other health-related characteristics was collected from study participants at baseline via self-administrated questionnaires (available online: http://www.ukbiobank.ac.uk/wp-content/uploads/2011/06/Touch_screen_questionnaire.pdf?phpMyAdmin=trmKQlYdjjnQIgJ%2CfAzikMhEnx6). Anthropometric measurements were obtained at the baseline visit using standardized protocols, while blood samples were collected at this time at the assessment centers, and then minimally processed and shipped for additional processing and storage within 24 hours of collection at UK Biobank's centralized automated laboratory (13). UK Biobank received

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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ethical approval from the North West Multi-center Research Ethics Committee. All participants gave written informed consent to the study at the time of enrollment.

Diabetes and related exposures

Participants who reported a diagnosis of diabetes by a doctor and/or use of antidiabetic medications at baseline visit were considered to be diabetics. Glycated hemoglobin was measured in frozen packed red blood cells by Bio-Rad Variant II Turbo analyzer using high-performance liquid chromatography (Bio-Rad Lab. Inc). Glycated hemoglobin levels were categorized according to established criteria: <31 mmol/mol as low, 31–<39 mmol/mol as normal, 39–<48 mmol/mol as increased risk for diabetes, and ≥48 mmol/mol as high risk for diabetes (14).

Other exposure information

Demographic information included age at enrollment, race (white vs. non-white), education (</≥ high school), and socioeconomic status (Townsend Deprivation Score; ref. 15) categorized by quintiles. Additional lifestyle and health-related factors were self-reported smoking status (never, past, and current), pack-years smoked (number of years smoked multiplied by the average number of cigarettes/day) for ever (past and current) smokers; alcohol consumption (never, special occasion, 1–3 drinks/month, 1–2 drinks/week, 3–4 drinks/week, daily); physical activity (MET-hours/week), calculated by multiplying the number of hours/week of each reported leisure-time physical activity by the metabolic equivalent (MET) of that activity, summing across all activities, and categorizing the total by quintiles; self-report of ever having had colon cancer screening, prostate cancer screening, and breast cancer screening; family history of breast cancer among first-degree relatives; history of benign breast disease; age at menarche (<12, 12–13, ≥14 years); and number of live births (0, 1, 2–3, ≥4). History of hysterectomy, history of bilateral oophorectomy, ever use of oral contraceptives and of hormone replacement therapy, history of hypertension, and history of viral hepatitis were each dichotomized (no or yes) according to baseline responses.

Women were considered to be postmenopausal if they reported having had natural menopause or a bilateral oophorectomy, while those who did not provide information on their menopausal status were considered to be postmenopausal if they were at least 53 years of age. Body mass index (BMI) was calculated using weight and height (kg/m^2); vitamin D serum level was measured by CLIA analysis on a DiaSorin Ltd. LIASON XL and categorized by quartiles.

Table 1. Baseline characteristics of the study cohort by diabetes status and glycated hemoglobin level.

Characteristics	Diabetes		Glycated hemoglobin (mmol/mol)				
	No	Yes	<31	31–<39	39–<48	≥48	Missing
N	450,973	25,544	54,085	308,976	64,167	16,501	32,788
Self-reported diabetes, %	—	—	0.5	0.8	10.7	79.8	5.7
Age (y)	56.2 (8.1)	59.4 (7.3)	56.3 (8.0)	52.2 (8.1)	59.6 (7.0)	59.2 (7.3)	56.2 (8.1)
Women, %	54.8	38.8	54.4	54.9	52.2	37.6	56.3
Race white, %	94.4	86.6	96.0	95.6	89.5	85.5	88.8
Education, ≥college %	32.7	23.6	38.7	33.3	25.4	23.3	29.5
Deprivation index (Townsend)	−1.3 (3.1)	−0.4 (3.4)	−1.4 (3.0)	−1.4 (3.0)	−0.9 (3.2)	−0.4 (3.4)	−1.0 (3.3)
Smoking previous, %	33.8	42.3	32.7	33.9	36.1	40.8	32.7
Current, %	10.6	11.1	10.2	6.9	15.3	12.1	10.9
Pack-years (n)	9.6	15.3	7.6 (14.6)	5.2 (11.5)	12.6 (19.8)	14.9 (23.3)	7.6 (15.4)
Alcohol never, %	7.5	16.2	5.5	7.0	11.6	16.9	9.2
Special occasion	11.1	18.6	8.5	10.6	15.4	18.8	13.1
1–3 drinks/month	11.1	12.2	9.9	11.1	12.1	12.8	11.3
1–2 drinks/week	25.9	23.1	26.9	26.1	24.6	23.2	25.1
≤3–4 drinks/week	23.6	15.5	24.1	26.5	18.7	14.5	21.7
Daily, %	20.6	14.4	22.4	21.4	17.2	13.4	19.3
Diabetes, %	—	—	0.5	0.8	10.1	79.8	5.7
Diabetes medication, %	—	57.3	0.1	0.3	5.9	53.3	3.4
Diabetes duration (y)	—	8.9 (10.5)	7.8 (11.5)	6.3 (9.3)	6.4 (8.7)	10.5 (11.2)	8.7 (10.6)
Hypertension, %	24.7	62.0	17.9	23.8	39.0	57.5	27.3
Vitamin D (nmol/L)	48.9 21.0)	43.3 (20.6)	49.4 (21.0)	49.2 (21.5)	46.2 (20.6)	41.2 (19.8)	48.6 (21.2)
BMI (kg/m^2)	27.2 (4.6)	31.3 (5.9)	26.3 (4.1)	27.0 (4.5)	29.2 (5.4)	31.7 (5.9)	27.7 (5.1)
PA MET/week lowest quintile, %	15.6	22.2	16.6	15.3	17.2	23.8	14.6
Benign breast disease, %	1.7	1.4	1.6	1.7	1.5	1.3	1.7
Mammography screening, %	78.6	85.0	60.0	79.6	90.6	85.7	78.0
PSA screening, %	27.7	29.3	24.0	28.0	30.7	26.3	26.9
Colorectal cancer screening, %	29.9	36.3	23.1	30.1	36.4	33.6	29.8
History of hepatitis, %	0.4	0.3	0.3	0.4	0.3	0.3	0.4
Family history of breast cancer, %	11.0	10.2	10.3	10.7	10.2	9.6	10.3
Age at menarche (y)	13.0 (1.6)	12.8 (1.7)	13.0 (1.6)	13.0 (1.6)	12.9 (1.6)	12.8 (1.7)	13.0 (1.6)
Menopause, %	69.0	79.4	41.2	70.5	86.9	81.8	68.8
Nulliparous %	18.8	16.1	23.0	18.5	15.8	17.5	19.3
Hormone therapy, ever %	37.6	42.4	24.6	38.4	46.1	41.1	36.8
Oral contraceptive, ever %	81.5	72.3	86.9	81.9	74.7	70.8	79.5

Note: Results reported are means (standard deviation), unless otherwise specified.
Abbreviations: BMI, body mass index; MET, metabolic equivalent; PA, physical activity.

Outcome ascertainment

Ascertainment of cancer cases at baseline and throughout follow-up was conducted through the Health and Social Care Information Centre for participants residing in England and Wales and through the NHS for those residing in Scotland. Cancers were classified using the International Classification of Diseases, tenth revision (ICD-10), and grouped on the basis of their anatomic sites. In this analysis we studied the occurrence of cancers of the breast (ICD-10 C50), endometrium (C54), ovary (C56), prostate (C61), esophagus (C15), stomach (C16), colon (C17, C18), rectum (C20), pancreas (C25), kidney (C64), liver (C22), bladder (C67), lung (C34), thyroid (C73), and brain (C71), as well as melanoma (C43), multiple myeloma (C90), and diffuse large B-cell non-Hodgkin lymphoma (C83.3).

Analytic cohort

All cases of prevalent cancer ($n = 23{,}047$), except nonmelanoma skin cancers (C44), and all participants with missing information on diabetes and BMI ($n = 2{,}972$) were excluded from the analysis. After these exclusions, the study analytic cohort for the main analyses included 476,517 participants (54% women).

Statistical analyses

Baseline characteristics were summarized according to diabetes status and HbA1c categories using means and SDs for continuous variables, and percentages for categorical variables.

Individuals contributed person-time at risk from the date of recruitment until the date of cancer diagnosis, death, withdrawal from the study, or end of follow-up (March 31, 2016 for participants from England and Wales, and October 31, 2015 for those from Scotland), whichever came first. Unadjusted cancer-specific incidence rates per 1,000 person-years were estimated by diabetes status and HbA1c categories.

Cox proportional hazards regression models were used to estimate HRs and 95% confidence intervals (CI) for cancer risk associated with diabetes (no diabetes served as the reference group) and HbA1c levels (the 31–<39 mmol/mol category was used as the reference group; ref. 16). Follow-up time was used as the time scale. To test the associations of diabetes and HbA1c with cancer, two analytical models were created. The first one included adjustment for age, sex, race, education, smoking status, pack-years of smoking, alcohol intake, and physical activity; in addition, established risk factors for the cancers of interest were included in cancer-specific multivariable models as described in detail in the footnotes to **Table 2**. The second model included all the variables in the first model plus BMI, to determine whether it affected the associations of diabetes and glycated hemoglobin with cancer. Missing values for potential confounders were categorized as a separate category and retained in the models.

Sensitivity analyses were performed excluding both cancer cases occurring within two years of enrollment in the study and participants with less than two years of follow-up ($n = 3{,}505$). For analyses of endometrial cancer, women with a history of hysterectomy at baseline ($n = 17{,}331$) were excluded; similarly, for analyses of ovarian cancer, those with a history of bilateral oophorectomy ($n = 18{,}688$) were excluded.

Potential effect modification by sex was tested by fitting an interaction term (diabetes × sex) in the complete model (model 2). Sex-specific stratified analyses were conducted for those cancer sites for which the cross-product P value was < 0.2. Analyses stratified by BMI were carried out for cancer sites with at least 20 cases in each BMI category (excluding those with BMI <25 kg/m^2, since few cases occurred in this category).

We assessed the association between antidiabetic medications and cancer risk by comparing diabetic users and nonusers to the nondiabetic referent group. Duration of diabetes was analyzed in two ways: by categorizing it according to the median value reported (6 years), and by treating it as a continuous variable (1-year increment).

All analyses were performed using STATA 15 statistical software (STATA Corporation). P values < 0.05 (two-tailed) were considered to be statistically significant.

Data source

This research has been conducted using the UK Biobank Resource under application number 40086.

Results

A total of 25,544 (5.4%) study participants reported having received a diagnosis of diabetes from a doctor and/or were taking antidiabetic medications. Slightly more than half of those with diabetes reported use of antidiabetic medication (Supplementary Table S1), and more than 90% of those who reported a diagnosis of diabetes had glycated hemoglobin levels in the upper two categories (Supplementary Table S2).

Descriptive characteristics by diabetes status and HbA1c level are presented in **Table 1**. Compared with nondiabetics or individuals with a normal HbA1c level, those with diabetes or high HbA1c were more likely to be older, non-white, male, with lower education and higher deprivation index, to be current or past smokers, to have lower alcohol consumption, to be hypertensive, have higher BMI, and to be less engaged in recreational physical activity. They were also more likely to have had screening for breast and colorectal cancer. Diabetic women reported earlier menarche, less use of oral contraceptives and more use of hormone therapy, were more likely to have had children, and were more likely to be postmenopausal than nondiabetics.

The total follow-up time of the cohort was 3,389,457 person-years, with a median duration of follow-up of 7.1 years (interquartile range 6.4–7.8 years). In multivariable adjusted models (**Table 2**, model 1), diabetes was significantly positively associated with risk of cancers of the esophagus, stomach, colon, liver, kidney, bladder, breast among postmenopausal women, and endometrium, and significantly inversely associated with risk of prostate cancer (**Fig. 1**; **Table 2**). Risk of cancers of the pancreas, breast among premenopausal women, ovary, thyroid, lung, brain, melanoma, and of large diffuse B-cell non-Hodgkin lymphoma and multiple myeloma, was not found to be associated with diabetes. Except for lung cancer among ever smokers, for cancer at all other sites, the inclusion of BMI in the multivariable models (model 2) reduced the strength of the associations with diabetes; however, the associations remained statistically significant for cancers of the stomach, liver, bladder, endometrium, and prostate, and became significant for lung cancer among ever smokers.

Compared with participants in the normal range of HbA1c (31–<39 mmol/mol), those in the increased risk for diabetes category (39–<48 mmol/mol) had increased risk of cancers of the colon, liver, bladder, and lung among smokers (**Fig. 2**; **Table 2**). Participants in the high-risk HbA1c category (≥48 mmol/mol) had increased risk of cancers of the esophagus, liver, pancreas, and bladder, and reduced risk of prostate cancer.

Analyses stratified by sex indicated that diabetes and moderately high HbA1c levels were associated with higher risk of cancers of the stomach, kidney, lung, and bladder among women compared to men; for liver cancer, the risk associated with these categories was greater in men than in women (Supplementary Table S3).

Table 2. Incidence rates and multivariable-adjusted HRs (95% CIs) for the association of diabetes and glycated hemoglobin with site-specific cancer risk.

Cancer	Total	Diabetes diagnosis		Glycated hemoglobin categories (mmol/mol)				P_{trend}[n]
		ND	D	<31	31–<39	39–<48	≥48	
Esophagus								
No. of cases	560	496	64	34	341	100	49	
Person-years	3,387,469	3,216,034	171,435	386,215	2,197,954	451,096	114,773	
Rate/1,000	0.17	0.15	0.37	0.09	0.16	0.22	0.43	
HR (95% CI)[a]		1.00 (ref.)	1.38 (1.06–1.81)	0.81 (0.57–1.15)	1.00 (ref.)	0.97 (0.77–1.21)	1.57 (1.15–2.14)	0.017
HR (95% CI)[b]		1.00 (ref.)	1.29 (0.98–1.69)	0.82 (0.58–1.17)	1.00 (ref.)	0.92 (0.73–1.16)	1.44 (1.05–1.97)	0.076
Diabetes × sex $P_{interaction}$ = 0.557								
Stomach								
No. of cases	380	333	47	25	227	72	30	
Person-years	3,387,828	3,210,070	177,758	386,241	2,198,190	451,147	114,807	
Rate/1,000	0.11	0.10	0.26	0.06	0.10	0.16	0.26	
HR (95% CI)[a]		1.00 (ref.)	1.51 (1.10–2.07)	0.88 (0.59–1.35)	1.00 (ref.)	1.04 (0.80–1.37)	1.44 (0.98–2.13)	0.097
HR (95% CI)[b]		1.00 (ref.)	1.39 (1.01–1.92)	0.90 (0.59–1.36)	1.00 (ref.)	1.00 (0.76–1.32)	1.31 (0.87–1.95)	0.307
Diabetes × sex $P_{interaction}$ = 0.080								
Colon								
No. of cases	2,485	2,283	202	289	2,121	629	159	
Person-years	3,376,762	3,199,914	176,848	385,450	2,192,394	449,445	114,430	
Rate/1,000	0.74	0.71	1.14	0.75	0.97	1.40	1.39	
HR (95% CI)[a,c]		1.00 (ref.)	1.18 (1.02–1.37)	1.02 (0.90–1.15)	1.00 (ref.)	1.18 (1.06–1.31)	1.08 (0.89–1.31)	0.130
HR (95% CI)[b,c]		1.00 (ref.)	1.11 (0.96–1.29)	1.01 (0.88–1.18)	1.00 (ref.)	1.14 (1.02–1.27)	1.01 (0.83–1.23)	0.376
Diabetes × sex $P_{interaction}$ = 0.261								
Rectum								
No. of cases	958	879	79	87	598	156	43	
Person-years	3,387,589	3,209,850	177,739	386,162	2,198,134	451,137	114,783	
Rate/1,000	0.28	0.27	0.44	0.23	0.27	0.35	0.37	
HR (95% CI)[a,c]		1.00 (ref.)	1.25 (0.99–1.59)	1.04 (0.84–1.30)	1.00 (ref.)	1.06 (0.88–1.27)	1.05 (0.77–1.45)	0.193
HR (95% CI)[b,c]		1.00 (ref.)	1.24 (0.98–1.58)	1.04 (0.83–1.30)	1.00 (ref.)	1.05 (0.88–1.26)	1.04 (0.75–1.44)	0.218
Diabetes × sex $P_{interaction}$ = 0.782								
Liver								
No. of cases	324	254	70	29	156	73	44	
Person-years	3,388,097	3,210,310	177,786	386,246	2,198,350	451,187	114,826	
Rate/1,000	0.10	0.08	0.39	0.08	0.07	0.16	0.38	
HR (95% CI)[a,d]		1.00 (ref.)	2.94 (2.21–3.92)	1.41 (0.95–2.11)	1.00 (ref.)	1.62 (1.22–2.15)	3.26 (2.30–4.62)	<0.001
HR (95% CI)[b,d]		1.00 (ref.)	2.82 (2.10–3.78)	1.43 (0.96–2.14)	1.00 (ref.)	1.55 (1.17–2.07)	3.00 (2.09–4.30)	<0.001
Diabetes × sex $P_{interaction}$ = 0.006								
Pancreas								
No. of cases	245	224	21	12	140	52	20	
Person-years	3,388,226	3,210,406	177,820	386,268	2,198,409	451,227	114,836	
Rate/1,000	0.07	0.07	0.12	0.03	0.06	0.12	0.17	
HR (95% CI)[a]		1.00 (ref.)	1.19 (0.76–1.89)	0.71 (0.39–1.29)	1.00 (ref.)	1.32 (0.95–1.82)	2.00 (1.23–3.23)	<0.001
HR (95% CI)[b]		1.00 (ref.)	1.15 (0.72–1.83)	0.72 (0.40–1.29)	1.00 (ref.)	1.30 (0.95–1.82)	1.97 (1.20–3.22)	<0.001
Diabetes × sex $P_{interaction}$ = 0.791								
Kidney								
No. of cases	824	738	86	62	478	159	49	
Person-years	3,386,330	3,208,725	177,605	386,111	2,197,286	450,852	114,724	
Rate/1,000	0.24	0.23	0.49	0.17	0.22	0.36	0.44	
HR (95% CI)[a,e]		1.00 (ref.)	1.21 (0.96–1.53)	1.03 (0.78–1.37)	1.00 (ref.)	1.06 (0.86–1.29)	1.12 (0.81–1.55)	0.584
HR (95% CI)[e,b]		1.00 (ref.)	1.08 (0.86–1.37)	1.06 (0.80–1.41)	1.00 (ref.)	0.97 (0.79–1.20)	0.96 (0.69–1.33)	0.484
Diabetes × sex $P_{interaction}$ = 0.006								
Bladder								
No. of cases	695	609	86	49	383	153	54	
Person-years	3,386,452	3,208,858	177,594	386,138	2,197,420	450,836	114,707	
Rate/1,000	0.21	0.19	0.50	0.13	0.17	0.34	0.47	
HR (95% CI)[a,e]		1.00	1.44 (1.14–1.82)	1.07 (0.79–1.44)	1.00	1.30 (1.07–1.57)	1.56 (1.16–2.08)	0.002
HR (95% CI)[e,b]		1.00	1.40 (1.10–1.77)	1.08 (0.80–1.45)	1.00	1.27 (1.05–1.54)	1.49 (1.11–2.01)	0.008
Diabetes × sex $P_{interaction}$ = 0.003								
Breast – Premenopausal								
No. of cases	1,479	1,445	34	332	973	58	17	
Person-years	555,943	13,593	542,350	122,931	353,771	30,156	7,697	
Rate/1,000	2.66	2.67	2.30	2.70	2.75	1.92	2.21	

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Table 2. Incidence rates and multivariable-adjusted HRs (95% CIs) for the association of diabetes and glycated hemoglobin with site-specific cancer risk. (Cont'd)

Cancer	Total	Diabetes diagnosis		Glycated hemoglobin categories (mmol/mol)				P_{trend}[n]
		ND	D	<31	31–<39	39–<48	≥48	
HR (95% CI)[a,f]		1.00 (ref.)	0.92 (0.65–1.29)	0.96 (0.85–1.09)	1.00 (ref.)	0.74 (0.56–0.97)	0.85 (0.53–1.38)	0.049
HR (95% CI)[f,b]		1.00 (ref.)	0.94 (0.66–1.32)	0.96 (0.85–1.09)	1.00 (ref.)	0.73 (0.56–0.96)	0.85 (0.52–1.38)	0.053
Breast – Postmenopausal								
No. of cases	4,438	4,214	224	320	2,954	703	145	
Person-years	1,255,093	1,202,605	52,487	85,235	840,841	203,211	35,121	
Rate/1,000	3.53	3.51	4.18	3.75	3.51	3.46	4.13	
HR (95% CI)[a,f,g]		1.00 (ref.)	1.20 (1.05–1.37)	1.09 (0.97–1.22)	1.00 (ref.)	0.98 (0.90–1.07)	1.21 (1.02–1.43)	0.643
HR (95% CI)[f,g,b]		1.00 (ref.)	1.10 (0.96–1.27)	1.13 (1.01–1.20)	1.00 (ref.)	0.92 (0.85–1.00)	1.07 (0.90–1.27)	0.054
Endometrium								
No. of cases	902	818	84	63	535	180	49	
Person-years	1,497,965	1,449,563	48,402	184,485	993,483	179,877	31,746	
Rate/1,000	0.60	0.57	1.67	0.34	0.54	1.00	1.54	
HR (95% CI)[a,f,h]		1.00 (ref.)	2.35 (1.86–2.97)	0.88 (0.67–1.15)	1.00 (ref.)	1.48 (1.24–1.76)	2.24 (1.66–3.02)	<0.001
HR (95% CI)[f,h,b]		1.00 (ref.)	1.45 (1.14–1.83)	0.97 (0.74–1.26)	1.00 (ref.)	1.14 (0.96–1.37)	1.27 (0.93–1.72)	0.063
Ovary								
No. of cases	587	560	27	53	390	77	21	
Person-years	1,673,410	1,613,987	59,422	198,581	1,106,564	209,713	37,249	
Rate/1,000	0.35	0.35	0.45	0.27	0.35	0.37	0.56	
HR (95% CI)[a,f,h,i]		1.00 (ref.)	1.13 (0.76–1.67)	0.99 (0.74–1.33)	1.00 (ref.)	0.85 (0.66–1.09)	1.28 (0.82–2.01)	0.633
HR (95% CI)[b,f,h,i]		1.00 (ref.)	1.11 (0.75–1.66)	0.99 (0.74–1.33)	1.00 (ref.)	0.85 (0.66–1.10)	1.30 (0.82–2.05)	0.614
Prostate								
No. of cases	6,213	5,819	394	578	3,952	1,003	251	
Person-years	1,533,254	1,426,284	1,06,971	173,634	975,665	211,337	70,411	
Rate/1,000	4.05	4.08	3.68	3.33	4.05	4.75	3.56	
HR (95% CI)[a,l]		1.00 (ref.)	0.71 (0.64–0.79)	1.05 (0.96–1.15)	1.00 (ref.)	0.95 (0.88–1.02)	0.74 (0.65–0.84)	<0.001
HR (95% CI)[b,l]		1.00 (ref.)	0.73 (0.66–0.81)	1.05 (0.96–1.14)	1.00 (ref.)	0.97 (0.90–1.04)	0.77 (0.68–0.88)	<0.001
Lung among ever smokers								
No. of cases	1,989	1,790	199	86	1,064	570	120	
Person-years	1,529,459	1,433,909	95,550	153,913	974,862	234,122	61,494	
Rate/1,000	1.30	1.25	2.08	0.56	1.09	2.43	1.95	
HR (95% CI)[a]		1.00 (ref.)	1.07 (0.92–1.24)	0.84 (0.67–1.05)	1.00 (ref.)	1.36 (1.23–1.65)	1.05 (0.87–1.28)	0.001
HR (95% CI)[b]		1.00 (ref.)	1.18 (1.00–1.34)	0.83 (0.66–1.03)	1.00 (ref.)	1.43 (1.29–1.59)	1.19 (0.98–1.45)	<0.001
Diabetes × sex $P_{interaction} < 0.001$								
Lung among never smokers								
No. of cases	305	292	13	39	197	38	9	
Person-years	1855954	1,776,890	79,064	232,186	1,221,932	216,421	53,208	
Rate/1,000	0.16	0.16	0.16	0.17	0.16	0.18	0.17	
HR (95% CI)[a]		1.00 (ref.)	0.79 (0.45–1.39)	1.56 (1.10–2.21)	1.00 (ref.)	0.82 (0.58–1.18)	0.88 (0.42–1.64)	0.640
HR (95% CI)[b]		1.00 (ref.)	0.84 (0.48–1.49)	1.55 (1.09–2.19)	1.00 (ref.)	0.82 (0.56–1.18)	0.89 (0.45–1.77)	0.791
Diabetes × sex $P_{interaction} = 0.238$								
Thyroid								
No. of cases	269	253	16	29	177	36	14	
Person-years	3,387,584	3,216,070	171,514	386,167	2,197,982	451,160	114,813	
Rate/1,000	0.08	0.08	0.09	0.08	0.08	0.08	0.12	
HR (95% CI)[a]		1.00 (ref.)	1.22 (0.73–2.05)	0.99 (0.67–1.48)	1.00 (ref.)	0.93 (0.65–1.35)	1.55 (0.89–2.70)	0.483
HR (95% CI)[b]		1.00 (ref.)	1.14 (0.68–1.93)	1.01 (0.68–1.50)	1.00 (ref.)	0.90 (0.62–1.30)	1.42 (0.81–2.52)	0.727
Diabetes × sex $P_{interaction} = 0.479$								
Melanoma								
No. of cases	1,741	1,658	83	194	1,147	227	57	
Person-years	3,382,884	3,211,577	171,307	2,152,350	379,816	441,740	112,787	
Rate/1,000	0.51	0.52	0.48	0.50	0.52	0.50	0.50	
HR (95% CI)[a]		1.00 (ref.)	0.93 (0.74–1.16)	1.08 (0.93–1.26)	1.00 (ref.)	0.95 (0.82–1.10)	0.97 (0.74–1.27)	0.289
HR (95% CI)[b,m]		1.00 (ref.)	0.91 (0.73–1.14)	1.09 (0.93–1.27)	1.00 (ref.)	0.94 (0.81–1.09)	0.95 (0.72–1.25)	0.201
Diabetes × sex $P_{interaction} = 0.124$								
Brain								
No. of cases	495	467	28	51	312	82	20	
Person-years	3,387,942	3,216,425	171,518	386,228	2,198,209	451,190	114,833	
Rate/1,000	0.15	0.15	0.16	0.13	0.14	0.18	0.17	
HR (95% CI)[a,g]		1.00 (ref.)	0.89 (0.61–1.32)	1.13 (0.84–1.53)	1.00 (ref.)	1.09 (0.85–1.40)	1.00 (0.63–1.57)	0.951
HR (95% CI)[b,g]		1.00 (ref.)	0.91 (0.62–1.35)	1.13 (0.83–1.52)	1.00 (ref.)	1.11 (0.87–1.43)	1.03 (0.64–1.63)	0.936
Diabetes × sex $P_{interaction} = 0.212$								

(Continued on the following page)

Table 2. Incidence rates and multivariable-adjusted HRs (95% CIs) for the association of diabetes and glycated hemoglobin with site-specific cancer risk. (Cont'd)

Cancer	Total	Diabetes diagnosis		Glycated hemoglobin categories (mmol/mol)				P_{trend}[n]
		ND	D	<31	31–<39	39–<48	≥48	
NHL – DLBCL								
No. of cases	481	445	36	46	294	95	18	
Person-years	3,387,236	3,215,753	171,484	386,165	2,197,770	451,042	114,830	
Rate/1,000	0.14	0.13	0.21	0.12	0.13	0.21	0.16	
HR (95% CI)[a]		1.00 (ref.)	1.09 (0.77–1.54)	1.23 (0.90–1.68)	1.00 (ref.)	1.20 (0.95–1.52)	0.85 (0.52–1.37)	0.747
HR (95% CI)[b]		1.00 (ref.)	1.03 (0.72–1.47)	1.24 (0.91–1.70)	1.00 (ref.)	1.16 (0.91–1.47)	0.79 (0.48–1.28)	0.408
Diabetes × sex $P_{interaction} = 0.415$								
Multiple myeloma								
No. of cases	452	426	26	40	280	84	22	
Person-years	3,387,363	3,215,869	171,493	386,174	2,197,885	451,058	114,806	
Rate/1,000	0.13	0.13	0.15	0.10	0.13	0.19	0.19	
HR (95% CI)[a]		1.00 (ref.)	0.85 (0.57–1.28)	1.07 (0.77–1.50)	1.00 (ref.)	1.16 (0.91–1.50)	1.16 (0.75–1.80)	0.345
HR (95% CI)[b]		1.00 (ref.)	0.80 (0.53–1.20)	1.08 (0.77–1.51)	1.00 (ref.)	1.13 (0.88–1.45)	1.09 (0.69–1.70)	0.524
Diabetes × sex $P_{interaction} = 0.449$								

Abbreviations: DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma.
[a]HRs and 95% CIs — adjusted for age, sex, education (≥ college), non-white race, smoking status (present, past, current), smoking-years (packs), alcohol intake (never, special occasion, 1–3 drinks/week, 3–4 drinks/week, daily), and physical activity (quintiles of MET-hour/week; model 1, as described in the text).
[b]HRs adjusted as in [a] plus BMI (kg/m^2; model 2, as described in the text).
[c]HRs adjusted for colon cancer screening and hormone replacement therapy.
[d]HRs adjusted for history of hepatitis and hormone replacement therapy.
[e]HRs adjusted for self-reported hypertension and hormone replacement therapy.
[f]HRs adjusted for age at menarche, family history of breast cancer, number of live births, history of benign breast disease, use of contraceptive pills, history of mammogram screening.
[g]HRs adjusted for hormone replacement therapy.
[h]HRs adjusted for hormone therapy and menopausal status. The analysis excluded women with a history of hysterectomy.
[i]The analysis excluded women with a history of bilateral oophorectomy.
[l]HRs adjusted for prostate screening.
[m]HRs adjusted for serum Vitamin D (quintiles).
[n]*P* values for the tests for trend across glycated hemoglobin categories.

Women who were diabetic but did not report use of antidiabetic medications had an increased risk of cancer of the lung among smokers (**Table 3**), while the risk for colon cancer was increased among diabetic women using medications. For cancers at other anatomical sites, the risks for diabetic users and nonusers of antidiabetic medications did not differ from that in the nondiabetic group. After exclusion of individuals using diabetes medications from the analysis of the association between HbA1c and cancer, there was an increased risk of liver, bladder, and lung cancer among those in the HbA1c increased risk of diabetes category (39–<48 mmol/mol), and of esophageal, liver, and breast cancer among postmenopausal women, and of lung cancer among smokers, among those in the high risk of diabetes one (≥48 mmol/mol; **Table 3**).

When the analyses were stratified by diabetes duration (with nondiabetics as the reference group), the risk of cancers of the stomach, colon, rectum, liver, and endometrium associated with diabetes was increased among those with a shorter duration of diabetes (<6 years), while the risk of liver and bladder cancer was significantly increased among those with longer duration of diabetes (≥6 years; **Table 4**). For each additional year of diabetes duration, we observed a significant increase in risk of cancers of the liver, bladder, and endometrium, and a reduced risk of prostate cancer (**Table 4**).

Among overweight participants (BMI 25–<30 kg/m^2), diabetes was associated with increased risk of liver cancer in men, of endometrial cancer, and of lung cancer among smokers (**Table 5**). For obese participants (BMI ≥ 30 kg/m^2), diabetes was associated with increased risk of cancers of the colon, liver (all of these cases occurred in men), breast cancer in postmenopausal women, and endometrial cancer.

Analyses excluding the first two years of follow-up showed similar associations of diabetes and HbA1c levels with cancer risk to those observed overall (Supplementary Table S4).

Discussion

We examined the associations of diabetes and HbA1c level with risk of cancer at different anatomic sites in a large population-based cohort study in which we controlled for multiple potential confounding factors. We found that for both men and women, diabetes was associated with an increased risk of stomach and bladder cancer, while for cancer at other anatomic sites, the associations were sex-specific. Among women, diabetes was associated with increased risk of cancers of the stomach, kidney, endometrium, and lung among smokers, and among men, diabetes was associated with increased risk of liver cancer and a reduced risk of prostate cancer. Analysis of the association between high HbA1c levels (≥48 mmol/mol) and risk of cancer showed somewhat similar results to those observed for the associations of diabetes with risk of cancer of the esophagus, liver, pancreas, bladder, and prostate. Moreover, HbA1c levels below the threshold for diabetes diagnosis but higher than normal (39–<48 mmol/mol) were associated with increased risk of cancers of the colon, liver, bladder, and of lung among ever smokers. Because overweight and obesity are often present in conjunction with diabetes, we examined the effect of adjustment for BMI on the association between diabetes, elevated HbA1c, and cancer and found, for most cancer sites, a reduction in the magnitude of the associations, which remained significant for cancers of the stomach, liver, and bladder, while the association with lung cancer among ever smokers increased

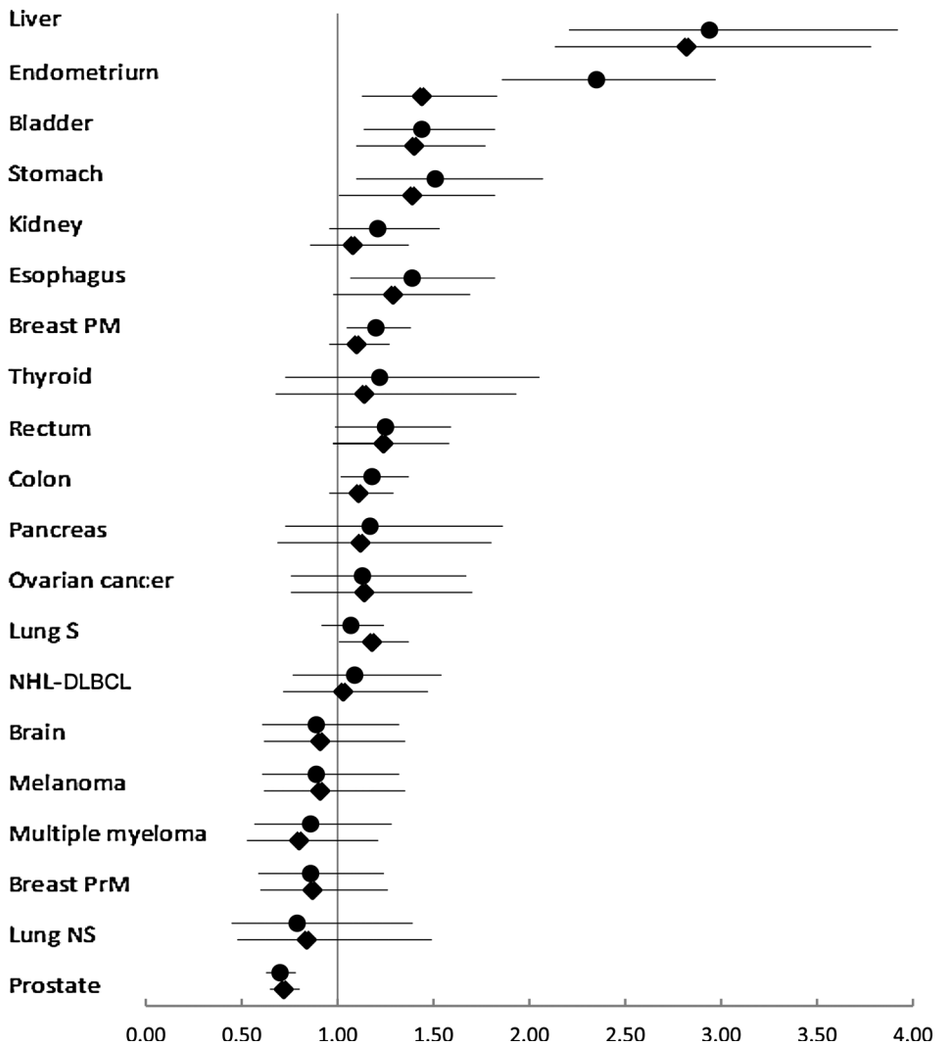

Figure 1.

HRs and 95% CIs for the association between diabetes status and cancer adjusted for: age, non-white race, education, alcohol intake, smoking status and cigarette-years, physical activity (●), and BMI (♦). HRs additionally adjusted for covariates reported in the footnotes of **Table 2**. DLBCL, diffuse large B-cell lymphoma; NS, nonsmokers; PM, postmenopausal; PrM, premenopausal; S, smokers.

in magnitude and statistical significance. Our results (summarized in Supplementary Table S5) showed that both diabetes and elevated HbA1c are associated with increased risk of cancers of the endometrium, liver, kidney, bladder, and lung among ever smokers, and with decreased risk of prostate cancer.

Although the overall risks of stomach, liver, kidney, bladder, and lung cancer are higher among men, women showed a higher and more statistically significant increase in risk in association with diabetes and high HbA1c for all these cancer sites except for the liver. Sex differences in the diabetes association with risk of cancer at several anatomic sites were reported recently in a meta-analysis of more than 120 cohorts, with results similar to those reported here for stomach, kidney, and liver cancer, suggesting a possible differential impact of high glucose level by sex (17), although the underlying mechanisms associated with any such differences are unclear.

Diabetes-associated hyperinsulinemia, insulin resistance, elevated insulin-like growth factor 1 (IGF-1), hyperglycemia, and inflammation are underlying metabolic conditions that may contribute to increased cancer risk through various mechanisms. Hyperinsulinemia and insulin resistance reduce apoptosis and promote cell proliferation leading to cancer progression. Insulin reduces the expression of IGF-1 binding protein, resulting in an increase in circulating free IGF-1 levels. Binding of IGF-1 with its receptors, highly expressed by cancer cells, triggers multiple pathways of cell survival and proliferation. Insulin also modulates estrogen production, a known tumorigenic factor in certain tissues (e.g., breast, endometrium; ref. 11). In addition, a sustained high level of glucose contributes to prolonged cancer cell proliferation and to apoptosis inhibition, which leads to uncontrolled cell growth, and stimulates expression of oxidative stress genes, thereby further stimulating cancer cell division (18). Diabetes is also associated with low-grade inflammation and elevated levels of inflammatory cytokines which increase insulin resistance and enhance tumorigenesis (19).

An increased risk of esophageal cancer was found amongst individuals with relatively high HbA1c levels (≥48 mmol/mol), and the results remained significant after adjustment for BMI and after the exclusion of diabetic medication users. Meta-analysis results have suggested a positive association of diabetes with esophageal cancer, although a high level of heterogeneity among studies and lack of adjustment for several confounding factors in many of the studies have been noted (20, 21). No data on HbA1c and esophageal cancer have been reported previously.

Among women, diabetes was associated with a statistically significant increase in risk of stomach cancer. In addition, there was a

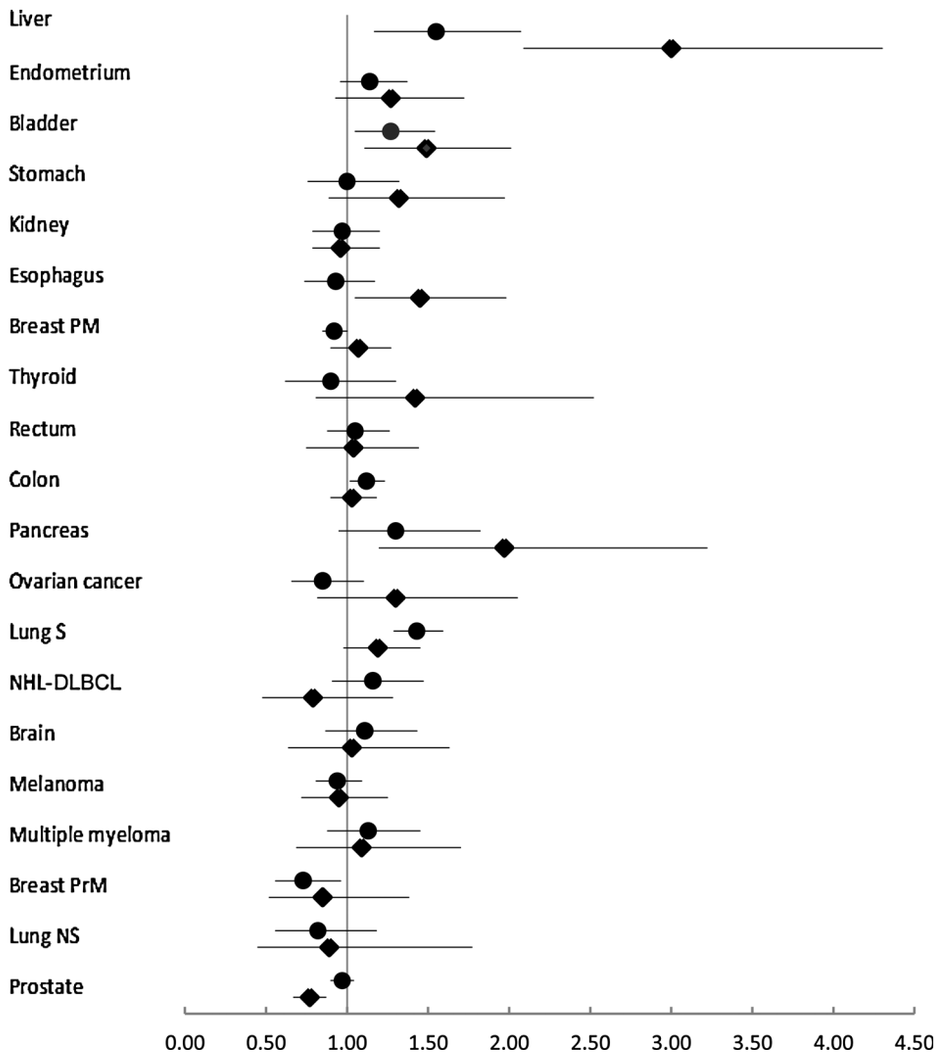

Figure 2.
HRs and 95% CIs for the association between glycated hemoglobin level 48–<53 mmol/mol (●) and ≥53 mmol/mol (♦), and cancer adjusted for: age, non-white race, education, alcohol intake, smoking status and cigarette-years, physical activity, and BMI. HRs additionally adjusted for covariates reported in the footnotes of **Table 2**. Normal HbA1c level (31–<48 mmol/mol) was used as reference category. DLBCL, diffuse large B-cell lymphoma; NS, nonsmokers; PM, postmenopausal; PrM, premenopausal; S, smokers.

positive association between HbA1c levels and risk, although this did not reach statistical significance. Previous studies on the association between diabetes and the risk of gastric cancer have been inconclusive in men, but have indicated an increased risk for diabetic women (22). Three previous studies have evaluated the association of HbA1c with the risk of gastric cancer and only one found a positive association when comparing those with medium-high versus low levels in a population-based sample (23). As for the other two studies, neither found an association between HbA1c levels and risk of stomach cancer. However, the first was conducted in a small sample with 25 cancer cases (10), while the other only included type II diabetic men and women (9).

In this study, elevated HbA1c (39–<48 mmol/mol) was associated with increased risk of colon cancer in both men and women, but not with rectal cancer. This is the first study that has evaluated the association of HbA1c with colon and rectal cancer separately. Consistent evidence has linked diabetes with an increased risk of colon cancer (24). However, the majority of previous prospective studies reported positive but statistically non-significant associations between increased HbA1c levels and colorectal cancer, with most of the results based on far fewer cancer cases than in this study (8, 25, 26). A case–control study of 1,026 colorectal cancer cases and a similar number of controls found increasing risk with increasing levels of HbA1c (27).

We did not observe an association between diabetes and pancreatic cancer. Although our results indicated a small increase in risk for those who reported a shorter duration of diabetes (<6 years), and reduction in risk among those with longer duration, neither of these estimates was statistically significant. In contrast to our findings, a meta-analysis that included 35 cohort studies and more than 50,000 pancreatic cancer cases indicated that diabetics had an increased risk for this cancer, especially within a short period from the diagnosis of diabetes (28). We found a significant positive association between HbA1c levels and risk of pancreatic cancer, particularly among those with high levels (≥48 mmol/mol), in agreement with other studies (29, 30). The pancreas is a key regulator of glucose homeostasis, and both hyperglycemia and hyperinsulinemia are considered to be contributors to tumorigenesis in this organ (31). However, it is possible that hyperglycemia is a marker of pancreatic cancer presence (28).

We observed strong positive associations of diabetes and HbA1c level with the occurrence of liver cancer, particularly among men, consistent with previous work suggesting that diabetes is an established risk factor for liver cancer (32). Of note, in the analysis stratified by BMI, the association of diabetes with liver cancer was stronger among

Table 3. Incidence rates and multivariable-adjusted HRs (95% CIs) for site-specific cancer risk in association with diabetic medication and by glycated hemoglobin levels.[a]

		Diabetics		Glycated hemoglobin categories (mmol/mol)[b]			
Cancer	**Nondiabetics**	**No diabetes medications**	**Diabetes medications**	**<31**	**31–<39**	**39–<48**	**≥48**
Esophagus							
No. of cases	496	30	34	34	339	91	26
Rate/1,000	0.15	0.40	0.33	0.09	0.15	0.21	0.48
HR (95% CI)	1.00 (ref.)	1.43 (0.98–2.07)	1.12 (0.78–1.60)	0.83 (0.58–1.18)	1.00 (ref.)	0.91 (0.71–1.15)	1.74 (1.15–2.62)
Stomach							
No. of cases	333	20	27	25	226	65	12
Rate/1,000	0.10	0.26	0.27	0.06	0.10	0.15	0.22
HR (95% CI)	1.00 (ref.)	1.46 (0.92–2.32)	1.33 (0.89–2.01)	0.92 (0.61–1.40)	1.00 (ref.)	0.97 (0.73–1.29)	1.27 (0.70–2.29)
Colon							
No. of cases	2,283	73	129	201	1,525	433	41
Rate/1,000	0.71	0.97	1.27	0.52	0.70	1.02	0.77
HR (95% CI)	1.00 (ref.)	0.96 (0.76–1.21)	1.22 (1.02–1.45)	1.01 (0.87–1.18)	1.00 (ref.)	1.11 (1.00–1.24)	0.79 (0.58–1.08)
Rectum							
No. of cases	879	33	46	87	597	141	17
Rate/1,000	0.27	0.43	0.45	0.23	0.27	0.33	0.32
HR (95% CI)	1.00 (ref.)	1.21 (0.85–1.72)	1.26 (0.93–1.72)	1.05 (0.84–1.32)	1.00 (ref.)	1.00 (0.83–1.21)	0.91 (0.56–1.48)
Liver							
No. of cases	254	46	24	29	152	62	14
Rate/1,000	0.08	0.45	0.32	0.08	0.07	0.15	0.26
HR (95% CI)	1.00 (ref.)	2.46 (1.60–3.78)	3.22 (2.30–4.52)	1.48 (0.99–2.22)	1.00 (ref.)	1.46 (1.07–1.98)	2.24 (1.27–3.93)
Pancreas							
No. of cases	224	8	13	12	140	46	13
Rate/1,000	0.07	0.11	0.13	0.03	0.06	0.11	0.24
HR (95% CI)	1.00 (ref.)	1.03 (0.50–2.10)	1.24 (0.70–2.22)	0.71 (0.39–1.29)	1.00 (ref.)	1.25 (0.89–1.76)	2.85 (1.59–5.11)
Kidney							
No. of cases	738	31	55	65	487	151	17
Rate/1,000	0.23	0.41	0.54	0.17	0.22	0.36	0.32
HR (95% CI)	1.00 (ref.)	0.97 (0.67–1.40)	1.16 (0.87–1.54)	1.03 (0.80–1.340	1.00 (ref.)	1.10 (0.91–1.33)	0.83 (0.51–1.35)
Bladder							
No. of cases	609	35	51	49	382	138	23
Rate/1,000	0.19	0.46	0.50	0.13	0.17	0.32	0.43
HR (95% CI)	1.00 (ref.)	1.39 (0.98–1.96)	1.44 (1.07–1.94)	1.07 (0.80–1.45)	1.00 (ref.)	1.23 (1.01–1.51)	1.43 (0.93–2.20)
Breast – Premenopausal							
No. of cases	1,445	16	18	332	969	56	6
Rate/1,000	2.7	2.0	2.7	2.7	2.7	2.0	1.4
HR (95% CI)	1.00 (ref.)	0.75 (0.43–1.29)	1.14 (0.69–1.89)	0.97 (0.85–1.10)	1.00 (ref.)	0.75 (0.56–1.02)	0.55 (0.21–1.47)
Breast – Postmenopausal							
No. of cases	4,214	108	116	320	2,944	674	81
Rate/1,000	3.5	4.5	3.9	3.8	3.5	3.5	4.7
HR (95% CI)	1.00 (ref.)	1.27 (1.04–1.56)	1.04 (0.85–1.28)	1.10 (0.98–1.24)	1.00 (ref.)	0.94 (0.85–1.03)	1.08 (0.81–1.43)
Endometrial							
No. of cases	818	39	45	63	530	169	21
Rate/1,000	0.58	1.62	1.72	0.34	0.53	0.98	1.30
HR (95% CI)	1.00 (ref.)	1.62 (0.85–1.28)	1.87 (1.34–2.60)	0.97 (0.75–1.27)	1.00 (ref.)	1.15 (0.96–1.38)	1.22 (0.79–1.91)
Ovary							
No. of cases	560	16	11	53	390	74	13
Rate/1,000	0.35	0.57	0.35	0.27	0.35	0.37	0.69
HR (95% CI)	1.00 (ref.)	1.53 (0.85–2.73)	0.63 (0.28–1.42)	0.99 (0.74–1.33)	1.00 (ref.)	0.85 (0.66–1.10)	1.62 (0.92–2.83)
Prostate							
No. of cases	5,819	170	224	578	3,939	946	115
Rate/1,000	1.82	2.25	3.49	1.51	1.81	2.24	2.15
HR (95% CI)	1.00 (ref.)	0.74 (0.63–0.86)	0.69 (0.58–0.82)	1.05 (0.96–1.15)	1.00 (ref.)	0.98 (0.91–1.05)	0.79 (0.65–0.95)
Lung among ever smokers							
No. of cases	1,790	96	103	86	1,060	532	66
Rate/1,000	1.25	2.39	1.86	0.56	1.09	2.42	2.34
HR (95% CI)	1.00 (ref.)	1.31 (1.06–1.61)	1.02 (0.83–1.26)	0.84 (0.67–1.05)	1.00 (ref.)	1.39 (1.24–1.55)	1.36 (1.06–1.76)
Lung among never smokers							
No. of cases	291	8	6	12	111	19	6
Rate/1,000	0.16	0.17	0.17	0.05	0.09	0.09	0.24
HR (95% CI)	1.00 (ref.)	0.86 (0.38–1.94)	0.89 (0.42–1.82)	1.53 (1.07–2.16)	1.00 (ref.)	0.86 (0.58–1.20)	0.59 (0.19–1.87)

(Continued on the following page)

Table 3. Incidence rates and multivariable-adjusted HRs (95% CIs) for site-specific cancer risk in association with diabetic medication and by glycated hemoglobin levels.[a] (Cont'd)

		Diabetics		Glycated hemoglobin categories (mmol/mol)[b]			
Cancer	Nondiabetics	No diabetes medications	Diabetes medications	<31	31–<39	39–<48	≥48
Thyroid							
No. of cases	251	5	13	29	176	32	6
Rate/1,000	0.08	0.07	0.13	0.08	0.08	0.08	0.11
HR (95% CI)	1.00 (ref.)	0.81 (0.33–1.98)	1.55 (0.87–2.77)	0.94 (0.44–1.99)	1.00 (ref.)	0.54 (0.23–1.28)	0.58 (0.08–4.37)
Melanoma							
No. of cases	1,656	32	53	194	1,141	213	24
Rate/1,000	0.52	0.42	0.52	0.50	0.52	0.51	0.45
HR (95% CI)	1.00 (ref.)	0.80 (0.56–1.14)	1.02 (0.77–1.35)	1.09 (0.93–1.27)	1.00 (ref.)	0.95 (0.81–1.10)	0.88 (0.58–1.32)
Brain							
No. of cases	466	17	12	311	51	78	13
Rate/1,000	0.15	0.22	0.12	0.13	0.14	0.18	0.24
HR (95% CI)	1.00 (ref.)	1.26 (0.77–2.05)	0.65 (0.37–1.17)	1.13 (0.83–1.52)	1.00 (ref.)	1.13 (0.88–1.46)	1.48 (0.84–2.59)
NHL-DLBCL							
No. of cases	445	12	24	46	290	88	6
Rate/1,000	0.14	0.16	0.24	0.12	0.13	0.21	0.11
HR (95% CI)	1.00 (ref.)	0.80 (0.45–1.44)	1.14 (0.74–1.74)	1.25 (0.91–1.71)	1.00 (ref.)	1.17 (0.92–1.50)	0.61 (0.27–1.37)
Multiple myeloma							
No. of cases	426	9	17	40	279	81	10
Rate/1,000	0.13	0.12	0.17	0.10	0.13	0.19	0.19
HR (95% CI)	1.00 (ref.)	0.65 (0.33–1.26)	0.86 (0.53–1.42)	1.08 (0.77–1.51)	1.00 (ref.)	1.16 (0.90–1.50)	1.09 (0.57–2.07)

Abbreviations: DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma.

[a]HRs and 95% CIs are adjusted for age, sex, education (≥ college), non-white race, smoking status (present, past, current), smoking-years (packs), alcohol intake (never, special occasion, 1–3 drinks/week, 3–4 drinks/week, daily), physical activity (quintiles of MET-hour/week), and BMI (kg/m^2; model 2, as described in the text). HRs for cancer risk at specific sites are additionally adjusted as reported in the footnotes of **Table 2**.

[b]The analysis by HbA1c categories included only individuals who did not use hypoglycemic medications.

overweight (25–<30 kg/m^2) individuals than among those who were obese (≥30 kg/m^2). Adjustment for other liver cancer risk factors, namely BMI, alcohol, and a history of hepatitis, did not significantly affect the strength of the associations. However, we did not have data on hepatitis B or C status. Data on the association between HbA1c and liver cancer are very scarce. Goto and colleagues reported a U-shaped association between HbA1c levels and liver cancer (26), whereas a retrospective case–control study indicated that HbA1c levels were significantly higher among patients with hepatocellular carcinoma than controls with other diseases (33). We observed a similar risk among all diabetics, whether or not they used diabetes medications, but a higher risk associated with longer duration of diabetes.

In our study, diabetes and elevated HbA1c levels were significantly associated with increased risk of kidney cancer in women, and with bladder cancer in both men and women, with a greater risk among women. Inclusion of BMI and hypertension in the models attenuated the associations, but they remained statistically significant. Previous studies have yielded similar results for the association of diabetes with risk of kidney cancer and bladder cancer, and for the sex-specific risk differences (17, 34, 35), but no previous study has reported on the association between HbA1c and the risk of kidney cancer separately from bladder cancer. Jonasson and colleagues found no association between HbA1c level and risk of kidney and other urinary cancers combined in a study restricted to diabetic subjects and with a small number of cases ($n = 86$; ref. 9). Similarly, Travier and colleagues reported no association between HbA1c and cancer of the urinary tract, but only 33 cases were included (10). Our results showed a strong association between increasing levels of glycated hemoglobin and risk of cancer at these two sites. High glucose levels are associated with renal blood vessel damage and altered urine filtration, which could affect the exposure of both the kidneys and the bladder to toxins and carcinogens. In addition, sustained high glucose levels are associated with urinary tract infection frequency and severity, particularly among women (36).

We observed significant positive associations of diabetes and HbA1c with risk of endometrial cancer and postmenopausal breast cancer; however, inclusion of BMI in the models substantially attenuated these associations, which remained statistically significant only for diabetes and endometrial cancer. In stratified analyses, we observed an increased risk of breast cancer among postmenopausal women with relatively high levels of HbA1c when the analysis was restricted to those not using diabetic medications and among those with BMI ≥30 kg/m^2. Results from several meta-analyses have suggested that diabetes is associated with a significant increase in risk of cancers of the endometrium and of the breast in postmenopausal women (37, 38); however, in contrast to our study, a number of previous studies did not adjust for relevant risk factors (1). No significant associations between HbA1c and breast cancer risk have been found in any previous cohort study despite large sample sizes (8–10, 39). One previous prospective study reported an increased risk of endometrial cancer in association with relatively high HbA1c (≥42 mmol/mol *vs.* <42 mmol/mol); however, the estimate of risk was only adjusted for age and ethnicity (10).

In this study, the associations of diabetes and HbA1c with risk of ovarian cancer failed to reach statistical significance. The magnitude of the association with diabetes was similar to that reported by a previous meta-analysis, which combined more than 7,500 ovarian cancer cases from case–control and cohort studies and concluded that diabetes was associated with an increased risk for ovarian cancer, despite some inconsistency among studies (40). No previous studies have reported on the association of HbA1C with ovarian cancer.

Table 4. HRs (95% CIs) for site-specific cancer risk associated with diabetes duration.[a]

	Diabetes duration			
	<6 years[b]	≥6 years[b]	1-Year increment	
Cancer	HR (95% CI)	HR (95% CI)	HR	*P*[c]
Esophagus	1.23 (0.81–1.88)	1.40 (0.96–2.05)	1.01	0.526
Stomach	1.58 (1.03–2.42)	1.23 (0.79–1.92)	1.01	0.165
Colon	1.22 (1.00–1.49)	1.14 (0.92–1.40)	1.00	0.628
Rectum	1.40 (1.04–1.90)	1.09 (0.77–1.55)	1.00	0.459
Liver	1.73 (1.07–2.78)	3.78 (2.72–5.27)	1.04	<0.001
Pancreas	1.32 (0.71–2.45)	0.93 (0.47–1.85)	0.99	0.713
Kidney	1.16 (0.84–1.59)	1.03 (0.74–1.41)	1.00	0.749
Bladder	0.96 (0.66–1.43)	1.89 (1.43–2.50)	1.02	<0.001
Breast premenopausal	0.67 (0.32–1.41)	0.91 (0.56–1.48)	1.00	0.804
Breast postmenopausal	1.18 (0.97–1.45)	1.11 (0.90–1.37)	1.01	0.061
Endometrium	1.94 (1.42–2.64)	1.30 (0.91–1.86)	1.02	0.050
Ovary	0.87 (0.41–1.85)	1.26 (0.69–1.31)	1.00	0.926
Prostate	0.64 (0.52–0.76)	0.72 (0.62–0.84)	0.98	<0.001
Lung among ever smokers	1.13 (0.90–1.40)	1.20 (0.99–1.47)	1.01	0.149
Lung among never smokers	0.43 (0.14–1.35)	1.15 (0.60–2.19)	0.99	0.541
Thyroid	1.19 (0.58–2.45)	1.06 (0.52–2.16)	1.02	0.093
Melanoma	0.79 (0.56–1.12)	1.06 (0.79–1.41)	1.00	0.737
Brain	0.90 (0.51–1.57)	0.92 (0.55–1.55)	1.01	0.526
NHL-DLBCL	0.55 (0.28–1.08)	1.44 (0.96–2.15)	1.02	0.053
Multiple myeloma	0.87 (0.50–1.52)	0.74 (0.42–1.29)	0.98	0.318

Abbreviations: DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma.

[a]HRs and 95% CI multivariable-adjusted for age, sex, education (≥ college), non-white race, smoking status (present, past, current), smoking-years (packs), alcohol intake (never, special occasion, 1–3 drinks/week, 3–4 drinks/week, daily), physical activity (quintiles of MET-hour/week), and BMI (kg/m^2; model 2, as described in the text). HRs for cancer risk at specific sites are additionally adjusted as reported in the footnotes of **Table 2**.

[b]Nondiabetic group was used as reference group.

[c]*P* value associated with the HR for 1-year increment of diabetes duration.

We performed separate analyses for lung cancer in smokers (ever) and nonsmokers due to the different etiology and pathophysiologic characteristics of the disease in the two groups. Among ever smokers, diabetes was a risk factor for lung cancer in women only, while levels of HbA1c in the increased risk for diabetes category (39–<48 mmol/mol) were associated with increased risk of this cancer in both men and women. Previous studies observed the highest risk among individuals with moderately high levels of HbA1c (8, 9); however, the results were not analyzed separately by smoking status. We did not observe altered risk of lung cancer in association with diabetes or HbA1c levels among never smokers.

Our study found an inverse association between diabetes and prostate cancer and a similar association between HbA1c and this outcome. A reduced risk of prostate cancer for men with diabetes has been observed previously in cohort studies of American and European populations (41). Some studies have suggested that the direction of this relationship depends on the duration of diabetes, with a reduction in risk occurring 10 years after the diagnosis of diabetes. We found a similar magnitude of reduction in risk regardless of the duration of diabetes. Previously reported data on HbA1c levels showed similar trends and magnitudes of association to those observed in this study, although they did not reach statistical significance (8). The plausibility of the observed inverse association is not clear, but several physiologic mechanisms associated with diabetes are under investigation including decreases in Leydig cell testosterone secretion, cancer-related growth factors (e.g., insulin-like growth factor and insulin-like growth factor binding protein-1, which decrease with increasing diabetes duration), PSA levels among diabetics, lower rate of health-seeking behavior, a protective effect of diabetes medication, and vascular damage in the prostate that could impact cancer growth (42).

We did not observe associations of diabetes or HbA1c with cancers of the thyroid or brain, or with malignant melanoma, diffuse large B-cell lymphoma, or multiple myeloma. Meta-analysis results on the association of diabetes with risk of these cancers are limited and inconclusive (1). With respect to HbA1c, one study has examined associations for melanoma and non-Hodgkin lymphoma, for which the results were not significant (10). Future consortia of large cohort studies may help to clarify these associations.

This study provides detailed analyses of the association of diabetes and HbA1c levels with risk of cancer at different anatomic sites conducted in a large cohort of individuals.

The HR estimates were adjusted for established risk factors for each of the cancer sites that were studied. The prospective nature of the study and the magnitude of the sample allowed us to evaluate the temporal relationship between measures of diabetes and a wide range of cancers, some of which are relatively rare and little studied. Measurements of glycated hemoglobin in this sample allowed us to test the association between chronic glycemic level and cancer regardless of reported diabetes status. We also analyzed the association of diabetes with different types of cancers based on the use of diabetes medications at baseline and on the duration of diabetes. Studies of the association between diabetic medications and cancer risk have shown evidence of altered risk of cancer depending on the type of medications and the cancer (43). However, we were unable to examine risk in association with different diabetes medications because the majority of participants using antidiabetic medications reported taking metformin alone (85.0%), or in combination with other drugs (10.4%), while only a small portion used other types of medication (4.6%).

The main limitation of the study is the lack of information on changes over time of the primary exposures (i.e., diabetes, use of

Table 5. Multivariable-adjusted HRs (95% CIs) for the association of diabetes with site-specific cancer risk stratified by levels of body mass index[a]

	BMI (kg/m^2) categories				
	<25	25–30		≥30	
Cancer	No. of cases[b] among diabetics	No. of cases among diabetics	HR (95% CI)	No. of cases among diabetics	HR (95% CI)
Esophagus	8	26	1.49 (0.98–2.26)	30	0.91 (0.60–1.37)
Stomach	4	15		28	
Colon	13	56	0.93 (0.71–1.22)	133	1.33 (1.09–1.61)
Rectum	9	30	1.24 (0.85–1.81)	40	1.23 (0.86–1.75)
Liver	6	24	3.19 (1.99–5.12)	40	2.61 (1.73–3.95)
Pancreas	6	4		11	
Kidney	6	26	1.30 (0.87–1.95)	54	1.33 (0.95–1.87)
Bladder	13	27	1.30 (0.85–2.01)	46	1.06 (0.71–1.59)
Breast premenopausal	4	8		22	
Breast postmenopausal	24	57	0.99 (0.76–1.29)	143	1.21 (1.01–1.44)
Endometrium	1	22	2.28 (1.45–3.59)	62	1.32 (1.00–1.75)
Ovary	2	7		18	
Prostate	46	188	0.83 (0.72–0.97)	160	0.64 (0.54–0.75)
Lung among ever smokers	28	76	1.30 (1.02–1.65)	95	1.00 (0.79–1.26)
Lung among never smokers	3	4		7	
Thyroid	5	5		8	
Brain	2	10		17	
Melanoma	8	36	0.69 (0.46–1.14)	60	1.07 (0.79–1.44)
NHL – DLBCL	3	9		24	
Multiple myeloma	1	11		14	

Note: In each category of BMI, the nondiabetic group was used as reference category.
Abbreviations: DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma.
[a]HRs and 95% CI adjusted for age, sex, education (≥ college), non-white race, smoking status (present, past, current), smoking-years (packs), alcohol intake (never, special occasion, 1–3 drinks/week, 3–4 drinks/week, daily), physical activity (quintiles of MET-hour/week), and BMI (kg/m^2; model 2, as described in the text). HRs for cancer risk at specific sites are additionally adjusted as reported in the footnotes of **Table 2**.
[b]No diabetes associated HRs were estimated for participants with BMI <25 kg/m^2 since few cancer cases occurred among diabetes in that category.

diabetes medications, HbA1c level), and potential confounders, which may have resulted in misclassification of the exposures and reduction in the strength of the associations. Diabetes was self-reported and some participants might not have been aware of their status or might not have recalled it correctly. We observed that 1.8% of participants in the study used antidiabetic medications but did not report having diabetes; their exclusion from the diabetes group did not change the results of the analyses. No distinction was made between type I and type II diabetes; however, we can assume that most of the reported diabetes cases were type II, given that <7% of the diabetics in this cohort had a diagnosis of diabetes before the age of 30 years and that approximately 90% of diabetic adults in the United Kingdom receive a type II diagnosis (44). A substantial portion of diabetic patients were not treated with medications despite high levels of HbA1c, possibly suggesting inadequate control of diabetes in this population. Hepatitis infection was self-reported and with no specification of the subtype. Finally, we did not have information on cancer stage and grade.

The results of this study suggest that diabetes and/or elevated HbA1c are associated with increased risk of cancers of the esophagus, stomach, colon, liver, pancreas, bladder, kidney, endometrium, and lung among ever smokers, and with decreased risk of prostate cancer, independently of other risk factors. These observations suggest the importance of diabetes and glycemic control to limit cancer risk and, at the same time, suggest that the biochemical and molecular mechanisms associated with elevated glucose levels may affect the progression of tumorigenesis in various organs differently. The results of this study support the previously found associations between HbA1c and the more common cancers and extend the evaluation of this exposure to less common cancers which have not been studied previously. The observation that glycated hemoglobin levels above and below the threshold used to diagnose diabetes are associated with many cancers constitutes new information and suggests the importance of glycemic control to potentially reduce cancer occurrence.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: R. Peila, T.E. Rohan
Development of methodology: R. Peila, T.E. Rohan
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): T.E. Rohan
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R. Peila, T.E. Rohan
Writing, review, and/or revision of the manuscript: R. Peila, T.E. Rohan
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): T.E. Rohan
Study supervision: T.E. Rohan

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