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RESEARCH ARTICLE

Diabetes mellitus and cancer incidence: the Atherosclerosis Risk in Communities (ARIC) cohort study

Hadith Rastad[1] · Mahboubeh Parsaeian[1] · Nooshin Shirzad[2,3] · Mohammad Ali Mansournia[1] · Kamran Yazdani[1]

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Abstract

Purpose To assess the association between diabetes mellitus (DM) and the incidence of cancer at different sites.

Methods Data from the baseline and first three follow-up visits of the Atherosclerosis Risk in Communities (ARIC) study, an ongoing cohort study of adults from four American communities, were used in this study. Of 15,792 persons aged 45–64 years old who participated in the baseline visit, the data of 15,118 participants were available for this study. For each cancer site, a conditional stratified Poisson regression model was fitted to estimate the adjusted relative rate and 95% confidence interval (adj. RR, 95% CI) of its incidence in diabetics compared to non-diabetics.

Results We excluded 850 participants with a history of cancer at baseline and 149 participants who developed cancer during 2 years after enrollment, leaving a total of 14,119 participants of whom 1721 were diabetics. Independent of age, body mass index, alcohol consumption, and physical activity, DM decreased the risk of all cancers combined (adj. RR: 0.77, 95% CI: 0.60, 0.98) and the risk of prostate cancer (adj. RR: 0.51, 95% CI: 0.27, 0.97) and increased the risk of colorectal cancer in non-menopausal women (adj. RR: 12.08, 95% CI: 2.06, 70.94).

Conclusions In conclusion, DM may be associated with an increased risk of colorectal cancer in non-menopausal women and a decreased risk of prostate cancer and all cancers combined.

Keywords Diabetes mellitus · Cancer · Cohort study · Poisson regression

Introduction

In 2016, an estimated 17.2 million new cancer cases were diagnosed across the world [1]. Cancer accounted for 8.93 million deaths in this year and remains to be the second leading cause of death globally, right behind cardiovascular diseases [2]. In addition, 415 million adults aged 20–79 years old were diagnosed with diabetes in 2015, which is projected to increase to 642 million by 2040 [3].

Some previous studies have suggested that DM might increase the risk of certain cancers; however, they have failed to provide robust evidence in this regard due to lack of taking confounding factors, latency period, and/or surveillance bias into consideration [4, 5]. It is noteworthy that because of the high prevalence of DM worldwide [3], even a small significant association could have important consequences on public health.

Hence, the purpose of this study was to assess the association between diabetes mellitus (DM) and risk of cancer at different sites after adjustment for relevant confounding factors considering a latency period.

Methods

Study design and participants

The data from the Atherosclerosis Risk in Communities (ARIC), an ongoing multicenter prospective cohort study in four U.S. communities, were used in this study. This

✉ Kamran Yazdani
kyazdani@tums.ac.ir

[1] Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, PO Box: 644614155, Tehran, Iran

[2] Department of Endocrinology, Vali Asr Hospital, Imam Khomeini Complex Hospital, Tehran University of Medical Sciences, Tehran, Iran

[3] Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Science Institute, Tehran University of Medical Sciences, Tehran, Iran

study was originally designed to investigate the etiology of atherosclerosis and its consequences as well as variations in the cardiovascular risk factors, medical care, and diseases. The design, measurement methods, and sampling strategy of the study have been described in details elsewhere [6].

In brief, from each of the randomly selected ARIC field centers (Washington County, MD; Forsyth County, NC; Jackson, MS; and Minneapolis, MN), a sample of approximately 4000 individuals aged 45–64 was initially recruited. A total of 15,792 participants completed baseline examinations from 1987 to 1989 (visit 1). After the baseline examinations, the participants were invited for four follow-up visits in 1990–1992 (visit 2), 1993–1995 (visit 3), 1996–1998 (visit 4), and 2011–2013 (visit 5). The data of 15,118 subjects collected during visit 1 (baseline) to visit 4 were available for use in this study.

The ARIC study protocol was approved by the Institutional Review Boards of the University of Minnesota, Johns Hopkins University, University of North Carolina, University of Mississippi Medical Center, and Wake Forest University. Written informed consent was obtained from participants at each clinical site [6]. Our study, which was part of a Ph.D. dissertation in epidemiology, was approved by the Graduate Council and the Ethics Committee of the School of Public Health (SPH), Tehran University of Medical Sciences.

Exposure and covariate measurements

Baseline characteristics, lifestyle data, medical history, and menopausal status (women) were obtained from visit 1 (baseline visit). In the ARIC study, the DM status was defined based on one or more of the following criteria: a fasting plasma glucose level of at least 126 mg/dl, a non-fasting plasma glucose level of at least 200 mg/dl, use of anti-diabetic medication(s) in the past 2 weeks, or self-report of a physician's diagnosis of diabetes. The body mass index (BMI, kg/m2) was calculated using the participants' weight and height. The participants were asked if they currently or formerly drank alcoholic beverages. For each participant, modified versions of the Baecke Physical Activity Questionnaire (PAQ) and the Willett Food Frequency Questionnaire (FFQ) were applied to measure the level of physical activity (during work, sport, and leisure time) and the amount of total energy intake, respectively. Women were also asked whether they had reached menopause (Yes or No).

In this study, the continuous variables of age, BMI, physical activity, total energy intake, fiber intake, and saturated fat intake as well as the multi-categorical variable of alcohol consumption were converted into binary variables using suitable cutoff points (Table 1).

Outcome measurements

A diagnosis of cancer (outcome), the cancer site, and the date of diagnosis were determined based on participants' self-reported data obtained through interviews at baseline and follow-up visits. *We excluded* cancers diagnosed in 2 years after enrollment to consider the minimum latency period for DM-related cancers. Therefore, our study included new cases of cancer that were identified between 1987 and 1998 among those participants who did not report cancer at the baseline visit and in the first 2 years of the study.

The types of cancer included in this study are presented in Table 2. We classified cancers of the nasal cavity, middle ear, lip, oral cavity, pharynx, larynx, and sinuses as "head and neck" cancer (HNC) according to the ICD-10 codes (C00 to C14 and C30 to C32) [7].

Data analysis

Descriptive part

In diabetic and non-diabetic groups:

- Baseline characteristics of the included participants are summarized and reported as mean (Standard Deviation (SD)) for continuous variables or frequency and percentage for categorical variables.
- Person-years at risk was calculated from baseline to the date of cancer diagnosis, death, loss to follow-up, or to the end of the fourth visit (1998), whichever occurred first.
- The crude incidence rate per 1000 person-years at risk and its 95% confidence interval were calculated for various cancer types.

Analytical part

To control for both main and interaction effects of confounding variables simultaneously, stratification on these variables is a main option. A useful approach for fitting stratified Poisson regression models is a 'conditional' Poisson analysis that avoids estimation of large numbers of stratum-specific parameters by conditions out their coefficients [8] . In this study, the following steps were taken to employ a conditional stratified Poisson regression model:

- Of the known risk factors for cancer [9], we asseseed the asociassion of the variabels of age, alcohol consumption, dietary factors (daily intake of total energy, fiber and saturated fat), physical activity and BMI with diabetes; finally, based on these findings, four variables were considered as potential confounders.

Table 1 Baseline characteristics of the participants in this study: 1987–1989

Variables		Total (N: 14,119) Percent(n) or mean (SD)	Non-diabetic (N:12,398) Percent(n) or mean (SD)	Diabetic (N:1721) Percent(n) or mean (SD)	*P*
Age	45–54	53.3 (7524)	54.8 (6800)	42.1 (724)	<0.001
	55–64	46.7 (6595)	45.2 (5598)	57.9 (997)	
Sex	Female	54.0 (7630)	54.1 (6702)	53.9 (928)	0.92
	Male	46.0 (6489)	45.9 (5696)	46.1 (793)	
Race	White	72.9 (10295)	75.4 (9354)	54.7 (941)	<0.001
	Black	27.1 (3824)	24.6 (3044)	45.3 (780)	
Alcohol consumption	Never	55.9 (7852)	58.4 (7213)	37.4 (639)	<0.001
	Currently or Former	44.1(6200)	41.6 (5132)	62.6 (1068)	
Total energy intake[a]	As recommended	87.4 (12048)	87.2 (10565)	88.6 (1483)	0.11
	Excessive	12.6 (1740)	12.8 (1549)	11.4 (191)	
Body Mass Index (BMI)[b]	Normal	32.8 (4609)	35.5 (4385)	13.1 (224)	<0.001
	Overweight or obese	66.2 (9444)	64.5 (7964)	86.9 (1480)	
Fiber intake[c]	At or above recommended	39.3 (5414)	39.1 (4747)	40.0 (667)	0.48
	Below recommended	60.7 (8379)	60.9 (7380)	60.0 (999)	
Saturated fat intake[d]	At or Below Recommended	19.5 (2691)	19.3 (2342)	21.0 (349)	0.11
	above recommended	80.5 (11102)	80.7 (9785)	79.0 (1317)	
Physical activity[e]	Non active	48.4 (6798)	46.7 (5764)	60.5 (1034)	<0.001
	Active	51.6 (7250)	53.3 (6574)	39.5 (676)	
Menopausal status	Non-Menopausal	29.0 (2201)	30.3 (2025)	19.1 (176)	<0.001
	Menopausal	71.0 (5398)	69.7 (4651)	80.9 (747)	

N Number, *SD* Standard Deviation

[a] As recommended: < 2000 kg per day for women and < 2500 kg per day for men / excessive: ≥ 2000 kcal per day for women and ≥ 2500 kcal per day for Men

[b] Normal: 18.5 < BMI < 25, overweight: 25 ≤ BMI <30, obese: 30 ≤ BMI

[c] At or above recommended fiber intake: ≥ 14 g/1000 kcal/day, below recommended fiber intake: < 14 g/1000 kcal/day

[d] At or below recommended saturated fat intake: < 18 g/1000 kcal/day, above recommended Saturated fat intake: ≥ 18 g/1000 kcal/day

[e] The median value of all subjects (7 scores) was used as a cutoff point for physical activity in this study; Active: score ≥ 7, and Non-Active: score < 7

- A variable named strata (with 16 levels) was defined by cross-classification of the important confounding variables of age at enrolment (45–54 vs. 55–65 years), BMI (<25 vs. ≥25), physical activity (active vs. less active), and alcohol consumption (formerly or currently vs. never).
- For each type of cancer, a dataset was generated that consisted of a total number of person-year and events, namely new cases of cancer cross-classified by the level of the exposure, DM, and the strata.
- By fitting a conditional stratified Poisson regression model, an adjusted parameter (Ln Relative Rate) was estimated separately to describe the association of diabetes with the risk of each type of cancer.

All *P* values were two-sided. *P* value less than 0.05 were considered significant. All analyses were performed using the SAS 9.2 (SAS Institute Inc., Cary, NC) and Stata 11.0 (Stata Corp, College Station, Texas, USA).

Results

Baseline characteristics of participants

After excluding participants with a history of cancer at baseline and participants who were diagnosed with cancer in the first 2 years of follow-up, a total of 14,119 subjects remained in the study of whom 1721 (12.2%) were diabetic at baseline (Fig. 1).

Table 1 presents the baseline characteristics of the included participants overall and by study group. Compared to non-diabetics, diabetic subjects were older, less physically active, and more overweight or obese. Moreover, they drank alcohol either at the time of the study or in the past more frequently.

The crude incidence rate of different cancers

Of 1080 various cancers detected between 1987 and 1998, 931 occurred after a minimum follow-up of 2 years, including

Table 2 The incidence rate, crude and adjusted relative rate of different cancer types in diabetics compared to non-diabetics in ARIC cohort study

Site of cancer	All		Diabetic		Non-Diabetic		Crude relative rate; 95% CI	Adjusted* relative rate; 95% CI
	(N:14,119)		(N:1721)		(N:12,398)			
	N of new cases	Incidence rate (95% CI)	N of new cases	Incidence rate (95% CI)	N of new cases	Incidence rate (95% CI)		
Skin	287	2.13 (1.89, 2.39)	27	1.67 (1.10, 2.43)	260	2.20 (1.90, 2.50)	0.76; 0.51,1.14	0.79; 0.51, 1.23
Breast†	169	2.30 (1.96,2.67)	18	2.05 (1.22, 3.24)	151	2.33 (1.97, 2.73)	0.88; 0.54, 1.45	0.93; 0.54, 1.62
Prostate	162	2.60 (2.20, 3.01)	12	1.62 (0.84, 2.84)	150	2.77 (2.35, 3.25)	0.59; 0.33, 1.06	**0.51; 0.27, 0.97**‡
Colon & Rectum	55	0.41 (0.31, 0.53)	9	0.56 (0.25, 1.05)	46	0.39 (0.28, 0.52)	1.44; 0.71, 2.94	1.34; 0.60, 2.97
Lung	42	0.31 (0.22, 0.42)	8	0.50 (0.21, 0.98)	34	0.29 (0.20, 0.40)	1.72; 0.80, 3.74	1.96; 0.83, 4.64
Uterus	38	0.52 (0.36, 0.71)	7	0.80 (0.32, 1.64)	31	0.48 (0.33, 0.68)	1.67; 0.73, 3.79	1.47; 0.59, 3.69
Head and Neck (HNC)	35	0.26 (0.18, 0.36)	1	0.06 (1.5×10^{-6}, 0.34)	34	0.29 (0.20, 0.40)	0.22; 0.03, 1.58	0.23; 0.03, 2.04
Bladder	34	0.25 (0.17, 0.35)	1	0.06 (1.5×10^{-6}, 0.34)	33	0.28 (0.19, 0.39)	0.22; 0.03, 1.63	0.24; 0.03, 2.16
Kidney	14	0.10 (0.06, 0.17)	1	0.06 (1.5×10^{-6}, 0.34)	13	0.11 (0.06, 0.19)	0.56; 0.07, 4.32	0.47; 0.05, 4.43
Lymphatic System	13	0.09 (0.05, 0.16)	1	0.06 (1.5×10^{-6}, 0.34)	12	0.10 (0.05, 0.18)	0.61; 0.08, 4.71	0.75; 0.08, 7.07
Stomach	12	0.09 (0.05, 0.15)	3	0.19 (0.04, 0.54)	9	0.08 (0.04, 0.14)	2.45; 0.66, 9.06	2.01; 0.47, 8.56
Cervix	9	0.12 (0.06, 0.23)	1	0.11 (2.9×10^{-6}, 0.64)	8	0.12 (0.05, 0.24)	0.92; 0.12, 7.38	0.64; 0.06, 6.44
Blood	8	0.06 (0.03, 0.11)	0	0.00 (0.00, 0.22)	8	0.07 (0.03, 0.13)	4. 6×10^{-8}; 0, NE [c]	7×10^{-6}; 0.00, NE
Thyroid	4	0.03 (8×10^{-6}, 0.07)	0	0.00 (0.00, 0.22)	4	0.03 (9×10^{-6}, 0.09)	4. 6×10^{-8}; 0, NE	7×10^{-6}; 0.00, NE
Ovary	4	0.05 (0.02, 0.14)	0	0.00 (0.00, 0.42)	4	0.06 (0.02, 0.16)	4. 6×10^{-8}; 0, NE	7×10^{-6}; 0.00, NE
Testicle	2	0.03 (4×10^{-6}, 0.11)	0	0.00 (0.00, 0.49)	2	0.04 (4×10^{-6}, 0.13)	4. 6×10^{-8}; 0, NE	7×10^{-6}; 0.00, NE
Others§	15	0.11 (0.06, 0.18)	0	0.00 (0.00, 0.22)	15	0.13 (0.07, 0.21)		
Unknown	28	0.21 (0.14, 0.30)	1	0.06 (1.5×10^{-6}, 0.34)	27	0.23 (0.15, 0.33)		
All	931	6.89 (6.46,7.35)	90	5.57 (4.47, 6.84)	841	7.07 (6.60, 7.56)	**0.79; 0.63–0.98**‡	**0.77; 0.60, 0.98**‡

N number, *CI* Confidence Interval, *NE* Non-Estimable

* Adjusted for age, Body Mass Index, Physical activity and alcohol consumption using stratified poisson regression; † For women only; ‡ $P < 0.05$; § Eye (1 case) Vagina (2 cases) Penis (1 case) Bone marrow (2 cases) Bone (2 cases) Gallbladder (2 cases) Spleen (1 case)

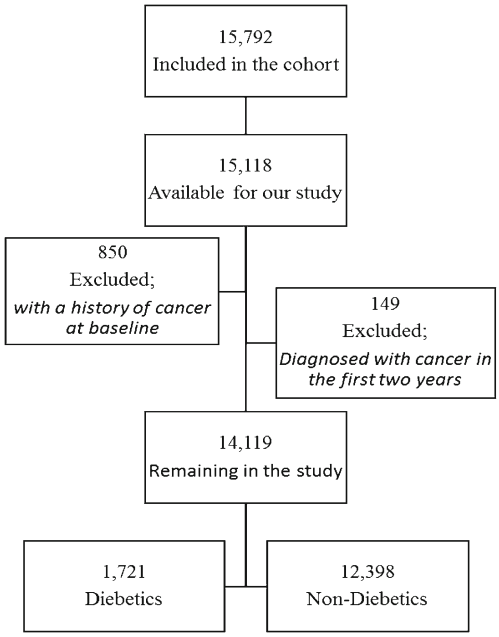

Fig. 1 Flow-chart of the included participants

23 different types of cancers and 28 unidentified cases. The mean follow-up time (SD) was 9.6 (1.5) and 9.4 (1.9) years in diabetics and non-diabetics, respectively. Table 2 shows that the crude incidence rate of all cancer sites combined was significantly lower in diabetics compared with non-diabetics, while there was no significant difference in site-specific crude incidence rates between the two groups.

Subgroup analysis (not shown) showed that in non-menopausal women, diabetics had a higher crude incidence rate of colorectal cancer compared to non-diabetics (crude Relative Rate (RR): 7.02, 95% CI: 1.68, 29.38; $P < 0.01$). In menopausal women, the crude incidence rate of skin cancer was lower in diabetics versus non-diabetics (crude RR:0.31, 95% CI: 0.12, 0.86; $P = 0.02$). The crude incidence rate of all cancer sites combined was lower in diabetic men compared to their non-diabetic counterparts (crude RR:0.73, 95% CI: 0.54, 0.99; $P = 0.04$). No significant differences were observed in ethnical subgroups (white and black ethnicities). (All P values >0.05).

Adjusted association between DM and risk of different cancers

The relative rates of different types of cancer adjusted for age, BMI, alcohol consumption, and physical activity are presented in Table 2. DM had a significant inverse association with the incidence rate of all cancers combined and prostate cancer after adjusting for confounding factors. The association of DM with the incidence of ovarian, testicular, thyroid, and blood cancers were not estimable.

Subgroup analysis showed a significant inverse association between DM and the incidence of all cancers combined in men (adjusted RR: 0.66; 95% CI: 0.47, 0.93; $P = 0.02$). In non-menopausal women, a significant association was observed between DM and the incidence of colorectal cancer (adj. RR: 12.08, 95% CI: 2.06, 70.94; $P < 0.01$), while this association was not observed in post-menopausal women (adj. RR: 1.79, 95% CI: 0.42, 7.67; $P = 0.41$). No significant associations were seen in other subgroups. (All P values >0.05).

Discussion

This study was done to examine the adjusted association between DM and the incidence of cancer at several sites using a conditional stratified Poisson regression model on the data of a prospective cohort (ARIC) study. After adjusting for confounding factors of age, BMI, physical activity, and alcohol consumption, it was found that DM reduced the risk of all cancers combined significantly. DM was also associated with a reduced risk of prostate cancer and all cancers combined in men, and an increased risk of colorectal cancer in non-menopausal women.

In 2013, a review of published meta-analyses and systematic reviews on the association between DM and risk of cancer development at several sites showed robust, unbiased evidence only for endometrial, breast, and colorectal cancer and intrahepatic cholangiocarcinoma while there was substantial uncertainty about other cancers [4]. Our findings did not support an association between DM and the risk of endometrial and breast cancer. There was a lack of data about cholangiocarcinoma in this study. However, the results showed a decreased risk of prostate cancer in male diabetic patients and an increased risk of colorectal cancer in non-menopausal women.

DM and prostate cancer

Consistent with our findings, an inverse association has been reported between DM and risk of prostate cancer in earlier studies [4]. On the other hand, a few studies have observed a direct association [10–12]; however, these studies have two major limitations, including a short follow-up period and/or not controlling important confounding factors such as obesity. The most probable explanations proposed for this inverse association are hypoinsulinemia [13], a genetic link [14, 15], and decreased circulating testosterone levels in men with DM [16, 17]. However, it is unknown whether diabetes decreases the level of intraprostatic androgen, which is supposed to be a stronger predictor of the risk of prostate cancer compared to its circulating levels [13, 18].

DM and colorectal cancer

Similar to our findings, Neilson et al. (2001) [19], in a population-based 12-year follow-up study, found a positive association between DM and the risk of colorectal cancer only in women (RR: 1.55, 95% CI: 1.04, 2.31) and not in men (RR: 0.66, 95% CI: 0.35, 1.24). On the other hand, a recent retrospective cohort study of over 34,000 diabetics and non-diabetics in each group showed an increased risk of colon cancer only in men (HR: 1.6, 95% CI: 1.2, 2.2) [20] although the observed association was not adjusted for important confounding factors such as obesity and alcohol consumption. Overall, large meta-analyses of observational studies have reported an average of 20–30% increase in the risk of colon cancer in both genders [21–26].

The probable mechanisms of this association are genetic links [27], slower colonic transit time [4, 28], and elevated serum insulin levels in diabetics [29–31]. However, it should be noted that metformin is likely to lower the risk of colorectal cancer [27].

DM and breast cancer

Similar to our findings, a pooled analysis of 182,542 Japanese women participating in 8 prospective cohort studies showed no significant association between DM and risk of breast cancer [32]. Moreover, a large case-control study conducted in 2017 found no significant association between DM and all breast cancer stages combined [33]; however, similar to other studies investigating the association of DM with cancer stage [33–35], a significant direct association was observed with higher stages. In a meta-analysis in 2013, De Bruijn et al. found a weakly significant association (HR: 1.23, 95% CI: 1.12, 1.34) between DM and breast cancer [36]; nonetheless, the effect of confounders was only controlled in one of the studies included in this meta-analysis. A possible site-specific mechanism is hyperinsulinemia. Insulin can affect the development and progress of breast cancer through various mechanisms, but it is more involved in the promotion and progression stages of breast tumorgenesis rather than the initiation stage of this process [37].

DM and uterus cancer

Consistent with our findings, Luo et al. conducted a cohort study of more than 88,000 post-menopausal women followed for an average of 11 years and reported a non-significant elevated risk of uterus cancer in diabetics adjusted for BMI when they only focused on the prevalence of DM at enrolment (HR: 1.16, 95% CI: 0.90, 1.48). However, this elevated risk became statistically significant after considering new DM cases (HR: 1.31, 95% CI: 1.08, 1.59). The reason may be high levels of insulin in newly diagnosed DM cases [38].

A meta-analysis of 16 studies including 13 case-control studies and 3 cohorts showed an elevated risk of uterine cancer in diabetic women [39]; however, most of the studies included in this meta-analysis were only adjusted for age.

It has been proposed that insulin can biologically develop this association through a direct effect on the uterine epithelial lining [5] and an indirect effect on the levels of insulin-like growth factors, sexual hormones, and adipokines [6].

Methodological issues

In this study, a conditional stratified Poisson regression model was fitted as a novel approach to adjust the confounding and interaction effects through applying a stratification method. This model was also fitted to reduce the number of parameters that need to be estimated by conditioning out the coefficients of stratum-specific parameters simultaneously [8].

After adjusting for the potential confounding variables, important changes were noticed; the non-significant crude rate ratio of prostate cancer became significant in people with DM compared to nondiabetics, while the crude rate ratio of skin cancer in women lost its significance. In this regard, Bonovas et al. performed a subgroup meta-analysis of the association between DM and risk of prostate cancer. The results showed that studies that controlled at least two potential confounders yielded a stronger summary relative risk (sRR) compared to studies with poor control (0 or 1) (sRR = 0.86, 95% CI: 0.73, 0.99 vs. sRR = 0.91. 95% CI: 0.88, 0.95) [40]. Similarly, Luo et al. reported that the significant association between DM (prevalent cases) and the risk of endometrial cancer became non-significant after adjusting for BMI [38].

The latency period for cancer development is considered one of the main methodological challenges in observational studies exploring the impact of DM on cancer incidence [5]. To address this consideration, we only included the new cases of cancer identified after 2 years of follow-up.

Strengths and limitations

In the ARIC study, to determine the DM status of the participants at baseline, fasting and non-fasting blood glucose tests were used in all subjects in addition to self-reports, minimizing the possibility of misclassification bias in exposure (DM).

One of the limitations was that the conversion of continuous and polytomous variables to dichotomous ones might have led to residual confounding although the likelihood ratio tests did not show this phenomenon. In addition, the type of DM was unknown in our study, but the majority of them had DM type 2 given the age of the participants. Furthermore, we could not control the effect of DM duration and the use of glucose-lowering treatments because of lack of sufficient data.

Conclusion

According to our findings, after adjustment for age, BMI, alcohol consumption, and physical activity, DM may only be associated with a reduced risk of all cancers combined and prostate cancer and an increased risk of colorectal cancer in menopausal women.

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Compliance with ethical standards

Competing interests The authors declare that they have no conflict of interest.

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