Prevalent diabetes and risk of total, colorectal, prostate, and breast cancers in an ageing population: meta-analysis of individual participant data from cohorts of the CHANCES consortium

Running title: Prevalent diabetes and cancer incidence

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ABSTRACT

Background

We investigated whether associations between prevalent diabetes and cancer risk are pertinent to older adults, and whether associations differ across sub-groups of age, body weight status, or levels of physical activity.

Methods

We harmonized data from seven prospective cohort studies of older individuals in Europe and the United States participating in the CHANCES consortium. Cox proportional hazard regression was used to estimate associations of prevalent diabetes with cancer risk (all cancers combined; and for colorectum, prostate, and breast). We calculated summary risk estimates across cohorts using pooled analysis and random effects meta-analysis.

Results

A total of 667,916 individuals were included with an overall median (P25-P75) age at recruitment of 62.3 (57-67) years. During a median follow-up time of 10.5 years, 114,404 total cancer cases were ascertained. Diabetes was not associated with risk of all cancers combined (hazard ratio [HR] = 0.94; 95% confidence interval [CI]: 0.86-1.04; $I^2=63.3\%$). Diabetes was positively associated with colorectal cancer risk in men (HR = 1.17; 95% CI: 1.08-1.26; $I^2=0\%$) and a similar HR in women (1.13; 95% CI: 0.82-1.56; $I^2=46\%$), but with a confidence interval including the null. Diabetes was inversely associated with prostate cancer risk (HR = 0.81; 95% CI: 0.77-0.85; $I^2=0\%$), but not with postmenopausal breast cancer (HR = 0.96; 95% CI: 0.89-1.03; $I^2=0\%$). In exploratory sub-group analyses, diabetes was inversely associated with prostate cancer risk only in men with overweight or obesity.

Conclusions

Prevalent diabetes was positively associated with colorectal cancer risk and inversely associated with prostate cancer risk in older Europeans and Americans.

INTRODUCTION

In 2015, 415 million people were estimated to live with diabetes, of whom more than 90% had type 2 diabetes, and this prevalence seems set to increase and affect all regions and countries of the world (1). The risk factors of type 2 diabetes include genetics, age, family history of diabetes, unhealthy diet, obesity, and physical inactivity (2).

A 2018 meta-analysis of 121 cohort studies reported that diabetes was positively associated with the incidence of all cancers combined, in both men and women. The pooled adjusted RRs were 1.19 (95% CI: 1.13-1.25) for men; and 1.27 (95% CI: 1.21-1.32) for women (3). Several prospective studies and meta-analyses have suggested that type 2 diabetes significantly increases the risk of breast (4) and colorectal cancers (5), but decreases the risk of prostate cancer (6). These are among the most frequent cancers and account together for 31% of total cancer cases globally (7). As noted in an umbrella review of meta-analyses (5), heterogeneity between studies investigating associations between diabetes and cancer risk was often large (5), which hampers the possibility of drawing robust conclusions across study settings. Different study designs with various definitions of prevalent diabetes and different level of adjustment for confounders may at least partly explain the large heterogeneity in previous meta-analyses. The relationship between diabetes and cancer risk may also be different in older people, who likely lived with diabetes for longer durations. Yet, previous studies have not specifically considered associations in ageing populations, such as in our study, where study participants had a median age of 60 or older at recruitment in four of the seven included cohorts.

The current evidence suggests that the association between type 2 diabetes and cancer development may be partially explained by shared pre-disposing risk factors, such as physical inactivity and overweight ($\text{BMI} \geq 25 \text{ kg/m}^2$) or obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) (8). Higher levels of physical activity were consistently associated with a lower risk of several cancers, in

particular those of the breast and colorectum (9,10) as well as type 2 diabetes (8). Similarly, obesity is an established risk factor for many cancers (11,12) and type 2 diabetes (13). More insight is needed as to whether associations between diabetes and cancer is direct, i.e. due to specific metabolic consequences of diabetes, or modified by common underlying risk factors.

We utilized data from the Consortium on Health and Ageing: Network of cohorts in Europe and the United States (CHANCES) to evaluate the association between prevalent diabetes at enrolment into the cohorts with later cancer development, while accounting for a common set of confounders. We assessed all cancers combined in seven cohorts, those of the colorectum and breast in four cohorts, and prostate in three cohorts. We focused on the most common cancers in Europe and the United States, for which respective data on incident cancer was available in at least three of the seven participating cohorts. We also assessed effect modification by age, body weight status, and levels of physical activity.

METHODS

Study population

The CHANCES project harmonized data from prospective cohort studies in Europe and the United States to investigate determinants of healthy ageing. Details on CHANCES have been provided previously (14). Seven CHANCES cohorts provided data for the current analysis, summarized in Table 1:

- the National Institutes of Health-AARP (NIH-AARP) study, which is a prospective cohort of men and women in the United States, aged 50–71 years at recruitment;
- the study centres in Greece, Spain, Sweden, and the Netherlands of the EPIC-Elderly study, which is a subset of the European Prospective Investigation into Cancer and Nutrition (EPIC) project that consists of men and women aged 60 years or older at recruitment;

- the Epidemiological Study for Prevention, Early Detection, and Optimized Therapy of Chronic Diseases at Old Age (ESTHER), a population-based cohort covering the entire federal state of Saarland in Germany, aged 50-75 years at recruitment;
- the FINRISK study, from which we included men and women aged 24-74 years in Finland,
- the PRIME Belfast study, a cohort of male residents aged 50–60 years of Belfast and the surrounding area in the United Kingdom;
- the Northern Sweden MONICA study, which is a prospective cohort of men and women, aged 25–74 years in Sweden; and
- the TROMSØ study, which recruited men and women in Norway between 1994 and 1995 (4th wave) aged 50–84 years.

Data collection and assessment of the covariates

Data on age, sex, alcohol consumption, smoking status, physical activity, level of education, and reproductive history (in women) were collected at baseline. Height and weight were measured at baseline in EPIC-Elderly, PRIME Belfast, and TROMSØ. BMI was calculated as weight (kg) divided by height (meter) squared. ESTHER and NIH-AARP collected self-reported weight and height at baseline, while no anthropometry data were available from FINRISK and Northern Sweden MONICA. Information regarding physical activity was self-reported in all cohort studies and was assessed either in terms of intensity, meaning exercise intensive enough to cause sweating, or in terms of time engaged in sport activities, depending on data availability. Vigorous physical activity (dichotomous: yes, no) was defined as at least 1 h per week of physical activity intense enough to cause perspiration, being out of breath or a faster heartbeat. Only the latter was available from most cohorts, except FINRISK and Northern Sweden cohorts, and was the best available harmonized indicator of physical activity across cohorts.

At baseline, all cohorts collected data on self-reported and/or documented diabetes. In the NIH-AARP and the Northern Sweden MONICA cohort, we lacked information about whether diabetes was type 1 or type 2, but type 2 diabetes accounts for more than 90% of the diabetes in this age group (15). Most cohorts (PRIME Belfast, FINRISK, Northern Sweden MONICA, TROMSØ,) had information on documented diabetes. In the ESTHER cohort, 55 cases of diabetes (5% of all cases of diabetes) were self-reported, while NIH-AARP and EPIC studies collected self-reported diabetes. Documented diabetes was defined as a diagnosis of diabetes, based on fulfillment of any of the following criteria: 1) 2-h plasma glucose ≥ 11.1 mmol/l (200 mg/ml) during an OGTT performed in accordance with the World Health Organization's recommendations (16), using a glucose load containing the equivalent of 75 grams anhydrous glucose dissolved in water; 2) HbA1c ≥ 48 mmol/mol (6.5%); 3) Fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl); fasting was defined as no caloric intake for at least 8hrs; 4) documented diagnosis of diabetes by a medical doctor; or 5) clinical or death certificate diagnosis indicating diabetes (Code 250 of ICD-8, Code 250 of ICD-9, Code E11 of ICD-10); and 6) documented current treatment of diabetes. For the remainder of the manuscript diabetes refers to type 2 diabetes acknowledging that a low proportion of patients were also of type 1.

Outcome ascertainment

All cohorts participating in this study provided follow-up cancer incidence information for all anatomical sites combined. Four cohorts (EPIC-Elderly, ESTHER, TROMSØ, and NIH-AARP) also provided information on site-specific incidence for breast and colorectal cancers while three (EPIC-Elderly, ESTHER, and NIH-AARP) also provided information on prostate cancer incidence. Study participants with history of cancer or prevalent cancer at baseline were excluded.

Cancer incidence was ascertained by active follow-up, record linkage with national/regional cancer registries, national hospital discharge register and causes of death register (17,18). The main endpoints were total cancer incidence as defined by codes C00-C97 according to the 10th edition of the ICD-10. Additional endpoints were incidence of colon and rectum (C18 -20), (C25), breast (C50), and prostate cancer (C61). Vital status was obtained from regional or state registries for all cohorts.

Statistical analyses

Means and SDs, or percentages as appropriate, of selected baseline characteristics of the study population were computed in relation to diabetes status.

Cox proportional hazards models with age as the time metric were used to estimate cause-specific HR and 95% CI for associations of prevalent diabetes with total, colorectal, prostate, and postmenopausal breast cancers. Age at entry was defined as the participant's age at recruitment, and exit time was age at diagnosis of cancer, death, loss to follow-up or censoring at the end of the follow-up period. The proportionality of hazards was verified based on the slope of the Schoenfeld residuals over time. Analyses were conducted for each individual cohort separately. Models were stratified by sex and adjusted for known or suspected cancer risk factors including: categories of smoking status, educational level, vigorous physical activity (yes/no), country (EPIC-Elderly only), and continuous variables of age, alcohol consumption, and BMI (Table 1). The linearity assumption for the continuous covariates was verified using fractional polynomials. A dummy category for missing data was created for categorical covariates, and continuous missing data were replaced by the median value of the population data. The results across cohorts were then combined using Der Simonian and Laird random effects meta-analysis (19). The heterogeneity of associations across studies was assessed using the I^2 score (20).

To investigate effect modification, all cohorts were pooled into one dataset. Stratified analyses were conducted according to age groups (< 60, 60-<65, 65-<70, and ≥ 70 years), predefined WHO cut-off points of weight status (normal BMI, $<25 \text{ kg/m}^2$; overweight, $25 - <30 \text{ kg/m}^2$ and obese, $\geq 30 \text{ kg/m}^2$) to facilitate clinical interpretation, and vigorous physical activity defined as at least 1 h per week of intense physical activity (yes/no). Multiplicative interaction was assessed by adding an interaction term between diabetes status and in turn age groups, weight status, and levels of physical activity to the multivariable Cox proportional hazards models and the significance of these were assessed by likelihood ratio tests. In contrast to our main analysis, which were based on a strong prior hypothesis, we penalized the more exploratory subgroup analyses for multiple testing using Bonferroni correction and estimated corresponding 98% CI ($100 - 5/k$; $k=24$ tests).

For sensitivity analysis, we repeated our analyses using fixed effect meta-analysis and pooled (individual-patient level) analyses to assess the robustness of the findings and to rule out sampling variability contributing to I^2 in our random effects meta-analysis. We also repeated our main analysis after excluding cancer cases ascertained within less than two years of follow-up to assess reverse causation. To assess whether defining diabetes (self-reported versus documented) affected associations with total cancer incidence, we performed the random effects meta-analysis by cohorts with self-reported (or mixture of documented and self-reported) diabetes status (i.e. NIH-AARP, EPIC-Elderly, and ESTHER [since a certain proportion was self-reported]) versus cohorts with documented diabetes (FINRISK, PRIME Belfast, Northern Sweden, and TROMSØ). This was not feasible for site-specific cancers, because not all cohorts could provide data on site-specific cancers and thus NIH-AARP and EPIC-Elderly dominated these analyses. Lastly, to assess whether imputation of missing values affected observed associations, we repeated the pooled analysis after excluding participants with missing values in any covariate (complete-case analysis).

All statistical tests were two-sided and P values < 0.05 were considered statistically significant ($P < 0.002$ in subgroup analyses). All analyses were performed using STATA version 14 (College Station, Texas, USA).

RESULTS

Population characteristics

Table 1 presents key characteristics of the cohorts and study participants. A total of 663,916 Participants (85.3% from NIH-AARP) was recruited between 1982 and 2009, with an overall median (P25-P75) age at recruitment of 62.2 (57-67) years (median age ranging from 46 years in FINRISK to 64 years in EPIC-Elderly). The proportion of individuals with diabetes was 9.3% ($n=61,587$) ranging from 3.3% in the Northern Sweden study to 12.3% in ESTHER. During a median follow-up of 10.5 years, 114,404 total cancer cases were ascertained (89.7% in NIH-AARP). Selected characteristics of the participants by diabetes status are shown in Supplementary Table 1. Total cancer and colorectal cancer were more common in individuals with diabetes than those without, while breast cancer and prostate cancer were less frequent. Individuals with diabetes were older, had a higher BMI, were less physically active, had a lower alcohol consumption, and had attained a lower educational level.

Meta-analysis of diabetes and cancer risk

We found no evidence for an association between prevalent diabetes and total cancer incidence. After adjusting for age, sex, BMI, alcohol consumption, physical activity, smoking, and education, the pooled HR from the random effects meta-analysis was 0.94 (95% CI: 0.86-1.04) in men and women combined (Figure 1). Similar risk estimates were obtained after stratification by sex (Figure 1). Substantial heterogeneity was observed across studies for both sexes combined ($I^2 = 63.3\%$, P heterogeneity = 0.012). This was mostly due

to the heterogeneity in women ($I^2 = 59.3\%$, P heterogeneity = 0.031), where the association was significantly positive in the AARP study and null in all other studies (Figure 1).

Diabetes was positively associated with colorectal cancer incidence in sex-stratified analyses with a pooled HR of 1.17 (95% CI: 1.08-1.26; $I^2 = 0\%$) in men, and a pooled HR in women equal to 1.13 (95% CI: 0.82-1.56; $I^2 = 46\%$) (Figure 2).

Diabetes was inversely associated with prostate cancer incidence with a pooled HR equal to 0.81 (95% CI: 0.77-0.85), and no heterogeneity across cohorts ($I^2 = 0\%$, P heterogeneity = 0.96) (Figure 3).

Regarding breast cancer in women, where postmenopausal cancer represented 93% of the cases, diabetes was not associated with risk. The corresponding pooled HR was equal to 0.96 (95% CI: 0.89-1.03) (Supplementary Figure 1). There was no heterogeneity across cohorts ($I^2 = 0\%$, P heterogeneity = 0.86), and no notable changes in results were observed when stratifying by menopausal hormone therapy (P interaction = 0.12).

Sensitivity analyses

In contrast to the random effects meta-analysis, we found a positive association between diabetes and total cancer incidence in both fixed effect meta-analysis and pooled analysis (Supplementary Table 2). However, the I^2 from the fixed effect meta-analysis was 63% (P heterogeneity = 0.012), which suggests that variability in observed associations was due to between study heterogeneity rather than chance, and results of the random effects meta-analysis more appropriately summarize the overall association across studies. Similarly, unlike the results of the random effects meta-analysis, we found a positive association between diabetes and risk of colorectal cancer in women in the fixed effect meta-analysis, but with a large variability of 46% (P heterogeneity = 0.135). In contrast, results for colorectal cancer in men and for cancers of the prostate and breast were comparable with the random effects meta-analysis with no heterogeneity across studies (Supplementary Table 2).

Results after excluding the first two years of follow-up were unchanged (data not shown). Results of a complete-case analysis were comparable with the analysis using imputation (Supplementary Table 2). Stratification of cohorts by diabetes ascertainment (self-reported versus documented) resulted in similar pooled HRs for risk of total cancer and overlapping 95% CIs in both groups of cohorts (Supplementary Figure 2).

Effect modification by age groups, body weight status, and physical activity

After pooling all cohorts into one dataset, we found no evidence for effect modification of associations between diabetes and cancer incidence by age groups (Supplementary Table 3).

For BMI, a significant effect modification was observed for prostate cancer (P interaction < 0.001), where the inverse association with diabetes remained among overweight (BMI = 25- <30 kg/m²; HR = 0.77, 98% CI: 0.71-0.83) and obese individuals (BMI ≥ 30 kg/m²; HR = 0.81, 98% CI: 0.73-0.89), but was attenuated among normal weight individuals (BMI <25 ; HR = 0.94, 98% CI: 0.83-1.07) (Supplementary Table 4). There was some evidence for effect modification for total cancer in men and women combined (P interaction < 0.044), with a positive association observed among obese individuals (HR = 1.06, 98% CI: 1.01-1.10) and overweight individuals (HR = 1.04, 95% CI: 1.00-1.07), but not in normal weight individuals (HR = 1.01, 98% CI: 0.95-1.07) (Supplementary Table 4).

For physical activity, we observed little evidence for effect modification (Supplementary Table 5).

DISCUSSION

In this meta-analysis of individual-level participant data, bringing together seven prospective cohort studies of middle-aged and older populations in Europe and the United States with harmonized assessment of confounders and prevalent diabetes, collected prior to cancer diagnoses, we found little evidence for an association between prevalent diabetes and

development of all cancers combined. In analyses of data from the participating cohorts that provided information by anatomical site of cancer, we observed a positive association with risk of colorectal cancer in men, an inverse association with prostate cancer, and no association for risk of postmenopausal breast cancer. In sub-group analyses testing effect modification by body weight status, we observed stronger inverse associations for prostate cancer among overweight and obese individuals, as compared to normal weight individuals, with diabetes.

Previous research has shown that some cancers develop more commonly in patients with diabetes, while prostate cancer occurs less often in men with diabetes (5). The positive association between diabetes and colorectal cancer is consistent with previous findings (3,21). Our findings on the persistence of these associations into older age groups highlight the relevance of public health advice on diabetes prevention for reducing colorectal cancer risk. Further research into the underlying mechanisms of diabetes in colorectal cancer development at various age groups would also be important.

For prostate cancer, our results confirm earlier evidence showing an inverse association between diabetes and prostate cancer incidence (5,22,23). Specifically, a meta-analysis of summary data based on 9 studies reported an inverse association between diabetes and prostate cancer, with the RR being slightly stronger for low grade (RR = 0.74; 95% CI: 0.64-0.86) and localized disease (RR = 0.72; 95% CI 0.67-0.76) compared with high grade (RR = 0.78; 95% CI: 0.67-0.90) and advanced disease (RR = 0.85; 95% CI: 0.75-0.97) (24). Similarly, a meta-analysis of summary data reported a pooled RR of prostate cancer for the highest vs. lowest category of fasting blood glucose of 0.88 (95% CI: 0.78-0.98, n=15 studies) (25). A large meta-analysis with bias analysis reported a RR of 0.83 (95% CI: 0.79-0.88) for associations between diabetes and prostate cancer incidence, but bias analysis for unmeasured confounding suggested that this association was unlikely to be causal (23).

A Mendelian randomization (MR) approach using genetic variants as proxies for glycemic traits did not find strong evidence for a role of fasting glucose, glycated hemoglobin, and diabetes in prostate cancer (27). Assuming that all assumption for a MR analysis were met, this suggests that the observed associations in our study are potentially not causal. Men with diabetes have a lower level of prostate specific antigens than men without it (28) which may lead to less frequent diagnosis of prostate cancer, in particular for low-grade and localized disease.

In contrast to some previous observational studies (21,29), we found no evidence for an association between diabetes and the risk of postmenopausal breast cancer. Nevertheless, our findings are consistent with a MR analysis, which also showed a lack of association between genetically predicted diabetes and other glycemic traits, and breast cancer risk (27). In the meta-analysis of Ling et al., bias analysis also suggested that associations between diabetes and breast cancer risk were unlikely to be causal (23).

BMI and physical activity are modifiable factors that have been consistently related to risk of both diabetes (30,31) and cancers (12,32). The strength of association between diabetes and cancer risk may vary according to BMI and levels of physical activity (33). A prospective study reported that the increased risk of cancers associated with diabetes was limited to people less physically active or overweight/obese (34). In that study, diabetes was associated with risk of overall cancer with an HR of 1.15 (95% CI: 1.01–1.31) among men and women with diabetes, who reported low levels of physical activity (< 2.0 h per week) and 1.21 (95% CI: 1.07–1.37) among overweight or obese people ($\text{BMI} \geq 25 \text{ kg/m}^2$) (34). In our study, the associations for diabetes with colorectal and breast cancers risks were generally similar across BMI categories, whereas for total cancer and prostate cancer, associations were stronger with higher BMI, suggesting that the interaction between BMI and diabetes status may have different consequences according to tissue type or organ. Consistent with this

finding, Fall et al. (35) also observed a strong inverse association with prostate cancer among men with diabetes and a high BMI. We note that BMI was considered as a common cause of both diabetes and cancer (i.e. a confounder). In an alternative and possibly less likely scenario, BMI could be a mediator of the diabetes-cancer association (e.g. by diabetes therapy leading to weight gain); stratifying on BMI would then return an estimate of the direct effect of diabetes on cancer risk, which is less straightforward to interpret. We found some evidence that vigorous physical activity appears to offset some of the positive associations between diabetes and risk of total cancer (Supplementary Table 5). However, after multiple testing correction, the confidence interval of the interaction term included the null. A similar lack of power (Supplementary Text 1) concerns our exploratory subgroup analysis of diabetes associated with total cancer across BMI categories, and therefore follow-up studies are required.

We found little evidence that cancer risk associated with diabetes varied across age groups in our study (Supplementary Table 3). However, the focus of the CHANCES consortium was on older adults, which resulted in a relatively narrow age range of individuals at recruitment (inter-decile range: 53 to 69 years).

It has been hypothesized that associations between diabetes and cancer may be direct, or indirect due in part to shared predisposing risk factors such as obesity and physical inactivity (8). Indeed, plausible biologic mechanisms implicated in cancer initiation and progression include hyperinsulinemia (either endogenous due to insulin resistance or exogenous due to administered insulin), hyperglycemia, and chronic inflammation (36). Insulin activates a number of signaling pathways, which may lead to cellular proliferation (37). Hyperglycemia can affect tumor cells by increasing proliferation, inducing mutations (36,38), and inducing production of circulating growth factors (insulin/IGF-1) and inflammatory cytokines (39), which is associated with increased cancer risk (40).

Investigations using detailed information on glycemic control could help provide insight into the mechanisms behind the diabetes-cancer link. The inverse association observed between diabetes and prostate cancer may be explained by reduced testosterone levels among men with diabetes (41), although residual confounding cannot be excluded.

The current study has several strengths including: the large study size and large number of cancer cases among diabetes patients (11,176), thus providing sufficient statistical power for most analyses; and the prospective design of the cohorts with availability of individual-level data allowing for data harmonization and homogenous adjustment for confounding.

The results of this study should be interpreted considering the following limitations. Site-specific data on incident cancer was only available in three (prostate cancer) and four (breast and colorectal cancers) of the seven cohorts, respectively. Second, Cox PH regression assumes that all individuals under observation experience either the primary outcome (here: cancer) or non-informative censoring (26), which may not be best suited to estimating predictive relationships. We were, however, not able to estimate absolute risks due to lack of data on specific censoring events. Instead, we estimated cause-specific hazard ratios to answer the etiological question whether incidence of total cancer, and of common site-specific cancers, is higher among people with diabetes as compared to people without diabetes. This approach returns the total effect of the association between diabetes and risk of cancer that is not mediated through other conditions. This should be a valid cause-specific estimate for relative risk irrespective of whether people with diabetes also developed another condition, such as a cardiovascular disease, prior or after diabetes. We acknowledge the lack of information on the duration and treatment of diabetes. Some treatments, in particular biguanide metformin may reduce cancer incidence (13). However, Kowal et al., 2015, provided evidence that metformin has no protective effect on the incidence of cancer among

individuals with diabetes (42), or specifically with prostate cancer risk (43). No information
 was available about dynamic changes in or cumulative effects of risk factors such as BMI and
 physical activity during follow-up or about the subsequent initiation of medications that
 might affect cancer incidence. While this may have affected the identification of interactions,
 we doubt that any such effects could offer plausible explanations for the disparate findings
 across cancer sites and would rather attenuate any observed risk estimates. The
 disproportionate weight of the large AARP study, which contributed a much larger number of
cancer cases than the other studies combined, may also be a potential limitation, ~~specifically~~
~~for total cancer~~. To counter this, a random effects model was used in the main analysis, which
 gives smaller studies a relatively larger weight in the meta-analysis. However, the reported
results of the supplementary fixed effect meta-analysis and of the effect modification in the
pooled analysis should be interpreted with caution, because these findings may be driven by
the AARP study. In some of the included cohorts, diabetes was assessed by self-report.
 However, sensitivity analysis revealed similar associations with total cancer when sub-
 dividing cohorts by diabetes ascertainment (self-reported vs. documented). We also cannot
 exclude the possibility of residual confounding from unmeasured confounding factors,
 including diet, blood lipid concentrations and blood pressure, and by incomplete adjustment
 for physical activity, because both moderate-to-vigorous and light-intensity physical activity
 have also been shown to reduce cancer mortality (44) and the risk of breast (45) and total
 cancer (46).

Conclusions

Overall, our analysis among older populations in Europe and the United States did not
 demonstrate an association between diabetes and the risk of all cancers combined or
 postmenopausal breast cancer. We corroborate and extend previous evidence that diabetes
 appears to be a risk factor for colorectal cancer among older populations. Our observed

371 inverse association with prostate cancer risk contrasts with findings using an instrumental
372 variable approach. Further research is needed to confirm our findings and to consider
373 duration and treatment of diabetes.

ADDITIONAL INFORMATION

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Where authors are identified as personnel of the International Agency for Research on Cancer/ World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/ World Health Organization.

Authors' contributions

AA designed the analyses, analyzed the data, interpreted the results, and drafted the manuscript. IR, HF, and MJ contributed to the acquisition of data. IR and HF contributed to the statistical analysis and drafting of the manuscript. AA, HF, MJ, KKT, AT, PB, BVG, OM, TW, FK, BS, JMOM, SM, SS, KK, HB, and IR critically reviewed the manuscript. PB and AT coordinated the CHANCES Consortium. All authors read and approved the final manuscript. IR is the guarantor of this work.

AA, HF, and IR take responsibility as guarantors of the manuscript and affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; that any discrepancies from the study as planned have been explained; access to data; and the decision to submit and publish the manuscript.

Ethics approval and consent to participate

All studies participating in CHANCES were conducted in accordance with the Declaration of Helsinki. For each study, investigators satisfied the local requirements for ethical research, including obtaining informed consent from participants.

Consent to publish

Not applicable.

Availability of data and materials

The CHANCES participating cohorts' data are available only to the collaborating scientists from the respective CHANCES participating centers. The data may be available upon request for some of the participating centers but not for all due to relevant data protection laws.

Competing interests

The authors declare that they have no competing interests.

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Figure 1: Random effects meta-analysis of the association between diabetes and total cancer risk.

Models were adjusted for country, age (years), smoking status (never/ever), educational level (primary or less/primary or less than college or university/college or university), alcohol consumption (g/day), BMI, (kg/m²), and vigorous physical activity (yes/no).

The size of each box indicates the relative weight of each study in the meta-analysis; the horizontal bars show the 95% confidence intervals (CI). Diamonds represent the combined HRs and 95% CI.

Figure 2: Random effects meta-analysis of the association between diabetes and colorectal cancer risk.

Models were adjusted for country, age (years), smoking status (never/ever), educational level (primary or less/primary or less than college or university/college or university), alcohol consumption (g/day), BMI, (kg/m²), and vigorous physical activity (yes/no).

The size of each box indicates the relative weight of each study in the meta-analysis; the horizontal bars show the 95% confidence intervals (CI). Diamonds represent the combined HRs and 95% CI.

Figure 3: Random effects meta-analysis of the association between diabetes and prostate cancer risk.

Models were adjusted for country, age (years), smoking status (never/ever), educational level (primary or less/primary or less than college or university/college or university), alcohol consumption (g/day), BMI, (kg/m²), and vigorous physical activity (yes/no).

The size of each box indicates the relative weight of each study in the meta-analysis; the horizontal bars show the 95% confidence intervals (CI). Diamonds represent the combined HRs and 95% CI.