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Effect of adipose tissue quantity and dysfunction on the risk of cancer in individuals with and without type 2 diabetes

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ABSTRACT

Objective: To determine the role of waist circumference and metabolic dysfunction in the risk of cancer in individuals with type 2 diabetes (T2D) and to compare this to individuals without T2D.
Methods: Individuals with (n = 1925) and without T2D (n = 10,204) were included from the UCC-SMART cohort. Incident cancer diagnoses were obtained by linkage with the Netherlands Cancer Registry. Metabolic dysfunction was defined as ≥ 3 adapted NCEP ATP-III metabolic syndrome criteria. The effects of waist circumference and metabolic dysfunction on cancer were assessed using Cox proportional hazards models, adjusted for confounders.
Results: During a median follow-up of 8.3 years (IQR 4.2–13.1), 1740 individuals were diagnosed with cancer. Incidence rates of total cancer were 19.3 and 15.5/1000 person-years for individuals with and without T2D, respectively. In individuals without T2D, a higher waist circumference was associated with an increased risk of colorectal (per standard deviation: HR 1.23; 95%CI 1.03–1.46), urinary tract (HR 1.28; 95%CI 1.05–1.56) and total cancer (HR 1.06; 95%CI 1.02–1.13). Metabolic dysfunction was related to an increased risk of colorectal (HR 1.35; 95%CI 1.01–1.82), lung (HR 1.37; 95%CI 1.07–1.75) and total cancer (HR 1.13; 95%CI 1.01–1.25) in individuals without T2D. In individuals with T2D, no significant associations were found.
Conclusion: Incidence rates of cancer are higher among individuals with T2D. However, higher waist circumference and metabolic dysfunction are only associated with an increased cancer risk in patients without T2D. These findings provide novel insights into the role of metabolic dysfunction in the occurrence of cancer.

1. Introduction

Cancer is the second leading cause of death globally. In 2020, there were 18 million incident cancer cases worldwide and cancer was accountable for nearly one in six deaths. The incidence is expected to rise to 28 million cases per year in 2040 [1], underlining the importance of cancer prevention. A growing body of evidence demonstrates that type 2 diabetes (T2D) is an important risk factor for several types of cancer [2,3]. A large meta-analysis, including over 32 million people, reported T2D to be associated with a 15% (95% confidence interval [95%CI] 10–21%) increased risk of total cancer, compared to the individuals without T2D [3].

The pathophysiologic mechanism that underlies this increased risk is not entirely clear. In individuals without T2D, the quantity of adipose tissue as well as the degree of adipose tissue dysfunction is associated with an increased risk of cancer [4]. Adipose tissue expansion, defined as an increase in the number or volume of adipocytes, can lead to adipose tissue dysfunction. Adipose tissue dysfunction involves a pathological shift in the function of adipose tissue, driven by genetic and environmental factors, which in turn may lead to altered secretion of pro-inflammatory and pro-carcinogenic factors [4,5]. For individuals with T2D, there is no direct evidence on the association between adipose

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tissue dysfunction and the risk of cancer. Because individuals with T2D have already progressed towards clinically overt insulin resistance, it could be argued that adipose tissue dysfunction rather than the quantity of adipose tissue explains the variation in cancer risk in these individuals.

Obesity is an important risk factor for T2D through the development of adipose tissue dysfunction contributing to insulin resistance [5]. Studies investigating the association between quantity of adipose tissue and the risk of cancer in individuals with T2D mainly used body mass index (BMI) to quantify adiposity. For example, a recent meta-analysis concluded that each 5-unit increase in BMI was associated with a 6% higher risk of total cancer (RR 1.06, 95%CI 1.01–1.10) [6]. BMI can however not distinguish between lean and fat mass and provides no indication of body mass distribution [7]. Waist circumference more accurately reflects the amount of visceral adipose tissue and is a simple and inexpensive yet effective alternative [8].

While the association between adipose tissue quantity and incident cancer has been studied in individuals with and without T2D [9,10], the association between adipose tissue dysfunction and cancer risk has only been investigated in individuals without T2D [11]. In addition, none of these associations has been investigated in a population at high risk of CVD. There is a complex relationship between obesity, CVD and cancer, which is mediated by several factors, including body fat distribution and inflammation. Investigating the associations between adipose tissue quantity and dysfunction and incident cancer in a population at high risk of CVD may provide additional insights in these interrelated pathways. The aim of this study therefore was to evaluate the relation between waist circumference and incident cancer and the relation between adipose tissue dysfunction, determined by the presence of metabolic dysfunction, in individuals with and without T2D in a population with established CVD or severe cardiovascular risk factors.

2. Materials and methods

2.1. Subjects

The study population consisted of participants from the Utrecht Cardiovascular Cohort - Second Manifestations of ARTerial Disease (UCC-SMART) study. This is an ongoing, single-center prospective cohort study, designed to observe and analyze trends over time. It includes patients from 18 years of age referred to the University Medical Center Utrecht with established cardiovascular disease (CVD) or severe cardiovascular risk factors. The design and rationale of the UCC-SMART study have been described elsewhere [12]. For the current study, data from individuals included in the UCC-SMART study without pre-existent diabetes and with pre-existent T2D was used, thus excluding individuals with type 1 diabetes. T2D was defined as a self-reported history of T2D, use of oral glucose-lowering medication or insulin, or a fasting serum glucose concentration of $\geq$ 7 mmol/L combined with initiation of diabetes treatment (dietary advice, weight reduction or medication) within 1 year from inclusion. Individuals with a history of cancer (n = 540) were excluded. Study inclusion for the UCC-SMART cohort used for this study occurred between January 1999 and December 2020, as waist circumference has been systematically assessed from January 1999 onwards. The UCC-SMART study was approved by the Medical Ethical Review Committee of the UMC Utrecht and all participants provided written informed consent.

2.2. Data collection and study definitions

At baseline, participants completed a standardized questionnaire on medical history, cardiovascular risk factors and medication use. They also underwent physical examination, collection of fasting blood samples and an abdominal ultrasound. Adipose tissue quantity was assessed using waist circumference. Waist circumference was measured horizontally at the midpoint between the iliac crest and lower costal margin. The mean of two measurements was calculated. If the 2 measurements differed by > 2 cm, a third was taken and the mean of the closest 2 was calculated. Adipose tissue dysfunction was assessed using the presence of metabolic dysfunction. Metabolic dysfunction was defined as the presence of three or more of the following five traits: 1) systolic blood pressure (SBP) $\geq$ 130 mmHg, diastolic blood pressure (DBP) $\geq$ 85 mmHg, or treatment for hypertension; 2) fasting serum triglycerides $\geq$ 1.7 mmol/L or treatment for elevated triglycerides; 3) fasting high-density cholesterol (HDL-C) < 1.0 mmol/L in men or < 1.3 in women, or treatment for low HDL-C; 4) fasting glucose $\geq$ 5.6 mmol/L or use of glucose-lowering agents; 5) elevated C-reactive protein (CRP [$\geq$2 mg/L]). The first four criteria are similar to the criteria of the National Cholesterol Education Program (NCEP) ATP-III [13] for the definition of metabolic syndrome, with the waist circumference criterion replaced by elevated C-reactive protein (CRP) [14].

2.3. Data analyses

Missing data for smoking (0.5%), alcohol intake (1.2%), waist and hip circumference (2.8%), SBP (0.1%), DBP (0.5%), HDL-C (0.6%), triglycerides (0.6%), fasting glucose (0.5%) and CRP (8.5%) were singly imputed using predictive matching based on all covariate as well as outcome data. CRP values > 20 mg/L (n = 302) were set to 'missing' and imputed as well, as a CRP level above this threshold is more likely to be associated with an acute inflammatory response rather than adipose tissue dysfunction. Cox proportional hazards models were used to estimate hazard ratios (HRs) and corresponding 95% CIs describing the relation between both waist circumference and the presence of metabolic dysfunction and incident cancer, for both individuals with and without T2D. For the analyses of separate cancer types, the first diagnosis of that specific cancer type was taken as the outcome event, which means that this may not have been the first diagnosis of cancer during follow-up for a certain patient. To adjust for potential confounding factors, the models investigating the relation between waist circumference and incident cancer were adjusted for the following pre-specified confounders: age, sex, smoking status, pack-years of smoking and alcohol intake. The models investigating the relation between the metabolic dysfunction and incident cancer were adjusted for the same confounders. Potential effect modification by T2D, sex and smoking status was tested by adding multiplicative interaction terms to the models. Linearity between determinant and outcome was assessed in the fully adjusted models. The proportional hazards assumptions, tested visually by plotting scaled Schoenfeld residuals against time, were not violated. All analyses were performed with R statistical software (version 4.0.3; R foundation for Statistical Computing, Vienna, Austria). All p-values were two-sided, with statistical significance set at 0.05.

2.4. Follow-up and outcome assessment

Participants received annual questionnaires on outpatient clinic visits and hospitalizations. The outcome of interest for this study was total cancer and cancer types according to anatomical location. Data on cancer incidence was obtained by linking the UCC-SMART database to the Netherlands Cancer Registry (NCR), a population-based cancer registry with nationwide coverage since 1989. They receive notifications of all new cancer diagnoses in the Netherlands through the Dutch Nationwide Pathology Databank (*PALGA*) and hospital discharge diagnoses. Each cancer case is coded by trained registration clerks based on information gathered from medical files at the hospital [15,16]. Benign neoplasms (ICD-10 codes D10–36), in situ neoplasms (D00-D09), non-melanoma skin cancer (C44), polycythemia vera (D45), myelodysplastic syndromes (D46) and neoplasms of unknown or uncertain behavior (D37-D44 and D47-D48) were excluded. For the analysis of the association between adipose tissue quantity and incident cancer and the association between adipose tissue dysfunction and incident cancer, incidence of total cancer (consisting of the cancer types specified in

Supplementary Table S1) and of the five most common cancer types were analyzed. These included cancer of the lung (ICD-10 code C34), prostate (C61), colorectum (C18-C20), urinary tract (C64-C66 and C67-C68) and breast (C50). In addition, cancer cases were classified according to stage at diagnosis for individuals with and without metabolic dysfunction (data not shown). Incidence rates and HRs for the five most common cancer types after the types mentioned above were presented in Supplementary Table S2.

2.5. Sensitivity analyses

In order to further examine the association between the quantity of adipose tissue and incident cancer, the analyses were repeated with BMI and visceral adipose tissue (VAT). Weight and length were used to calculate BMI in kg/m^2. As the relation between BMI and total cancer was nonlinear for individuals without T2D (p for non-linearity <0.005), the nadir (the BMI value associated with the lowest hazard) instead of HR was reported. The nadir was derived as the minimum of the quadratic function that models the relation between BMI and incident cancer in individuals without T2D. VAT was measured by ultrasonography as the distance between the peritoneum and psoas muscles or lumbar spine using electronic calipers using an EPIQ-7 ultrasound machine (Philips Medical Systems, Eindhoven, The Netherlands). To further evaluate the association between adipose tissue dysfunction and incident cancer, the analyses were repeated using two other markers: the estimated glucose disposal rate (eGDR) in case of T2D and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) in case of absence of T2D. In individuals with type 1 diabetes and T2D, eGDR (mg/kg/min) is a validated alternative for the hyperinsulinemic euglycemic clamp, which is the reference standard for quantifying insulin resistance [17, 18]. It was calculated as follows: eGDR = 24.31 – (12.22 × WHR) – (3.29 × HT) – (0.57 × HbA1c), where WHR is waist-to-hip ratio, HT represents history of hypertension (0 = no, 1 = yes) and HbA1c level in %. Hypertension was defined as a baseline SBP ≥ 140 mmHg, a baseline DBP ≥ 90 mmHg or treatment with antihypertensive medication. Hip circumference was measured at the horizontal level around the buttocks that yielded the maximum measurement. As eGDR decreases with increasing insulin resistance, the HR with corresponding 95%CI denotes the decrease in risk for the event per 1 unit increase in eGDR. HOMA-IR was calculated according to the following formula: [fasting insulin (mU/L) × fasting glucose (mmol/L)] / 22.5 [19].

To evaluate the presence of reverse causality, analyses were repeated after excluding patients who were diagnosed with cancer within one, two and five year(s) after inclusion. Furthermore, because adiposity and adipose tissue dysfunction are particularly associated with an increased risk of postmenopausal breast cancer and not to premenopausal breast cancer, analyses were repeated in women who were postmenopausal at the time of a breast cancer diagnosis. Postmenopausal was defined as age 50 or older, which is the average age at menopause in the Netherlands [20].

3. Results

3.1. Baseline characteristics

A total of 10,204 participants without prevalent T2D and 2038 participants with T2D were included. Baseline characteristics stratified for the presence of T2D are shown in Table 1. Compared to individuals without T2D, individuals with T2D had a higher mean age (61 ± 10 years versus [vs.] 56 ± 12 years), were more often male (70% vs. 64%), had a higher mean waist circumference (101 ± 13 vs. 93 ± 13 cm) and more often fulfilled at least 3 criteria of metabolic dysfunction (79% vs. 48%).

Table 1
Baseline characteristics stratified by presence of T2D.

	No T2D (n = 10,204)	T2D (n = 1925)
Age (years)	56 ± 12	61 ± 10
Male sex	6488 (64)	1356 (70)
History of CVD	6542 (64)	1284 (67)
Diabetes duration (years)	-	4 (1–10)
HOMA-IR	2.3 (1.5–3.5)	-
eGDR (mg/kg/min)	7.1 (6.2–8.6)	5.6 (4.7–6.5)
Metabolic dysfunction	4877 (48)	1522 (79)
Current smoking	2733 (27)	460 (24)
Former smoking	4338 (43)	952 (49)
Number of pack-years	9 (0–25)	12 (0–31)
Current alcohol use	7545 (74)	1160 (60)
Medication use		
Blood pressure lowering medication	6700 (66)	1540 (80)
Oral glucose lowering medication	-	1303 (68)
Insulin	-	472 (25)
Statin	5498 (54)	1289 (67)
Systolic blood pressure (mmHg)	139 ± 22	144 ± 21
Diastolic blood pressure (mmHg)	83 ± 13	83 ± 12
Body mass index (kg/m^2)	26.6 ± 4.3	29.1 ± 5.0
Waist circumference (cm)	93 ± 13	101 ± 13
Visceral adipose tissue (cm)	8.4 ± 2.6	10.3 ± 2.8
Laboratory values		
LDL-cholesterol (mmol/L)	3.0 ± 1.2	2.6 ± 1.1
HDL-cholesterol (mmol/L)	1.3 ± 0.4	1.2 ± 0.3
Non-HDL-cholesterol (mmol/L)	3.8 ± 1.3	3.5 ± 1.3
Triglycerides (mmol/L)	1.3 (1.0–1.9)	1.6 (1.2–2.4)
eGFR (ml/min/1.73 m^2)	82 ± 18	78 ± 21
Fasting glucose (mmol/L)	5.7 ± 0.7	8.6 ± 2.8
HbA1c (mmol/mol)	37 ± 5	54 ± 14
HbA1c (%)	5.6 ± 0.4	7.1 ± 1.3
CRP (mg/L)	1.7 (0.9–3.7)	2.2 (1.0–4.6)

Data are presented as n (%), mean ± standard deviation or median (interquartile range).
Abbreviations: CRP, C-reactive protein; CVD, cardiovascular disease; eGDR, estimated glucose disposal rate; eGFR, estimated glomerular filtration rate (calculated with Chronic Kidney Disease Epidemiology Collaboration formula); HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-estimated insulin resistance; LDL, low-density lipoprotein; T2D, type 2 diabetes.

3.2. Association between waist circumference and incident cancer

During a total follow-up of 107,575 person-years (median 8.2 years; interquartile range [IQR] 4.1–13.1), 1740 individuals were diagnosed with cancer, of which 325 individuals had pre-existent T2D. Prostate (n = 338 [19.4% of the total number of cancer cases]), lung (n = 333 [19.1%]), colorectum (n = 246 [14.1%]), urinary tract (n = 180 [10.3%]) and breast (n = 145 [8.3%]) cancer were most often diagnosed (Fig. 1). Incidence rates were 19.3 and 15.5 per 1000 person-years for individuals with and without T2D, respectively. The resulting incidence rate ratio (IRR) for individuals with vs. without T2D was 1.24 (95%CI 1.10–1.40). Classification of cancer cases according to stage at diagnosis showed no large differences between individuals with and without metabolic dysfunction (data not shown).

In individuals without T2D, a higher waist circumference was independently associated with a higher risk of colorectal (per standard deviation [SD]: 1.23; 95%CI 1.03–1.46), urinary tract (HR 1.28; 95%CI 1.05–1.56), and total cancer (HR 1.06; 95%CI 1.02–1.13). In individuals with T2D, no significant associations between waist circumference and incident cancer were observed (Fig. 2). No interaction was observed by T2D in the relation between waist circumference and total cancer (p for interaction = 0.88), nor in the relation between waist circumference and specific cancer types (p for interaction all >0.05). In addition, no interaction was observed by sex and smoking status in these associations (p for interaction all >0.05). Results for models only adjusted for age and sex are provided in Supplementary Table S3.

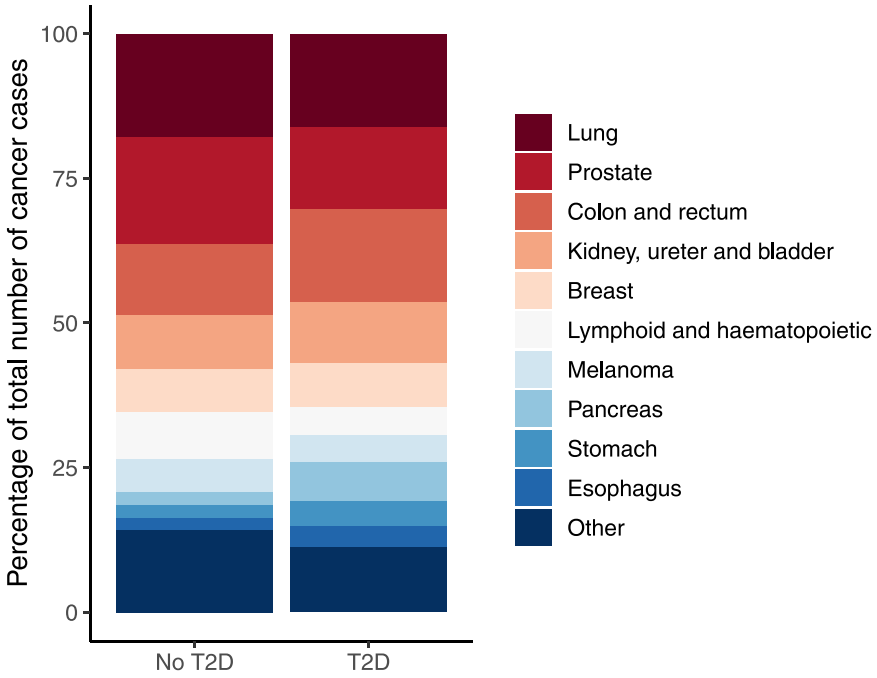

Fig. 1. Distribution of cancer types stratified by presence of type 2 diabetes. Category 'other' includes: lip, oral cavity and pharynx, small intestine, liver and bile ducts, gallbladder, nasal cavity, middle ear, accessory sinus, larynx and trachea, bone and articular cartilage of limb, mesothelial and soft tissue, vulva or vagina, cervix uteri or corpus uteri, ovarium, penis or testis, eye, brain and other parts of central nervous system, thyroid gland and ill-defined, secondary and unspecified sites. Abbreviations: T2D, type 2 diabetes.

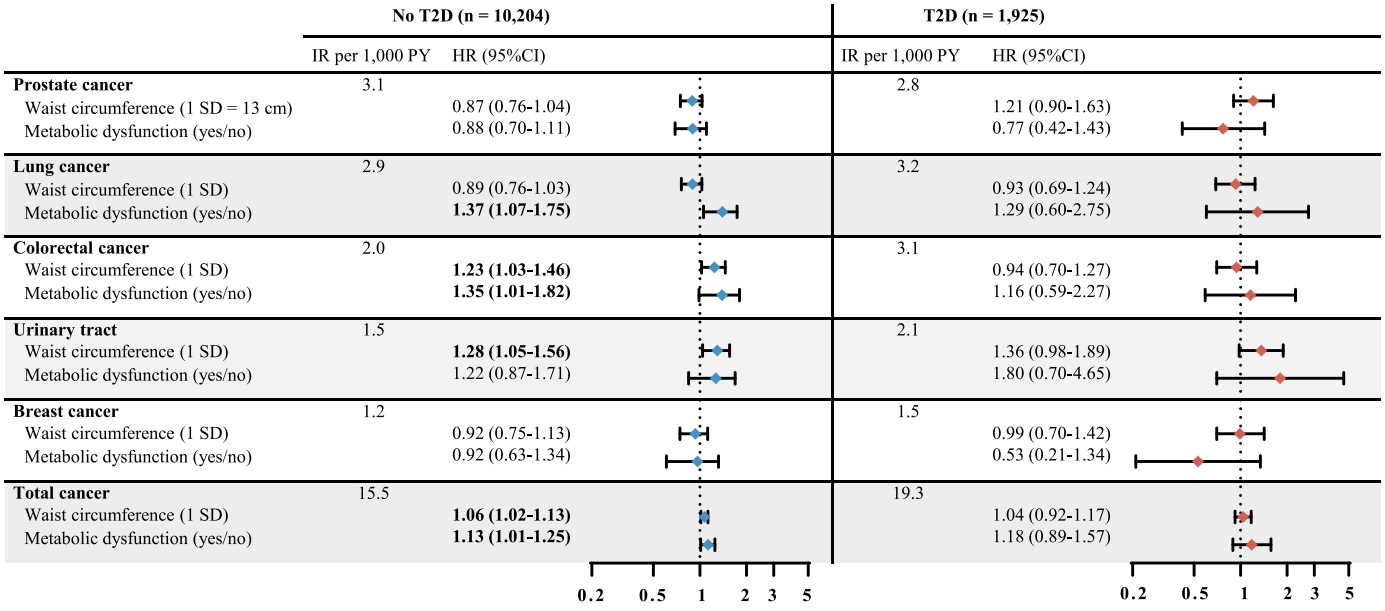

Fig. 2. Association between waist circumference and metabolic dysfunction and risk of cancer. Models were adjusted for age, sex, smoking status, pack-years of smoking and alcohol intake. Abbreviations: HR, hazard ratio; IR, incidence rate; PY, person-years; SD, standard deviation; T2D, type 2 diabetes.

3.3. Association between metabolic dysfunction and incident cancer

In individuals without T2D, the presence of metabolic dysfunction was associated with an increased risk of lung (HR 1.37; 95%CI 1.07–1.75), colorectal (HR 1.35; 95%CI 1.01–1.82) and total cancer (HR 1.13; 95%CI 1.01–1.25). Again, no significant associations were observed in individuals with T2D (Fig. 3). There was no effect modification by T2D in the association between metabolic dysfunction and total cancer (p for interaction = 0.58). Also, no effect modification by T2D in the association between metabolic dysfunction and specific cancer types was found (p for interaction all >0.05). Finally, no interaction was observed by sex and smoking status in these associations (p for interaction all >0.05).

3.4. Sensitivity analyses

When repeating the analyses with BMI and ultrasonographically measured VAT instead of waist circumference, there were no significant associations with incident cancer (Supplementary Table S3 and S4), except for the association between BMI and urinary tract cancer in

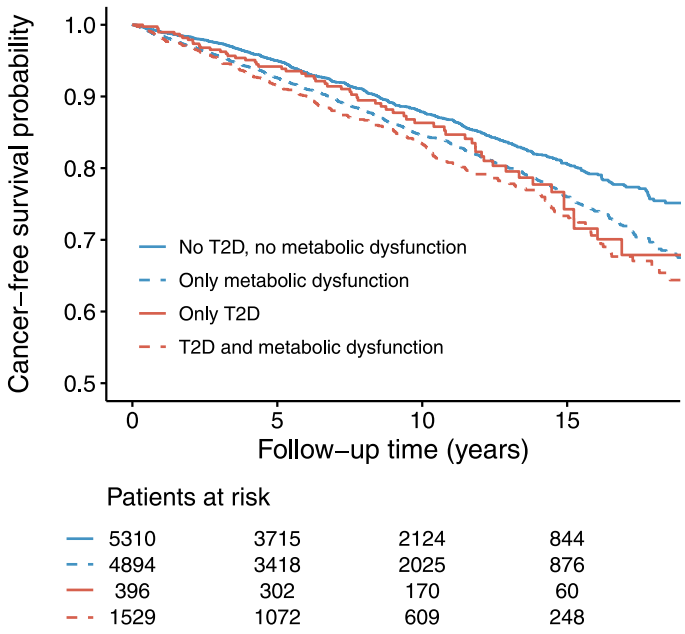

Fig. 3. Cancer-free survival according to presence of type 2 diabetes and metabolic dysfunction. Abbreviations: T2D, type 2 diabetes.

individuals without T2D (per SD: HR 1.24 [95%CI 1.06–1.45]). With regard to the association between BMI and total cancer in individuals without T2D, the nadir was 29.5 kg/m^2 (Supplementary Fig. S1). No significant associations were observed for HOMA-IR and eGDR as measures of adipose tissue dysfunction in relation to incident cancer, for both individuals with and without T2D. The possibility of reverse causality was evaluated by excluding patients who were diagnosed with cancer within 1 (n = 158), 2 (n = 278) or 5 (n = 689) year(s) and this did not result in substantial changes in HRs (data not shown). Exclusion of premenopausal breast cancer cases (n = 17, all without T2D) resulted in stronger but still not statistically significant associations between waist circumference and metabolic dysfunction and the risk of cancer (data not shown).

4. Discussion

The present study shows that incidence rates of cancer are higher among individuals with T2D compared to individuals without T2D. In individuals without T2D, a higher waist circumference was related to an increased risk of colorectal, urinary tract and total cancer. The presence of metabolic dysfunction was related to a higher risk of colorectal, lung and total cancer in the non-T2D individuals. In individuals with T2D, no association between both waist circumference and metabolic dysfunction and the risk of cancer was found.

The association between quantity of adipose tissue and the risk of cancer in individuals without T2D is well recognized [9,21–23]. A study in participants from the UK Biobank reported an increase in risk of total cancer (HR 1.04; 95% 1.03–1.05) per SD increase in waist circumference [24], which is comparable to the increase found in the current study. Of the five cancer types analyzed in the present study, colorectal, kidney (being part of the broader 'urinary tract cancer' endpoint) and postmenopausal breast cancer are considered to be obesity-related [21]. Cancer, in particular obesity-related cancer, shares many risk factors with CVD, including obesity, diabetes, hyperlipidemia and smoking [25]. This will be discussed in more detail later. Although optimal cutoff values in waist circumference differ between men and women [8], no interaction by sex was observed in the association with incident cancer. Moreover, no significant associations were observed between BMI and risk of cancer. In individuals without T2D, BMI had a U-shaped relation with total cancer, with an optimal BMI value of 29.8 kg/m^2. This finding of a non-linear relation with higher BMI values being associated with a lower risk of cancer has been observed in previous studies [7,26] and may be explained by the inability of BMI to discriminate fat mass and lean body mass.

The current study also demonstrated that the presence of metabolic dysfunction confers an increased risk of cancer in individuals without T2D. This notion is supported by previous studies [11,27,28]. A meta-analysis found the presence of the metabolic syndrome to be related to liver, colorectal and bladder cancer in men and endometrial, pancreatic, colorectal and postmenopausal breast cancer in women [11]. The existence of an association between metabolic dysfunction and incident colorectal cancer was confirmed by the current study. In individuals with T2D, the association between metabolic dysfunction and cancer has not been investigated before.

The current study also showed a statistically significant association between metabolic dysfunction and the risk of lung cancer, while this type of cancer is not considered to be obesity-related. A possible explanation is that lung cancer is strongly related to chronic low-grade inflammation through multiple pathways [29], of which one may have its origin in metabolic dysfunction. Metabolic dysfunction is characterized by chronic low-grade inflammation due to secretion of numerous adipocytokines by visceral adipose tissue. Altered secretion of several of these adipocytokines, including leptin, adiponectin, plasminogen activator inhibitor-1, tumor necrosis factor-alpha and interleukin-6 plays an important role in carcinogenesis and cancer progression through not only inflammation but also insulin resistance [4]. The CANTOS trial, a randomized controlled trial of canakinumab in patients with a history of a myocardial infarction, supports the existence of a link between inflammation and lung cancer. This trial showed that targeting inflammation by an interleukin-1β antibody lowered the incidence of CVD, as well as lung cancer and lung cancer mortality [30,31]. Another hypothesis in the association between metabolic dysfunction and cancer is that metabolic dysfunction may be a surrogate marker of other cancer risk factors, such as low physical activity, smoking habits and diet [11]. It should be noted that CRP levels, being part of the metabolic dysfunction definition, are generally higher in patients with cancer compared to patients without cancer [32]. However, it is unlikely that high CRP levels in the current study were a consequence rather than a cause of cancer, as exclusion of patients who were diagnosed with cancer within the first years did not result in substantial changes in HRs.

The link between the quantity of adipose tissue, adipose tissue dysfunction and T2D is not fully elucidated. In lean, healthy individuals, adipose tissue is mainly stored in subcutaneous depots. From there, stored triglycerides can be mobilized when needed. In addition, the depot functions as an insulator to prevent heat loss [33]. When the storage capacity of the subcutaneous depots is exceeded, adipose tissue starts to accumulate in other areas. These areas include epicardial, perivascular, intrahepatic, retroperitoneal, mesenteric and omental fat, of which the latter three can be considered 'visceral fat' [33]. Visceral fat releases free fatty acids (FFA) into the portal circulation. These FFA lead to dyslipidemia by directly influencing the lipid metabolism as well as hepatic insulin resistance through FFA uptake by the liver. Visceral fat thereby contributes to the components of metabolic dysfunction, including inflammation [34]. Importantly, some individuals with obesity mainly accumulate fat in their subcutaneous depots and thereby remain insulin-sensitive, although their BMI would classify them as being obese. This phenomenon is also known as 'metabolically healthy obese' and these individuals have a lower risk of developing T2D and CVD. Hence, the risk of obesity-related complications is mainly driven by the distribution of adipose tissue [33].

As mentioned before, obesity is strongly related to insulin resistance through altered secretion of adipocytokines. If pancreatic beta cells become unable to compensate for the reduced insulin sensitivity, this eventually leads to T2D. Insulin resistance is thought to increase the risk of cancer mainly via insulin and insulin-growth factor-1, which contribute to cell proliferation and inhibit apoptosis. The IRR for total cancer for individuals with vs. without T2D found in the current study was comparable to the IRRs found in other studies [35,36]. It is worth noting that as of 2014, a population-based colorectal cancer screening program was introduced in the Netherlands for individuals aged 55–75 years, which has led to a decrease in overall and advance staged colorectal cancer [37].

This study also shows that in individuals with T2D, neither waist circumference nor the presence of metabolic dysfunction was statistically significant associated with incident cancer. A first possible explanation is that individuals with T2D have reached such a far state of insulin resistance that not only the quantity of adipose tissue, but also the presence of metabolic syndrome no longer determines their cancer risk. It is important to note that T2D is a heterogenous disease. A previous study identified five subgroups with differing disease progression and risk of diabetes complications, labelled as 'severe autoimmune diabetes (SAID) ', 'severe insulin-deficient diabetes (SIDD)', 'severe insulin-resistant diabetes (SIRD)', 'mild obesity-related diabetes (MOD)' and 'mild age-related diabetes (MARD)' [38]. As our study population consisted of patients with or at high risk of CVD, the majority of our study population with T2D can probably be categorized as having SIRD and MOD. A second explanation for the absence of a significant association may be that the components of metabolic dysfunction are influenced by treatment but are not causally related to incident cancer. This would also explain why 'only' 79% of the individuals with T2D fulfilled 3 or more criteria of metabolic dysfunction in the present study. Finally, the lack of significant associations could of course also be caused by limited statistical power. It should be noted that the point estimates for the association between waist circumference and total cancer as well as the association between metabolic dysfunction and total cancer in individuals with T2D is similar to that for individuals without T2D, though with a wider confidence interval.

The findings of this study emphasize the importance of obesity prevention. As obesity is not only a risk factor for cancer but also for CVD, obesity prevention is even more important in the current study population at high risk of a (subsequent) CVD event. The overlap in risk factors for cancer and CVD suggests that these diseases also share underlying genetic and molecular pathways, such a systemic low-grade inflammation [29]. Weight reduction reduces both visceral obesity and insulin resistance [5] and thereby potentially lowers the risk of cancer. A posthoc analysis of the Look AHEAD trial showed that an intensive life style intervention aimed at weight loss may lower the incidence of obesity-related cancers by 16% (HR 0.84; 95%CI 0.68–1.04) in individuals with T2D, although the study was likely underpowered [39].

Strengths of the present study include the prospective study design with long term and complete follow-up, attained through linkage with the Netherlands Cancer Registry. This registry is considered to have a near complete coverage [16]. Potential limitations also need consideration. Despite the large number of total cancer events, the number of some site-specific cancers was insufficient to detect potential significant relations, particularly in individuals with T2D. The limited statistical power may also explain the lack of statistical evidence for effect modification by T2D. Therefore, we decided to present the results for people with and without T2D separately, allowing readers to evaluate the associations within each group. In addition, as with all etiologic studies, residual confounding cannot be ruled out. Information on possible confounders for some cancer sites, such as socioeconomic status and lifestyle including dietary pattern, was not available.

In conclusion, although a higher waist circumference and metabolic dysfunction are associated with an increased risk of cancer in patients without T2D, this was not the case in patients with T2D. These findings provide novel insights into the role of metabolic dysfunction in the occurrence cancer and underline the importance of obesity prevention.

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Ethical statement

The authors declare that the study was conducted in accordance with the Declaration of Helsinki and was carried out with the adequate understanding and written consent of participants. Formal approval to conduct the study has been obtained from the Medical Ethical Review Committee of the UMC Utrecht, which can be provided upon request.

CRediT authorship contribution statement

Marga Helmink: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Jan Westerink**: Conceptualization, Methodology, Supervision, Validation, Writing – review & editing. **Steven Hageman**: Methodology, Validation, Writing – review & editing. **Miriam Koopman**: Validation, Writing – review & editing. **Manon van der Meer**: Validation, Writing – review & editing. **Martin Teraa**: Validation, Writing – review & editing. **Ynte Ruigrok**: Validation, Writing – review & editing. **Frank Visseren**: Conceptualization, Methodology, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

All authors declare no conflict of interest. The UCC-SMART study was financially supported by a grant of the University Medical Center Utrecht, the Netherlands. The supporting sources had no involvement in study design, analysis, interpretation, writing of the results, or the decision to submit for publication.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.orcp.2023.09.004.

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