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SHORT COMMUNICATION

Diabetes influences cancer risk in patients with increased carotid atherosclerosis burden

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Abstract *Background and aims:* Atherosclerosis and cancer share several risk factors suggesting that at least in part their pathogenesis is sustained by common mechanisms. To investigate this relation we followed a group of subjects with carotid atherosclerosis at baseline up for malignancy development.
Methods and results: we carried out an observational study exploring cancer incidence (study endpoint) in subjects with known carotid atherosclerosis at baseline (n = 766) without previous cancer or carotid vascular procedures. During the follow-up (160 ± 111 weeks) 24 cancer occurred, corresponding to an overall annual incidence rate of 0.11%. 10 diagnosis of cancer occurred in individuals with a carotid stenosis >50% (n = 90) whereas 14 in patients with a carotid stenosis <50% patients (n = 676) ($p < 0.001$). Respect to patients without cancer, diabetes was markedly more common in subjects with cancer diagnosis during the FU (37.3%vs75.0%, $p < 0.001$). After controlling for classic risk factors, carotid stenosis >50% (HR = 2.831, 95% CI = 1.034–5.714; p = 0.036) and diabetes (HR = 4.831, 95%CI = 1.506–15.501; p = 0.008) remained significantly associated with cancer diagnosis.
Conclusions: to our knowledge this is the first study reporting a significant risk of cancer development in subjects with diabetes and high risk of cerebrovascular events, highlighting the need of a carefully clinical screening for cancer in diabetic patients with overt carotid atherosclerosis.

Introduction

Atherosclerosis and cancer are chronic multifactorial diseases, often co-existing, which are the two most important causes of mortality worldwide [1]. The two disorders share several risk factors suggesting that at least in part their pathogenesis is sustained by common mechanisms [2].

In atherosclerosis and cancer an uncontrolled cell proliferation and a cell cycle progression have been implicated, although at different extent, as a pivotal process resulting from the interplay among several factors including genetic defects, low-grade inflammation and oxidative stress [3]. Angiogenesis and apoptosis, both hallmarks of atherosclerosis and cancer evolution, are often triggered by intracellular metabolic stimuli resulting from synergic effects of risk factors such as obesity, hyperglycemia, hypertension and hypertriglyceridemia [4].

Recently, Fasehee H and collegues reported a tumorigenesis proteomic profile in advanced atherosclerotic plaque of

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human coronary artery [5]. Therefore, increasing evidences suggest that individuals with atherosclerotic plaques might host several biochemical characteristics of neoplastic cell proliferation.

Type 2 diabetes (T2D) is a strong risk factor for atherosclerosis and its complications [6] but multiple studies have claimed that T2D is also associated with an increased risk of cancer at several sites including liver, pancreas, endometrium, colorectum, breast and bladder [7].

The aim of the study was to investigate the unexplored but possible relation between clinical atherosclerosis and new cancer diagnosis. To this purpose, we followed a group of subjects with known carotid atherosclerosis at baseline up for malignancy development.

Methods

In this single-center, observational study we analyzed a large cohort of participants (n = 3444) performing a carotid ultrasound evaluation at the Center for Atherosclerosis of the Policlinico Tor Vergata in Rome in 2014–2018. All individuals underwent an extensive demographic and clinical data registration. Hypertension was defined as systolic BP level of ≥140 mmHg and/or diastolic BP level of ≥90 mmHg or if patients taking any medication or other treatment for hypertension. Dyslipidemia was defined if patients taking any treatment for dyslipidemia such as statins and/or ezetimibe or fibrates.

During the carotid ultrasound evaluation participants gave written informed consent and the Institutional Ethics Review Board of the University of Rome Tor Vergata approved this study. Exclusion criteria included previous carotid vascular procedures, previous cancer, liver disease, renal insufficiency, heart failure, coagulopathy or any other severe systemic disease.

The follow-up was performed by phone interview and lasted up to 4 years (6–48 months). The study endpoint was a new diagnosis of any type of cancer. Information on endpoint was sought by phone interviews and confirmed by review of hospital records. Completed data were available for 766 subjects. We excluded from analysis 1698 patients who did not answer to phone interview and 980 patients for missing data on clinical or demographic information.

Carotid ultrasound analysis

Cohort participants performed a carotid ultrasound at the beginning of follow up. Carotid ultrasounds were conducted using the Esaote Mylab System (Ref 101620000) using a VF 13–5 linear array transducer. Guidelines from Expert Consensus Recommendations of the American Society of Neuroradiology were used for the study protocol [8]. As study convention we defined the presence of significant carotid atherosclerosis burden in case of carotid plaque in one or more carotid arteries as having wall thickening >50% of the thickness of the surrounding wall. Two different blinded experts (RS and LS) red all images and measurements with replicate readings performed on 5% of the cohort participants with results indicating an intraclass correlation value of 0.93.

Statistical analysis

Patients' characteristics were reported as mean and standard deviation (±SD) for continuous variables whereas percentages were used for categorical ones. Correlations between continuous variables were estimated using Spearman correlation. Time-to-event data were analyzed by means of log-rank test or univariate Cox-models for categorical or continuous variables, respectively. Significance of cancer diagnosis was also assessed at multivariate Cox-modeling, after adjusting for possible relevant confounders. The maximum events to number of predictors ratio was fixed at eight (Table 3), and the model was chosen by minimizing the Akaike Information Criterion (AIC) in a forward fashion. All calculations were made by using a standard statistical package (SPSS for Windows 16.0 e Chicago, Illinois, USA).

Results

Clinical characteristics of patients, divided upon presence of one or more carotid plaques >50% (CP>50%), are summarized in Table 1. Respect to subjects without significant carotid atherosclerosis (CP<50%), CP>50% individuals were markedly older ($p < 0.001$) whereas sex distribution, BMI, CRP and pharmacological therapy were similar.

Table 1 Baseline demographic and clinical characteristics of patients divided upon presence of carotid plaques stenosis >50% or <50%.

	CP>50% (n = 90)	CP<50% (n = 676)	p
Age (y)	76.2 ± 9.1	59.9 ± 16.9	<0.001
BMI	26.8 ± 4.9	28.2 ± 5.4	0.128
CRP	9.8 ± 25.0	7.2 ± 17.8	0.738
Female (%)	47.7	46.6	0.472
Smokers o former smokers (%)	63.3	55.0	0.084
Diabetes (%)	53.3	36.5	0.002
Hypertension (%)	81.1	61.5	<0.001
Dyslipidemia (%)	57.7	44.2	0.010
Number of cancer diagnosis during FU	10	14	<0.001
Pharmacological Therapy			
Metformin (%) *	47	52	0.412
Oral hypoglycemic agents (%)*§	35	35	0.884
Insulin (%)*	18	13	0.239
Angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists (%)	83	78	0.338
Diuretics (%)	35	25	0.135
Calcium-antagonist (%)	35	34	0.766
Beta-blockers (%)	51	46	0.291
Antiplatelet agents (%)	86	81	0.117
Statins (%)	55	57	0.659

CP>50%: Individuals with carotid placques stenosis >50%; CP<50% Individuals with carotid placques stenosis <50%. (*) Therapy referred to only diabetic patients. (§) Oral hypoglycemic agents different from Metformin.

Table 2 Clinical characteristics of patients according to the presence or absence of cancer.

	A (n = 24)	B (n = 742)	p
Age (y)	73.5 ± 10.1	61.5 ± 17.0	0.001
BMI	28.0 ± 6.1	28.1 ± 5.3	0.957
CRP	5.8 ± 4.5	7.8 ± 20.1	0.669
Female (%)	37.5	47.0	0.238
Smokers o former smokers (%)	50.0	56.2	0.344
Diabetes (%)	75.0	37.3	<0.001
Hypertension (%)	92.6	63.0	0.002
Dyslipidemia (%)	62.5	45.2	0.072
Carotid plaques stenosis >50% (%)	41.6	11.0	<0.001

A: Individuals with diagnosis of cancer during follow up. B: Individuals without cancer diagnosis during follow up.

Among the classic atherosclerotic risk factors CP>50% patients were more frequently affected by diabetes, hypertension and dyslipidemia but the rate of current or former smokers was similar.

During the follow-up (160 ± 111 weeks) 24 cancer diagnosis occurred, corresponding to an overall annual incidence rate of 0.11%. Individual with CP>50% had a higher rate of cancer diagnosis during the FU respect to CP<50% participants ($p < 0.001$). In fact, as shown in Table 1, 10 cancers occurred in CP>50% subjects (n = 90) whereas 14 in CP<50% patients (n = 676). In CP>50% subjects we observed 1 bladder, 3 breast, 1 lung, 2 colorectal, 1 prostate, 1 pancreas and 1 rhynopharynx cancers respect to 3 prostate, 4 lung and 3 breast, 3 colorectal cancers and 1 lymphoma in CP<50% participants (Supplementary Table).

Then we sorted study participants according to the presence/absence of cancer during the FU (Table 2). When compared with no cancer individuals, subjects who had cancer during the follow-up were significantly older ($p < 0.001$), more frequently affected by hypertension ($p = 0.002$) and with higher carotid atherosclerotic burden ($p < 0.001$) but with a similar rate of smoking habit, dyslipidemia, and equivalent BMI and CRP. Of note, respect to patients without cancer, diabetes was markedly more common in subjects with cancer during the FU (37.3%vs75.0%, $p < 0.001$).

The presence of carotid atherosclerotic plaques >50% was significantly associated with cancer diagnosis at follow up (HR = 5.691, 95%CI = 2.527−12.814, $p < 0.001$).

Table 3 Cox regression model for cancer diagnosis.

	Hazard ratio (HR)	95% CI for HR		p
Age (y)	1.051	1.002	1.101	0.044
Sex (male)	2.418	0.808	7.235	0.114
Active smoke or former smoke	2.766	0.908	6.628	0.102
BMI	0.986	0.891	1.090	0.776
Diabetes	4.831	1.506	15.501	0.008
Hypertension	1.934	0.403	9.292	0.410
Dyslipidemia	0.713	0.259	1.963	0.713
Carotid placques stenosis >50%	2.831	1.034	5.714	0.036

Finally, we created a multivariate model for cancer diagnosis including sex, age, BMI, smoke habit, hypertension, diabetes, dyslipidemia and presence of carotid plaques >50% as covariates. Carotid stenosis >50% (HR = 2.831, 95%CI = 1.034−5.714; p = 0.036) and diabetes at the baseline (HR = 4.831, 95%CI = 1.506−15.501; p = 0.008) remained significantly associated with cancer diagnosis (Table 3).

Discussion

In this study, after adjustment for several common oncogenic risk factors, we found a significant association between elevated carotid atherosclerotic burden and subsequent cancer diagnosis. Interestingly, among classic risk factors only diabetes remained significantly associated with study outcome. Our data suggest a specific interaction between diabetes and atherosclerosis to increase cancer risk. We can speculate that diabetes through several mechanisms including hyperinsulinemia, hyperglycemia, IGF, increased ROS and inflammation, may influence simultaneously atherosclerotic and the neoplastic process, acting as an accelerating and bridging mechanism [9,10]. Since both diabetes and atherosclerosis are characterized by an altered lipid metabolism but dyslipidemia did not emerge as independent risk factor in our analysis, we speculate that a lipid metabolic pathway not related to cholesterol metabolism might interconnect diabetes, atherosclerosis and cancer. Actually, very recently, LXR-623 (WAY-252623), a liver X receptor agonist involved in glucose homeostasis, able to reduce atherosclerotic plaque progression, was indicated as a possible antitumor agent in breast cancer and in glioblastoma cells [11].

The causative effect of diabetes and how this relates to increased cancer risk is still not fully understood even if seems to be linked through metabolic control. Hyperglycemia causes continuous ROS exposure, affects mitochondrial oxidative phosphorylation and increases mitochondrial DNA mutations [4]. Similarly, LOX-1, a lectin-like 50-kD receptor belonging to class E scavenger receptors, reducing NO levels elicits smooth muscle cell proliferation [12], stimulates monocyte chemotaxis raising inflammatory citokines, endothelial dysfunction and plaque formation. Interestingly, Ox-LDL and LOX-1 are also involved in several mechanisms closely linked to tumorigenesis such as cell transformation state in diverse cancer cell lines and in tumor growth. Thus, individuals with high levels of circulating ox-LDL and LOX-1 expression, such as diabetic patients, seem to be more prone to develop cancer, implying a mechanistic overlap in the pathobiology of atherogenesis, diabetes and tumorigenesis. Recently, Ling J and colleagues demonstrated that the down regulation of matrix metalloproteinase (MMP) inhibitor TIMP3 is the target of CDK8 mediated colon cancer growth in the liver [13]. Interestingly, we previously reported that a similar down regulation of TIMP3 causes insulin resistance in type 2 diabetic patients leading to an increased generation of TNF-alpha and IL-6 levels [14,15]. Of note TIMP3 is also reduced in atherosclerotic plaques [16].

Noteworthy, even if the positive association between tobacco smoking and the risk of various sited of cancer has been consistently observed, in our study smoking habit was not significantly associated to increased cancer risk. One possible explanation is that in our study the number of smoked cigarettes such as the number of involuntary smokers are missing [17].

This work has some limitations. First, it is not possible to understand the extent to which diabetes and atherosclerosis could together, if present simultaneously, increase the risk of cancer. Another important limitation is the limited number of covariates available for regression model respect to relative large number of subjects included in the study. On the contrary, we collected information about pharmacological therapy. Although we did not observe any significant influence of pharmacological therapy on results, this clinical information is certainly a strength of the study. In fact, metformin, diuretic family, statins and aspirin have been reported to modulate cancer risk in various reports [18]. In conclusion, even if this report needs replication in prospective larger studies, to our knowledge this is the first study reporting a significant risk of cancer development in subjects with diabetes and high risk of cerebrovascular events, highlighting the need of a carefully clinical screening for cancer in patients with overt clinical atherosclerosis.

Declaration of Competing Interest

All the authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.11.016.

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