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Original Article

Cardiol Res. 2025;16(3):202-211

Progression of Atherosclerosis and Hypothesis on the Relationship Between Microvascular Dysfunction, Cardiovascular Risk, and Cancer

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Abstract

Background: The extent of atherosclerosis in healthy men and women was measured using ultrasound in the carotid artery and whether the progression could be predicted using the classic risk factors was investigated. A hypothesis was also formulated as to how microvascular dysfunction and atherosclerosis, on the one hand, and cardiovascular disease and cancer, on the other hand, might be related. To describe the relationship between atherosclerosis and cancer, the classic risk factors and plaque burden were compared.

Methods: From 2009 to 2024, 10,597 subjects (44% women) aged 20 - 65 years without signs of cardiovascular disease were examined using ultrasound of the carotid artery. The sum of all plaque areas (total plaque area (TPA)) and the maximum plaque thickness were measured. Follow-up examinations were carried out on 4,520 subjects (42% women) aged 40 - 65 years. In 2,397 men without cancer or cardiovascular events during follow-up, the classic risk factors and plaque burden were compared between 55 men who had a solid tumor and 188 men who had a cardiovascular event, and whether patients with cancer and a cardiovascular event exhibited different risk profiles was examined.

Results: In the age group of 35 - 65 years, 12% of men and 4.2% of women had advanced atherosclerosis (types III and IVb). In the age group of 40 - 65 years, 2,592 men and 1,928 women were followed up. Low to moderate atherosclerosis was present in 2,052 (79.2%) men and 1,761 (91.3%) women. Advanced atherosclerosis developed in 139 (6.8%) men and 39 (2.2%) women, which could not be predicted by the classical risk factors ($P > 0.05$). The mean follow-up time was 73 months (6.1 years) for men and 75 months (6.3 years) for women. Patients without cancer or cardiovascular disease have lower risk factors and lower plaque burden compared to men with cancer or cardiovascular events. Patients with cancer have very similar high-risk factors and high plaque burden compared to patients with cardiovascular disease.

Conclusion: By measuring the plaque burden on the carotid artery, a good risk stratification can be achieved in every age group. A follow-up examination every 3 - 5 years is advisable, as a rapid progression of the disease cannot be predicted taking into account the classic risk factors. Early treatment of advanced atherosclerosis improves the prognosis for cardiovascular diseases and possibly also for certain types of cancer. Patients with cancer and cardiovascular events show a similar risk profile and plaque burden.

Keywords: Microvascular dysfunction; Atherosclerosis; Cardiovascular risk; Cancer; Carotid ultrasound

Introduction

Atherosclerosis is the most common cause of death in industrialized countries. It is a systemic disease of the arteries that manifests itself in the entire vascular system. Cardiovascular diseases such as heart attacks, strokes, and peripheral arterial disease (PAD) are the most common. The small vessels can also be affected, which manifests itself in the heart through coronary microvascular dysfunction [1]. There is evidence that cancer is also associated with atherosclerosis and impaired microcirculation [2-10]. In every age group, there are people with a high plaque burden and rapid progression of the disease within a few years.

Ultrasound examination of the carotid artery can detect people with advanced disease in the subclinical stage and treat them early, which can improve the prognosis [10]. The extent of the disease can be easily determined by measuring plaque area (total plaque area (TPA)) and maximum plaque thickness with ultrasound. The aim of the study was to investigate the extent of atherosclerosis by sex and age group and whether the individual course of the disease can be predicted. Furthermore, the classic risk factors and plaque burden were compared in men with new cardiovascular events and cancer.

A hypothesis was formulated as to how microvascular dysfunction and atherosclerosis on the one hand and cardiovascular disease and cancer on the other hand could be related.

Manuscript submitted January 17, 2025, accepted March 31, 2025
Published online April 11, 2025

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doi: https://doi.org/10.14740/cr2049

Materials and Methods

Study design

This was a retrospective study. All described investigations and evaluations on humans were conducted with the approval of the responsible ethics committee. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Study population

Between 2009 and 2024, an ultrasound examination of the carotid artery was offered as part of occupational health screening in companies in various sectors (chemicals, glass, pharmaceuticals, administration, metal, social services, paper, printing, ceramics, IT, university, university of applied sciences, and retail) in the region around Koblenz.

A total of 10,597 subjects (44% women) aged 20 - 65 years without signs of cardiovascular disease were examined by ultrasound of the carotid artery, and the sum of all plaque areas (TPA) and the maximum plaque thickness were measured.

A portable ultrasound device from Kontron Medical, type Imagic Agile, with a 10 MHz linear scanner was used.

Carotid plaque measurements

The measurement method was performed as previously published [10]. The classification of ultrasound findings was developed in an independent population of patients who were examined 1 day before a planned coronary angiography.

A low risk corresponds to ultrasound findings types I and IIa, a medium risk to findings types IIb and IVa, and a high risk to findings types III and IVb.

Follow-up examinations were carried out on 3,813 subjects (42% women) with a low to medium risk aged 40 - 65 years (follow-up men 57.8%, women 51.1%).

Baseline and follow-up examinations

At baseline and follow-up examinations, history of previous cancer and cardiovascular disease (myocardial infarction, stroke, coronary artery bypass grafting (CABG), and percutaneous transluminal coronary angioplasty (PTCA)) was obtained. Follow-up examinations were carried out on 3,813 subjects (42% women) with a low to medium risk aged 40 - 65 years (follow-up men 57.8%, women 51.1%). The proportion of subjects who changed from a low and medium risk of plaque to a high risk was determined and whether this was predictable taking into account the classic risk factors (lipids, hypertension, diabetes, smoking, familial risk, and body mass index).

In 2,397 men without cancer or cardiovascular events during follow-up, the classic risk factors and plaque burden were compared between 55 men who had a solid tumor and 188 men who had a cardiovascular event, and whether patients with cancer and a cardiovascular event exhibited different risk profiles was examined. Due to the low cancer incidence in women with 15 cases, a statistical evaluation was not carried out.

Myocardial infarction, stroke, CABG, and PTCA or angiographically proven coronary stenosis > 50% were classified as cardiovascular events.

Clinical intervention and patient management

Patients at high risk (types III and IVb ultrasound findings) received a letter to their family doctor to start treatment with a statin, for example, atorvastatin. Two hundred fifty-nine (47.9%) men and 98 (58.7%) women received a statin. In 15 subjects, statin use was irregular. If the duration of use was less than 50% of the follow-up period, it was considered no treatment, and vice versa. In 11 subjects, statins were not tolerated and had to be discontinued. The statin dose remained constant between the first and second visits and was adhered to by the patients.

Statistical analysis

The baseline characteristics of all subjects by risk group were described (continuously scaled: mean, standard deviation; categorically scaled: absolute and relative frequencies) and compared using *t*-test.

For each age group from 20 to 65 years, percentile curves of the plaque area (TPA) were created for men and women and the percentage of subjects with advanced atherosclerosis (type III-IVb findings) was shown.

Results

To better evaluate the factors associated with carotid atherosclerosis at baseline, the population was divided into two groups: low to moderate atherosclerosis (types I, IIa, IIb, and IVa findings in ultrasound) and high risk (types III and IVb) (Table 1).

Figures 1 and 2 show the percentile curves of TPA in men and women by age group (20 - 65 years).

In the age group 25 - 65 years, 5,672 men and 4,652 women were examined.

The proportion of men and women with advanced arteriosclerosis (types III and IVb) is shown in Figure 3. Five hundred eighty-four (10.3%) men and 180 (3.9%) women have advanced atherosclerosis type III/IVb.

In the age group of 40 - 65 years, 2,592 men and 1,928 women were followed up.

Low to moderate atherosclerosis (types I, IIa, IIb, and IVa findings in ultrasound) was present in 2,052 (79.2%) men and 1,761 (91.3%) women. During follow-up, 139 (6.8%) men and

Table 1. Baseline Characteristics of All Subjects by Risk Groups

Characteristics	Male, type I, IIa, IIb, IVa	Male, type III, IVb	P value	Female, type I, IIa, IIb, IVa	Female type, III, IVb	P value
N	2,052	540		1,761	167	
Age	50 ± 7	54 ± 6	< 0.0001	50 ± 7	55 ± 6	< 0.0001
BMI, kg/m^2	27.47 ± 4.08	27.94 ± 4.20	0.002	25.40 ± 4.68	26.02 ± 4.72	0.101
Current smoker	458 (22.3%)	238 (43.5%)	< 0.0001	339 (19.3%)	79 (47.3%)	< 0.0001
LDL-cholesterol, mg/dL	150 ± 33	159 ± 40	< 0.0001	143 ± 33	160 ± 40	0.002
HDL-cholesterol, mg/dL	51 ± 12	48 ± 11	0.001	65 ± 15	63 ± 14	0.116
Triglycerides, mg/dL	170 ± 117	188 ± 123	0.001	112 ± 58	143 ± 71	0.005
SBP, mm Hg	126 ± 15	135 ± 19	< 0.0001	122 ± 16	131 ± 19	0.0002
DBP, mm Hg	82 ± 8	84 ± 10	< 0.0001	78 ± 9	86 ± 12	0.143
Diabetes mellitus	76 (3.7%)	47 (8.6%)	< 0.0001	25 (1.4%)	11 (6.6%)	0.009
Antihypertensive therapy	440 (21.4%)	206 (37.7%)	< 0.0001	318 (18.1%)	80 (47.9%)	< 0.0001
Positive family history	450 (21.9%)	159 (29.1%)	0.034	485 (27.5%)	65 (38.9%)	< 0.0001
PROCAM risk	6.5±6.5%	14.4±11.1%	< 0.0001	1.5±2.4%	5.1±5.4%	< 0.0001
TPA, mm^2	32 ± 33	150 ± 64	< 0.0001	16 ± 24	123 ± 63	< 0.0001
Max. plaque thickness, mm	1.7 ± 0.5	2.9 ± 0.8	< 0.0001	1.6 ± 0.4	3.1 ± 0.6	< 0.0001
Event (MACE, CABG, PTCA, stenosis)	60 (2.9%)	128 (23.4%)	< 0.0001	4 (0.2%)	13 (7.8%)	< 0.0001
Carcinoma	21 (1.0%)	34 (6.2%)	< 0.0001	12 (0.7%)	3 (1.8%)	0.289
Follow-up, months (min. - max.)	73 (3 - 156)	74 (3 - 145)	0.032	74 (2 - 155)	75 (2 - 139)	0.836
Death of all causes	14 (0.7%)	42 (7.7%)	< 0.0001	6 (0.3%)	0	< 0.0001
Death of CVD	5 (0.2%)	17 (3.1%)	0.0004	2 (0.1%)	0	< 0.0001
Death of carcinoma	4 (0.2%)	20 (4.4%)	< 0.0001	1 (0.06%)	0	< 0.0001

The mean values with the standard deviations or the percentages are shown. BMI: body mass index; CABG: coronary artery bypass grafting; CVD: cardiovascular disease; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MACE: major adverse cardiovascular event; PROCAM: Prospective Cardiovascular Munster Study; PTCA: percutaneous transluminal coronary angioplasty; SBP: systolic blood pressure; TPA: total plaque area.

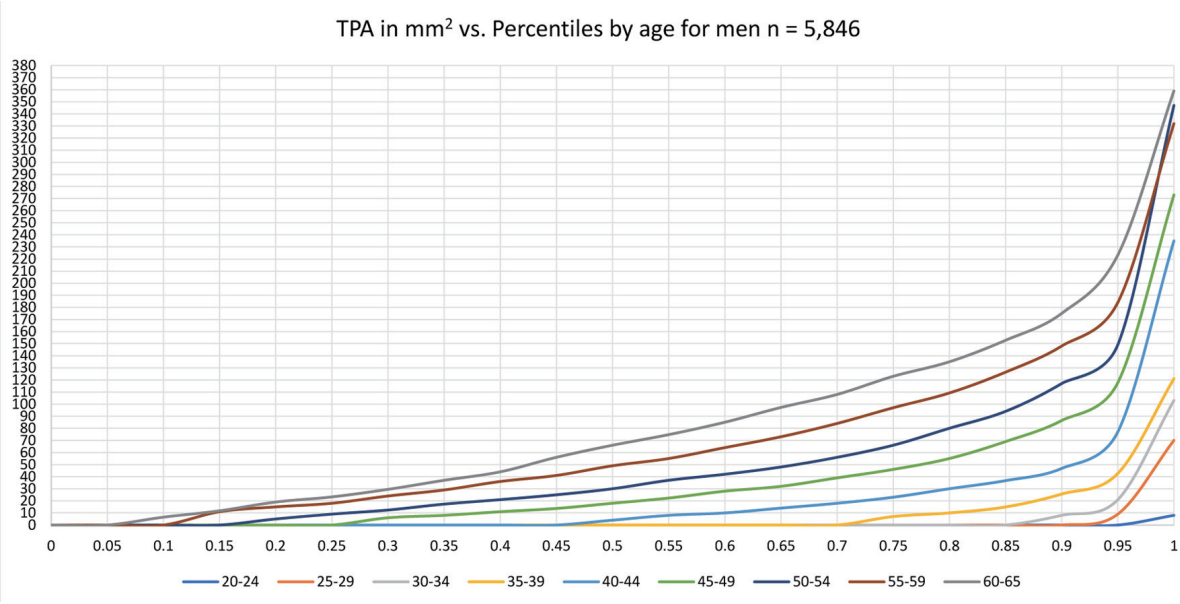

Figure 1. TPA percentiles by age for men. TPA: total plaque area.

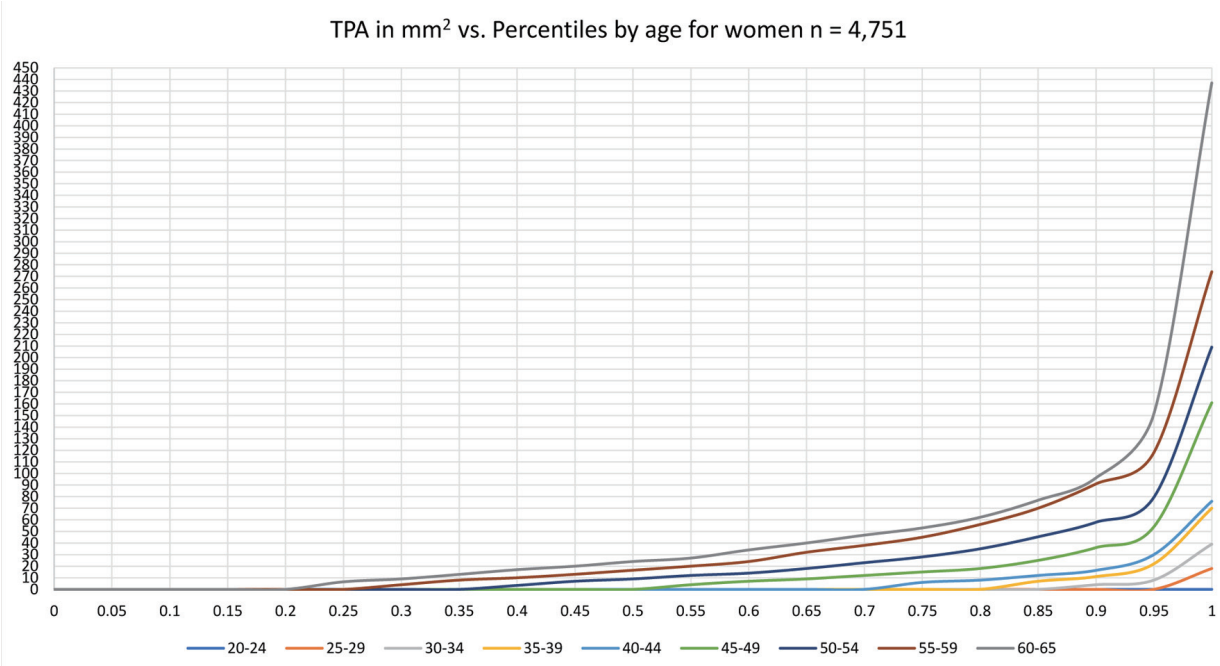

Figure 2. TPA percentiles by age for women. TPA: total plaque area.

39 (2.0%) women developed advanced atherosclerosis type III or IVb (Tables 2-4), which could not be predicted by the classic risk factors ($P > 0.05$). The mean follow-up time was 73 months (6.3 years) for men and 75 months (5.8 years) for women.

Patients with cancer and a cardiovascular event have a significantly higher risk profile and greater plaque burden than men without cancer or cardiovascular events (Tables 5 and 6), whereas patients with cancer and cardiovascular events have a very similar risk profile and plaque burden (Table 7). The following cancers have occurred: nine bronchial, six colon, two bladder, three brain, four stomach, two renal, three pancreas, 17 prostate, one base of the tongue, one esophagus, four unknown, one gallbladder, one larynx, and one lymphoma.

Discussion

Atherosclerosis is an inflammatory disease of the arteries and remains the most common cause of death in industrialized nations. The first plaques can be found in men at the age of 24 and in women at the age of 26. There are men and women in every age group who already have advanced atherosclerosis, which is associated with a high risk of cardiovascular disease [10]. This proportion increases with age. This means that in

Age	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-65	n
Type III, IVb Men	0.3%	0.8%	2.2%	4.5%	9.5%	12.5%	22.2%	26.8%	n = 5,672
Type III, IVb Women	0.0%	0.0%	0.9%	0.9%	2.8%	4.1%	8.0%	9.2%	n = 4,652

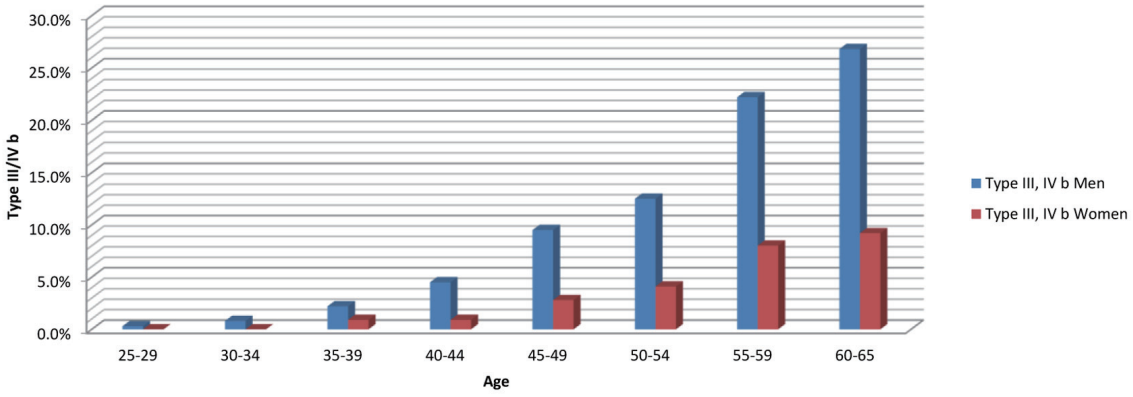

Figure 3. Proportion of men and women with advanced atherosclerosis.

Table 2. Proportion of Men With Progression to High Plaque Risk

	Men, type I, IIa, IIb, IVa	Progression in type III, IVb	P value (*t*-test)
N	1,913	139	
Age	50 ± 6	50 ± 5	0.5042
BMI, kg/m^2	27.47 ± 4.08	27.80 ± 4.48	0.4030
Current smoker	423 (22.1%)	40 (28.8%)	0.0954
LDL-cholesterol, mg/dL	150 ± 33	153 ± 32	0.2661
HDL-cholesterol, mg/dL	51 ± 11	52 ± 13	0.4186
Triglycerides, mg/dL	169 ± 116	174 ± 133	0.6990
SBP, mm Hg	127 ± 16	130 ± 17	0.0047
DBP, mm Hg	81 ± 8	83 ± 10	0.0763
Diabetes mellitus	67 (3.5%)	9 (6.5%)	0.1662
Antihypertensive therapy	409 (21.4%)	34 (24.5%)	0.4240
Positive family history	423 (22.1%)	27 (19.4%)	0.4436
PROCAM risk	6.5±6.4%	8.1±7.5%	0.0360
TPA, mm^2	30 ± 33	53 ± 30	< 0.00001
Max. plaque thickness, mm	1.7 ± 0.5	1.79 ± 0.5	0.000017

The mean values with the standard deviations or the percentages are shown. BMI: body mass index; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; PROCAM: Prospective Cardiovascular Munster Study; SBP: systolic blood pressure; TPA: total plaque area.

every age group, there is a further proportion of test subjects who develop rapid progression of atherosclerosis within a few years. It can be seen that the expected percentage of subjects with rapid progression of the disease is in good agreement with the actual percentage (Table 4). For example, in the age group of 40 - 44 years, 4.5% of men have advanced atherosclerosis types III and IVb; in the age group of 45 - 49 years, it is already 9.5%. It is therefore to be expected that approximately 4% of men in the age group of 40 - 44 years have a rapid progression of atherosclerosis and switch to high risk. In this group, 477 subjects with a low-medium risk of plaque (types I, IIa, IIb, and IVa) were followed up. Of the 477 subjects, 24 (5%)

Table 3. Proportion of Women With Progression to High Plaque Risk

	Women, type I, IIa, IIb, IVa	Progression in type III, IVb	P value (*t*-test)
N	1,722	39	
Age	50 ± 6	51 ± 6	0.1942
BMI, kg/m^2	25.41 ± 4.80	24.03 ± 5.92	0.0186
Current smoker	351 (20.4%)	12 (30.8%)	0.1767
LDL-cholesterol, mg/dL	143 ± 32	146 ± 35	0.6567
HDL-cholesterol, mg/dL	65 ± 15	65 ± 13	0.9377
Triglycerides, mg/dL	112 ± 59	118 ± 60	0.5433
SBP, mm Hg	121 ± 16	126 ± 18	0.1116
DBP, mm Hg	78 ± 9	78 ± 9	0.9849
Diabetes mellitus	27 (1.6%)	0 (0%)	< 0.0001
Antihypertensive therapy	308 (17.9%)	8 (20.5%)	0.6998
Positive family history	475 (27.6%)	10 (25.6%)	0.7876
PROCAM risk	1.5±2.5%	1.8±2.4%	0.5312
TPA, mm^2	17 ± 24	48 ± 34	< 0.0001
Max. plaque thickness, mm	1.6 ± 0.4	2.1 ± 0.5	< 0.0001

The mean values with the standard deviations or the percentages are shown. BMI: body mass index; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; PROCAM: Prospective Cardiovascular Munster Study; SBP: systolic blood pressure; TPA: total plaque area.

Table 4. Proportion of Men and Women With Progression to High Plaque Risk by Age Group

	25 - 29	30 - 34	35 - 39	40 - 44	45 - 49	50 - 54	55 - 59	60 - 65
Type III, IVb, men	0.3%	0.8%	2.2%	4.5%	9.5%	12.5%	22.2%	26.8%
No. of men examined with follow-up				477	584	499	335	147
No. of which change in type III/IVb, men				24	40	46	26	2
Change with follow-up, men				5.0%	6.8%	9.2%	7.8%	1.4%
Type III, IVb, women	0.0%	0.0%	0.9%	0.9%	2.8%	4.1%	8.0%	9.2%
No. of women examined with follow-up				348	486	480	324	125
No. of which change in type III/IVb, women				7	5	15	10	2
Change with follow-up, women				2.0%	1.0%	3.1%	3.1%	1.6%

developed rapid progression. Who is affected cannot be predicted with the classic risk factors (all P-values > 0.05 except for systolic blood pressure P < 0.05 in men). This is probably also the reason why the classic risk scores only work to a very limited extent [11, 12].

It is therefore important to look at the disease and not just the classic risk factors. As advanced or rapidly progressing atherosclerosis is associated with a high risk of cardiovascular disease, which can be significantly reduced with early treatment with a statin, it is useful to measure the plaque burden on the carotid artery with ultrasound in men and women from the age of 35 or 45 and to repeat this examination after 3 - 5 years, so that test subjects with rapid progression of atherosclerosis are not overlooked. The examinations are offered to employees at companies every 3 years. This means that employees are examined without selection, but unfortunately not all of them. Participation in the study is voluntary. Therefore, the follow-up is not complete. In some companies, the examination only took place once.

In addition, there is evidence that advanced atherosclerosis and microvascular dysfunction are not only associated with an increased risk of cardiovascular events, but also with an increased risk of cancer [2-10]. Men with cancer and cardiovascular events show a very similar risk profile and a significantly increased plaque burden compared to men without events (Tables 5-7). Microvascular dysfunction probably affects not only the prearterioles and arterioles of the coronary vessels, but also other organs [13, 14].

Structural (obstruction and perivascular fibrosis) and functional changes (increased vascular tone caused by increased production of endothelin, prostacyclin, peptide Y or decreased production of nitric oxide NO) occur [1]. Hypoxia affects the proliferation and expression of the genes hypoxia-inducible factor-1-alpha (HIF-1α) and JMJD1A in head and neck tumor

Table 5. Comparison of Risk Factors in Men With Cancer and Without Cancer, CVD

	Men without cancer, CVD	Men with cancer	P value (*t*-test)
N	2,397	55	
Age	50 ± 6	55 ± 5	0.00003
BMI, kg/m^2	27.48 ± 4.08	27.18 ± 4.48	0.53300
Current smoker	603 (25.2%)	23 (41.8%)	0.01738
LDL-cholesterol, mg/dL	151 ± 33	151 ± 32	0.94355
HDL-cholesterol, mg/dL	50 ± 11	52 ± 13	0.52725
Triglycerides, mg/dL	172 ± 116	198 ± 133	0.26128
SBP, mm Hg	128 ± 16	135 ± 17	0.02165
DBP, mm Hg	82 ± 8	84 ± 10	0.05588
Diabetes mellitus	103 (4.3%)	2 (3.6%)	0.79888
Antihypertensive therapy	572 (23.9%)	19 (34.5%)	0.10744
Positive family history	549 (22.9%)	13 (23.6%)	0.90068
PROCAM risk	7.5±6.4%	12.8±7.5%	0.03379
TPA, mm^2	49 ± 33	103 ± 30	< 0.00001
Max. plaque thickness, mm	2.1 ± 0.5	2.6 ± 0.5	0.00037

The mean values with the standard deviations or the percentages are shown. BMI: body mass index; CVD: cardiovascular disease; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; PROCAM: Prospective Cardiovascular Munster Study; SBP: systolic blood pressure; TPA: total plaque area.

Table 6. Comparison of Risk Factors in Men With CVD and Without Cancer, CVD

	Men without cancer, CVD	Men with CVD	P value (*t*-test)
N	2,397	188	
Age	50 ± 6	54 ± 6	< 0.00001
BMI, kg/m^2	27.48 ± 4.08	28.10 ± 4.08	0.0161
Current smoker	603 (25.2%)	85 (45.2%)	< 0.00001
LDL-cholesterol, mg/dL	151 ± 33	161 ± 33	0.00065
HDL-cholesterol, mg/dL	50 ± 11	48 ± 11	0.00275
Triglycerides, mg/dL	172 ± 116	194 ± 116	0.01691
SBP, mm Hg	128 ± 16	133 ± 16	0.00153
DBP, mm Hg	82 ± 8	83 ± 8	0.12071
Diabetes mellitus	103 (4.3%)	20 (10.6%)	0.00620
Antihypertensive therapy	572 (23.9%)	68 (36.2%)	0.00081
Positive family history	549 (22.9%)	58 (30.9%)	0.02357
PROCAM risk	7.5±6.4%	14.9±6.4%	< 0.00001
TPA, mm^2	49 ± 33	133 ± 33	< 0.00001
Max. plaque thickness, mm	2.1 ± 0.5	2.7 ± 0.5	< 0.00001

The mean values with the standard deviations or the percentages are shown. BMI: body mass index; CVD: cardiovascular disease; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; PROCAM: Prospective Cardiovascular Munster Study; SBP: systolic blood pressure; TPA: total plaque area.

cells [8]. Natural killer (NK) cells are the first line of defense against infections and cancer cells. Hypoxia upregulates the transcription factor-1α (HIF-1α), which slows down the activity of NK cells in tumor defense [15]. Rashid et al consider HIF-1α to be an important transcription factor in cancer development. Hypoxia acts as an overarching driver and master regulator of cancer development [16].

Haverich and Boyle have written a very interesting book on atherosclerosis pathogenesis and microvascular dysfunction [17]. There is a physiological growth process of the intima

Table 7. Comparison of Risk Factors in Men With CVD and With Cancer

	Men with CVD	Men with cancer	P value (*t*-test)
N	188	55	
Age	54 ± 6	55 ± 5	0.9690
BMI, kg/m^2	28.10 ± 4.08	27.18 ± 4.48	0.0650
Current smoker	85 (45.2%)	23 (41.8%)	0.6857
LDL-cholesterol, mg/dL	161 ± 33	151 ± 32	0.0677
HDL-cholesterol, mg/dL	48 ± 11	52 ± 13	0.0731
Triglycerides, mg/dL	194 ± 116	198 ± 133	0.8708
SBP, mm Hg	133 ± 16	135 ± 17	0.4497
DBP, mm Hg	83 ± 8	84 ± 10	0.4753
Diabetes mellitus	20 (10.6%)	2 (3.6%)	0.0413
Antihypertensive therapy	68 (36.2%)	19 (34.5%)	0.8620
Positive family history	58 (30.9%)	13 (23.6%)	0.3092
PROCAM risk	14.9±6.4%	12.8±7.5%	0.4608
TPA, mm^2	133 ± 33	103 ± 30	0.0153
Max. plaque thickness, mm	2.7 ± 0.5	2.6 ± 0.5	0.5322

The mean values with the standard deviations or the percentages are shown. BMI: body mass index; CVD: cardiovascular disease; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; PROCAM: Prospective Cardiovascular Munster Study; SBP: systolic blood pressure; TPA: total plaque area.

Table 8. Baseline Characteristics for All Subjects With Low and Intermediate Risk With and Without Follow-Up

	Male, type I, IIa, IIb, IVa follow-up	Male without follow-up	P value	Female, type I, IIa, IIb, IVa follow-up	Female without follow-up	P value
N	2,052	1,494		1,761	1,684	
Age	50 ± 7	50 ± 8	0.122	50 ± 7	50 ± 4	0.158
BMI, kg/m^2	27.47 ± 4.08	27.60 ± 4.08	0.375	25.40 ± 4.68	25.63 ± 4.98	0.174
Current smoker	458 (22.3%)	335 (22.4%)	0.966	339 (19.3%)	337 (20.0%)	0.778
LDL-cholesterol, mg/dL	150 ± 33	150 ± 40	0.719	143 ± 33	145 ± 35	0.361
HDL-cholesterol, mg/dL	51 ± 12	50 ± 20	0.072	65 ± 15	64 ± 12	0.487
Triglycerides, mg/dL	170 ± 117	171 ± 122	0.896	112 ± 58	119 ± 64	0.123
SBP, mm Hg	126 ± 15	128 ± 16	0.181	122 ± 16	123 ± 19	0.095
DBP, mm Hg	82 ± 8	82 ± 11	0.066	78 ± 9	79 ± 10	0.067
Diabetes mellitus	76 (3.7%)	56 (3.7%)	0.985	25 (1.4%)	33 (1.9%)	0.205
Antihypertensive therapy	440 (21.4%)	363 (24.3%)	0.058	318 (18.1%)	333 (19.8%)	0.151
Positive family history	450 (21.9%)	307 (20.5%)	0.305	485 (27.5%)	448 (26.6%)	0.639
PROCAM risk	6.5±6.5%	6.5±9.46%	0.693	1.5±2.4%	1.8±2.7%	0.058
TPA, mm^2	32 ± 33	30 ± 26	0.068	16 ± 24	15 ± 27	0.052
Max. plaque thickness, mm	1.7 ± 0.5	1.6 ± 0.4	0.713	1.6 ± 0.4	1.6 ± 0.5	0.072

The mean values with the standard deviations or the percentages are shown. BMI: body mass index; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; PROCAM: Prospective Cardiovascular Munster Study; SBP: systolic blood pressure; TPA: total plaque area.

starting with 1 - 2 cell layers at birth to 25 - 30 layers at the age of 25 - 30 years. The thin-walled arteries are supplied by diffusion from the lumen. From a critical thickness of 29 lamellae, hypoxic conditions occur in the media and adventitia, triggering angiogenic processes and the formation of vasa vasorum. The vasa vasorum supply the medium and large arteries with nutrients and oxygen from the outside to the inside. Disturbed perfusion of the vasa vasorum leads to neovascularization and immature endothelial structures, which promote the deposition of atherogenic substances and the supply of inflammatory cells and ultimately plaque formation. Atherosclerosis is initiated by impaired microcirculation. Hypertension, smoking, and reduced physical activity are risk factors for the development of functional and structural changes in the prearterioles and arterioles. Hypoxia occurs in the affected organs. Plaque formation occurs in the large and medium-sized arteries (coronary vessels, aorta, carotid artery, and femoral artery are seen as an organ), coronary microvascular dysfunction in the heart leads to a reduction in the coronary flow reserve, and in other organs, microvascular-induced hypoxia may downregulate the immune system, thereby slowing down tumor defense. In addition, there is evidence that there is a connection between neurodegenerative diseases such as glaucoma and Alzheimer's and impaired microcirculation [18].

Impaired microcirculation could be the key to cardiovascular events and certain cancers and thus premature death.

The good news is that treatment, or prevention, is simple and costs little to nothing compared to later treatment: smoking cessation, 30 min of aerobic endurance training at least three times/week, early treatment of hypertension, and statin therapy for advanced atherosclerosis. There are numerous studies that describe the positive influence of endurance training for the prevention of several types of solid cancer (e.g., bowel, prostate, breast) and cardiovascular diseases [19, 20]. Improved microcirculation through endurance training could explain the positive preventive effect for both disease groups.

Carotid screening with ultrasound opens up a very good opportunity for the prevention of cardiovascular diseases and possibly also cancer.

Conclusion

Ultrasound examination of the carotid artery can identify people with advanced atherosclerosis. A follow-up examination with low or moderate plaque burden after 3 - 5 years is useful, so that subjects with rapid progression of atherosclerosis can be detected at an earlier stage. Early treatment of advanced atherosclerosis improves the prognosis for cardiovascular diseases and possibly also for certain types of cancer.

Limitations

The follow-up in the group with low and medium risk ultrasound in men and women is only 54%. The examinations are offered to employees at companies every 3 years. This means that employees are examined without selection, but unfortunately not all of them. Therefore, the follow-up is not complete. In some companies, the examination only took place once. In total, 1,494 men (42.1%) and 1,684 women (48.9%) were not followed up.

This number is high and may lead to bias, but there is no significant statistical difference between subjects with or without follow-up (Table 8).

The link between microvascular dysfunction and certain types of cancer is a hypothesis and needs to be confirmed by further studies.

Acknowledgments

None to declare.

Financial Disclosure

This study has not been supported by any external funding.

Conflict of Interest

The authors confirm that they have no conflict of interest.

Informed Consent

All patients provided informed consent.

Author Contributions

WB and MR discussed the approach and the findings of this study with AA intensively and gave AA valuable feedback. All examinations have been done by AA.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

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