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Research Article

Cancer Risk in Patients with Manifest Vascular Disease: Effects of Smoking, Obesity, and Metabolic Syndrome

Rob C.M. van Kruijsdijk[1], Yolanda van der Graaf[2], Petra H.M. Peeters[2], and Frank L.J. Visseren[1], on behalf of the Second Manifestations of ARTerial disease (SMART) study group

Abstract

Background: Patients with vascular disease may be at increased risk of cancer because of shared risk factors and common pathogenesis.

Methods: Patients with vascular disease (n = 6,172) were prospectively followed for cancer incidence. Standardized incidence ratios (SIRs) were calculated to compare the cancer incidence of the study population with that of the general population. Multivariable-adjusted hazard ratio's (HRs) of cancer were estimated for smoking status, pack-years, body mass index, waist circumference and visceral adipose tissue (VAT), and metabolic syndrome (MetS).

Results: During a median follow-up of 5.5 years, 563 patients were diagnosed with cancer. Patients with vascular disease were at increased risk of cancer [SIR = 1.19; 95% confidence interval (CI), 1.10–1.29]. Specifically, risk of lung cancer (SIR = 1.56; 95% CI, 1.31–1.83), as well as bladder cancer (SIR = 1.60; 95% CI, 1.11–2.24) and cancer of the lip, oral cavity, or pharynx in men (SIR = 1.51; 95% CI, 0.89–2.39), and colorectal (SIR = 1.71; 95% CI, 1.11–2.53) and kidney cancer (SIR = 2.92; 95% CI, 1.05–6.38) in women was increased. A relation between smoking and cancer risk was observed (HR for current smokers = 1.37; 95% CI, 1.05–1.73), whereas an increase in VAT was associated with higher breast cancer risk in women (HR = 1.42; 95% CI, 1.03–1.96). No relation between MetS and cancer risk was found.

Conclusions: Patients with vascular disease have a 19% higher cancer risk compared to the general population. Smoking increased cancer risk and abdominal obesity is a risk factor for breast cancer in female patients with vascular disease.

Impact: These results call for awareness of the increased cancer risk in patients with vascular disease among physicians and underline the necessity of lifestyle improvement not only for reducing cardiovascular risk. *Cancer Epidemiol Biomarkers Prev; 22(7); 1267–77. ©2013 AACR.*

Introduction

Cardiovascular disease and cancer constitute a major burden on global health and share several important modifiable risk factors, including tobacco smoking and excess bodyweight (1–4). Over recent decades, survival of cardiovascular events has substantially improved, whereas the number of patients with prevalent cardiovascular disease is ever growing (3, 4). Although secondary prevention in clinical practice focuses on the recurrence of vascular events (5, 6), these patients might also be at increased risk of cancer as there are shared risk factors for both cardiovascular disease and cancer.

The atherogenic and carcinogenic effects of smoking, as well as the increased risk of vascular disease in persons with excess body weight are well established (7–9). The relation between excess bodyweight and increased cancer risk, however, has now also been established (10–13). Increased body mass index (BMI) is related with both an increased incidence and mortality of various cancer types, including endometrial, colorectal, and postmenopausal breast cancer as well as several other common cancers (10, 13). Underlying mechanisms are not fully clear, but it is assumed that adipose tissue dysfunction plays an important role by inducing insulin resistance, inflammation, and changes in serum levels of adipokines (e.g., leptin and adiponectin) and sex steroids, and thereby promoting cell proliferation and survival, as well as invasive growth, metastasis, and angiogenesis (14). An indicator of the metabolic changes associated with obesity is the presence of metabolic syndrome (MetS), which is a cluster of metabolic risk factors including abdominal obesity, hypertension, dyslipidemia, and hyperglycemia (15). Individual MetS components as well as MetS as an entity are related to the occurrence of several types of

Authors' Affiliations: [1]Department of Vascular Medicine; and [2]Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, the Netherlands

Corresponding Author: Frank L.J. Visseren, Department of Vascular Medicine, University Medical Centre Utrecht, P.O. Box 85500, 3508 GA Utrecht, the Netherlands. Phone: 31-88-7555555; Fax: 31-88-7555488; E-mail: f.l.j.visseren@umcutrecht.nl

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cancer in the general population (16–18). MetS as well as other established risk factors for cancer such as obesity and smoking are highly prevalent in patients with vascular disease (19). To date, however, knowledge about cancer incidence and the effect of these various risk factors in patients with vascular disease is limited. Therefore, we assessed cancer incidence in patients with clinical manifest vascular disease and evaluated the effects of smoking, obesity, and MetS on cancer risk in a prospective cohort study.

Materials and Methods

Study population, data collection, and follow-up

Patients originated from the Second Manifestations of ARTerial disease (SMART) study (20), an ongoing prospective cohort study at the University Medical Center Utrecht (UMCU) in the Netherlands. Patients aged 18 to 80 years newly referred to the UMCU with clinically manifest cerebrovascular disease, coronary heart disease (CAD), peripheral arterial disease, abdominal aortic aneurysm, or a marked cardiovascular risk factor (hypertension, dyslipidemia, or diabetes mellitus) are included in the SMART study. The central aims of the SMART study are to determine the prevalence of concomitant arterial disease and of risk factors for arterial disease in a high-risk population and to study the incidence of future cardiovascular events. A detailed description of the study has been published previously (20). In short, patients underwent baseline examinations, including a questionnaire covering medical history, symptoms and risk factors for cardiovascular disease, menopausal status for female patients (21), and current medication use. Furthermore, a standardized diagnostic protocol was conducted including physical examination (height, weight, systolic and diastolic blood pressure) and laboratory tests to determine metabolic markers fasting serum glucose and lipid levels. Since January 1999, additional measurements of waist circumference and visceral adipose tissue (VAT) have been done. Waist circumference was measured halfway between the lower rib and iliac crest. VAT was estimated by ultrasonography. A detailed description of this procedure has been published previously (22). Patients were biannually asked to complete a questionnaire on hospitalization and outpatient clinic visits for follow-up. Information on cancer diagnosis was obtained by linking the SMART database with the Netherlands Cancer Registry. Age- and gender-specific cancer incidence rates in the Netherlands in the period of 1997 to 2010 were also acquired from the Cancer Registry (23), whereas mortality rates were obtained from Statistics Netherlands (24). The local ethics committee approved the study and all participants gave their written informed consent. For this study, data of patients with manifest vascular disease included between September 1996 and March 2011 ($n = 6{,}172$) were used. Two hundred fifty-eight patients (4.2%) were lost to follow-up because of migration or withdrawal from the study.

Definitions

MetS was defined according to the revised National Cholesterol Education Program (NCEP-R) criteria (15). Participants were diagnosed with MetS when complying with 3 or more of the following abnormalities:

1. Abdominal obesity: waist circumference $\geq$102 cm in men or $\geq$ 88 cm in women.
2. Hypertension: blood pressure $\geq$130 mm Hg systolic or $\geq$ 85 mm Hg diastolic or use of blood pressure–lowering agents.
3. Hypertriglyceridemia: serum triglycerides $\geq$1.70 mmol/L (150 mg/dL).
4. Reduced HDL-cholesterol: serum HDL-cholesterol < 1.03 mmol/L (40 mg/dL) in men or < 1.3 mmol/L (50 mg/dL) in women.
5. Elevated fasting glucose: fasting serum glucose $\geq$ 5.6 mmol/L (100 mg/dL) or use of glucose-lowering agents.

If waist circumference was not available ($n = 863$), a BMI higher than 30 kg/m^2 was used as determinant for abdominal obesity (25). This method was evaluated in the subset of patients of whom waist circumference was available, which resulted in a positive predictive value of 91% [95% confidence interval (CI), 89%–93%] and a negative predictive value of 74% (95% CI, 73%–76%). Pack-years of smoking were calculated with the formula: (number of years smoked $\times$ mean number of cigarettes smoked per day)/20. Cancer incidence data were coded according to the 10th revision of the International Classification of Diseases (ICD-10; ref. 26). The main endpoint of interest was defined as the first primary invasive neoplasm, excluding non-melanoma skin cancer. For women who were premenopausal at baseline, age 50 years was used as proxy for menopause to determine menopausal status at time of cancer diagnosis (27).

Data analyses

Standardized incidence ratios (SIR), adjusted for age (5-year age groups), sex (when not stratified by), and calendar year were calculated for all observed cancers. Corresponding 95% CIs were computed assuming a Poisson distribution. To compare cancer incidence with the incidence of recurrent vascular events (i.e., myocardial infarction, ischemic stroke, or vascular death), cumulative incidences, as functions of years since study enrollment, were estimated accounting for competing risk of death by causes other than the endpoint under study.

Patients who had a history of cancer before enrollment ($n = 232$) were excluded from further analysis. Missing data for smoking status ($n = 28$; 0.5%), pack years of smoking ($n = 23$; 0.4%), BMI ($n = 10$; 0.2%), and alcohol use ($n = 28$; 0.5%) were singly imputed by weighted probability matching on the basis of multivariable regression using covariate and outcome data (using the aregImpute-function in R, Hmisc-package; ref. 28). Proportional subdistribution hazards regression models (29, 30) were

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fitted to estimate HRs with corresponding 95% CIs of incident cancer associated with (i) smoking status [never (reference), past, current] and pack-years of smoking [0 (reference), 1 to <30 and ≥30]; (ii) BMI, waist circumference, and VAT per SD increment; (iii) presence of MetS and number of MetS components [categorized into 3 groups, i.e., 0–1 (reference), 2–3, and 4–5 components]. Death was treated as competing event. Relations between the determinants and total incident cancer as well as the 3 most common male and female cancer sites (i.e., cancer of the colon/rectum, lower respiratory tract, breast, and prostate) were examined. Two models were fitted: a crude model and a model adjusted for age, sex (when not stratified by), and additional adjustments depending on the association examined: (i) BMI (continuous) and alcohol drinking status (never, past, or current alcohol use) for the association between smoking and cancer incidence; (ii) smoking status, pack-years of smoking, and alcohol drinking status for the association between measures of adiposity and cancer incidence; and (iii) smoking status, pack-years of smoking, and alcohol drinking status for the association between MetS/number of MetS components and cancer incidence. The proportionality assumption for all models was checked graphically by plotting the scaled Schoenfeld residuals against failure time, but no violations were observed. For the adiposity measures, the linearity assumption was evaluated by adding these determinants to the respective models as a restricted cubic spline function. Subsequently, the presence of nonlinearity was formally assessed using a Wald test. No significant nonlinearity was detected (P-values > 0.05). Potential effect modification by age, sex, and smoking status was tested for by adding multiplicative interaction terms to the models. No effect modification was found (P-values for interaction > 0.05). Furthermore, analyses were repeated after exclusion of patients who were diagnosed with cancer within 1 year after inclusion ($n = 84$) to evaluate the presence of reverse causality. This procedure did not result in substantial changes of HRs, thus final analyses were conducted retaining these patients. Statistical analyses were conducted in Microsoft Excel 2003 and in R, version 2.15.1 (R Development Core Team, Vienna, Austria; packages: "cmprsk," "rms," and "Hmisc").

Results

Baseline characteristics

A total of 6,172 patients with manifest vascular disease were included in this study, of whom 1,589 (26%) were female. Baseline characteristics according to sex are shown in Table 1. A majority of the study population consisted of smokers (84% ever and 32% current smokers among men and 70% ever and 36% current smokers among women). Mean BMI was 26.9 kg/m^2 in men and 26.8 kg/m^2 in women. MetS was present in 53% of men and in 55% of women. CAD was the most common vascular disease in both men (66%) and women (44%). Four percent of the participants had a history of cancer.

Table 1. Baseline characteristics

	Men ($n = 4,583$)	Women ($n = 1,589$)
Age (years)	60 (10)	59 (12)
Smoking, current	1,477 (32)	564 (36)
Smoking, ever	3,688 (84)	1,111 (70)
Pack years of smoking[a]	20 (6–35)	12 (0–29)
Alcohol consumption, current	2,428 (53)	643 (41)
BMI (kg/m^2)	27 (4)	27 (5)
VAT (cm)	10 (3)	8 (2)
Metabolic syndrome components		
Waist circumference (cm)	98 (11)	89 (13)
Systolic blood pressure (mm Hg)	141 (20)	143 (21)
Diastolic blood pressure (mm Hg)	80 (10)	78 (10)
Serum triglycerides (mmol/L)	1.4 (1.0–2.1)	1.4 (1.0–1.9)
High density lipoprotein (mmol/L)	1.2 (0.3)	1.4 (0.4)
Fasting serum glucose (mmol/L)	5.8 (5.4–6.5)	5.6 (5.2–6.4)
Metabolic syndrome[b]	2,434 (53)	867 (55)
Number of components:		
0–1	762 (17)	338 (21)
2–3	2,626 (57)	772 (49)
4–5	1,194 (26)	477 (30)
Other metabolic parameters		
Total cholesterol (mmol/L)	4.8 (1.2)	5.2 (1.3)
Low-density lipoprotein (mmol/L)	2.9 (1.0)	3.0 (1.1)
C-reactive protein (mg/L)	2.0 (1.0–4.4)	2.4 (1.1–5.1)
eGFR (mL/min/1.73 m^2)[c]	77 (18)	72 (18)
Medication use		
Use of blood pressure–lowering medication	3,446 (75)	1,100 (69)
Use of glucose-lowering medication	624 (14)	226 (14)
Use of statins	3,016 (66)	945 (60)
Use of aspirin	3,409 (74)	1,056 (67)
Medical history		
Coronary artery disease	3,022 (66)	699 (44)
Cerebrovascular disease	1,155 (25)	616 (39)
Peripheral arterial disease	841 (18)	403 (25)
Abdominal aortic aneurysm	459 (10)	86 (5)
Cancer (excluding non-melanoma skin cancer)	171 (4)	61 (4)
Diabetes mellitus	799 (17)	269 (18)

Data are mean (SD), percentage of group, or median (interquartile range).

[a]Only for ever smokers.

[b]According to NCEP-R criteria.

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Table 2. Standardized incidence ratios for incident cancer in patients with manifest vascular disease

	Men ($n = 4,583$)			Women ($n = 1,589$)			Total ($n = 6,172$)		
Cancer site (ICD-10 code)	**Observed**	**Expected**	**SIR (95% CI)**	**Observed**	**Expected**	**SIR (95% CI)**	**Observed**	**Expected**	**SIR (95% CI)**
Lip, oral cavity, pharynx (C00–C14)	18	10.2	1.76 (1.04–2.78)	0	1.7	–	18	11.9	1.51 (0.89–2.39)
Esophagus (C15)	14	16.2	0.87 (0.47–1.45)	1	1.6	0.63 (0–3.58)	15	17.8	0.84 (0.47–1.39)
Stomach (C16)	15	8.9	1.69 (0.95–2.80)	2	1.6	1.27 (0.12–4.64)	17	10.4	1.63 (0.95–2.61)
Colon, rectum (C18–C20)	58	62.1	0.93 (0.71–1.21)	25	14.6	1.71 (1.11–2.53)	83	76.7	1.08 (0.86–1.34)
Pancreas (C25)	10	9.4	1.07 (0.51–1.96)	4	2.6	1.54 (0.40–3.97)	14	12.0	1.17 (0.64–1.96)
Larynx, trachea/bronchus/lung (C32–C34)	110	79.8	1.38 (1.13–1.66)	31	10.9	2.86 (1.94–4.05)	141	90.6	1.56 (1.31–1.83)
Melanoma of skin (C43)	19	11.7	1.62 (0.97–2.53)	6	3.8	1.59 (0.57–3.47)	25	15.5	1.61 (1.04–2.38)
Breast (C50)	–	–	–	31	28.5	1.09 (0.74–1.54)	31	28.5	1.09 (0.74–1.54)
Corpus uteri (C54)	–	–	–	9	5.1	1.76 (0.80–3.35)	9	5.1	1.76 (0.80–3.35)
Ovary (C56)	–	–	–	3	3.4	0.88 (0.17–2.60)	3	3.4	0.88 (0.17–2.60)
Prostate (C61)	91	104.5	0.87 (0.70–1.07)	–	–	–	91	104.5	0.87 (0.70–1.07)
Kidney (C64)	18	11.1	1.62 (0.96–2.56)	6	2.1	2.92 (1.05–6.38)	24	13.2	1.82 (1.17–2.71)
Bladder (C67)	34	21.2	1.60 (1.11–2.24)	1	1.7	0.58 (0–3.29)	35	22.9	1.53 (1.06–2.12)
Lymph/hematopoietic tissue (C81–C96)	30	33.3	0.90 (0.61–1.29)	10	7.5	1.34 (0.64–2.47)	40	40.8	0.98 (0.70–1.34)
Other	44	40.4	1.09 (0.79–1.46)	12	18.6	0.64 (0.33–1.13)	56	59.1	0.95 (0.72–1.23)
All [excluding non-melanoma skin cancer (C44)]	461	408.8	1.13 (1.03–1.24)	141	95.1	1.48 (1.25–1.75)	602	503.9	1.19 (1.10–1.29)

Abbreviation: SIR, standardized incidence ratio (quotient of observed and expected numbers of incident cancer cases).

Presented SIRs are adjusted for age (5-year age groups), sex (when not stratified by) and calendar year.

The sum of the number of expected cancer cases in men and women might differ from the total number of expected cancer cases because of rounding.

The observed and expected numbers of cancers include multiple separate cases of incident cancer in individual patients.

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Cancer incidence

During a total follow-up of 36,461 person-years (median follow-up 5.5 years, interquartile range 2.9–8.6 years), 429 men (8.5%) and 134 women (7.9%) were diagnosed with cancer. Compared with the general Dutch population, a higher cancer incidence was observed in patients with manifest vascular disease (SIR = 1.19; 95% CI, 1.10–1.29), particularly in women (SIR = 1.48; 95% CI, 1.25–1.75; Table 2). In both men and women, incidence of cancer of the lower respiratory tract (SIR = 1.38; 95% CI, 1.13–1.66 and SIR = 2.86; 95% CI, 1.94–4.05) was increased. Men also had an excess risk of bladder cancer (SIR = 1.60; 95% CI, 1.11–2.24) and cancer of the lip, oral cavity, or pharynx (SIR = 1.76; 95% CI, 1.04–2.78), whereas women had a higher risk of colorectal cancer (SIR = 1.71; 95% CI, 1.11–2.53) and kidney cancer (SIR = 2.92; 95% CI, 1.05–6.38). In addition, the incidence of melanoma of the skin was significantly higher in men and women combined (SIR = 1.61; 95% CI, 1.04–2.38), but not in men or women separately. Figure 1 displays the observed and expected cumulative incidence curves for cancer and the observed recurrent vascular events in men and women.

Smoking and incident cancer risk

Table 3 shows the HRs for incident cancer by smoking status and pack-years of smoking in patients with manifest vascular disease without a history of cancer at baseline. Both former and current smokers had a higher risk of incident cancer compared to never smokers (HR = 1.33; 95% CI, 1.03–1.73 and HR = 1.37; 95% CI, 1.05–1.80, respectively). Compared to never smokers, the risk of cancer of the lower respiratory tract in former smokers was 2-fold higher (HR = 2.65; 95% CI, 1.22–5.78) and was 4-fold higher in current smokers (HR = 4.60; 95% CI, 2.13–9.92). An increase in risk for cancer of the lower respiratory tract was observed for number of pack-years (for 1 to <30 pack-years: HR = 2.41; 95% CI, 1.11–5.22; for ≥30 pack-years: HR = 5.14; 95% CI, 2.37–11.14).

Measures of adiposity and incident cancer risk

The risk of incident cancer per SD increase in BMI, waist circumference, and VAT is shown in Table 4. Among men, BMI, waist circumference, and VAT were inversely related to overall cancer risk, with HRs of 0.86 (95% CI, 0.77–0.97), 0.87 (95% CI, 0.77–0.99), and 0.89 (95% CI, 0.77–1.02) per SD increase, respectively. An inverse relation was also seen between the different measures of adiposity and cancers of the lower respiratory tract and prostate, but only the inverse relation between BMI and prostate cancer was statistically significant (HR = 0.79; 95% CI, 0.64–0.97). Increase in VAT significantly increased the risk of breast cancer in women (HR = 1.42; 95% CI, 1.03–1.96). Ninety-two percent of women diagnosed with breast cancer were postmenopausal at the time of diagnosis.

Metabolic syndrome and incident cancer risk

No significant association between MetS and cancer risk was observed in men (HR = 0.92; 95% CI, 0.76–1.13) or women (HR = 0.96; 95% CI, 0.66–1.40; Table 5). In

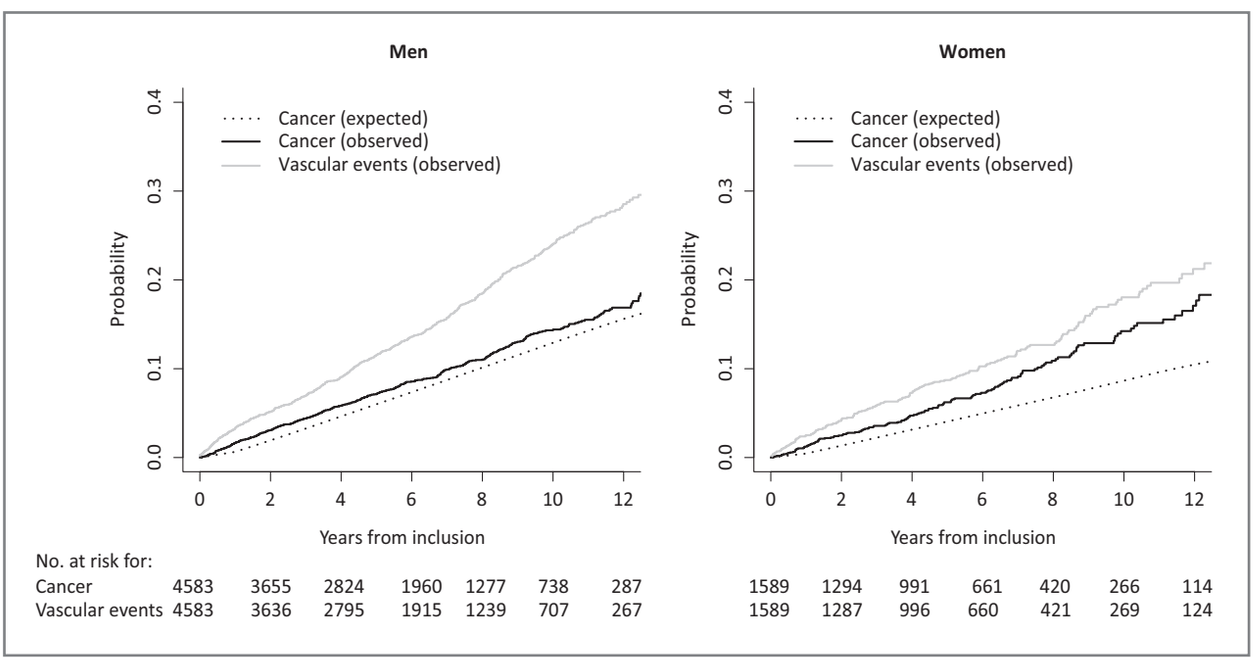

Figure 1. Cumulative incidence of cancer and recurrent vascular events in patients with manifest vascular disease.

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Table 3. Hazard ratios with 95% Confidence Intervals for smoking status and pack-years of smoking for risk of incident cancer in patients with manifest vascular disease without a history of cancer at baseline

Cancer site (ICD-10 code)	Smoking status			Pack-years of smoking		
	Never	Former	Current	0	1 to <30	≥30
All [excluding non-melanoma skin cancer (C44)]						
Men						
No. of patients	729	2,252	1,431	729	2,308	1,375
No. of events	46	210	135	46	185	160
Crude model	1.00 (reference)	1.41 (1.03–1.94)	1.29 (0.92–1.80)	1.00 (reference)	1.18 (0.85–1.63)	1.65 (1.19–2.30)
Adjusted model[a]	1.00 (reference)	1.25 (0.91–1.72)	1.41 (1.00–1.98)	1.00 (reference)	1.15 (0.83–1.59)	1.56 (1.12–2.16)
Women						
No. of patients	464	520	544	464	726	338
No. of events	34	49	42	34	57	34
Crude model	1.00 (reference)	1.35 (0.87–2.10)	0.93 (0.59–1.46)	1.00 (reference)	1.04 (0.68–1.59)	1.27 (0.79–2.05)
Adjusted model[a]	1.00 (reference)	1.49 (0.95–2.32)	1.14 (0.72–1.82)	1.00 (reference)	1.25 (0.81–1.91)	1.46 (0.90–2.37)
Men and women						
No. of patients	1,193	2,772	1,975	1,193	3,034	1,713
No. of events	80	259	177	80	242	194
Crude model	1.00 (reference)	1.36 (1.06–1.75)	1.16 (0.89–1.51)	1.00 (reference)	1.12 (0.87–1.44)	1.53 (1.18–1.99)
Adjusted model[a]	1.00 (reference)	1.33 (1.03–1.73)	1.37 (1.05–1.80)	1.00 (reference)	1.21 (0.93–1.56)	1.59 (1.22–2.07)
Colon, rectum (C18–C20)						
Men and women						
No. of patients	1,193	2,772	1,975	1,193	3,034	1,713
No. of events	11	39	21	11	34	26
Crude model	1.00 (reference)	1.49 (0.76–2.92)	1.00 (0.48–2.09)	1.00 (reference)	1.15 (0.58–2.26)	1.50 (0.74–3.03)
Adjusted model[a]	1.00 (reference)	1.66 (0.82–3.39)	1.37 (0.64–2.94)	1.00 (reference)	1.42 (0.70–2.88)	1.77 (0.84–3.73)
Larynx, trachea/bronchus/ lung (C32–C34)						
Men and women						
No. of patients	1,193	2,772	1,975	1,193	3,034	1,713
No. of events	8	51	59	8	48	62
Crude model	1.00 (reference)	2.69 (1.28–5.65)	3.91 (1.87–8.18)	1.00 (reference)	2.23 (1.05–4.71)	4.95 (2.37–10.32)
Adjusted model[a]	1.00 (reference)	2.65 (1.22–5.78)	4.60 (2.13–9.92)	1.00 (reference)	2.41 (1.11–5.22)	5.14 (2.37–11.14)
Breast (C50)						
Women						
No. of patients	464	520	544	464	726	338
No. of events	7	11	7	7	16	2
Crude model	1.00 (reference)	1.49 (0.59–3.81)	0.73 (0.25–2.08)	1.00 (reference)	1.41 (0.58–3.41)	0.36 (0.07–1.71)
Adjusted model[a]	1.00 (reference)	1.41 (0.52–3.83)	0.64 (0.21–1.91)	1.00 (reference)	1.34 (0.50–3.54)	0.35 (0.07–1.69)
Prostate (C61)						
Men						
No. of patients	729	2,252	1,431	729	2,308	1,375
No. of events	9	41	29	9	39	31
Crude model	1.00 (reference)	1.41 (0.68–2.89)	1.43 (0.68–3.02)	1.00 (reference)	1.27 (0.62–2.62)	1.65 (0.79–3.47)
Adjusted model[a]	1.00 (reference)	1.21 (0.58–2.50)	1.64 (0.77–3.51)	1.00 (reference)	1.23 (0.59–2.54)	1.55 (0.74–3.26)

[a]Model adjusted for age, sex (when not stratified by), BMI, and alcohol use.

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Table 4. HRs with 95% CIs for incident cancer per SD increase in BMI, waist circumference, and VAT in patients with manifest vascular disease without history of cancer at baseline

Cancer site (ICD-10 code)	BMI (kg/m^2)	Waist circumference (cm)	VAT (cm)
All [excluding non-melanoma skin cancer (C44)]			
Men			
No. of patients	4,412	3,904	3,496
No. of events	391	303	244
1 SD	3.6	10.6	2.4
Crude model	0.83 (0.74–0.93)	0.91 (0.81–1.02)	0.94 (0.83–1.08)
Adjusted model[a]	0.86 (0.77–0.97)	0.87 (0.77–0.99)	0.89 (0.77–1.02)
Women			
No. of patients	1,528	1,356	1,221
No. of events	125	95	77
1 SD	4.8	12.8	2.4
Crude model	1.01 (0.85–1.20)	1.10 (0.91–1.33)	1.08 (0.89–1.30)
Adjusted model[a]	0.97 (0.80–1.18)	1.05 (0.84–1.31)	1.00 (0.80–1.24)
Men and women			
No. of patients	5,940	5,260	4,717
No. of events	516	398	321
1 SD	4.0	11.9	2.6
Crude model	0.88 (0.80–0.97)	0.97 (0.88–1.07)	0.98 (0.88–1.10)
Adjusted model[a]	0.89 (0.81–0.99)	0.91 (0.81–1.02)	0.90 (0.80–1.02)
Colon, rectum (C18–C20)			
Men and women			
No. of patients	5,940	5,260	4,717
No. of events	71	57	46
1 SD	4.0	11.9	2.6
Crude model	0.95 (0.76–1.19)	0.91 (0.70–1.18)	0.88 (0.68–1.15)
Adjusted model[a]	0.96 (0.76–1.22)	0.87 (0.65–1.17)	0.80 (0.60–1.09)
Larynx, trachea/bronchus/lung (C32–C34)			
Men and women			
No. of patients	5,940	5,260	4,717
No. of events	118	82	62
1 SD	4.0	11.9	2.6
Crude model	0.83 (0.66–1.03)	1.03 (0.82–1.30)	1.02 (0.79–1.30)
Adjusted model[a]	0.85 (0.68–1.07)	0.94 (0.70–1.25)	0.89 (0.66–1.21)
Breast (C50)			
Women			
No. of patients	1,528	1,356	1,221
No. of events	25	17	14
1 SD	4.8	12.8	2.4
Crude model	0.88 (0.63–1.23)	1.03 (0.65–1.62)	1.31 (0.96–1.79)
Adjusted model[a]	0.88 (0.62–1.25)	1.14 (0.67–1.96)	1.42 (1.03–1.96)
Prostate (C61)			
Men			
No. of patients	4,412	3,904	3,496
No. of events	79	57	51
1 SD	3.6	10.6	2.4
Crude model	0.73 (0.60–0.88)	0.90 (0.73–1.11)	0.89 (0.65–1.21)
Adjusted model[a]	0.79 (0.64–0.97)	0.87 (0.69–1.10)	0.85 (0.62–1.17)

[a]Model adjusted for age, sex (when not stratified by), smoking status, pack-years of smoking, and alcohol use.

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Table 5. HRs with 95% CI for incident cancer according to metabolic syndrome in patients with manifest vascular disease without a history of cancer at baseline

	Number of metabolic syndrome components[a]			Metabolic syndrome	
Cancer site (ICD-10)	**0–1**	**2–3**	**4–5**	**No**	**Yes**
All [excluding non-melanoma skin cancer (C44)]					
Men					
No. of patients	734	2,531	1,146	2,064	2,347
No. of events	69	224	98	188	203
Crude model	1.00 (reference)	0.91 (0.69–1.19)	0.87 (0.64–1.18)	1.00 (reference)	0.93 (0.76–1.13)
Adjusted model[b]	1.00 (reference)	0.84 (0.64–1.10)	0.83 (0.61–1.13)	1.00 (reference)	0.92 (0.76–1.13)
Women					
No. of patients	323	742	461	694	832
No. of events	24	57	44	53	72
Crude model	1.00 (reference)	1.13 (0.70–1.80)	1.23 (0.75–2.02)	1.00 (reference)	1.07 (0.75–1.52)
Adjusted model[b]	1.00 (reference)	0.99 (0.61–1.60)	1.05 (0.63–1.75)	1.00 (reference)	0.96 (0.66–1.40)
Men and women					
No. of patients	1,057	3,273	1,607	2,758	3,179
No. of events	93	281	142	241	275
Crude model	1.00 (reference)	0.97 (0.77–1.23)	0.96 (0.74–1.25)	1.00 (reference)	0.96 (0.81–1.14)
Adjusted model[b]	1.00 (reference)	0.87 (0.68–1.10)	0.88 (0.67–1.14)	1.00 (reference)	0.92 (0.77–1.10)
Colon, rectum (C18–C20)					
Men and women					
No. of patients	1,057	3,273	1,607	2,758	3,179
No. of events	8	46	17	32	39
Crude model	1.00 (reference)	1.84 (0.87–3.90)	1.33 (0.57–3.09)	1.00 (reference)	1.02 (0.64–1.63)
Adjusted model[b]	1.00 (reference)	1.66 (0.79–3.51)	1.16 (0.51–2.67)	1.00 (reference)	0.95 (0.59–1.52)
Larynx, trachea/bronchus/lung (C32–C34)					
Men and women					
No. of patients	1,057	3,273	1,607	2,758	3,179
No. of events	17	64	37	51	67
Crude model	1.00 (reference)	1.21 (0.71–2.07)	1.38 (0.78–2.46)	1.00 (reference)	1.11 (0.77–1.60)
Adjusted model[b]	1.00 (reference)	1.04 (0.60–1.78)	1.14 (0.63–2.05)	1.00 (reference)	1.00 (0.68–1.46)
Breast (C50)					
Women					
No. of patients	323	742	461	694	832
No. of events	7	11	7	13	12
Crude model	1.00 (reference)	0.75 (0.29–1.93)	0.65 (0.22–1.88)	1.00 (reference)	0.70 (0.32–1.56)
Adjusted model[b]	1.00 (reference)	0.80 (0.30–2.09)	0.68 (0.22–2.04)	1.00 (reference)	0.73 (0.31–1.76)
Prostate (C61)					
Men					
No. of patients	734	2,531	1,146	2,064	2,347
No. of events	17	46	16	45	34
Crude model	1.00 (reference)	0.76 (0.44–1.33)	0.58 (0.29–1.15)	1.00 (reference)	0.65 (0.42–1.02)
Adjusted model[b]	1.00 (reference)	0.70 (0.40–1.24)	0.58 (0.30–1.15)	1.00 (reference)	0.68 (0.44–1.07)

[a]According to NCEP-R criteria, abdominal obesity: waist circumference > 102 cm in men or >88 cm in women; hypertension: ≥130 mm Hg systolic or ≥85 mm Hg diastolic; hypertriglyceridemia: serum triglycerides ≥ 1.70 mmol/L (150 mg/dL); low HDL-cholesterol: serum HDL-cholesterol < 1.04 mmol/L (40 mg/dL) in men or <1.29 mmol/L (50 mg/dL) in women; high fasting glucose: fasting serum glucose ≥ 5.6 mmol/l (100 mg/dL).

[b]Model adjusted for age, sex (when not stratified by), smoking status, pack-years of smoking, and alcohol use.

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addition, the number of metabolic syndrome components did not significantly affect overall cancer risk.

Discussion

In patients with manifest vascular disease, cancer incidence was 19% higher than expected based on cancer incidence in the general population. Specifically, risk of cancer of the lower respiratory tract as well as cancer of the bladder and lip, oral cavity, or pharynx in men and colorectal and kidney cancer in women was higher compared to the general population. Our results indicate that smoking is a strong risk factor for cancer risk in these patients. Adiposity was associated with a lower risk of overall incident cancer, but with a higher risk of breast cancer in women, whereas there was no relation between MetS and cancer risk.

These findings are in line with observations of an increased risk of smoking-related cancers in patients with vascular disease in previous hospital discharge register studies (31–33). However, inconsistent results have been reported for cancers that are not known to be related to smoking, such as colorectal and prostate cancer (1, 32, 34–36). For colorectal neoplasms, several studies found an increased risk in patients with CAD (1, 32) whereas other studies found no relation (35, 36). Observations in this study of a higher incidence of colorectal cancer, but also of melanoma of the skin, compared to the general population, indicate that other factors besides tobacco smoking may also have a role. In contrast to previous studies, the design of this study allowed to prospectively evaluate and quantify the effects of possible explanatory factors for the observed increased cancer risk. Twenty-six percent of the study population were female, which is similar to the percentage of women among patients with vascular disease of the same age category in the general population (24).

Although obesity is a known risk factor for colorectal cancer in the general population (13, 37), no association between any of the adiposity measures and colorectal cancer risk was observed in our study population. Meta-analyses of population-based studies indicate that, in addition to colorectal cancer, increase in BMI is associated with a higher risk of esophageal adenocarcinoma, endometrial, postmenopausal breast, and high-grade prostate cancer, as well as several less common cancers (12, 13, 38). Conversely, inverse associations with BMI have been reported for lung and low-grade prostate cancer (12, 13, 38). The modestly lower overall cancer risk with increasing BMI observed in this study might have been caused by the relatively large number of lung and prostate cancer cases (38% of total cases). Indeed, inverse associations of BMI with prostate and lung cancer were found, although the latter was not statistically significant.

Insulin resistance and chronic low-grade inflammation are considered as culprits in the relation between obesity and cancer (14). Especially abdominal obesity is associated with a state of insulin resistance and low-grade inflammation (39, 40) and VAT might therefore be a better determinant for certain cancers than BMI or waist circumference, as the latter measures are known to misclassify individuals in terms of VAT and metabolic risk (41). Correspondingly, we observed that an increase in VAT was related to an increased risk for breast cancer risk, whereas BMI and waist circumference were not.

To our knowledge, this is the first prospective study investigating the effect of MetS on cancer risk in patients with vascular disease. This study confirms previous findings from population-based cohorts that MetS is not related to overall cancer risk (42, 43), or risk of cancers of the lung or prostate (17). However, in contrast to the present findings in patients with vascular disease, MetS has been linked to an increased risk of colorectal and postmenopausal breast cancer in the general population, as was recently confirmed in a meta-analysis (17). Furthermore, in a cross-sectional study among patients undergoing coronary angiography, a relation was observed between CAD and advanced colonic lesions, which was stronger in persons with MetS (1). The lack of a relation between BMI or MetS and colorectal cancer risk in this study warrants further research to determine which factors are responsible for this difference between patients with vascular disease and the general population.

The increased risk of cancer in patients with vascular disease warrants awareness among clinicians. Pharmaceutical treatment and lifestyle modifications of shared risk factors, such as smoking cessation, are likely to reduce both (recurrent) vascular events and cancer in these patients. Although targeting (abdominal) obesity may decrease breast cancer risk, the inverse relation between BMI and prostate and lung cancer risk suggests that lowering BMI might not be favorable for the risk of these cancers. The net benefit of such interventions should be determined in studies that consider both cancer and vascular disease concurrently. In addition to shared risk factors, a possible common pathogenesis, such as chronic inflammation in both atherosclerosis and colorectal carcinogenesis, may also have a role in the relation between vascular disease and cancer risk (44). A better understanding of such mechanisms might provide novel therapeutic strategies targeting both vascular disease and cancer.

Several potential limitations of our study should be considered. Relative cancer risk in patients with vascular disease might have been underestimated by using the general Dutch population—in which vascular disease is highly prevalent—as reference group to calculate SIRs. Despite the substantial number of possible confounders that was adjusted for in the models, information on other possible confounders for some specific cancer sites, such as physical activity, genetic, and dietary factors, was not available. In addition, due to the relatively small number of cases

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the study might have been underpowered to detect significant relations with several site-specific cancers. Furthermore, the limited number of cases did not allow stratification by cancer-specific features (e.g., low-/high-grade prostate cancer) in analyses of individual cancer types, hereby reducing comparability with previous studies.

Notable strengths of our study include the prospective design and the completeness of cancer diagnoses, attained through a linkage of the SMART cohort with the Netherlands Cancer Registry, which is considered to have a near complete coverage (45). The proportion of study participants who were lost to follow-up was low, reducing the risk of bias. Furthermore, the study population is at high risk of vascular death, which is a competing event for incident cancer and may therefore complicate the interpretability of the risk estimates. We addressed this problem by using competing risk models (29). Hence, the HRs that are presented can be directly interpreted in terms of risk.

In conclusion, patients with vascular disease have a 19% higher cancer risk compared to the general population in a median follow-up of 5.5 years. Smoking is a risk factor for cancer in men and women, and abdominal obesity increased the risk of breast cancer in female patients with clinical manifest vascular disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: R.C.M. van Kruijsdijk, Y. van der Graaf, F.L.J. Visseren

Development of methodology: R.C.M. van Kruijsdijk, Y. van der Graaf, F.L.J. Visseren

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R.C.M. van Kruijsdijk, Y. van der Graaf, P.H. Peeters, F.L.J. Visseren

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R.C.M. van Kruijsdijk, P.H. Peeters, F.L.J. Visseren

Writing, review, and/or revision of the manuscript: R.C.M. van Kruijsdijk, Y. van der Graaf, P.H. Peeters, F.L.J. Visseren

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R.C.M. van Kruijsdijk, Y. van der Graaf

Study supervision: Y. van der Graaf, P.H. Peeters, F.L.J. Visseren

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Rob C.M. van Kruijsdijk, Yolanda van der Graaf, Petra H.M. Peeters, et al.

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