Increased prevalence of coronary atherosclerosis in cancer survivors: a retrospective matched cross-sectional study with coronary CT angiography

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Increased prevalence of coronary atherosclerosis in cancer survivors: A retrospective matched cross-sectional study with coronary CT angiography

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Abstract

Background Cancer and cancer treatment may accelerate the development of cardiovascular disease. With the improved prognosis of cancer survivors, cardiovascular events are increasing in this patient group. However, it is unknown whether the prevalence of coronary atherosclerosis is increased in patients with a history of cancer. This study aims to evaluate the prevalence and severity of coronary atherosclerosis in different age groups of cancer survivors compared to matched controls.

Methods Consecutive cancer survivors aged > 30 years who underwent evaluation for stable coronary artery disease with coronary computed tomography angiography (CCTA) were included in this retrospective study. Propensity score matching was performed and cancer survivors were matched 1:2 to a control population without oncological history. The presence of coronary atherosclerosis was assessed in both groups.

Results The study population consisted of 312 cancer survivors and 624 matched controls. Median age at CCTA scan was 59.2 [50.3-67.5] years and 66.0% was female. Coronary atherosclerosis was observed in 257 (82.4%) cancer survivors compared to 459 (73.6%) control patients with an Odds Ratio (OR) of 1.68 [95% CI: 1.19-2.36], $P = .003$. Mainly younger cancer survivors aged between 30 and 59 years had an increased prevalence of coronary atherosclerosis with an OR of 2.21 [95% CI: 1.40-3.49] compared to control patients ($P = .001$). In addition, thoracic radiotherapy showed a significant association with increased prevalence of atherosclerosis in the younger population with an OR of 3.29 ([95% CI: 1.70-6.38], $P < .001$).

Conclusions Patients with a history cancer have an increased prevalence of coronary atherosclerosis on CCTA compared to matched patients without cancer. This effect was most pronounced in younger patients aged 30 to 59 years. (Am Heart J 2025;282:134–145.)

Background

Cancer and cardiovascular diseases (CVD) are leading causes of death worldwide.[1,2] Major improvements in cancer treatment have led to a substantial rise in cancer survivors over the last 30 years. However, due to longer survival, the cardiotoxic side effects of cancer therapies have become more apparent in this patient population, increasing the risk of cardiovascular disease and death.[3] This underlines the importance of monitoring long-term cardiotoxicity after cancer treatment.[4,5]

Cancer and CVD share many (modifiable) risk factors including smoking, diabetes mellitus (DM), obesity and hypertension. These shared risk factors contribute to the development of atherosclerotic disease in cancer survivors, in addition to the cardiovascular risks associated with cancer therapies. Prior research reported that traditional risk factors for CVD are associated with an

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increased risk of cancer development and - vice versa - that a healthy lifestyle decreases the risk of future cancer.[6] Moreover, childhood cancer survivors demonstrated an elevated risk of future CVD, which was further increased in the presence of traditional modifiable cardiovascular risk factors,[7] indicating the importance of lifestyle modification in cancer survivors. Moreover, clonal haematopoiesis of intermediate potential (CHIP), which arises from somatic mutations in hematopoietic stem cells, increases the risk of both haematological malignancies as well as CVD.[8,9]

In recent years, this close connection between cancer and atherosclerosis has garnered growing interest. Aside from similarities in pathogenesis between cancer and atherosclerosis, such as oxidative stress and inflammation, some cancer therapies also accelerate the development of atherosclerosis, for instance (thoracic) radiotherapy, which leads to endothelial damage and premature development of coronary atherosclerosis. Moreover, other systemic cancer therapies have also been reported to contribute to atherogenesis and the acceleration of atherosclerosis, such as anthracyclines (by producing reactive oxygen species), plant alkaloids (by increasing the permeability of blood vessels) and alkylating agents, which lead to increased oxidative stress and thrombosis.[9-12] However, research has predominantly focused on cardiovascular events, including heart failure and stroke, rather than addressing the underlying process contributing to those events, namely atherosclerosis itself. Therefore, there remains a notable gap in research on the association between the development of atherosclerosis in the population of cancer survivors.

In order to successfully monitor the (long-term) cardiovascular adverse events of cancer therapies, different modalities for screening and monitoring are recommended by the European Society of Cardiology (ESC) Guidelines on cardio-oncology.[13] For the early detection of atherosclerosis in specific groups of cancer survivors, the guidelines recommend noninvasive screening. While the specific screening modality is not explicitly specified, coronary computed tomography angiography (CCTA) is favored over coronary artery calcium (CAC) score due to its ability to identify stenosis severity and plaque morphology, which is a limitation of CAC score.[14,15] Limited studies have focused on the use of CCTA as screening method for cardiovascular disease in cancer survivors, however, this modality seems useful in the assessment of cardio-oncology patients with chest pain.

Therefore, this study aims to assess the association between cancer and the prevalence and severity of atherosclerosis as evaluated via CCTA in a cohort of cancer survivors, matched to a control group of individuals without a history of cancer through propensity score analysis.

Methods

Study population

We conducted a retrospective cross sectional study among consecutive cancer survivors who underwent evaluation for stable CAD with CCTA between 2010 and 2023 in the Leiden University Medical Center (LUMC). Eligible patients with a history of cancer and > 30 years of age were matched with propensity score technique to patients without a history of cancer. A propensity score was calculated using the following variables: age, sex, body mass index (BMI), hypercholesterolemia, hypertension, diabetes, use of statins and smoking status. Based on propensity scores, patient were matched 1:2. Cancer diagnosis was specified as a history of cancer, which was defined as all malignant neoplasms excluding non-melanoma skin cancer. Cancer diagnosis was determined with imaging, biomarkers or pathology. Smoking was defined as current or past smoking, hypercholesterolemia as a total cholesterol > 5 mmol/L or LDL-cholesterol > 3 mmol/L, diabetes mellitus as a history of diabetes mellitus type II or glucose levels > 11.1 mmol/L and hypertension as a history of hypertension or use of antihypertensive medication. The study was approved by the local Medical Ethical Committee (METC-LDD G20.045) and complies with the declaration of Helsinki. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

CCTA scan indication

Patients were referred for clinically indicated CCTA scans for evaluation of stable CAD either for suspected CAD or preprocedural evaluation before liver transplantation, electrophysiological interventions, transcatheter interventions or cardiothoracic surgery.

Data collection

Demographic patient data, medication and cardiovascular risk factors were collected from the institutional database consisting of 7000 patients who underwent CCTA at the LUMC. Cardiac CT reports were derived from the departmental Cardiology Information System (EPD-Vision, The Netherlands). Data on oncological characteristics, including the date of cancer diagnosis and treatment data were collected from pharmacy records (HiX Version 6.1 Chipsoft, The Netherlands).

CCTA acquisition

All patients were scanned using a 320-row volumetric scanner (Acquillon ONE Canon Medical Systems, Otawara, Japan). According to our hospital's protocol, metoprolol was prescribed in the outpatient clinic as preparation for the CT scan and a single dose metoprolol was administered orally (25-150 mg) 60 minutes prior

to the examination if the heart rate was > 65 beats per minute. If the target heart rate was not achieved after 60 minutes, metoprolol was administered intravenously (2.5-10 mg). Sublingual nitroglycerin spray was given 5 minutes prior to examination. Scan parameters were set according to BMI. Tube voltage ranged between 80 and 135 kV, tube current was set between 210 and 900 mA, gantry rotation time was 275 to 350 ms and the scan range chosen differed between 12 and 16 cm. Contrast administration was also dependent on BMI and ranged between 30 and 150 ml, which was administered in 11 seconds (FlowSens Medes) and followed by a 30 to 60 ml saline flush at 10 seconds. To reduce radiation dose, prospective ECG-triggering was performed if possible. Image analysis of the coronary arteries was performed using dedicated postprocessing software (Vitrea FX 7.12; Vital Images, Minnetonka, Minnesota, USA).

CCTA analysis

CCTA scans were reported by consensus of experts in the field according to the 17-segment model described by the American Heart Association.[16] The CCTA scans were reviewed by 2 independent researchers. In the case of disagreement, scans were reviewed by a third researcher to achieve consensus. The severity of coronary artery stenosis was collected for the segments of the main coronary arteries: the left main coronary artery (LM), the left anterior descending artery (LAD), the left circumflex artery (LCx) and right coronary artery (RCA) and was graded as 0, 0% to 24%, 25% to 49%, 50% to 69%, 70% to 99% or chronic total occlusion (CTO). Wall irregularities were defined as atherosclerosis without plaque. Plaque characteristics were assessed and defined as noncalcified, mixed or calcified for plaques with lumen narrowing ≥ 25%.[17] Significant stenosis was defined as lumen narrowing > 50%. Agatston calcium scores and percentiles were collected if available. CAC scores were also scored binary and given a score of zero in the absence of atherosclerosis, presence of wall irregularities or presence of noncalcified plaques and a score of 1 in the presence of mixed or calcified plaques. Semiquantitative plaque analysis to determine atherosclerotic plaque burden was performed using an adapted version of the CT-adapted Leaman score (CT-LeSc),[18] which is shown in Appendix A. To calculate this score, 3 different weighting factors are used: the coronary segment taking system dominance into account, the degree of stenosis with a multiplication factor of 1 for obstructive (≥ 50%) stenosis and 0.615 for nonobstructive stenosis and the plaque composition with a multiplication factor of 1.5 noncalcified or mixed plaques and 1 for calcified plaques. The CT-LeSc was determined for the segments of the main coronary arteries: proximal, mid and distal LAD, proximal, mid and distal RCA, proximal and distal LCx and LM. The total CT-LeSc per coronary artery was calculated by the sum of its segments and a total CT-LeSc per patient was derived from the sum of all segments.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median with interquartile range [IQR], depending on whether they follow a normal distribution. Categorical variables are shown as percentages or frequencies. Mixed-effect models were used for analyses, which utilize random effects to account for the propensity-based matching. Specifically, to compare the baseline characteristics of normally distributed continuous variables, the mixed-effects model was performed to assess differences between the exposure and control group. For non-normally distributed data, the mixed-effects generalized linear model with gamma distribution was performed to assess for differences between the groups. The mixed-effects logistic regression model, was used to evaluate differences in binary, nominal and ordinal variables between groups. Logistic regression analysis was performed to estimate the Odds Ratio's (OR) in the whole propensity-score matched study population to assess the risk of atherosclerosis or significant stenosis. In the unbalanced subpopulations, a mixed-effects logistic regression analysis with random effects was conducted to adjust for baseline imbalances between subgroups, accounting for the matched triplets. E-values were calculated to assess the potential impact of unmeasured confounders on the outcomes. To calculate E-values, the risk ratio (RR) was calculated by the square root (sqrt) of the OR and inserted in this formula: E-value = RR + sqrt {RR x (RR-1)}. A 2-sided *p*-value of < .05 was considered as statistically significant. All analyses were performed in STATA version 17.0 (StataCorp 2021, Texas, United States).

Results

Baseline characteristics

The study population consisted of 312 cancer survivors and 624 propensity score matched controls. The balancing property was met in all matched patients with mean propensity scores of 0.12 ± 0.06 in the exposure group and 0.12 ± 0.08 in the control group ($P = .59$)

The median age at the time of CCTA was 59.3 [50.4-67.5] years and 618 (66.0%) of the patients were female. No significant differences were found in the baseline characteristics of both groups (Table 1). In cancer survivors, the median time between cancer diagnosis and CCTA scan was 10.3 [4.5-19.1] years and median age at cancer diagnosis was 50.0 [31.5-60.1] years. Most common primary cancer diagnoses in our population were breast cancer (n = 72, 23.1%), Hodgkin lymphoma (n = 70, 22.4%) and melanoma (n = 25, 8.0%). Radiotherapy was applied as treatment in 185 cancer survivors (59.3%) of whom 139 (75.1%) were treated with thoracic

Table 1. Baseline characteristics of the study population

	Total (n = 936)	No cancer (n = 624)	Cancer (n = 312)	*P*-value
Age at CT scan, yrs	59.4 [50.4-67.5]	58.9 [50.1-67.0]	60.3 [50.6-68.9]	.41
Female	618 (66.0%)	412 (66.0%)	206 (66.0%)	1.00
BMI, kg/m^2	25.3 [23.0-28.3]	25.2 [23.0-28.3]	25.7 [22.7-28.3]	.94
Cardiovascular risk factors				
Smoking	117 (12.5%)	78 (12.5%)	39 (12.5%)	.96
Hypercholesterolemia	498 (53.2%)	334(53.5%)	164 (52.6%)	.70
Diabetes Mellitus	86 (9.5%)	64 (10.5%)	22 (7.4%)	.11
Hypertension	282 (30.1%)	187 (30.0%)	95 (30.4%)	.86
Statin use	175 (18.7%)	119 (19.1%)	56 (17.9%)	.65
CT indication				.30
Evaluation CAD	886 (94.7%)	594 (95.2%)	292 (93.4%)	
Preprocedural	50 (5.3%)	30 (4.8%)	20 (6.4%)	

BMI = body mass index; CAD = coronary artery disease.

Table 2. Oncological characteristics

	Patients with a history of cancer (n = 312)
Age at cancer diagnosis, yrs	50.0 [31.5-60.1]
Primary cancer type	
Breast	71 (22.8%)
Hodgkin lymphoma	70 (22.4%)
Melanoma	26 (8.3%)
Prostate	19(6.1%)
Leukemia	17 (5.4%)
Colorectal	16 (5.1%)
Other	93 (29.8%)
Distant metastasis	15 (4.8%)
Second malignancy	34 (10.9%)
Treatment	
Chemotherapy	153 (49.2%)
Radiotherapy	185 (59.5%)
Thoracic radiotherapy	139 (74.7%)
Total body irradiation	6 (4.3%)
Immune checkpoint inhibitors	1 (0.3%)

radiotherapy, 153 (49.0%) patients were treated with chemotherapy and 1 patient (0.3%) was treated with immune checkpoint inhibitors (Table 2). In the group of cancer survivors, 292 patients (93.4%) underwent CCTA for stable CAD evaluation for suspected CAD compared to 594 (95.2%) in the control group and CCTA as preprocedural evaluation was performed in 20 cancer survivors (6.4%) compared to 30 control patients (4.8%), $P = .31$.

Presence of coronary atherosclerosis in cancer vs no cancer

Cancer survivors had a significant higher prevalence of coronary atherosclerosis. In this population, 257 patients (82.4%) had atherosclerosis in at least 1 of the main coronary arteries and in the control population this was present in 459 patients (73.6%). Cancer survivors showed an OR of 1.68 [95% CI: 1.19-2.36] for atherosclerosis ($P = .003$) with a corresponding E-value of 2.12. No significant differences in the grade of stenosis or presence of atherosclerosis in specific coronary segments were observed between the 2 groups. Table 3 shows an overview of the CCTA characteristics including the CADRADs in both patient groups. Cancer was significantly associated with the presence of atherosclerosis when adjusted for thoracic radiotherapy with an OR of 2.03 [95% CI: 1.29-3.20] ($P = .002$) and E-value of 2.44.

Coronary atherosclerosis related to age

In our study population, 486 patients were aged 30 to 59 years of whom 151 were cancer survivors and 335 were control patients. The majority of the patients was female (63.8%). The control population was older and had a significant higher prevalence of diabetes mellitus (Table 4). In this younger subgroup, cancer survivors had a significant higher prevalence of coronary atherosclerosis: 112 patients with cancer (74.1%) showed coronary atherosclerosis compared to 211 (63.0%) control patients. When adjusted for baseline imbalances, younger cancer survivors had an OR of 2.21 [95% CI: 1.40-3.49] for atherosclerosis compared to control patients ($P = .001$) with an E-value of 2.59. The population aged $\geq$ 60 years consisted of 450 patients of whom 68.4% (n = 308) were female. A history of cancer was present in 161 (35.8%) patients and 289 (64.2%) patients had no prior malignancy. Cancer survivors had a significantly higher median BMI (26.5 vs 25.7 kg/m^2, $P = .049$) and age at CT scan (68.8 vs 67.4 years, $P = .035$). No significant differences in other cardiovascular risk factors were found. In this older population, there was no significant difference in the prevalence of coronary atherosclerosis between the 2 groups: 90.0% (n = 145) of the cancer survivors had coronary atherosclerosis compared to 85.8% (n = 248) patients in the control population with an OR of 1.50 [95% CI: 0.81-2.78] for patients with a history of cancer compared to the control group ($P = .20$). Also

Table 3. CCTA characteristics

	Total (n = 936)	No cancer (n = 624)	Cancer (n = 312)	P-value
Age at CT scan, yrs	59.3 [50.4-67.5]	58.9 [50.1-67.0]	60.3 [50.6-68.9]	.41
Dominant System				.79
Right dominant	803 (85.8%)	534 (85.6%)	268 (85.9%)	
Left dominant	100 (10.6%)	68 (10.9%)	32 (10.2%)	
Balanced	33 (3.5%)	22 (3.5%)	11 (3.5%)	
Atherosclerosis	716 (76.5%)	459 (73.6%)	257 (82.4%)	.003
Lumen narrowing > 50%	111 (11.9%)	72 (11.5%)	39 (12.5%)	.67
CADRADs				.084
0	220 (23.5%)	165 (26.4%)	55 (17.6%)	.003
1	286 (30.6%)	187 (30.0%)	99 (31.7%)	.58
2	319 (34.1%)	200 (32.1%)	119 (38.1%)	.06
3	64 (6.8%)	41 (6.6%)	23 (7.4%)	.64
4	37 (4.0%)	25 (4.0%)	12 (3.8%)	.91
4A	32 (3.4%)	21 (3.4%)	11 (3.5%)	.90
4B	5 (0.5%)	4 (0.6%)	1 (0.3%)	.53
5	13 (1.4%)	8 (1.3%)	5 (1.6%)	.69
Agatston calcium score (n = 646)	0 [0-17]	0 [0-10]	0 [0-35]	.21
0	433 (67.0%)	312 (69.3%)	121 (61.7%)	.06
1-99	117 (18.1%)	79 (17.6%)	38 (19.4%)	.58
100-399	51 (7.9%)	34 (7.6%)	17 (8.7%)	.66
≥ 400	45 (7.0%)	25 (5.6%)	20 (10.2%)	.035
Calcium score percentile (n = 646)				
0%	433 (67.0%)	312 (69.3%)	121 (61.7%)	.059
0-25%	11 (1.9%)	9 (2.0%)	3 (1.5%)	.68
25-50%	46 (7.1%)	34 (7.6%)	12 (6.1%)	.52
50-75%	54 (8.4%)	36 (8.0%)	18 (9.2%)	.62
75-90%	45 (7.0%)	28 (6.2%)	17 (8.7%)	.26
> 90%	56 (8.7%)	31 (6.9%)	25 (12.8%)	.015

CADRADs = Coronary Artery Disease-Reporting and Data System; CCTA = coronary computed tomography angiography.

Table 4. Baseline characteristics of the younger population (30-59 years)

	Total (n = 486)	No cancer (n = 335)	Cancer (n = 151)	P-value
Age at CT scan, yrs	50.7 [44.7-55.5]	50.7 [45.7-55.8]	50.4 [40.9-55.2]	.014
Female	310 (63.8%)	216 (64.5%)	94 (62.3%)	.98
BMI, kg/m^2	25.0 [23.0-28.1]	25.2 [23.2-28.5]	24.6 [22.2-27.2]	.052
Cardiovascular risk factors				
Smoking	64 (13.2%)	48 (14.3%)	16 (10.6%)	.30
Hypercholesterolemia	255 (52.5%)	173 (51.6%)	82 (54.3%)	.53
Diabetes Mellitus	40 (8.5%)	37 (11.3%)	3 (2.1%)	.003
Hypertension	95 (19.5%)	73 (21.8%)	22 (14.6%)	.073
Statin use	67 (13.8%)	51 (15.2%)	16 (10.6%)	.22

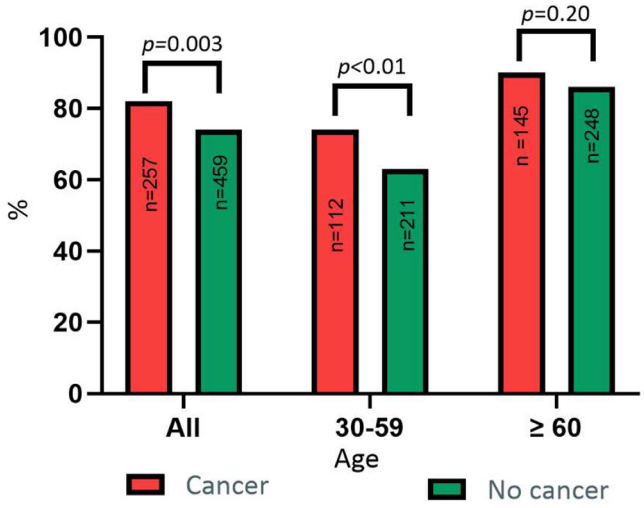
BMI = body mass index.

after adjusting for BMI and age at CT scan, no significant association between cancer and atherosclerosis was observed ($P = .71$). These results show that in younger cancer survivors, coronary atherosclerosis is significantly more prevalent compared to the control population, whereas older cancer survivors have a similar prevalence of atherosclerosis compared to the control population. Figure 1 shows an overview of the risk of atherosclerosis for the different patient groups. In Figure 2, an example of severe coronary stenosis in a cancer survivor is shown, compared to a propensity score matched patient without atherosclerosis.

Proatherogenic systemic cancer treatment and atherosclerosis

We assessed the different systemic cancer treatments and classified proatherogenic treatment according to state-of-the-art literature.[9] In total, 157 cancer survivors (16.8%) were treated with proatherogenic systemic cancer treatment: 81 (26.0%) with anthracyclines, 111 (35.6%) with alkylating agents, 100 (32.1%) with plant alkaloids, 41 (13.1%) with antimetabolites, 27 (8.7%) with hormonal therapies and 11 (3.5%) with tyrosine kinase inhibitors and/or immune checkpoint inhibitors. Adjusted for age at CT scan and hypertension, mixed-

Figure 1. Presence of coronary atherosclerosis. This figure shows the presence of coronary atherosclerosis in any of the main coronary arteries for cancer survivors and the control group. Overall, cancer survivors have a significant higher prevalence of atherosclerosis, mostly driven by the subgroup of patients aged 30 to 59 years. Odds Ratios were calculated by using logistic regression analysis and in the subpopulations mixed-effects logistic regression analysis with random effects was performed to adjust for imbalanced covariates.



effects logistic regression analysis showed an OR of 1.72 ([95% CI: 1.09-2.71], $P = .019$, E-value = 2.16) for the presence of atherosclerosis in patients treated with proatherogenic systemic cancer therapies. In the younger population, when corrected for baseline imbalances (age at CT scan and DM), a significant increased OR of 2.22 [95% CI: 1.28-3.86] for atherosclerosis was found ($P = .005$) with an E-value of 2.60. In the older population, treatment with proatherogenic systemic cancer therapies did not increase the risk of atherosclerosis.

Radiotherapy and atherosclerosis

In our population of cancer survivors, 139 patients (44.6%) were treated with thoracic radiotherapy for various malignancies: Hodgkin lymphoma (n = 66), breast cancer (n = 56), Non-Hodgkin's lymphoma (n = 6), leukemia (n = 5), lung cancer (n = 2), multiple myeloma (n = 1), mediastinal metastases (n = 2) and sarcoma (n = 1). The median time between cancer diagnosis and CCTA scan was 10.3 [4.5;19.1] years. These patients did not have a significant higher prevalence of atherosclerosis compared to patients not treated with thoracic radiotherapy (79.1% vs 76.0% respectively), with an OR of 1.20 [95% CI: 0.77-1.87], $P = .42$. However, when adjusted for unbalanced baseline covariates (age at CT, gender, BMI, hypertension, DM and statin use), the calculated OR was 2.19 (95% CI: 1.34-3.58, $P = .002$, E-value = 2.57) for the risk of atherosclerosis for patients treated with thoracic radiotherapy.

In the group of older patients aged ≥ 60 years, no increased prevalence of atherosclerosis was found for patients treated with vs without thoracic irradiation. In the older population, 54 patients (33.3%) were treated with thoracic radiotherapy of whom 45 (83.3%) showed atherosclerosis compared to 348 patients (87.9%) who were not treated with thoracic radiotherapy. There were significant more female patients in the group of patients treated with thoracic radiotherapy, but also adjusted for gender, mixed-effects logistic regression did not show a significant association between thoracic radiotherapy and atherosclerosis. However, in the younger population aged 30 to 59 years, 85 patients (56.3%) were treated with thoracic radiotherapy of whom 65 (76.5%) showed atherosclerosis compared to 258 patients (64.3%) who were not treated with thoracic radiotherapy with an OR of 1.89 [95% CI: 1.06-3.40], $P = .032$. There were significant baseline imbalances for age, BMI and DM. When thoracic radiotherapy was adjusted for these covariables, an OR of 3.29 ([95% CI: 1.70-6.38], $P < .001$) for atherosclerosis with a corresponding E-value of 3.33 was calculated. Coronary atherosclerosis in relation to thoracic radiotherapy is visualized in Figure 3 for the different patient groups.

Plaque composition

We assessed all plaque morphologies in the whole study population for plaques with a minimal lumen narrowing of 25%. In cancer survivors, a significant higher prevalence of calcified plaques was observed compared

Figure 2. CCTA scans of a matched pair of patients. Figure 2A shows the multiplanar reconstruction and 3D-view of a coronary CT scan of a 73-year-old female breast cancer survivor, who was treated with surgical excision and chemotherapy. Cardiac risk factors were hypertension, diabetes, obesity and smoking. The figure shows that her RCA is totally occluded from the mid-RCA. Figure 2B shows the multiplanar reconstruction and 3D-view of a coronary CT scan of a 41-year-old female patient without a history of cancer who was propensity score matched to the patient in Figure 2A. She had non-anginal complaints in the presence of smoking and obesity as risk factors. Her RCA does not show atherosclerosis.

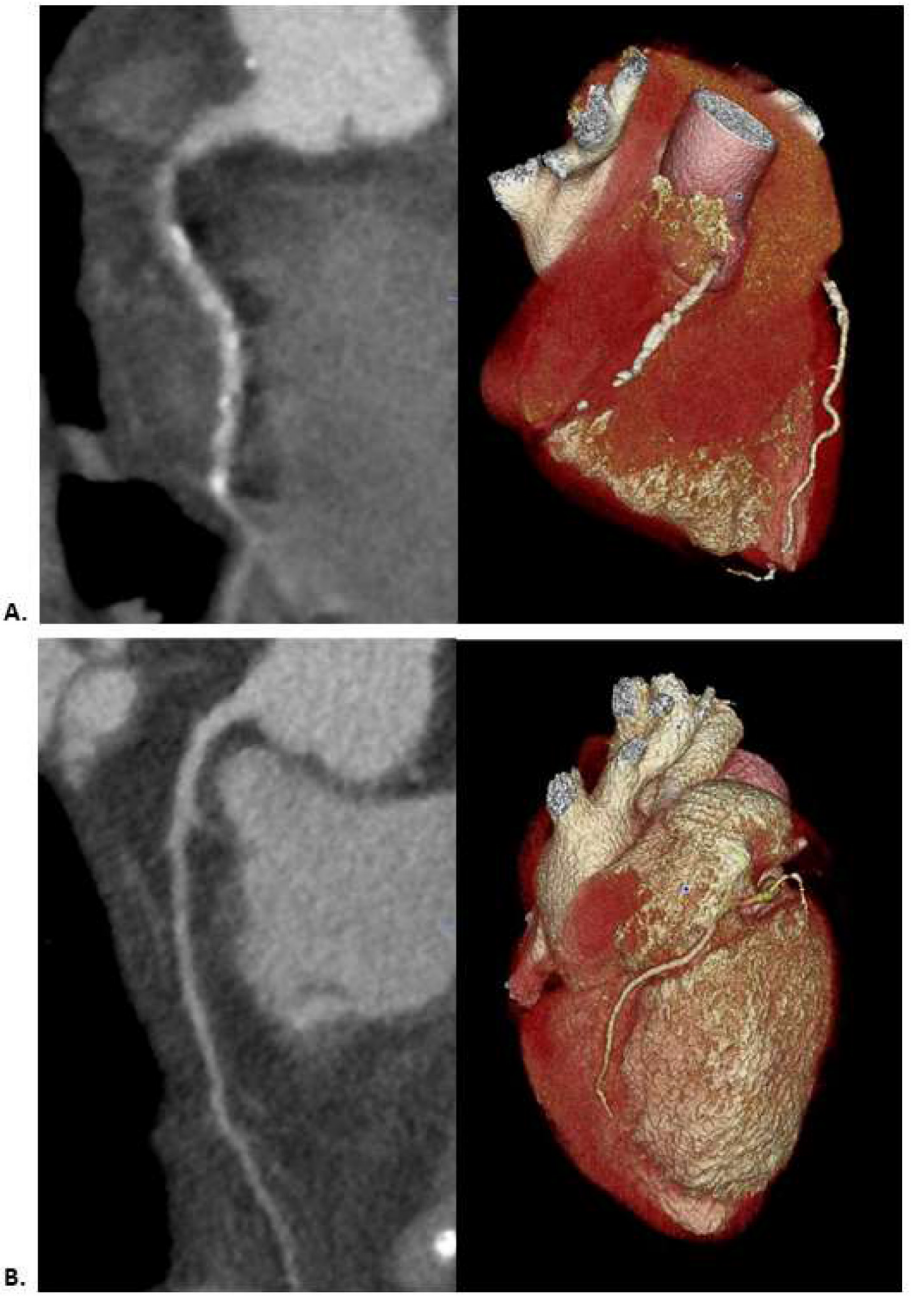
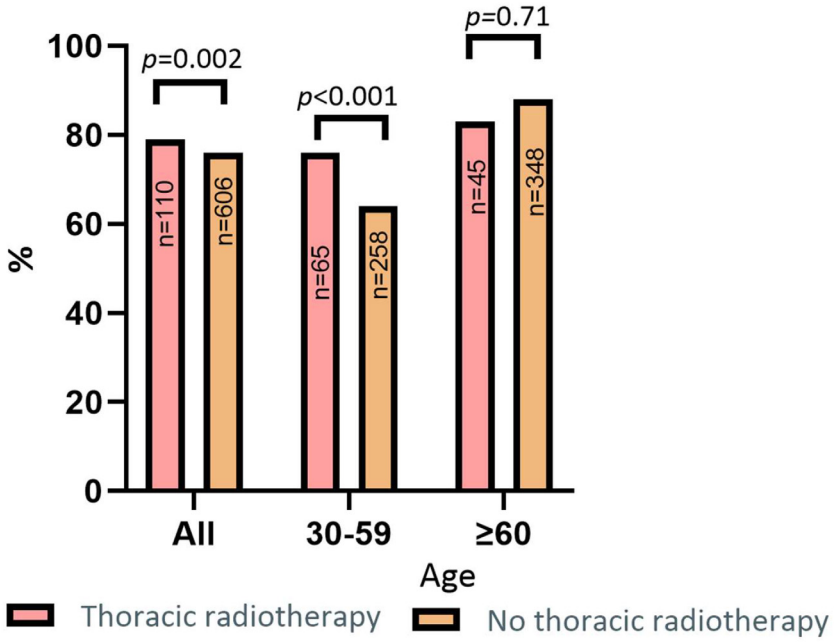


Figure 3. Presence of Coronary Atherosclerosis in Patients Treated With and Without Thoracic Radiation.
Figure 3 shows the presence of coronary atherosclerosis in cancer patients treated with and without thoracic radiotherapy. In the younger population aged 30 to 59, thoracic radiotherapy is associated with an increased prevalence of atherosclerosis. Odds Ratios were calculated by using logistic regression analysis and in the subpopulations mixed-effects logistic regression analysis with random effects was performed to adjust for imbalanced covariates.



to patients without cancer (14.4% vs 9.3% respectively, $P = .019$). No significant differences were observed for the prevalence of noncalcified and mixed plaques between the 2 groups. Noncalcified plaques, including wall irregularities, were present in 40 cancer survivors (12.8%) and 103 control patients (16.5%), $P = .14$. Mixed plaques were present in 84 (26.9%) cancer survivors and 140 control patients (22.4%), $P = .13$. Calcified plaques and mixed plaques were significantly more prevalent in cancer survivors treated without radiotherapy compared to cancer survivors treated with radiotherapy (18.5% vs 9.4%, $P = .025$ and 34.1% vs 18.0%, $P = .002$, respectively). Also, calcified and mixed plaque morphologies were significantly more prevalent in the elderly patients aged $\geq$ 60 years compared to patients $<$ 60 years (15.8% vs 6.6%, $P < .001$ and 35.3% vs 13.4%, $P < .01$, respectively).

Prevalence of significant stenosis

There was no significant difference in the presence of significant stenoses in cancer survivors vs the control population. The median time between cancer diagnosis and presence of significant stenosis as assessed by CCTA was 7.6 [1.6-12.8] years. A significant stenosis in any of the main coronary arteries was present in 39 cancer survivors (12.5%) and 72 control patients (11.5%) with an OR of 1.10 [95% CI: 0.72-1.66] for cancer survivors compared to the control population ($P = .67$).

Semi-quantitative plaque analysis

The CCTA-Adapted Leaman Score (CT-LeSc) was adapted (Appendix A) and used to determine the plaque burden in the main coronary arteries for plaques with lumen narrowing $>$ 25%. No significant differences in CT-LeSc between the 2 groups were observed. The total CT-LeSc per patient was available in 415 patients with values of 5.60 $\pm$ 3.77 in cancer survivors compared to 5.47 $\pm$ 3.92 in the control population ($P = .74$). In the LAD the scores were 4.49 $\pm$ 2.28 and 4.32 $\pm$ 2.19 respectively ($P = .51$). An overview of all CT-LeSc scores is shown in Table 5. When stratifying the population by age, no significant differences were found between patients with and without cancer aged 30 to 59 years or $\geq$ 60 years. In the whole study population, older patients had a significant higher CT-LeSc score compared to patients aged 30 to 59 years with a mean total CT-LeSc of 5.91 $\pm$ 3.88 vs 4.79 $\pm$ 3.72 ($P = .004$). However, after stratification for cancer, the older population did not show higher CT-LeSc compared to the younger population with cancer (5.94 $\pm$ 3.67 vs 4.86 $\pm$ 3.91, $P = .10$). We also determined CAD-RADS 2.0 including plaque modifier (P) scores according to the expert con-

Table 5. CT-adapted leaman score

CT-LeSc	Total (n = 936)	No cancer (n = 624)	Cancer (n = 312)	*P-value*
LM (n = 58)	4.52 ± 0.96	4.58 ± 0.95	4.41 ± 0.99	.50
RCA (n = 216)	1.39 ± 0.96	1.43 ± 1.01	1.30 ± 0.86	.34
LAD (n = 349)	4.38 ± 2.22	4.32 ± 2.19	4.49 ± 2.28	.51
RCx (n = 133)	1.50 ± 0.70	1.49 ± 0.50	1.51 ± 0.92	.88
Per patient (n = 415)	5.52 ± 3.86	5.47 ± 3.92	5.60 ± 3.77	.74

LAD = left anterior descending artery; LM = left main coronary artery; RCA = right coronary artery; RCx = right circumflex artery.

sensus document for semi-quantitative plaque analysis.[19] These results are presented in Appendix B. No significant differences in CADRADS 2.0 scores were observed between cancer survivors and the control population.

Coronary artery calcium score

Agatston calcium scores were available for 196 (62.8%) cancer survivors and 450 control patients (72.1%) ranging from 0 to 3457 and 0 to 5160 respectively. Calcium scores were also scored binary retrospectively. Cancer survivors showed a significant higher prevalence of a CAC score higher than zero compared to the control population (62.2% vs 50.2%, $P = .001$) and a higher prevalence of a calcium score > 90th percentile (12.8% vs 6.9%, $P = .016$). In all 716 patients with atherosclerosis, a CAC sore of zero was observed in almost one third of the patients (n = 209, 29.2%). In the presence of coronary atherosclerosis, cancer survivors still had a significant increased prevalence of a CAC score higher than zero compared to control patients (75.5% vs 68.2%, $P = .040$). In the subgroups stratified for age, no significant differences were observed. In the older population ≥ 60 years, 393 patients had coronary atherosclerosis and the prevalence of a CAC score higher than zero in cancer survivors was 89.0% vs 82.3% in the control population ($P = .08$). In the younger population (30-59 years), 323 patients had coronary atherosclerosis and the prevalence of a CAC score higher than zero in cancer survivors was 58.0% vs 51.7% in the control population ($P = .27$).

Discussion

Our study shows that coronary atherosclerosis is more prevalent in cancer survivors compared to a propensity score matched control cohort. This difference in the presence of atherosclerosis is mainly observed in younger patients aged < 60 years, suggesting that cancer induces early onset and/or rapid progression of atherosclerosis in this patient population. Moreover, the younger cancer survivors treated with thoracic radiotherapy and proatherogenic systemic cancer therapies showed a significant increased prevalence for atherosclerosis compared to patients not treated with these therapies. Therefore, the results of the current study suggest that mainly in the younger population, the impact of cancer and thoracic radiotherapy on the development of atherosclerosis is higher than in the older population.

Cancer and atherosclerosis

Many risk factors for cancer and cardiovascular disease, including hypertension and obesity, induce an inflammatory state, which plays a role in both carcinogenesis and atherogenesis. Cardiovascular risk factors, such as hyperlipidemia, smoking and hypertension contribute to the development of atherosclerosis by initiating a process in which leukocytes are recruited to the blood vessel walls due to the expression of adhesion molecules by endothelial cells. A chronic proinflammatory state, which can be triggered by shared risk factors for cancer and cardiovascular disease, induces oxidative stress, which is an underlying mechanism of the development of atherosclerotic plaques by lipid peroxidation.[20] Prior research showed that cancer and CAD are independent risk factors for each other and that patients with atherosclerotic CVD are at increased risk of developing cancer compared to patients without CVD.[21-23] A study by Aleman et al. observed that the major cause of long-term death after Hodgkin lymphoma is not attributed to the primary cancer itself, but to cardiovascular disease or a secondary malignancy.[24] Also, a study by Whelton et al. observed that cancer or CVD as the leading cause of death was dependent on the CAC score at baseline.[25] Moreover, we observed a higher prevalence of atherosclerosis for patients aged 30 to 59 treated with thoracic radiotherapy consequent with various studies that have reported an association between thoracic radiotherapy and cardiovascular disease.[26,27] However, we did not observe this difference in the older population or whole study population. This may be explained by the heterogeneity of our cancer population and the number of patients (approximately 50%) who were treated with thoracic radiotherapy, but not treated with mediastinal radiotherapy with associated higher mean heart radiation dose as was often performed in patients with Hodgkin lymphoma. In line, almost 40% of the patients treated with thoracic radiotherapy were diagnosed with breast cancer, which is associated with lower mean heart radiation dose.[28] In the past decades, new techniques have been developed to minimize the mean heart radiation dose without affecting tumor response, includ-

ing the deep breath inspiration hold technique and proton beam therapy.[29,30] The pathophysiology of radiation-induced CAD differs from conventional atherosclerosis and may accelerate more rapidly due to both microvascular and macrovascular damage of the endothelium.[31] In our patient cohort a higher proportion of younger cancer survivors was treated with thoracic radiotherapy compared to older cancer survivors, most likely due to a higher prevalence of Hodgkin lymphoma in younger patients aged < 59 years compared to older patients (41.1% vs 5.0%), which is generally treated with mantle field radiotherapy. Younger patients also had a higher prevalence of leukemia (8.6% vs 2.5%), for which treatment most often includes (low-dose) total body irradiation. However, breast cancer was more common in the older population (34.8% vs 10.0%) and although new techniques for minimizing radiation dose in breast cancer patients have been developed, the majority of breast cancer patients in our cohort was treated with older techniques, involving more radiation exposure to the heart. Due to these differences in cancer diagnoses between the groups, younger patients were possibly more likely to develop coronary atherosclerosis, as they were treated with more aggressive thoracic irradiation techniques. However, future studies should focus on the impact of (premature) atherosclerosis on cardiovascular events to assess the clinical relevance of atherosclerosis at younger age. As current results suggest that mainly in younger patients, cancer is a risk factor for the development of coronary atherosclerosis and radiotherapy may accelerate the onset and progression of coronary atherosclerosis in younger cancer survivors, defining strategies for long-term cardiovascular monitoring is of great importance in patients with a history of cancer.

Monitoring of CAD in cancer survivors

The ESC guidelines[13] on cardio-oncology recommend to perform a baseline cardiovascular toxicity risk assessment and to consider primary or secondary prevention strategies. Patients with cancer have an increased risk of CAD and acute coronary syndrome, due to shared pathophysiological pathways and cardiovascular risk factors.[20] However, specific cancer therapies, such as immune checkpoint inhibitors, radiotherapy and alkylating agents may also contribute to the development of coronary atherosclerosis. Especially cancer survivors treated with radiation doses exposing the heart and/or high dose anthracyclines are at increased risk of late cancer therapy-related cardiac dysfunction and have a twofold increased risk of cardiac death.[13] The guidelines recommend regular cardiovascular monitoring after cancer therapy, including noninvasive screening for CAD in patients treated with high-dose radiotherapy as radiation increases the risk of acceleration of atherosclerosis as well as other vasculopathies. Functional imaging and/or CCTA is recommended in asymptomatic cancer survivors treated with irradiation, but the preferred method is not specified. In our study, although a significant higher prevalence of a CAC score higher than zero was observed in patients with atherosclerosis for the whole patient group, this could not be extrapolated to the younger population. As this younger population shows a significant higher prevalence of atherosclerosis without a significant higher prevalence of a CAC score higher than zero, this raises the question whether performing calcium scoring is sufficient in patients < 60 years with a history of cancer to detect atherosclerosis. Therefore, performing anatomical imaging using CCTA instead of CAC score should be considered in younger patients with a history of cancer. Moreover, as chest irradiation shows poorer outcomes mainly driven by the results in younger cancer survivors, additional approaches, such as ischemia testing should be considered to determine patients at risk of CVD in an early stage and initiate a more sophisticated approach, including more frequent cardiovascular monitoring. Although we did not observe significant differences in the prevalence of severe atherosclerosis, our results showed a higher incidence of premature (nonsevere) atherosclerosis in younger cancer survivors. Development of atherosclerosis raises the risk of noncalcified plaque rupture and severe stenosis, which could both ultimately lead to significant obstructions and ACS. As atherosclerosis seems to develop at a younger age after cancer diagnosis compared to the general population, lifestyle modification should be emphasized in this population and patients should be encouraged to quit smoking, have enough physical activity and manage a healthy diet to limit the development of cardiovascular risk factors and disease including hypertension, hyperglycemia and hyperlipidemia. Moreover, timely initiation of (intensive) lipid lowering therapy should be considered in these patients. Together with lifestyle education, this should decrease the risk of rapid progression of atherosclerosis. Especially in the younger patient population, but also in the general population of cancer survivors with higher ischemic burden, a more extensive monitoring approach, including routinely follow-up visits and ischemia testing or coronary catheterization should be considered. The guidelines do not make any recommendations regarding noninvasive screening for CAD in patients who are not treated with radiotherapy. However, our study shows that patients without prior thoracic radiotherapy also have an increased risk of developing CAD. Our data demonstrating an association between cancer and development of atherosclerosis is important, as there are currently no cardiovascular risk calculators that include cancer as a risk factor for CVD. Larger studies are needed to confirm this and to determine the patient groups at risk and screening intervals that may be applied in clinical practice.

Limitations

This study has some limitations. First of all, it is a retrospective cross-sectional study and, therefore, no temporal relationship between cancer and atherosclerosis could be established. Additionally, as patients in the control group were more likely referred for evaluation of CAD due to thoracic complaints, selection bias may be present in this group, potentially contributing to an underestimation of our results as cancer survivors were mostly referred for routinely evaluation of CAD after cancer therapy. Moreover, as thoracic radiation doses were not reported, the association between radiation doses and the presence of (obstructive) CAD could not be assessed. Also, as the prevalence of significant stenoses were limited, the relationship between a history of cancer and/or radiotherapy on the prevalence of significant stenoses could not be established. Furthermore, a large proportion of our cohort had available Agatston calcium scores, but these scores were not collected for the whole study population, due to change in scanning protocol. As there were no serial CCTA scans available, the exact time between cancer diagnosis and development of atherosclerosis and significant stenosis could not be determined. Finally, quantitative plaque analysis was not performed, as it is not commonly used in clinical practice. In contrast, semi-quantitative plaque analysis allows for broader interpretation to assess the need for cardiovascular monitoring and therapy initiation.

Conclusions

Patients with a history cancer have an increased prevalence of coronary atherosclerosis on CCTA compared to matched patients without a history of cancer, and this effect was most pronounced in patients aged < 60 years. Defining monitoring and prevention strategies in this growing patient population is warranted.

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Declaration of competing interest

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CRediT authorship contribution statement

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Supplementary materials

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References

1. Herrington W, Lacey B, Sherliker P, et al. Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease. Circ Res 2016;118:535–46.
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49.
3. Herrmann J, Yang EH, Iliescu C, Marmagkiolis K. Response by Herrmann et al to Letter Regarding Article, "Vascular toxicities of cancer therapies: the old and the new-an evolving avenue. Circulation 2016;134:e466–e4e7.
4. Lyon AR, Dent S, Stanway S, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. Eur J Heart Fail 2020;22:1945–60.
5. Shapiro CL. Cancer survivorship. N Engl J Med 2018;379:2438–50.
6. Lau ES, Paniagua SM, Liu E, et al. Cardiovascular risk factors are associated with future cancer. JACC CardioOncol 2021;3:48–58.
7. Armstrong GT, Oeffinger KC, Chen Y, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. J Clin Oncol 2013;31:3673–80.
8. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med 2014;371:2488–98.
9. Velusamy R, Nolan M, Murphy A, et al. Screening for coronary artery disease in cancer survivors: JACC: CardioOncology State-of-the-art review. JACC CardioOncol 2023;5:22–38.
10. Florido R, Daya NR, Ndumele CE, et al. Cardiovascular disease risk among cancer survivors. J Am Coll Cardiol 2022;80:22–32.
11. Min SS, Wierzbicki AS. Radiotherapy, chemotherapy and atherosclerosis. Curr Opin Cardiol 2017;32:441–7.

12. Tapia-Vieyra JV, Delgado-Coello B, Mas-Oliva J. Atherosclerosis and cancer; A resemblance with far-reaching implications. Arch Med Res 2017;48:12–26.
13. Lyon AR, Lopez-Fernandez T, Couch LS, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J 2022;43:4229–361.
14. Tjessem KH, Bosse G, Fossa K, et al. Coronary calcium score in 12-year breast cancer survivors after adjuvant radiotherapy with low to moderate heart exposure - relationship to cardiac radiation dose and cardiovascular risk factors. Radiother Oncol 2015;114:328–34.
15. van Nimwegen FA, Schaapveld M, Janus CP, et al. Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. JAMA Intern Med 2015;175:1007–1017.
16. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation. 2002;105:539–42.
17. Dalager MG, Bottcher M, Thygesen J, et al. Different plaque composition and progression in patients with stable and unstable coronary syndromes evaluated by cardiac CT. Biomed Res Int 2015;2015:401357.
18. Gonçalves PD, Garcia-Garcia HM, Dores H, et al. Coronary computed tomography angiography-adapted Leaman score as a tool to noninvasively quantify total coronary atherosclerotic burden. Int J Cardiovas Imag 2013;29:1575–84.
19. Cury RC, Leipsic J, Abbara S, et al. CAD-RADS 2.0 - 2022 coronary artery Disease - Reporting and Data system.: an expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Cardiology (ACC), the American College of Radiology (ACR) and the North America Society of Cardiovascular Imaging (NASCI). J Am Coll Radiol 2022;19:1185–212.
20. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. Circulation 2016;133:1104–14.
21. Bell CF, Lei X, Haas A, et al. Risk of cancer after diagnosis of cardiovascular disease. JACC CardioOncol 2023;5:431–40.
22. Li J, Zhao J, Lei Y, et al. Coronary atherosclerotic disease and cancer: risk factors and interrelation. Front Cardiovasc Med 2022;9:821267.
23. Dzaye O, Berning P, Dardari ZA, et al. Coronary artery calcium is associated with increased risk for lung and colorectal cancer in men and women: the Multi-Ethnic Study of Atherosclerosis (MESA). Eur Heart J-Card Img 2022;23:708–16.
24. Aleman BM, van den Belt-Dusebout AW, Klokman WJ, et al. Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol 2003;21:3431–9.
25. Whelton SP, Al Rifai M, Dardari Z, et al. Coronary artery calcium and the competing long-term risk of cardiovascular vs cancer mortality: the CAC Consortium. Eur Heart J Cardiovasc Imaging 2019;20:389–95.
26. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013;368:987–98.
27. Milo MLH, Thorsen LBJ, Johnsen SP, et al. Risk of coronary artery disease after adjuvant radiotherapy in 29,662 early breast cancer patients: A population-based Danish Breast Cancer Group study. Radiother Oncol 2021;157:106–13.
28. Correa CR, Litt HI, Hwang WT, et al. Coronary artery findings after left-sided compared with right-sided radiation treatment for early-stage breast cancer. J Clin Oncol 2007;25:3031–7.
29. Lin LL, Vennarini S, Dimofte A, et al. Proton beam versus photon beam dose to the heart and left anterior descending artery for left-sided breast cancer. Acta Oncol 2015;54:1032–9.
30. Zagar TM, Kaidar-Person O, Tang X, et al. Utility of deep inspiration breath hold for left-sided breast radiation therapy in preventing early cardiac perfusion defects: A prospective study. Int J Radiat Oncol Biol Phys 2017;97:903–9.
31. Venkatesulu BP, Mahadevan LS, Aliru ML, et al. Radiation-induced endothelial vascular injury: A review of possible mechanisms. JACC Basic Transl Sci 2018;3:563–72.