ORIGINAL RESEARCH

Cancer and Its Association With the Development of Coronary Artery Calcification: An Assessment From the Multi-Ethnic Study of Atherosclerosis

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***Background*—**Although cancer and its corresponding therapies are associated with increased ischemic heart disease, the temporal relationship between cancer and the development of coronary artery calcium (CAC), a marker of subclinical atherosclerosis, is unknown.

***Methods and Results*—**Among 3122 men and women free of cardiovascular disease and cancer in the Multi-Ethnic Study of Atherosclerosis trial, CAC scoring was performed at baseline (2000–2002) and at follow-up (2010–2012). Over this 10-year period, 85 men (age 63.6±8.3 years) and 50 women (age 62.1±9.8 years) were diagnosed with cancer (predominantly breast, lung, or uterine [52%] in women and prostate or colorectal [78%] in men). The other 2987 subjects (age 59.6±9.2 years for men, 59.7±9.4 years for women) remained cancer free. The incidence of new CAC (baseline Agatston score of zero converting to detectable CAC) was modeled with relative risk regression and compared for cancer versus no cancer. Increase in pre-existing CAC was compared in these groups using linear regression of log transformed CAC. The incidence of CAC was independently associated with cancer history (relative risk 1.32 [*P*=0.04] and 1.29 [*P*=0.01] for women and men, respectively). In participants with CAC at baseline, a clear difference of CAC progression was not observed between cancer and noncancer participants (*P*=0.6 for women, *P*=0.2 for men).

***Conclusions*—**A diagnosis of cancer is associated with the development of CAC even after accounting for atherosclerotic risk factors. However, in individuals with pre-existing CAC, it is not clear whether the presence of cancer accelerates CAC over time.
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Key Words: cancer • cardiotoxicity • coronary artery calcium • subclinical atherosclerosis risk factor

In comparison with the general population, survivors of several cancers including breast cancer, lymphoma, and testicular cancer experience an increase in the risk of coronary arterial atherosclerotic-related events including myocardial infarction, coronary artery disease, and angina.[1–3] Coronary artery calcium (CAC), quantified by multidetector computed tomography (CT) and the Agatston score, has become a well-established, quantifiable marker of coronary arterial atherosclerotic burden and predictor of cardiovascular events.[4] Prior studies have demonstrated in small series of Hodgkin's lymphoma survivors that CAC is elevated,[5,6] but these findings were not replicated in breast cancer survivors.[7] In addition, no prior studies have investigated the longitudinal change of CAC with a cancer diagnosis as compared to the general population.

Accordingly, we performed this cohort analysis to investigate the relationship of cancer and its treatment to incidence and progression of subclinical atherosclerosis. To achieve this objective, we utilized the Multi-Ethnic Study of Atherosclerosis (MESA), a large cohort followed for ≈10 years with serial assessments of cardiovascular risk factors as well as quantification of subclinical vascular disease (ie, coronary artery calcification). We hypothesized that a diagnosis of cancer would be associated with increased progression of CAC over time when compared to cancer-free participants.

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Methods

Study Design and Population

The MESA is a prospective cohort study designed to study the prevalence, risk factors, and progression of subclinical cardiovascular disease. A detailed description of the study design and methods has previously been published.[8] MESA enrolled a cohort of 6814 participants aged 45 to 84 years from 4 race/ethnic groups in 6 US communities (Forsyth County, NC; New York, NY; Chicago, IL; Baltimore, MD; St. Paul, MN; and Los Angeles, CA) between 2000 and 2002. All participants were free of clinically diagnosed cardiovascular disease (heart attack, angina, stroke, transient ischemic attack, heart failure, undergone prior cardiac procedure including angioplasty, bypass surgery, valve surgery, or pacemaker implantation) and were not undergoing active treatment for cancer. Each site attempted to recruit equal numbers of men and women with prespecified age and race/ethnicity proportion goals. The MESA study was approved by the institutional review boards of each study site, and written informed consent was obtained from all participants.

The MESA study conducted a baseline examination that included CAC scans (henceforth referred to as "baseline") between 2000 and 2002 on 6814 participants, with 6421 reporting no prior history of cancer. A repeat CT CAC scan was obtained at the 5th follow-up exam, conducted between years 2010 and 2012, (henceforth referred to "follow-up") and was performed on a random 50% sample of the original MESA cohort (n=3305) who were part of the MESA Air ancillary study investigating air pollution and heart disease.[9] Of the 6421 participants without cancer at the baseline exam, 3122 had a CT CAC scan performed at the follow-up exam. During the nearly 10 years between exams, 135 participants developed cancer (Figure 1). In the 3299 participants who did not have the follow-up CT CAC scan at visit 5 (not selected, refusal, death, loss of follow-up), 411 developed cancer in the 10-year time period after Exam 1. The participants included in the analysis were compared with those excluded to assess for bias.

At both the baseline and the follow-up examinations, participant demographics, medical history, medication use, laboratory data, and anthropometric data were collected. Diabetes mellitus was defined as fasting glucose ≥126 mg/dL or use of hypoglycemic medications.[10] Use of antihypertensive and lipid-lowering medications were based on the review of prescription medication containers. Current smoking and former smoking history were combined to define a dichotomous variable of current/former smoking history versus never. Resting blood pressure was measured 3 times with subjects in a seated position, and the average of the second and third readings was used. Total and high-density lipoprotein cholesterol were measured from blood samples obtained after a 12-hour fast.

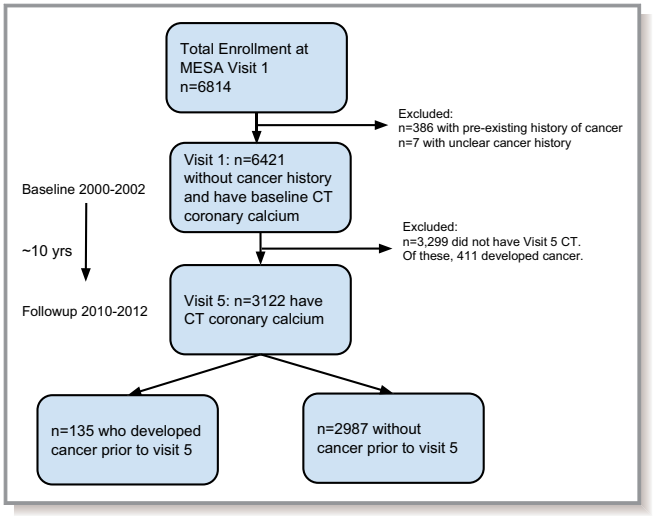

Figure 1. Flow diagram of MESA cohort who underwent serial coronary artery calcification assessments divided into cancer and no-cancer subgroups. CT indicates computed tomography; MESA, Multi-Ethnic Study of Atherosclerosis.

Measurement of CAC Score

Details of the MESA CT scanning and interpretation methods have been reported elsewhere.[11] At the baseline examination, scanning centers assessed CAC by either an electron-beam CT scanner (Chicago, Los Angeles, and New York field centers) or a multidetector CT system (Baltimore, Forsyth County, and St. Paul field centers). Certified technologists scanned all participants twice with corrections using phantoms of known physical calcium concentration. A radiologist or cardiologist read all CT scans at a central reading center (Los Angeles Biomedical Research Institute at Harbor–University of California Los Angeles, Torrance, CA), blinded to all clinical and demographic information of the patients. The amount of CAC was quantified with the Agatston score method[12] and a total score was determined by summing all individual lesions from the coronary vasculature (left main, left anterior descending, circumflex, and right coronary arteries). The mean score between the 2 scans was utilized in the analysis. At the follow-up examination, CAC was assessed using multidetector CT, and each participant was scanned once with corrections using a phantom of known physical calcium concentration.

Ascertainment of Cancer Status

Cancer history was determined in 2 ways. At the baseline examination, the questionnaire included questions regarding

history of cancer and the type of cancer ("breast," "prostate," "colon," "nonmelanoma skin," "blood [leukemia, lymphoma or other]," or "other") with the opportunity to free-text "other" types of cancer. Individuals with cancer prior to their MESA enrollment were excluded from analysis in order to ensure a baseline CAC scan prior to cancer and a follow-up scan after cancer diagnosis. Nonmelanoma skin cancers, owing to their superficial nature, were re-coded as the participant not having a cancer unless other cancers were chosen. Participants selecting "Don't Know" in regard to their cancer history were also excluded from the analysis (Figure 1).

The diagnosis of cancer during the MESA study was determined utilizing data gathered during prespecified MESA follow-up procedures after baseline examination. During the study, contact with the participants every 9 to 12 months regarding events including hospitalizations prompted a request for hospitalization records. The hospitalization records contained International Classification of Diseases, 9th Revision (ICD-9) diagnosis codes pertinent to that hospitalization. ICD 9 codes associated with cancer (140.-209.) were extracted from the records and re-coded into types of cancer (Table 1). Nonmelanoma skin cancers were re-coded not a cancer owing to their superficial nature. The time of cancer diagnosis was assumed to be the same as the hospitalization date.

Statistical Analysis

All analyses were stratified by sex due to expected sex differences in cancer type and sex-specific difference in distribution of CAC.[13] Means and standard deviations were calculated for normally distributed variables; medians and quartile 1 and 3 values were reported for raw CAC scores. Counts and percentages were calculated for categorical variables. Differences in continuous variables were compared using Student *t* tests (for normally distributed variables) or the Kruskal–Wallis test (for non-normally distributed variables). Categorical variables were compared using χ^2 test or Fisher's exact test in the appropriate situations.

Longitudinal progression of CAC and its association with intervening cancer diagnosis was performed in a 2-part model as recommended for CAC due to the highly skewed nature of the variable.[14,15] Analysis for the association of cancer diagnosis and baseline prevalence and magnitude of pre-existing CAC with adjustments for risk factors was performed in a similar manner. The first analysis modeled the probability of the incidence of CAC as it relates to cancer history. Incidence was defined as progressing from no CAC (Agatston score=0) to detectable CAC at follow-up (Agatston score>0). Due to the magnitude of CAC incidence, the rare disease criterion of assuming the relative risk to be closely approximated by odds ratios was not met and thus, relative risk regression with log link with Gaussian error (the preferred binomial error failed to converge) was implemented.[14] Robust standard errors were used to ensure valid statistic inferences. Multivariable regressions were modeled for CAC incidence utilizing known risk factors associated with subclinical atherosclerosis. Model 1 included the continuous variable of age and the categorical covariate of race/ethnicity (white, black/African American, Hispanic, Chinese American) and cancer history. Model 2 (based upon the risk factors in 2013 ACC/AHA Guidelines[16]) included age and race/ethnicity as well the continuous covariates of total cholesterol, high density lipoprotein, and systolic blood pressure. Categorical variables in Model 2 included use of antihypertension medications, use of lipid-lowering medication, current or former smoking status, history of diabetes, and cancer history.

In those with prevalent CAC at baseline (defined as baseline Agatston score>0), the linear association between cancer history and the change in CAC was analyzed using a technique previously described.[15] The dependent variable in the linear regression model is $\text{Log}(\text{CAC}_{\text{Followup}}+25)-\text{Log}(\text{CAC}_{\text{Baseline}}+25)$, where log is the natural logarithm. The constant of 25 was chosen based upon prior literature demonstrating its benefit of resulting in improved normality[15] (Thus, throughout the study, any reference to log transformed score implies that a constant of 25 was added prior to the natural logarithm calculation). Multivariable regression was also employed using the same covariate models as described above. All statistical analyses were performed using SAS statistical software version 9.3 (SAS Institute, Cary, NC).

Table 1. Cancer Type Stratified by Gender

Cancer in Women	Number in Group (% of Group)	Cancer in Men	Number in Group (% of Group)
1. Breast	13 (26)	1. Prostate	55 (65)
2. Lung	8 (16)	2. Colon/ Rectal	11 (13)
3. Uterine	5 (10)	3. Kidney	3 (4)
4. Colon/rectal	4 (8)	4. Lymphoma	2 (2)
5. Lymphoma	2 (4)	5. Leukemia	2 (2)
All others	18 (36)	All Others	12 (14)
Total cancer participants	50	Total cancer participants	85

Results

Fifty women and 85 men had cancer diagnosis occurring during the MESA follow-up period, and 1583 women and 1404

men without a cancer history underwent CAC assessment at both baseline and follow-up. The cancer types between the men and women differed as shown in Table 1. The time between the scans at baseline and follow-up was not different in participants with and without cancer (Table 2). The mean time from cancer diagnosis to follow-up CT scan was 4.8 years for women and 4.2 years for men. Baseline demographics and characteristics of the MESA participants with and without cancer, stratified by sex, are also shown in Table 2. At baseline, women in the cancer subgroup were less likely to be Hispanic and had higher mean systolic blood pressure as compared to women without cancer. The prevalence of CAC at baseline was higher in women in the cancer group. After adjusting for baseline covariates shown in Table 2, the difference in CAC prevalence remained significant (P=0.03). The men with cancer were older, with a trend towards more participants receiving antihypertensive medications as compared to the men without cancer group. The unadjusted prevalence of CAC at baseline was also higher in men in the cancer group but not significant with adjustment for baseline co-variates (P=0.4).

In the analysis of incidence of CAC, there were 27 women without CAC at baseline in the cancer group and 16 (59%) developed detectable CAC at follow-up. In the cancer-free group, 1084 women had CAC=0 at baseline and from these, 456 (42%) developed CAC at follow-up. In the unadjusted model, the relative risk of progressing from no CAC to detectable CAC was 1.41 (P=0.03) in those with cancer as compared to those without (Figure 2). Table 3 demonstrates that even after adjustments for risk factors, there was a 32% (P=0.04) increased risk of transitioning from a zero CAC score to detectable CAC if a woman had been diagnosed with cancer between the 2 scans.

Of the 23 men without CAC at baseline in the cancer group, 18 (78%) went on to develop a non-zero score at follow-up. In the cancer-free group, 630 men had CAC=0 at baseline. Of these, 323 (51%) developed CAC at follow-up (Figure 2). In men without prevalent CAC, the cancer group was older (P=0.004), had increased receipt of antihypertensives (P=0.001), and were current or past smokers (P=0.01). The unadjusted relative risk of progressing from no CAC to detectable CAC was 1.52 (P=0.003) in those men with cancer as compared to those without (Table 3). Even after adjusting for risk factors, there was a 29% (P=0.01) increased risk of transitioning from a zero CAC score to detectable in men with cancer as compared to noncancer participants.

Twenty-three women in the cancer group and 499 without cancer had detectable CAC at the baseline examination. In

Table 2. Baseline Characteristics According to Future Cancer Status and Stratified by Sex

Characteristic	No Cancer Women, n=1583	Cancer Women, n=50	*P* Value	No Cancer Men, n=1404	Cancer Men, n=85	*P* Value
Race/ethnicity:						
White	579 (36%)	23 (46%)	0.2	572 (41%)	40 (47%)	0.3
Chinese	185 (12%)	3 (6%)	0.2	182 (13%)	6 (7%)	0.1
Black	452 (29%)	20 (40%)	0.08	329 (23%)	26 (31%)	0.1
Hispanic	367 (23%)	4 (8%)	0.009*	321 (23%)	13 (15%)	0.1
Age, y	59.7 (9.4)	62.1 (9.8)	0.08	59.6 (9.2)	63.6 (8.3)	<0.0001*
Current/former smoker	639 (40%)	22 (44%)	0.6	789 (56%)	53 (62%)	0.3
On antihypertensives	551 (35%)	23 (46%)	0.1	455 (32%)	45 (53%)	<0.0001*
Diabetes	144 (9%)	6 (12%)	0.5	154 (11%)	12 (14%)	0.4
On lipid meds	225 (14%)	9 (18%)	0.5	241 (17%)	14 (16%)	0.9
Total cholesterol, mg/dL	200.3 (34.7)	201.5 (44.9)	0.8	188.9 (33.3)	186.8 (40.1)	0.6
HDL, mg/dL	56.5 (15.3)	55.4 (16.4)	0.6	44.6 (11.3)	43.3 (9.7)	0.3
Systolic blood pressure, mm Hg	124.1 (21.7)	131.2 (23.7)	0.02*	123.9 (17.9)	127.2 (19.3)	0.1
Time from CAC baseline to CAC follow-up, y	9.7 (0.6)	9.7 (0.6)	0.7	9.6 (0.6)	9.5 (0.5)	0.1
Time from cancer diagnosis to CT scan, y	—	4.8 (3.1)		—	4.2 (2.7)	
Prevalent CAC at baseline	499 (32%)	23 (46%)	0.03*	774 (55%)	62 (73%)	0.001*
Baseline CAC scores median, (Q1, Q3)	0 (0, 9.6)	0 (0, 109.1)	—	5.3 (0.0, 107.8)	48.7 (0, 168.8)	—

Values are mean±SD or n (%). CAC indicates coronary artery calcium; CT, computed tomography; HDL, high-density lipoprotein; Q1, quartile 1; Q3, quartile 3.
*P<0.05.

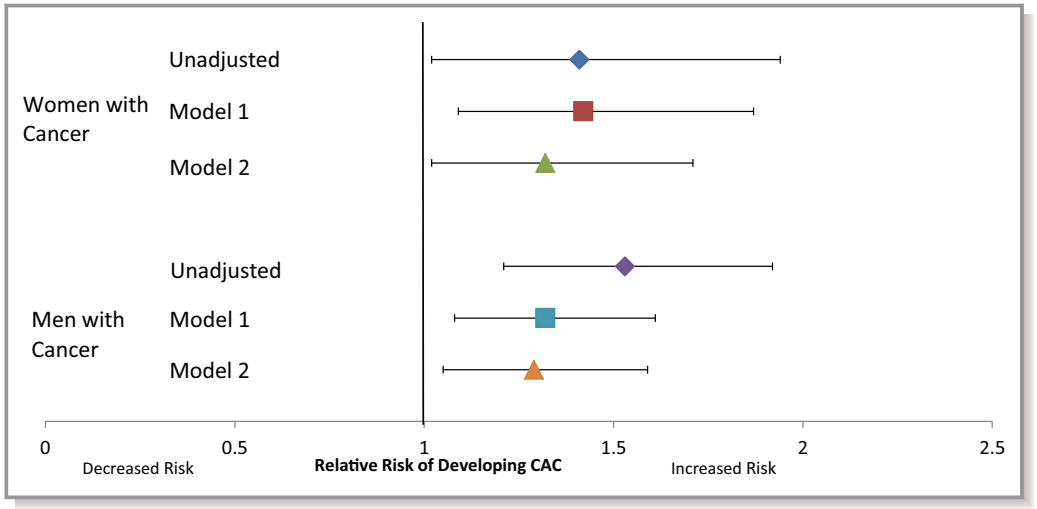

Figure 2. Unadjusted and adjusted relative risk of the incidence (defined as undetectable coronary artery calcium [CAC] at baseline transitioning to presence of CAC at follow-up) of coronary artery calcification over 10 years in those with cancer versus those without, stratified by sex. Both women and men with cancer experience significantly higher incidence of CAC as compared to participants without a cancer history, even after adjusting for known cardiovascular risk factors (Model 1: age and race/ethnicity. Model 2: model 1 and lipid medication, total cholesterol, high-density lipoprotein, on hypertension medication, systolic blood pressure, current or former smoker, and history of diabetes).

women, both the baseline CAC score (log transformed) and the follow-up CAC score were higher in the cancer compared with the cancer-free participants with cancer group (Table 4). However, after adjusting for risk factors, the baseline difference in CAC score was no longer significant (P=0.07). After adjustment for risk factors, the difference in the log-transformed CAC scores between follow-up and baseline (ie, the progression of pre-existing CAC) was not statistically different between the 2 groups (P=0.5). This finding is also reflected in the lack of significance in the β coefficient associated with cancer in the unadjusted linear regression model results (β=−0.10, 95% CI of −0.40 to 0.18). Furthermore, with risk factor adjustments in Models 1 and 2, the relationship between CAC change and cancer was not significant (β for Model 1=−0.05, 95% CI of −0.34 to 0.24; β for Model 2=−0.09, 95% CI of −0.37 to 0.20) as the confidence interval contains 0 in all analyses.

In men with pre-existing CAC, there were 62 in the cancer group and 774 without cancer. The men in the cancer group were more likely to be using antihypertensive medications (P=0.05) and a lower high-density lipoprotein (P=0.02). There was no difference in the baseline transformed CAC score, the follow-up transformed CAC score, nor in the subtracted difference (ie, the progression of CAC) in the transformed values between the men with cancer and noncancer groups (Table 4). Similarly, this is also reflected in the lack of significance in the β coefficient associated with cancer in the unadjusted linear regression model (β=0.08, 95% CI of −0.25 to 0.08). After risk factor adjustments in Models 1 and 2, the relationship between CAC progression and cancer as represented by the β coefficient associated with cancer status was not significant (β for Model 1=0.13, 95% CI of −0.04 to 0.29; β for Model 2=0.11, 95% CI of −0.05 to 0.27).

Additional analysis was performed comparing baseline data on the 135 with cancer that were included in the study versus the 411 with cancer that were excluded due to not having a follow-up CT CAC. This comparison revealed that in women, the cancer types and distribution were similar for the top 4 cancers but the excluded women were almost 5 years older (P=0.003). Ethnicity and cardiovascular risk factors were similar between those with cancer that were included versus those excluded. In men with cancer, those excluded

Table 3. Unadjusted and Adjusted Relative Risk of Incidence of Coronary Artery Calcification (ie, Score=0 at Baseline Visit Progressing to Detectable at Follow-up) in Participants With Cancer (n=27 Women, n=23 Men) as Compared to Those Without Cancer (n=1084 Women, n=630 Men), Stratified by Sex

Relative Risk	Unadjusted Model (95% CI)	Model 1 (95% CI)	Model 2 (95% CI)
Women	1.41 (1.02–1.94)	1.42 (1.09–1.87)	1.32 (1.02–1.71)
Men	1.53 (1.21–1.92)	1.32 (1.08–1.61)	1.29 (1.05–1.59)

Model 1: age and race/ethnicity. Model 2: Model 1 and lipid medication, total cholesterol, high-density lipoprotein, on hypertension medication, systolic blood pressure, current or former smoker, and history of diabetes.

Table 4. Progression of CAC (Log Transformed) in Those With Prevalent CAC at Baseline (CAC Score >0) According to Cancer History and Stratified by Sex, Unadjusted

Characteristics	No Cancer Women, n=499	Cancer Women, n=23	*P* Value	No Cancer Men, n=774	Cancer Men, n=62	*P* Value
Baseline CAC	46.9 (12.3, 152.3)	111.2 (30.8, 409.1)	—	87.0 (20.8, 295.1)	87.6 (27.8, 310.2)	—
Baseline log (CAC)	4.5 (1.0)	5.1 (1.2)	0.007*	4.9 (1.2)	4.9 (1.1)	0.8
Follow-up CAC	247.9 (102.3, 598.6)	456.1 (172, 982.7)	—	390.7 (147.7, 902.8)	505.9 (190.7, 994.0)	—
Follow-up log(CAC)	5.6 (1.1)	6.1 (1.1)	0.04*	6.0 (1.1)	6.1 (1.1)	0.4
Difference in log transformed scores	1.1 (0.7)	1.0 (0.7)	0.5	1.2 (0.6)	1.2 (0.6)	0.3

Values are mean±SD or median (25% quartile, 75% quartile). Log (CAC) represents log (CAC score+25). Difference in log transformed scores is log (follow-up CAC score+25)−log(baseline CAC score+25). CAC indicates coronary artery calcium score; log, natural logarithm.
*$P<0.05$.

had more lung cancer (20% of group), more gastrointestinal cancers (liver, esophagus, small intestine, 9%) and less prostate cancer (25% versus 65%) as compared to the included participants. The excluded men were also almost 5 years older ($P<0.0001$) and had a slightly higher high-density lipoprotein ($P=0.03$) but otherwise, were similar with regard to ethnicity and other risk factors listed in Table 2.

Discussion

There were 3 important findings in this study. First, the baseline prevalence of CAC was higher in women in the cancer group as compared to those without cancer, a finding that persisted even after adjusting for baseline risk factor differences. Second, a diagnosis of cancer and its treatment was associated with the increased incidence of developing coronary artery calcification in men and women even after accounting for atherosclerotic risk factors. Finally, a significant association could not be determined between cancer and the longitudinal progression of pre-existing CAC in men or women. These findings suggest that cancer, its therapies, or a common antecedent risk factor may contribute to the development of subclinical atherosclerosis.

To the best of our knowledge, this is the first longitudinal study investigating the relationship of incident cancer with progression of CAC. The study was performed in an ethnically diverse patient population with a large comparator group who underwent concurrent examinations and CT scans. In addition, the cancer diagnoses (Table 1) and assumed treatments were contemporary, using data from 2000 to 2012.

In this study, both women and men who were diagnosed with cancer during the study had a higher baseline prevalence of CAC as compared to individuals who did not. This increased prevalence is in part explained by the difference in baseline risk factors such as age and race/ethnicity.[17] In women in the cancer group, there was a trend toward increased age, fewer Hispanics, and a higher mean systolic blood pressure. However, upon adjusting for these differences, the prevalence of CAC remained significantly higher in the cancer group, suggesting an unrecognized subclinical vascular disease difference between the 2 groups even before the diagnosis of cancer. This raises the possibility of a common antecedent process between the development of cancer and the development of coronary artery calcification. In men with cancer, increased average age, a strong risk factor for CAC, was at least in part responsible for this baseline difference in CAC prevalence because after accounting for this difference, the prevalence of CAC in the 2 groups was no longer present. The reason for the difference in men and women in this regard is likely complex; one potential reason for the difference is that the cancer types (such as breast and ovarian) specific to women may have a stronger link to the proposed common antecedent risk factor (for example, chronic inflammation).[18]

Despite the baseline differences in prevalence, an increased incidence of developing CAC over the next decade was found in both men and women diagnosed with cancer as compared to individuals without cancer (Figure 2). Previous research has demonstrated that age, race/ethnicity, smoking, diabetes, and hypertension are known risk factors for increased incidence of CAC.[15] Even after accounting for these risk factors in the 2 models, a history of cancer (diagnosed prior to follow-up CT by a mean of 4.8 years for women and 4.2 years for men) was associated with an increased incidence of CAC (Table 3).

For those with CAC at baseline, we assessed whether the progression of pre-existing CAC was associated with cancer diagnosis. Though both the initial and follow-up CAC scores in women with cancer were higher than individuals without cancer, the unadjusted change between the 2 groups was not different. With adjustments of known cardiovascular risk factors, the change in CAC remained similar in those with and those without incident cancer. In men with prevalent CAC, there was no difference in the baseline CAC scores between the groups, nor was there a difference in the change in CAC between examinations. With accounting for the cardiovascular risk factors, cancer was not found to be a factor in the progression of pre-existing CAC.

In individuals with pre-existing CAC, we did not demonstrate a significant increase in CAC in men or women with cancer. There are several potential explanations for this complex relationship. First, other typical risk factors for atherosclerosis have also shown an increase in the incidence of CAC over time but not progression of pre-existing CAC. Low-density lipoprotein and high-density lipoprotein have a similar relationship to the one found here for cancer: they both are associated with the incidence of CAC but not the progression of pre-existing CAC.[15] Another possible explanation for the significant association of cancer and CAC incidence with no significant increase in pre-existing CAC progression is that the statistical approach utilized may affect the outcomes. Recent publications have demonstrated that varying statistical definitions of CAC progression can lead to divergent associations with risk modifiers.[19,20] Similarly, the relatively low number of participants with cancer limited the power of this analysis to detect a difference.

Previous research investigating CAC and its association with cancer and/or its therapies has been focused on cross-sectional data and obtained differing results. Two cross-sectional studies have associated cancer, prior to therapy, with increased CAC scores. In a cohort of breast cancer patients prior to chemotherapy or radiation, Mast et al demonstrated increased CAC in middle-aged women (55 to 64 years) as compared to MESA age-matched controls.[21] In men, coronary stenoses as assessed by CT angiogram were associated with colorectal adenoma, a precursor to cancer, in a Korean cohort study adjusting for cardiovascular risk factors.[22] More advanced polyps were associated with more severe coronary obstruction.

In addition, several studies have investigated the potential impact of cancer and its therapies on CAC. One series of 9 Hodgkin's lymphoma patients, median age of 45 years, treated with mediastinal radiation an average 26 years earlier, reported that 6/9 were above the 90th percentile for age and gender CAC scores from published reference values.[5] A similar series of 47 Hodgkin's lymphoma patients treated with radiation found abnormally high CAC scores as compared to published values for CAC.[6] However, these positive findings were not seen in a recent study by Tjessem et al. This study investigated a cohort of 236 breast cancer survivors who had undergone radiation±chemotherapy and compared their CAC with published general population CAC scores showing a similar age-matched distribution.[7]

We demonstrated an increase in the incidence of CAC over time in individuals diagnosed with cancer compared with noncancer controls. Our study differs from prior studies in several ways. First, the present study included a wide range of cancers, though predominated in women by breast, lung, and uterine (52% of the women) and in men, prostate and colorectal (78%). Additionally, our comparison group was selected from the same study, as opposed to using previously published CAC values or historical controls. Finally, our study was longitudinal and was able to evaluate incident CAC.

There are many potential mechanisms for the association between cancer and progression of coronary arterial calcification. Prior studies have shown that certain chemotherapies for cancer are associated with an increase in atherosclerotic risk factors including hypertension[23] and metabolic syndrome.[24] Several chemotherapeutic regimens have been suggested to cause acute ischemic events. Anti-metabolites 5-fluorouracil and its prodrug capecitabine have been associated with acute cardiac ischemic events with an incidence ranging from 3% to 9% with capecitabine and 1% to 68% with fluorouracil.[25] A broad range of mechanisms have been proposed including vasospasm, arteritis, thrombosis, direct myocardial and endothelial damage, and myocarditis.[26] Newer small-molecule tyrosine kinase inhibitors have also been implicated with acute ischemia. Cardiac ischemia or infarct occurred in 3% of individuals treated with sorafenib compared to <1% of placebo in a trial treating renal cell carcinoma.[27] Radiation therapy has also been associated with ischemic cardiovascular events[1–3] in cancer survivors with hypothesized mechanisms of endothelial injury, arteriosclerosis and fibrosis of the coronary vasculature, and prothrombotic state.[28] Finally, the progression of the atherosclerosis may be independent of the therapies to treat cancer and may be due to the intertwined processes of chronic inflammation and cancer,[18] as inflammation has been associated with the development of coronary atherosclerosis.[29]

Study Limitations

There are some notable limitations to this study. First, the follow-up CT CAC score (performed in the ancillary MESA Air study) was performed on ≈50% of the original MESA population. As described in the Results section, the excluded cancer participants differed from the cancer participants included in the analysis. In women, the excluded women were almost 5 years older on average. In men as well, the excluded cancer participants averaged almost 5 years older and the cancer type distribution differed, with more lung and gastrointestinal cancers and less prostate cancers in the excluded group. Intuitively, this makes sense as older participants or those with cancers with increased morbidity and mortality (eg, lung) are less likely to follow up electively due to death or frailty.

Furthermore, the method of diagnosing cancer during the course of the study depended upon using ICD 9 codes, which required hospitalization for any cause. Participants diagnosed with cancer who were never hospitalized would be incorrectly classified. Finally and importantly, this study does not have

details regarding the patients' cancer diagnosis including the specific histological subtype of cancer or its staging. The cancer treatment is unknown, including whether chemotherapy was given, which chemotherapy, and whether surgery and radiation were also part of the treatment plan. Due to this limitation, we are unable to determine associations with specific treatments or cancers and thus, determination of cause is speculative. However, this study, as an initial investigation, raises some important questions about cancer and its relationship to progression of subclinical atherosclerosis.

In conclusion, this cohort analysis demonstrated that a diagnosis of cancer is associated with the development of subclinical atherosclerosis as determined by coronary artery calcification. This relationship is complex, as demonstrated by the association of increased prevalence of CAC in women prior to a cancer diagnosis. Further research is needed to delineate the details of this relationship and determine which cancers and/or therapies or shared cancer–atherosclerosis risk factors/pathways are responsible for the onset of subclinical atherosclerosis in these patients.

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Disclosures

All authors have completed and submitted the International Committee of Medical Journal Editors Form for Disclosure of Potential Conflicts of Interest. None of the authors disclosed a financial or other conflict of interest.

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