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ORIGINAL RESEARCH

Morphological Plaque Characteristics and Clinical Outcomes in Patients With Acute Coronary Syndrome and a Cancer History

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BACKGROUND: Although patients with a cancer history have a 2 to 3 times higher risk for acute coronary syndrome (ACS), the morphological characteristics of ACS culprit plaque in those patients and their relations with clinical outcomes remain unknown.

METHODS AND RESULTS: This retrospective, multicenter, observational cohort study included consecutive patients with ACS who underwent optical coherence tomography-guided emergent percutaneous coronary intervention. Patients were categorized into those without a cancer history, those with a cancer history, and those currently receiving cancer treatment. ACS culprit lesions were classified as plaque rupture, plaque erosion, or calcified nodule using optical coherence tomography. Plaque erosion frequency was significantly higher in culprit lesions of patients with current cancer and patients with cancer history than in those of patients without cancer history (56.3% versus 61.7% versus 36.5%). Calcified nodule incidence was significantly higher in patients without cancer history than in patients with current cancer and patients without cancer history (patients with current cancer: 12.4% versus patients without cancer history: 25.5% versus patients without cancer history: 12.6%, $P<0.001$). Cancer history was independently associated with nonplaque rupture (plaque erosion or calcified nodule) in ACS culprit lesions (odds ratio, 4.00; $P<0.001$). Cancer history was independently associated with major adverse cardiovascular events (hazard ratio [HR], 1.98; $P=0.002$). Nonplaque rupture in ACS culprit lesions was independently associated with major adverse cardiovascular events (HR, 1.60; $P=0.011$).

CONCLUSIONS: Patients with a cancer history had significantly worse clinical outcomes after ACS than those without a cancer history. Those with a cancer history had significantly higher plaque erosion and calcified nodule incidences in the ACS culprit lesions, which might partly explain their worse clinical outcomes.

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Key Words: acute coronary syndrome ■ cancer history ■ optical coherence tomography ■ plaque morphology

Cardiovascular disease and cancer are associated with an aging population and share common risk factors.[1] Patients with a cancer history have a 2- to 3-fold higher risk of acute coronary syndrome (ACS),[2] which lasts up to 10 years following cancer diagnosis.[3] Patients with both cancer and cardiovascular disease have worse survival rates than those with cancer alone.[4]

The 3 most common underlying mechanisms contributing to ACS are plaque rupture (PR), plaque erosion (PE), and calcified nodule (CN).[5] Optical coherence tomography (OCT) is a high-resolution intravascular

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CLINICAL PERSPECTIVE

What Is New?

- This is the first study that reveals the differences in morphological plaque characteristics of patients with acute coronary syndrome with or without a cancer history using optical coherence tomography and assesses their relationship with clinical outcomes.
- Patients with a cancer history had significantly higher plaque erosion or calcified nodule in culprit lesions and had worse clinical outcomes after acute coronary syndrome compared with those without a cancer history.

What Are the Clinical Implications?

- Patients with a cancer history have different plaque morphology in culprit lesion (often plaque erosion or calcified nodule rather than plaque rupture), which might partly explain their worse clinical outcomes.
- Patients with a cancer history may require different treatment for culprit lesions and post-ACS therapy compared with those without cancer, which may improve their clinical outcomes.

Nonstandard Abbreviations and Acronyms

CCP	patient with current cancer
CN	calcified nodule
HCP	patient with cancer history
MACE	major adverse cardiovascular event
NCP	patient without cancer history
OCT	optical coherency tomography
PE	plaque erosion
PR	plaque rupture
TLR	target lesion revascularization
TVR	target vessel revascularization

imaging technology that allows for better discrimination of plaque characteristics (eg, lipidic plaque, fibrous plaque, calcified plaque, thin-cap fibroatheroma), visualization of coronary plaque morphology, and detection of intracoronary thrombi. Based on these features, OCT can be used to classify ACS culprit plaque into PR, PE, and CN in vivo.[6]

Cancer is associated with increased coagulability, platelet activation, and aggregability, potentially leading to thrombus formation in the coronary artery.[7] Furthermore, cancer treatments, including chemotherapy, are associated with vascular endothelial disorders, which may be associated with PE causing ACS.[8] Additionally, patients who received radiation therapy are more likely to have fibrosis and calcification of the vessel wall.[9] Thus, we hypothesized that ACS culprit lesions of patients with cancer may differ from those without cancer, potentially explaining the worse long-term outcomes of patients with cancer who develop ACS. Therefore, this study aimed to clarify differences in morphological plaque characteristics of patients with ACS with or without a cancer history using OCT and to assess their relationship with clinical outcomes.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Population

The Kobe University ACS-OCT registry is a retrospective, multicenter, observational cohort study that explores the morphological plaque characteristics of ACS culprit lesions using OCT. Consecutive patients with ACS who underwent OCT-guided primary percutaneous coronary intervention (PCI) at 4 institutions (Kobe University Graduate School of Medicine, Kobe, Japan; Osaka Saiseikai Nakatsu Hospital, Osaka, Japan; Hyogo Prefectural Awaji Medical Center, Sumoto, Japan; Hyogo Brain and Heart Center, Himeji, Japan) from January 2010 to December 2018 were included. ACS included ST-segment–elevation myocardial infarction (MI), non-ST-segment–elevation MI, and unstable angina pectoris defined by the Fourth Universal Definition of Myocardial Infarction Guidelines.[10] Patients with in-stent restenosis, those with culprit lesions predilated using a balloon of ≥2.0 mm before OCT imaging, and those with insufficient OCT image quality were excluded.

We divided the enrolled patients according to cancer status (with or without a cancer history) and the timing of the treatment accordingly: (1) patients with current cancer (CCP)—those with ongoing cancer treatment or diagnosis within 1 year before ACS; (2) patients with cancer history (HCP)—those with a cancer history who were diagnosed more than 1 year before ACS; and (3) patients without cancer history (NCP). This study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of Kobe University Hospital. Written informed consent was waived because the data were collected retrospectively. This study was registered on the University Hospital Medical Information Network Clinical Trial Registry (UMIN000038442).

OCT Image Analysis and Definitions

OCT images were acquired using a frequency-domain OCT system (ILUMIEN; Abbott Vascular, Santa Clara,

CA, USA) with a Dragonfly Optis OCT imaging catheter (Abbott Vascular). Offline OCT analysis was performed using a dedicated software (Light Lab Imaging Inc., Westford, MA, USA). OCT was performed for patients with ACS as previously reported.[11] A 0.014-inch conventional standard guide wire was positioned distally in the target vessel, and the OCT catheter (C7 and C8 Dragonfly, Abbott Vascular) was advanced to the distal end of the target lesion. For image acquisition, blood in the lumen was replaced with contrast media or low-molecular-weight dextran. OCT was performed from as far distal as possible to the ostium of each vessel including the entire length of the lesion of interest using an integrated automated pullback device at 36 mm/s. The use of thrombus aspiration before the initial OCT examination was left to the operator's discretion. The images were digitally stored offline. All OCT images were analyzed by 2 experienced investigators (A. N. and K. T.) who were blinded to the angiographic data and clinical presentations, including history of cancer.

The morphological plaque characteristics of ACS culprit lesions were classified into 3 types: PR, PE, and CN (Figure S1) based on the following criteria. PR was defined as the presence of a fibrous cap discontinuity with a clear cavity formed inside the plaque. PE was defined as the presence of an attached thrombus overlying an intact and visualized plaque, luminal surface irregularity at the culprit lesion in the absence of thrombus, or attenuation of underlying plaque by thrombus without superficial lipid or calcification immediately proximal or distal to the site of thrombus. CN was defined as fibrous cap disruption detected over a calcified plaque characterized by protruding calcification, superficial calcium, or the presence of substantive calcium proximal and/or distal to the lesion.[12] The tissue characteristics of the underlying plaque were defined using previously established criteria: (1) lipid (low-signal region with diffuse border); (2) fibrous (homogeneous, high backscattering region); or (3) calcification (an area with low backscattering signal and a sharp border inside a plaque).[6,13] Thin-cap fibroatheroma was defined as a plaque with a lipid arc >90° with a minimal fibrous cap thickness <65 μm.[14] Intracoronary thrombus was defined as a mass (diameter >250 mm) attached to the luminal surface or floating within the lumen, including red (red blood cell-rich) thrombus, defined by high backscattering and high attenuation, or white (platelet-rich) thrombus, defined by homogeneous backscattering with low attenuation.[6] Microchannels were defined as signal-poor voids that were sharply delineated in multiple contiguous frames.[15] Spotty calcification was defined as a calc arc <90 and a calc length <4 mm.[16] Fibrous cap thickness was measured as follows. Three candidate frames were selected to measure the minimum fibrous cap thickness by visually screening all contiguous frames, and the fibrous cap thickness was then measured at the thinnest part of the fibrous cap on each frame. The minimum fibrous cap thickness was determined as the smallest fibrous cap thickness among the candidate frames.[14] When there was a discordance between the observers, a consensus reading was obtained from a third investigator (S. N.).

Clinical Data Collection and Definition of Cancer History

Besides baseline patient and lesion characteristics, we retrospectively recorded cancer status and treatment details, including the medical history of previous and current cancer types, and whether patients currently had the disease, had completed treatment within a year, or had completed treatment over a year ago.

We also collected clinical event data after ACS until the occurrence of an end point. Collected clinical events included noncardiac death, cardiac death, nonfatal MI, and any revascularization for coronary vessels (target lesion revascularization [TLR], target vessel revascularization [TVR], and non-TVR), stroke/transient ischemic attack, and heart failure with admission. Cardiovascular events were ascertained from a review of medical records and confirmed by direct contact with the patients, their families, or physicians. Cardiac death was defined as death due to MI, congestive heart failure, arrhythmia, or documented sudden cardiac death. Clinical end points were major adverse cardiovascular events (MACE: composite of cardiac death, nonfatal MI, and any revascularization for coronary vessels, stroke/transient ischemic attack, and heart failure with admission), and coronary ischemic event (composite of cardiac death, nonfatal MI, and any revascularization for coronary vessels).

Statistical Analysis

Continuous variables with normal distributions are expressed as mean±SD. Variables with nonnormal distributions are expressed as median and interquartile range (25th–75th). Student's *t* test or analysis of variance was used to evaluate parametric continuous variables. The Mann–Whitney *U* test or Kruskal–Wallis test was used for nonparametric variables followed by post hoc testing only if $P<0.05$. Categorical variables are expressed as frequencies with percentages and compared using χ^2 or Fisher's exact test followed by residual analysis only if $P<0.05$. We used the Kaplan–Meier method to estimate the clinical event after ACS and the log-rank test to compare the distributions of survival times among groups. Cox proportional hazard analysis was used to assess predictors of clinical events. Survival time was defined as the time from the onset date of ACS to the occurrence of MACE. Patients who did not experience MACE were censored at the time of

last available contact or at the time of death. Regarding the patient background, age, sex, body mass index, family history of coronary artery disease, smoking, comorbidities (hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, and hemodialysis), previous treatment history (MI, cerebral infarction, and peripheral artery disease), type of MI, and number of stenosis vessels (single or multivessel) were used as covariables. Regarding the OCT findings, the morphological plaque characteristics on OCT findings, OCT measurements (minimum lumen area and the length of culprit lesion), and the presence of thin-cap fibroatheroma were used as covariables. Baseline variables with $P<0.10$ in the univariate regression analysis were included in the multivariate logistic regression models. The results are presented as hazard ratios (HRs) with 95% CIs. Logistic regression analysis was performed to identify independent factors associated with non-PR ACS. The same variables as those used in Cox proportional hazard analysis were used as covariates. Not only baseline variables with $P<0.10$ in the univariate regression analysis but also the variables that have been previously reported to be related to non-PR such as age, sex, and the hemodialysis were included in the multivariate logistic regression models. Results are presented as odds ratios (ORs) with 95% CIs. For all tests, a value of $P<0.05$ was considered significant. All statistical analyses were performed using SPSS version 25 (IBM Inc., Armonk, NY, USA); $P<0.05$ was considered statistically significant.

RESULTS

Patient Flow and Baseline Characteristics

A total of 511 patients underwent primary PCI for ACS under OCT guidance during the study period. After excluding 36 patients diagnosed with in-stent restenosis or stent thrombosis and 39 patients with unanalyzable OCT images due to poor image quality, 436 patients were finally enrolled (Figure 1). Among them, 63 patients (14.4%) had a history of cancer, including 16 (3.6%) CCPs and 47 (10.8%) HCPs. Detailed cancer-related characteristics are summarized in Table S1.

Comparisons of Clinical Characteristics, OCT Findings, and Clinical Events Between Patients With and Without a Cancer History

Patients with a cancer history (including CCPs and HCPs) were older and had a higher prevalence of hemodialysis than NCPs (Table 1). They also had a higher prevalence of non-ST-segment–elevation MI, whereas NCPs had a higher prevalence of ST-segment–elevation MI. Regarding laboratory variables

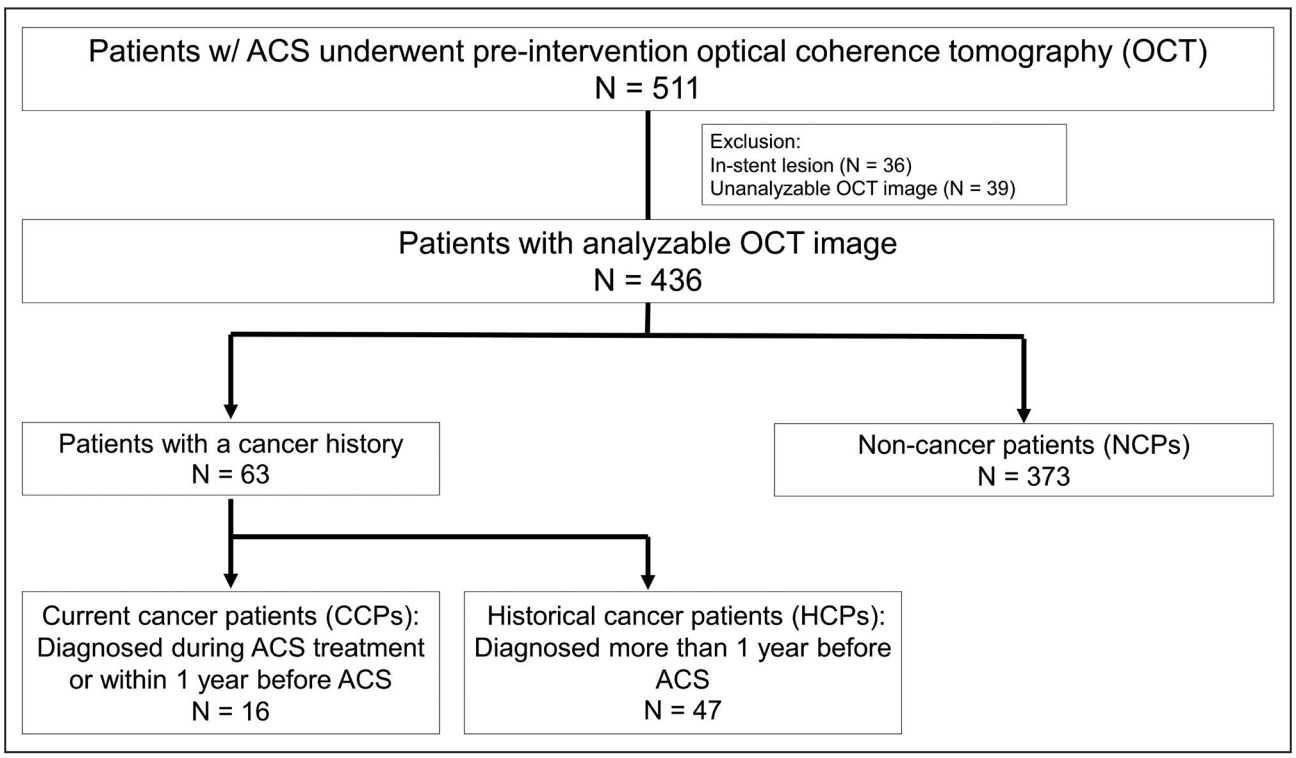

Figure 1. Patient flow diagram.
ACS indicates acute coronary syndrome; CCP, patient with current cancer; HCP, patient with cancer history; NCP, patient without cancer history; and OCT, optical coherence tomography.

Table 1. Baseline and Procedural Characteristics of Patients With and Without a Cancer History

	Overall (n=436)	Patients With a Cancer History (Current and Historical) (n=63)	Patients Without Cancer History (n=373)	*P* Value
Age, y	69.0 (60.0–77.0)	74.0 (67.0–81.0)	68.0 (59.0–75.5)	<0.001
Female sex, n	105 (24.1)	18 (28.6)	87 (23.3)	0.368
Body mass index, kg/m^2	23.3 (21.1–25.5)	22.8 (20.1–25.7)	23.4 (21.3–25.4)	0.522
Left ventricular ejection fraction, %	54.0 (45.3–60.0)	54.0 (45.2–60.0)	54.0 (45.2–60.0)	0.698
Smoking, n	282 (64.7)	41 (65.1)	241 (64.6)	0.943
Family history of coronary artery disease, n	63 (14.4)	8 (12.7)	55 (14.7)	0.669
Comorbidity, n				
Hypertension	304 (69.7)	43 (68.3)	261 (70.0)	0.784
Diabetes mellitus	175 (40.1)	29 (46.0)	146 (39.1)	0.302
Dyslipidemia	269 (61.7)	38 (60.3)	231 (61.9)	0.808
Hemodialysis	11 (2.5)	4 (6.3)	7 (1.9)	0.036
Peripheral artery disease	26 (6.0)	7 (11.1)	19 (5.1)	0.062
Previous MI	22 (5.0)	6 (9.5)	16 (4.3)	0.079
Previous PCI	38 (8.7)	9 (14.3)	29 (7.8)	0.090
Previous coronary artery bypass grafting	3 (0.7)	0 (0.0)	3 (0.8)	0.475
Clinical presentation for PCI, n				0.008
ST-segment–elevation MI	250 (57.3)	27 (42.9)	223 (59.8)*	
Non-ST-segment–elevation MI	138 (31.7)	29 (46.0)*	109 (29.2)	
Unstable angina pectoris	48 (11.0)	7 (11.1)	41 (11.0)	
Laboratory variables on admission				
Hemoglobin, g/dL	14.2 (12.9–15.4)	13.4 (12.0–14.6)	14.3 (13.0–15.6)	<0.001
Creatinine, mg/dL	0.81 (0.69–0.95)	0.83 (0.65–0.97)	0.80 (0.70–0.95)	0.477
Hemoglobin A1c, %	6.0 (5.7–6.7)	5.9 (5.6–7.0)	6.0 (5.7–6.7)	0.741
C-reactive protein, mg/dL	0.18 (0.06–0.63)	0.21 (0.07–1.20)	0.18 (0.06–0.50)	0.158
Brain natriuretic peptide, pg/mL	62.8 (24.6–191.0)	127.1 (44.5–305.9)	58.1 (22.9–163.5)	0.001
Peak creatinine kinase, IU/L	1188.5 (420.8–2678.5)	862.0 (335.0–2260.0)	1261.0 (429.5–2717.0)	0.189
Lesion characteristics				
Culprit vessel, n				0.703
Left main trunk	5 (1.1)	0 (0.0)	5 (1.3)	
Left anterior descending	223 (51.1)	31 (49.2)	192 (51.5)	
Left circumflex	65 (14.9)	11 (17.5)	54 (14.5)	
Right coronary artery	143 (32.8)	21 (33.3)	122 (32.7)	
Multivessel disease, n	165 (37.8)	24 (38.1)	141 (37.8)	0.965
Prethrombolysis in myocardial infarction flow grade, n				0.099
0 or 1	222 (50.9)	25 (39.7)	197 (52.8)	
2 or 3	214 (49.1)	38 (60.3)	176 (47.2)	
Procedural characteristics				
Thrombus aspiration, n	240 (55.0)	29 (46.0)	211 (56.6)	0.166
Door to balloon time, min	60.0 (44.0–90.0)	63.0 (45.0–78.5)	60.0 (44.0–90.0)	0.787
Medication at discharge				
Dual antiplatelet therapy, n	436 (100)	63 (100)	373 (100)	N/A
Statin, n	391 (89.7)	50 (79.3)	341 (91.4)	0.004
Renin-angiotensin system-inhibitors, n	324 (74.3)	37 (58.7)	287 (76.9)	0.002
β blocker, n	297 (68.1)	36 (57.1)	261 (70.0)	0.043

Values are median (interquartile range) or n (%). MI indicates myocardial infarction; and PCI, percutaneous coronary intervention.
*P<0.01 were adjusted by post hoc test for multiple comparisons among the groups.

on admission, HCPs had lower hemoglobin levels and higher brain natriuretic peptide levels than NCPs. They also received statins, renin-angiotensin system inhibitors, and beta blockers less frequently than NCPs. Lesion and procedural characteristics were not statistically different between groups (Table 1).

The patients with a cancer history (CCPs and HCPs) had a higher prevalence of PE and CN and a lower prevalence of PR than NCPs. Only 17.5% of patients with a cancer history had PR, whereas 50.9% of NCPs had PR in their ACS culprit lesions. Furthermore, 60.3% of patients with a cancer history had PE, whereas only 36.5% of NCPs had PE in their ACS culprit lesions (Table 2 and Figure 2A). Regarding dominant plaque characteristics, patients with a cancer history had a higher prevalence of calcified plaque, and NCPs had a higher prevalence of lipid plaque. There was no statistically significant difference in the prevalence of thrombus between HCPs and NCPs (82.5%, 89.3%, P=0.124). No other significant differences in OCT findings existed between groups (Table 2).

During a median follow-up period of 809 (405–1271) days, 140 patients (32.1%) experienced adverse events after the onset of ACS (52.4% of the patients with a cancer history [CCPs and HCPs] and 28.7% of NCPs). Kaplan-Meier analysis with log-rank test demonstrated that patients with a cancer history had significantly higher frequencies of cumulative incidence of all-cause death, MACE, and coronary ischemic events than NCPs (Figure 3). The patients with a cancer history had tendencies toward a higher frequency of TLR, TVR, and non-TVR than NCPs (Table S2 and Figure S2).

Subgroup Analysis Stratified by CCPs, HCPs, and NCPs

CCPs had the lowest prevalence of hypertension. HCPs were the oldest and had the highest prevalence of previous MI. Additionally, HCPs had a significantly higher prevalence of non-ST-segment–elevation MI, lower serum hemoglobin level, and higher serum brain natriuretic peptide levels than the other groups. NCPs had a significantly higher prevalence of ST-segment–elevation MI than the other groups (Table S3). The cancer details of CCPs and HCPs are summarized in Table S4.

Regarding the OCT analysis of the ACS culprit plaques, in CCPs and HCPs, PE was the most frequently observed, followed by PR and CN (PR, PE, CN: CCPs, 31.3%, 56.3%, 12.5%; HCPs: 12.8%, 61.7%, 25.5%, respectively). In NCPs, PR was the most frequently observed, followed by PE and CN (PR, PE, CN: 50.9%, 36.5%, 12.6%, respectively) (Figure 2 and Table 3). CN was most frequently observed in HCPs (CCP, HCP, and NCPs: 12.5% versus 25.5% versus 12.6%, respectively, P<0.01). Regarding dominant plaque characteristics, CCPs and HCPs had a significantly higher prevalence of calcified plaques than NCPs (37.5% versus 33.4% versus 15.1%, P<0.01, respectively) (Table 3).

Table 2. Optical Coherence Tomography Findings of ACS Culprit Lesions in Patients With and Without Cancer History

	Overall (n=436)	Patients With a Cancer History (Current and Historical) (n=63)	Patients Without Cancer History (n=373)	*P* Value
Length of culprit lesion, mm	22.0 (15.0–28.0)	20.0 (15.0–30.0)	22.0 (15.0–28.0)	0.513
Minimum lumen area, mm^2	1.22 (0.96–1.70)	1.12 (0.94–1.61)	1.22 (0.97–1.72)	0.562
Plaque classification at culprit lesion, n				<0.001
Plaque rupture	201 (46.1)	11 (17.5)	190 (50.9)*	
Plaque erosion	174 (39.9)	38 (60.3)*	136 (36.5)	
Calcified nodule	61 (14.0)	14 (22.2)*	47 (12.6)	
Dominant plaque characteristics, n				<0.001
Lipid plaque	298 (68.4)	33 (52.4)	265 (71.0)*	
Fibrous plaque	58 (13.3)	6 (9.5)	52 (13.9)	
Calcified plaque	80 (18.3)	24 (38.1)*	56 (15.1)	
Thrombus, n	385 (88.3)	52 (82.5)	333 (89.3)	0.124
Thrombus length, mm	7.9 (4.8–11.9)	6.3 (3.7–10.7)	7.9 (5.0–12.5)	0.388
Maximum thrombus height, mm	0.95 (0.67–1.22)	0.97 (0.64–1.16)	0.94 (0.68–1.22)	0.530
Thin-cap fibroatheroma, n	183 (42.0)	24 (38.1)	159 (42.6)	0.500
Minimum fibrous cap thickness, μm	70 (60–80)	70 (60–80)	70 (60–80)	0.927
Spotty calcification, n	102 (23.4)	15 (23.8)	87 (23.3)	0.933
Microchannel, n	79 (18.1)	12 (19.0)	67 (18.0)	0.836

Values are median (interquartile range) or n (%). ACS indicates acute coronary syndrome.
*P<0.01 were adjusted by residual analysis for multiple comparisons among groups.

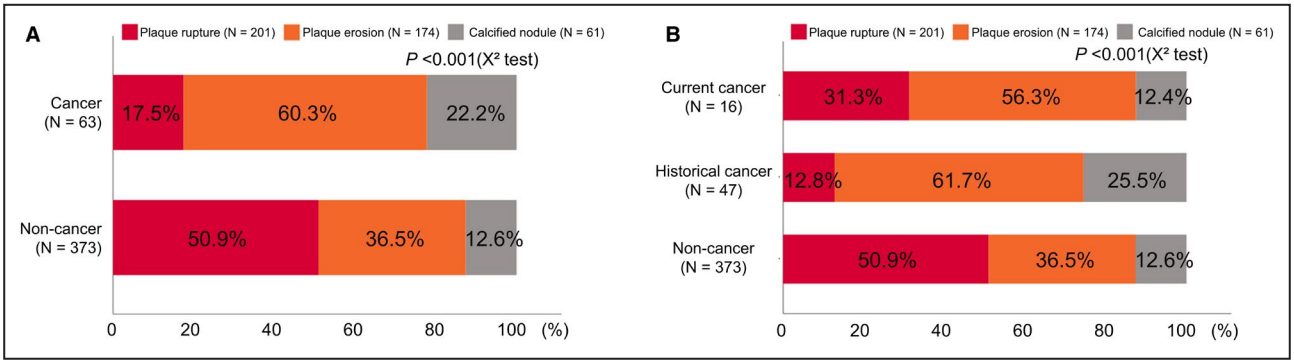

Figure 2. Percentage of morphological plaque characteristics by OCT.
A, Comparison between patients with and without a history of cancer. **B**, Comparison among patients without cancer history, with current cancer, and with cancer history.

During the follow-up period, 11 (68.8%) CCPs, 22 (46.8%) HCPs, and 107 (28.7%) NCPs experienced adverse events (Table S5). The cumulative incidence of all-cause death was the highest in HCPs, followed by CCPs and NCPs (all *P*=0.035), which was significantly higher in HCPs than in NCPs (*P*=0.009). The cumulative incidences of MACE and coronary ischemic events were the highest in CCPs, followed by HCPs and NCPs (*P*=0.011 and *P*=0.02, respectively). The cumulative incidence of MACE and coronary ischemic events was significantly higher in CCPs than in NCPs (*P*=0.003 and *P*=0.01, respectively), and a similar tendency was observed between HCPs and NCPs (Figure 4). CCPs had tendencies toward a higher frequency of TLR, TVR, and non-TVR than NCPs (Figure S3). There were no significant differences in the cumulative incidences of all adverse events between CCPs and HCPs.

Associated Factors for Clinical Events and Plaque Disruption

Four hundred thirty-six patients were included for each Cox model, and individuals were censored at death (n=12) or the end of follow-up (n=296). Cox proportional hazard analysis of patient background showed that cancer history (HR, 1.98; 95% CI, 1.29–3.03; *P*=0.002), statin nonuse at discharge (HR, 2.53; 95% CI, 1.52–4.20; *P*<0.001) and multivessel disease (HR, 2.43; 95% CI, 1.69–3.50; *P*<0.001) were independently associated with MACE (Table 4). Regarding morphological plaque characteristics of ACS culprit lesions, Cox proportional hazard analysis demonstrated that non-PR of culprit lesions (HR, 1.60; 95% CI, 1.11–2.29; *P*=0.011) were independently associated with MACE (Table 5). Logistic regression analysis showed that cancer history (OR, 4.00; 95% CI, 1.96–8.13; *P*<0.001) and diabetes mellitus (OR, 1.58; 95% CI, 1.05–2.40; *P*=0.030) were independently associated with non-PR ACS culprit lesions (Table 6). In the subgroup analysis of each culprit plaque morphology, logistic regression analysis showed that younger age (OR, 0.97; 95% CI, 0.96–0.99; *P*=0.002) and cancer history (OR, 3.37; 95% CI, 1.88–6.03; *P*<0.001) were independently associated with PE in ACS culprit lesions (Table S6). Moreover, older age (OR, 1.07; 95% CI, 1.04–1.10; *P*<0.001), diabetes mellitus (OR, 2.42; 95% CI, 1.35–4.33; *P*=0.003), and hemodialysis (OR, 6.23; 95% CI, 1.77–21.9; *P*=0.004) were independently associated with the presence of CN in the ACS culprit lesions (Table S7).

DISCUSSION

This retrospective study assessed the differences in OCT morphological plaque characteristics of patients with ACS with or without a cancer history and determined their relationship with clinical outcomes. The main findings can be summarized as follows: (1) patients with a cancer history were older and had a higher prevalence of hemodialysis and non-ST-segment–elevation MI than patients without cancer history; (2) in addition to nonreceived statin at discharge and multivessel disease, cancer history was independently associated with MACE after the onset of ACS; (3) cancer history was independently associated with the presence of non-PR in ACS culprit lesions; and (4) the presence of non-PR in ACS culprit lesions was independently associated with MACE after the onset of ACS.

Characteristics and OCT Findings of Patients With a Cancer History

Patients with a cancer history (CCPs and HCPs) had a significantly higher prevalence of PE and CN compared with NCPs. More specifically, among NCPs, 50.9% of ACS had developed because of PR, whereas in patients with a cancer history, only 17.5% of ACS had developed because of PR and 60.3% had occurred because of PE. Furthermore, the prevalence of ACS events because of CN was significantly higher

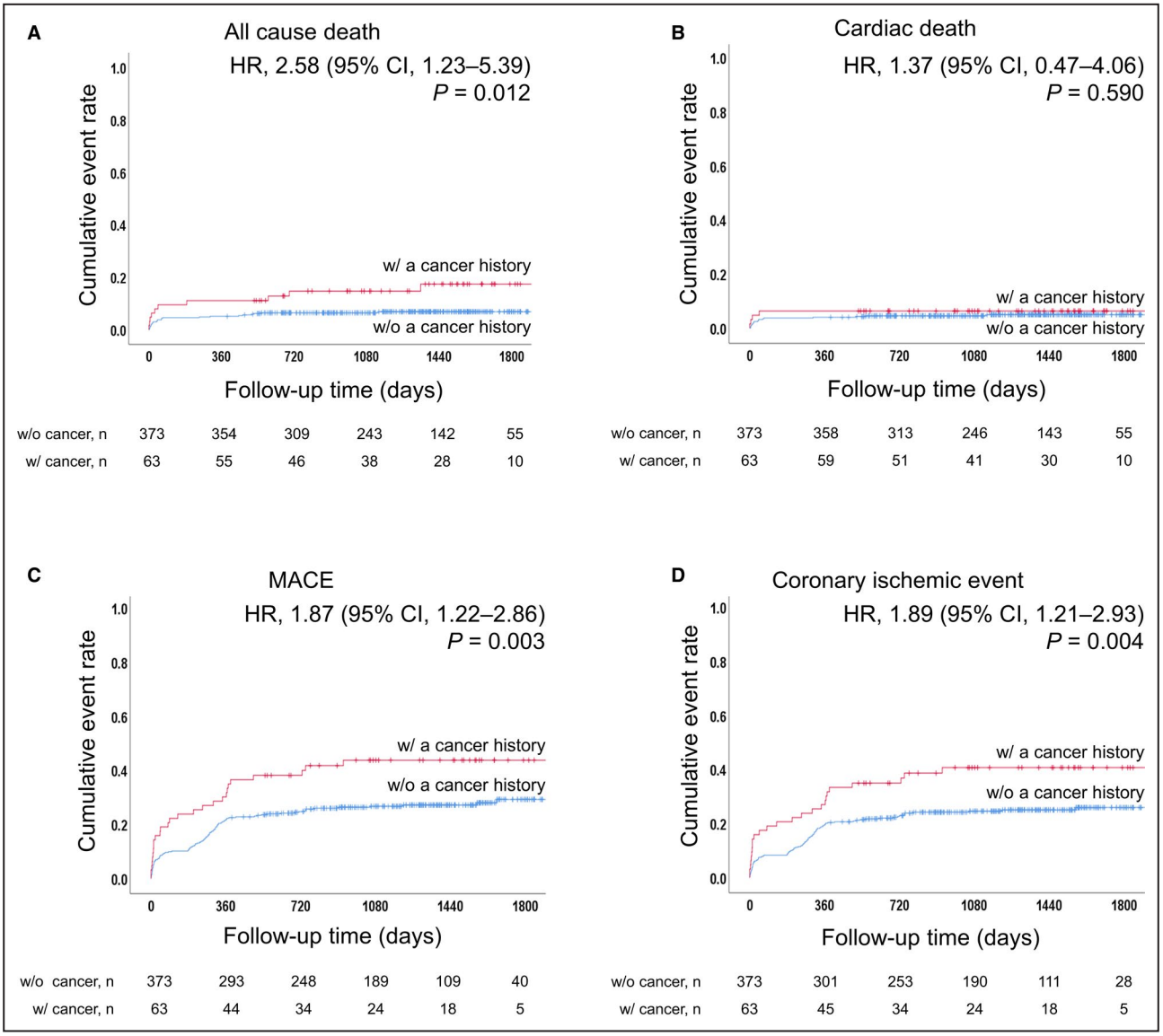

Figure 3. Kaplan-Meier curves showing the difference in the cumulative incidence of clinical events between patients with and without a cancer history.
A, All-cause death, (**B**) cardiac death, (**C**) MACE, and (**D**) coronary ischemic events. HR indicates hazard ratio; and MACE, major adverse cardiovascular event.

in patients with a cancer history than in NCPs (22.2% versus 12.6%; *P*<0.01). According to a previous OCT study, PR, PE, and CN incidence in ACS culprit lesions was 43.7%, 31.0%, and 7.9%, respectively.[6] Thus, PE and CN incidences in patients with a cancer history of the present study were extremely high, whereas those in NCPs were comparable with those reported in previous study. Additionally, we revealed that the presence of PE or CN (non-PR) in ACS culprit lesions was independently associated with a cancer history in patients with ACS. These results indicate that the mechanisms of ACS development in patients with a cancer history might differ from NCPs. A previous study reported that patients with a cancer history are exposed to an increased risk of cardiovascular disease through prothrombotic mechanisms and endothelial dysfunction resulting from the presence of cancer itself and oncological treatments, including radiotherapy or molecular-targeted agents.[9,17] Although speculative, chronic inflammation because of cancer and its treatment have been implicated in accelerating these tendencies. In general, cancer cells induce the secretion of proinflammatory cytokines, which promote endothelial damage and increase microvasculature permeability for procoagulating factors. These inflammatory responses, which can subsequently send feedback signals to tumor cells, could induce further progression of endothelial dysfunction and procoagulant

Table 3. Optical Coherence Tomography Findings of ACS Culprit Lesions Between Patients with Current Cancer, Cancer History, and Without Cancer History

	Overall (n=436)	Patients With Current Cancer (n=16)	Patients With Cancer History (n=47)	Patients Without Cancer History (n=373)	*P* Value for Overall
Length of culprit lesion, mm	22.0 (15.0–28.0)	24.0 (18.0–36.0)	18.0 (15.0–28.0)	22.0 (15.0–28.0)	0.407
Minimum lumen area, mm^2	1.22 (0.96–1.70)	1.32 (0.93–1.95)	1.12 (0.94–1.56)	1.22 (0.97–1.72)	0.658
Plaque classification at culprit lesion, n					<0.001
Plaque rupture	201 (46.1)	5 (31.3)	6 (12.8)	190 (50.9)*	
Plaque erosion	174 (39.9)	9 (56.3)	29 (61.7)*	136 (36.5)	
Calcified nodule	61 (14.0)	2 (12.5)	12 (25.5)*	47 (12.6)	
Dominant plaque characteristics, n					<0.001
Lipid plaque	298 (68.4)	8 (50.0)	25 (53.2)	265 (71.0)*	
Fibrous plaque	58 (13.3)	2 (12.5)	4 (8.5)	52 (13.9)	
Calcified plaque	80 (18.3)	6 (37.5)*	18 (38.3)*	56 (15.1)	
Thrombus, n	385 (88.3)	14 (87.5)	38 (80.9)	333 (89.3)	0.237
Thrombus length, mm	7.9 (4.8–11.9)	9.5 (5.7–15.5)	5.9 (3.2–9.9)	7.9 (5.0–12.5)	0.478
Maximum thrombus height, mm	0.95 (0.67–1.22)	0.97 (0.51–1.14)	0.96 (0.65–1.29)	0.94 (0.68–1.22)	0.709
Thin-cap fibroatheroma, n	183 (42.0)	5 (31.3)	19 (40.4)	159 (42.6)	0.648
Minimum fibrous cap thickness, μm	70 (60–80)	70 (60–97.5)	70 (60–80)	70 (60–80)	0.896
Spotty calcification, n	102 (23.4)	4 (25.0)	11 (23.4)	87 (23.3)	0.988
Microchannel, n	79 (18.1)	2 (12.5)	10 (21.3)	67 (18.0)	0.718

Values are median (interquartile range) or n (%). ACS indicates acute coronary syndrome.
*$P<0.01$ were adjusted by residual analysis for multiple comparisons among groups.

release. In addition, several chemotherapeutic agents and radiation therapy have been reported to induce endothelial dysfunction and apoptosis, thromboxane production, and platelet activation, all of which can potentially result in coronary artery thrombosis.[18] In particular, alkylating agents such as cisplatin have been reported to have toxic effects on endothelial cells and cause coronary thrombosis. Although the underlying mechanism remains uncertain, it was speculated to be an interaction between the cytotoxic effects on the endothelium leading to plaque erosion and subsequent platelet activation and coagulation cascade, which is further enhanced by the activating effect of cisplatin on platelet phospholipase A2.[19,20] In addition, tyrosine kinase inhibitors (ie, axitinib) are also known to induce coronary thrombosis because of thrombotic effects precipitated by the interaction with platelets and alteration in fibrinolytic capacities by neutralizing the inhibitory effect of vascular endothelial growth factor on the expression of PAI-1 (plasminogen activator inhibitor-1) in tumor cells.[21] In the present study, there were 5 patients who used such as chemotherapy drugs, and 4 of them presented with PE or CN. Thus, we speculate that chronic inflammation owing to the presence of cancer and the toxic effects of chemotherapy in combination with endothelial damage under prothrombotic status may explain the relatively higher incidence of ACS events caused by PE and CN in patients with cancer compared with NCPs.

In the present study, the proportion of ACS caused by CN and the presence of calcified plaque in ACS culprit lesions were more frequent in patients with cancer compared with NCPs. According to a recent clinical study using computed tomography, a diagnosis of cancer and its treatment was associated with an increased coronary artery calcification incidence.[22] Patients who received long-term radiation therapy are prone to subsequent calcifications in the vessel wall.[9,23] In the present study, there were 4 patients who underwent radiation and 2 of them presented with CN. Based on these findings together, we currently consider that the cancer treatment may influence the plaque morphology of the lesions causing ACS. Further studies with larger sample sizes are warranted to confirm this speculation.

Differences in Clinical Outcomes After ACS Onset According to a Cancer History

In this study, the incidence of MACE and coronary ischemic events after ACS was significantly higher in patients with a cancer history (CCPs and HCPs) than in NCPs. Previous studies have already reported that cancer is associated with significantly higher rates of adverse cardiovascular events including TLR after PCI in patients with coronary artery disease.[24,25] We also observed that the non-TVR incidence was

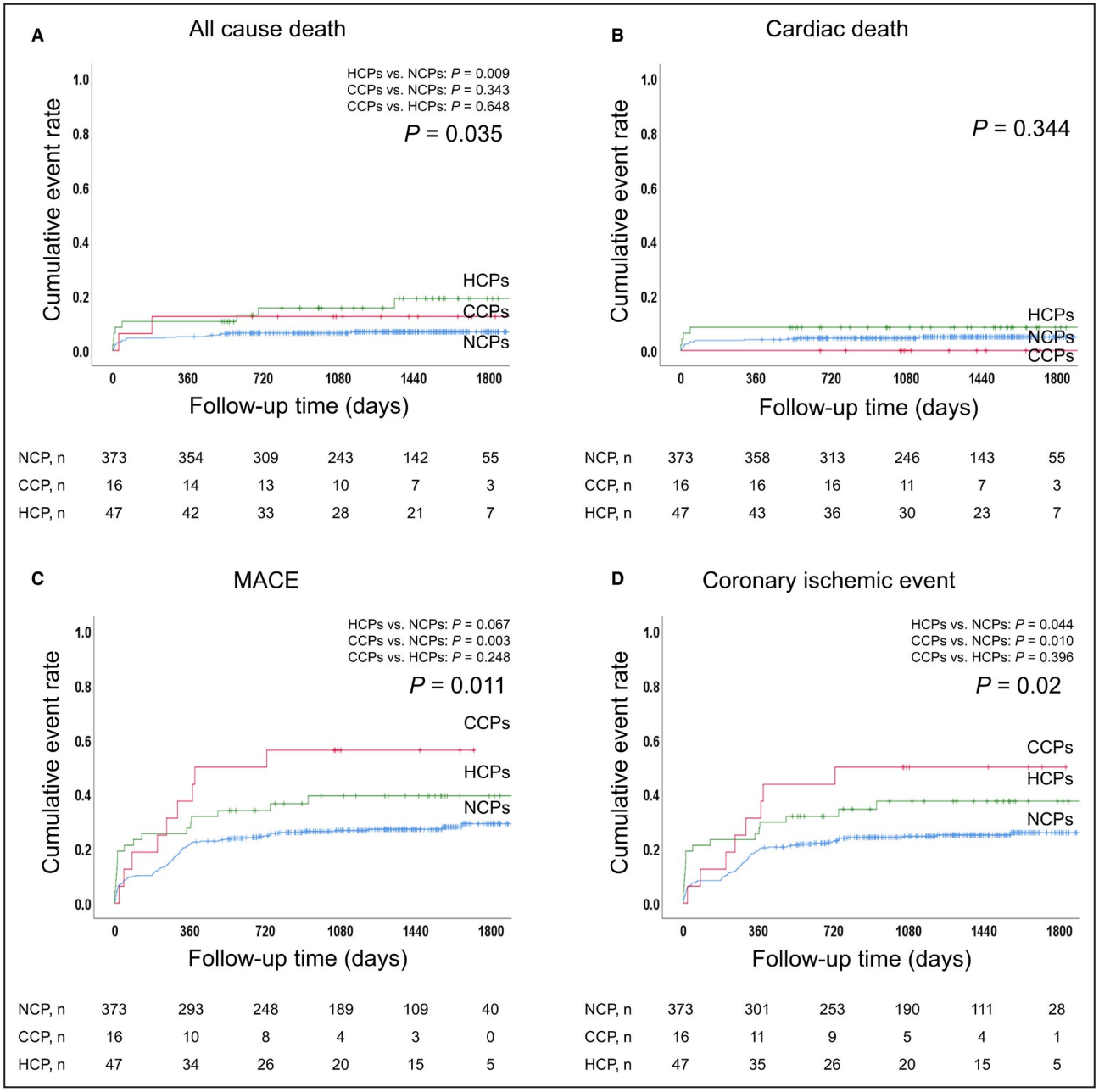

Figure 4. Kaplan-Meier curves showing the cumulative incidence of clinical events between current, historical, and noncancer patient groups.
A, All-cause death, (**B**) cardiac death, (**C**) MACE, and (**D**) coronary ischemic event. CCP indicates patient with current cancer ; HCP, patient with cancer history; MACE, major adverse cardiovascular event; and NCP, patient without cancer history.

significantly higher in patients with a cancer history than in NCPs, with a tendency toward higher incidences of TLR and TVR in patients with a cancer history. Although the detailed mechanisms of the relationship between a cancer history and higher cardiovascular event rates remain unclear, one might speculate that the presence of malignancies might increase vascular wall inflammation through the action of inflammatory cytokines and that this inflammation might cause progressive coronary arteriosclerosis. In the recent prospective randomized placebo-controlled CANTOS trial, Ridker et al demonstrated that anti-inflammatory therapy using canakinumab significantly reduced the incidence of recurrent cardiovascular events and cancer mortality without modifying serum glucose or lipid levels,[26] suggesting a pivotal role of inflammation in the process of both atherosclerosis and cancer development. In the present study, patients with a cancer history had a significantly higher prevalence of hemodialysis, previous

Table 4. Cox Proportional Hazards Regression Analyses for MACE After ACS

Variables	Univariate Regression			Multivariate Regression		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age, y	1.03	1.00–1.04	0.001			
Cancer history, n	1.87	1.22–2.86	0.004	1.98	1.29–3.03	0.002
Noncancer (ref.)						
Current cancer	2.67	1.35–5.29	0.005	2.16	1.09–4.31	0.028
Historical cancer	1.63	0.99–2.69	0.057	1.72	1.01–2.91	0.045
Male sex, n	0.88	0.71–1.10	0.258			
Body mass index, kg/m^2	0.98	0.93–1.03	0.417			
<18.5 (ref), n						
18.5–25, n	0.54	0.28–1.04	0.067			
>25, n	0.53	0.26–1.08	0.079			
Left ventricular ejection fraction <40%, n	2.00	1.30–3.08	0.002			
Family history of coronary artery disease, n	0.73	0.43–1.25	0.254			
Current smoking, n	0.82	0.57–1.17	0.269			
Hypertension, n	1.39	0.93–2.08	0.106			
Diabetes mellitus, n	1.26	0.89–1.79	0.192			
Dyslipidemia, n	0.72	0.51–1.02	0.062			
Hemodialysis, n	1.82	0.74–4.45	0.191			
Previous MI, n	1.99	1.04–3.79	0.037			
Peripheral artery disease, n	1.68	0.88–3.2	0.116			
ST-segment–elevation MI, n	1.06	0.75–1.51	0.742			
Multivessel disease, n	2.68	1.89–3.81	<0.001	2.43	1.69–3.50	<0.001
Chronic kidney disease, n	1.34	0.92–1.96	0.127			
Statin nonuse, n	3.27	2.04–5.24	<0.001	2.53	1.52–4.20	<0.001
Renin-angiotensin system-inhibitors non-use, n	1.28	0.86–1.91	0.221			
β-blocker non-use, n	0.99	0.67–1.46	0.943			

ACS indicates acute coronary syndrome; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; and RAS, renin angiotensin system.

MI, and peripheral artery disease, indicating more progressed atherosclerosis in these patients. Thus, we speculate that, in combination with older age and advanced atherosclerosis, a history of cancer itself can be an important risk factor for worse outcomes in patients with ACS. Furthermore, the incidence of MACE and coronary ischemic events were the highest in CCPs, followed by HCPs and NCP. These results might indicate that a more recent presence of cancer can result in a higher level of systemic inflammation, which might in turn increase the risk of adverse cardiovascular events after ACS.

Table 5. Cox Proportional Hazards Regression Analyses for MACE After ACS by Optical Coherence Tomography Findings

Variables	Univariate Regression			Multivariate Regression		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age, y	1.03	1.01–1.04	0.001	1.02	1.01–1.04	0.001
Male sex, n	0.78	0.50–1.20	0.258			
Non-PR, n	1.60	1.12–2.29	0.01	1.60	1.11–2.29	0.011
Plaque erosion (vs PR), n	1.56	1.06–2.28	0.024			
Calcified nodule (vs PR), n	1.74	1.05–2.88	0.033			
Minimum lumen area, mm^2	0.86	0.67–1.10	0.233			
Length of culprit lesion, mm	1.01	0.99–1.03	0.102			
Thin-cap fibroatheroma, n	1.06	0.75–1.50	0.749			

ACS indicates acute coronary syndrome; HR, hazard ratio; MACE, major adverse coronary events; and PR, plaque rupture.

Table 6. Logistic Regression Analyses for Nonplaque Rupture of ACS Culprit Lesion

Variables	Univariate Regression			Multivariate Regression		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age, y	1.00	0.99–1.02	0.675	0.99	0.97–1.01	0.432
Cancer history, n	4.91	2.48–9.70	<0.001	4.20	2.08–8.48	<0.001
Noncancer (ref.)						
Current cancer	2.28	0.78–6.70	0.133	2.01	0.65–6.21	0.225
Historical cancer	7.10	2.94–17.11	<0.001	5.64	2.27–14.02	<0.001
Male sex, n	0.83	0.54–1.30	0.420	0.82	0.50–1.35	0.436
Body mass index, kg/m^2	1.00	0.95–1.05	0.939			
<18.5 (ref), n						
18.5–25, n	1.04	0.50–2.14	0.921			
<25, n	1.20	0.56–2.60	0.639			
Left ventricular ejection fraction <40%, n	0.96	0.55–1.67	0.89			
Family history of coronary artery disease n	0.86	0.51–1.48	0.593			
Current smoking, n	1.13	0.76–1.67	0.546			
Hypertension, n	0.84	0.56–1.27	0.421			
Diabetes mellitus, n	1.57	1.07–2.32	0.022	1.54	1.02–2.32	0.039
Dyslipidemia, n	0.79	0.54–1.17	0.237			
Hemodialysis, n	2.33	0.61–8.89	0.217	1.34	0.30–6.06	0.704
Previous MI, n	1.53	0.63–3.72	0.350			
Peripheral artery disease, n	2.00	0.85–4.71	0.112			
ST-segment–elevation MI, n	0.64	0.44–0.94	0.023	0.71	0.47–1.07	0.105
Multivessel disease, n	1.27	0.86–1.88	0.230			
Chronic kidney disease, n	0.81	0.53–1.24	0.332			
Statin non-use, n	2.08	1.03–4.23	0.042	1.66	0.73–3.78	0.231
Renin-angiotensin system-inhibitor nonuse, n	1.61	1.02–2.52	0.038	1.23	0.73–2.07	0.439
β-blocker nonuse, n	1.70	1.12–2.57	0.014	1.41	0.88–2.24	0.152

ACS indicates acute coronary syndrome; MI, myocardial infarction; and OR, odds ratio.

Associated Factors With Adverse Events After the Onset of ACS

The presence of non-PR, including PE and CN, in ACS culprit lesions was associated with worse clinical outcomes during a median follow-up period of 26 months after the onset of ACS. The presence of cancer history was independently associated with the presence of non-PR. Thus, we speculated that besides the patient background specific to those with cancer, including older age and advanced atherosclerosis, morphological features of ACS culprit lesions might partially explain the relatively worse clinical prognosis in patients with a cancer history.

Currently, there are limited data regarding the potential relationship between morphological features of ACS culprit lesions and prognosis after the onset of ACS. In a previous study that enrolled 139 patients with ACS who underwent pre-PCI OCT, Niccoli et al reported that the MACE incidence was significantly higher in the PR group than in the non-PR group during a 3-year follow-up (32 patients [39.0%] versus 8 patients [14.0%]; *P*=0.001).[27] Another larger study enrolling 510 patients with ACS reported a significantly higher MACE incidence after PCI in the PR group than in the intact fibrous cap (PE) group (65 patients [19.8%] versus 20 patients [11.0%]; *P*=0.002, respectively).[28] Although both studies reported that PR-ACS was related to worse clinical outcomes than non-PR ACS, differences in culprit plaque classification might explain these contradicting results between these previous studies and the present one. Because the concept of CN as a culprit plaque of ACS is relatively new, previous studies have not adopted CN in the classifications of ACS culprit plaques in the analyses. Thus, the prognostic impact of non-PR ACS might be underestimated in these previous studies. Indeed, there have been several reports showing worse clinical outcomes after PCI for patients with ACS and CN. A large cohort study that enrolled 6855 patients with ACS who underwent PCI reported that moderate/severe calcification lesions were related to higher 1-year rates of MACE, stent thrombosis, and TLR than in those without ACS.[29] In a recent OCT study evaluating the prognostic impact of CN in 362 patients with ACS, Kobayashi et

al reported that CN was associated with a higher TLR incidence than PR-ACS.[30] These studies suggest that clinical outcomes after the onset of ACS with CN might be worse than PR. Further studies with larger sample sizes will be required to confirm the potential relationship among ACS culprit lesion morphology, cancer history, and future prognosis.

Study Limitations

This study has several limitations. First, as a retrospective, multicenter cohort study, the results may not be generalizable. Several clinicians may have been aware of the history of cancer and tailored the treatment to the patient. Second, all populations underwent OCT-guided PCI. Therefore, the results for patients who did not undergo PCI or OCT because of cardiogenic shock are unknown. Third, owing to the small sample size of patients with cancer, we could not evaluate the influences of various cancer treatments (chemotherapy, radiation, or surgery), as well as the different cancer types on the outcomes. Fourth, the OCT-defined PR may be underestimated because the presence of residual thrombus limits the detection of fibrous cap disruption on OCT. Moreover, detection of fibrous cap disruption is sometimes difficult on the surface of nodular calcification. Thus, the OCT-defined CN has not been completely established. These considerations warrant future prospective observational studies with the consideration of the treatment context of patients with cancerr.

CONCLUSIONS

Patients with a cancer history had significantly worse clinical outcomes after the onset of ACS compared with NCPs. They also had significantly higher incidences of PE and CN in ACS culprit lesions, which might partly explain the worse clinical outcomes after the onset of ACS in patients with a cancer history.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S7
Figures S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Cancer characteristics.

	N = 63
Type of cancer	
Neck/thyroid	7 (11.1)
Esophageal/gastric/colon/rectum	23 (36.5)
Liver/pancreas	5 (7.9)
Lung	4 (6.3)
Skin	2 (3.2)
Breast	1 (1.6)
Uterine/ovarian	7 (11.1)
Renal/bladder/prostate	10 (15.9)
Hematopoietic	0 (0)
Other	4 (6.3)
TNM staging category	
Stage I	49 (77.8)
Stage II	7 (11.1)
Stage III	5 (7.9)
Stage IV	2 (3.2)
Metastasis	6 (9.5)
Duration between cancer diagnosis and ACS onset	
Current (<1 yr)	16 (25.4)
Historical (1–5 yr)	20 (31.7)
Historical (>5 yr)	27 (42.9)
Any treatment for cancer	48 (76.2)
Only surgery	40 (63.4)
Only chemotherapy	2 (3.2)
Only radiation	1 (1.6)
Combination of surgery and chemotherapy	2 (3.2)
Combination of surgery and radiation	1 (1.6)
Combination of surgery and chemoradiation	2 (3.2)
Recurrence after ACS	2 (3.2)

Values are n (%). ACS, acute coronary syndrome; TNM, tumor, nodes, and metastases.

Table S2. All-cause death and adverse cardiovascular events during the follow-up period according to a cancer history.

Variables	Patient with a cancer history (CCPs and HCPs) (N = 63)	NCPs (N = 373)	HR (95% CI)	*P*-value
All-cause death, n	10 (15.9)	24 (6.4)	2.58 (1.23–5.39)	0.012
Cardiac death, n	4 (6.3)	18 (4.8)	1.37 (0.47–4.06)	0.590
Non-cardiac death, n	6 (9.6)	6 (1.6)	6.19 (2.00–19.2)	0.002
Pneumonia	3 (4.8)	2 (0.5)		
Acute abdomen	0 (0)	3 (0.8)		
Cerebellar hemorrhage	0 (0)	1 (0.3)		
Acute limb ischemia	1 (1.6)	0 (0)		
Unknown	2 (3.2)	0 (0)		
Non-fatal MI, n	1 (1.6%)	7 (1.9)	0.84 (0.10–6.85)	0.874
TLR, n	9 (14.3)	27 (7.2)	2.12 (0.99–4.50)	0.06
TVR, n	11 (17.5)	37 (9.9)	1.88 (0.96–3.69)	0.077
Non-TVR, n	15 (23.8)	49 (13.1)	2.01 (1.13–3.58)	0.027
Heart failure with admission, n	1 (1.6)	5 (1.3)	1.17 (0.14–10.0)	0.876
Stroke/TIA, n	1 (1.6)	7 (1.9)	0.87 (0.11–7.03)	0.874
MACE, n	27 (42.9)	101 (27.1)	1.87 (1.22–2.86)	0.003
Coronary ischemic event, n	25 (39.7)	92 (24.7)	1.89 (1.21–2.93)	0.004

Values are n (%). Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with the use of a Cox proportional hazards model. MACE was composite of cardiac death, non-fatal MI, any revascularization (TLR, TVR, and non-TVR), stroke/TIA, and heart failure with admission. Coronary ischemic event was composite of cardiac death, non-fatal MI, and any revascularization. CCP, current cancer patient; HCP, historical cancer patient; MACE, major adverse cardiovascular event; MI, myocardial infarction; NCP, non-cancer patient; TIA, transient ischemic attack; TLR, target lesion revascularization; TVR, target vessel revascularization.

Table S3. Differences in baseline procedural and patient characteristics between current, historical, and non-cancer patient groups.

	Overall (N = 436)	CCPs (N = 16)	HCPs (N = 47)	NCPs (N = 373)	*P*-value for overall
Age, yr	69.0 (60.0–77.0)	70.5 (65.3–79.8)	74.0 (67.0–83.0)*	68.0 (59.0–75.5)*	0.001
Female, n	105 (24.1)	6 (37.5)	12 (25.5)	87 (23.3)	0.418
Body mass index, kg/m^2	23.3 (21.1–25.5)	21.4 (20.5–25.7)	23.3 (20.0–26.0)	23.4 (21.3–25.4)	0.555
LVEF, %	54.0 (45.3–60.0)	50.0 (45.1–59.0)	55.5 (45.3–60.0)	54.0 (45.15–60.0)	0.594
Smoking, n	282 (64.7)	9 (56.3)	32 (68.1)	241 (64.6)	0.692
Family history of coronary artery disease, n	63 (14.4)	1 (6.3)	7 (14.9)	55 (14.7)	0.636
Comorbidity, n					
Hypertension	304 (69.7)	7 (43.8) †	36 (76.6)	261 (70.0)	0.046
Diabetes mellitus	175 (40.1)	9 (56.3)	20 (42.6)	146 (39.1)	0.368
Dyslipidemia	269 (61.7)	9 (56.3)	29 (61.7)	231 (61.9)	0.901
Hemodialysis	11 (2.5)	1 (6.3)	3 (6.4)	7 (1.9)	0.112
Peripheral artery disease	26 (6.0)	2 (12.5)	5 (10.6)	19 (5.1)	0.169
Previous myocardial infarction	22 (5.0)	0 (0.0)	6 (12.8) †	16 (4.3)	0.028
Previous PCI	38 (8.7)	1 (6.3)	8 (17.0)	29 (7.8)	0.100
Previous coronary artery bypass grafting	3 (0.7)	0 (0.0)	0 (0.0)	3 (0.8)	0.775
Laboratory variables on admission					
Hemoglobin, g/Dl	14.2 (12.9–15.4)	13.1 (11.9–15.1)	13.4 (12.0–14.5)*	14.3 (13.0–15.6)*	0.001
Creatinine, mg/dL	0.81 (0.69–0.95)	0.83 (0.71–0.96)	0.83 (0.64–0.98)	0.80 (0.70–0.95)	0.777

Hemoglobin A1c, %	6.0 (5.7–6.7)	6.3 (5.5–7.9)	5.9 (5.6–6.6)	6.0 (5.7–6.7)	0.699
C-reactive protein, mg/dL	0.18 (0.06–0.63)	0.71 (0.09–1.73)	0.15 (0.06–0.84)	0.18 (0.06–0.50)	0.175
Brain natriuretic peptide, pg/mL	62.8 (24.6–191.0)	73.5 (19.1–333.7)	129.8 (49.4–311.0)*	58.1 (22.9–163.5)*	0.002
Peak creatinine kinase, IU/L	1188 (421–2678)	1436 (421–2641)	860 (194–2083)	1261 (429–2717)	0.287
Lesion characteristics					
Clinical presentation for PCI, n					0.023
ST elevation MI	250 (57.3)	11 (68.8)	16 (34.0)	223 (59.8) †	
Non-ST elevation MI	138 (31.7)	5 (31.2)	24 (51.1) †	109 (29.2)	
uAP	48 (11.0)	0 (0.0)	7 (14.9)	41 (11.0)	
Culprit vessel, n					0.747
Left main trunk	5 (1.1)	0 (0.0)	0 (0.0)	5 (1.3)	
Left anterior descending	223 (51.1)	10 (62.5)	21 (44.7)	192 (51.5)	
Left circumflex	65 (14.9)	1 (6.3)	10 (21.3)	54 (14.5)	
Right coronary artery	143 (32.8)	5 (31.3)	16 (34.0)	122 (32.7)	
Multivessel disease, n	165 (37.8)	8 (50.0)	16 (34.0)	141 (37.8)	0.524
Pre TIMI flow grade, n					0.054
0 or 1	222 (50.9)	8 (50.0)	17 (36.2)	197 (52.8)	
2 or 3	214 (49.1)	8 (50.0)	30 (63.8)	176 (47.2)	
Procedural characteristics					
Thrombus aspiration, n	240 (55.0)	9 (56.3)	20 (42.6)	211 (56.6)	0.120
Door to balloon time, min	60.0 (44.0–90.0)	65.0 (58.0–90.0)	57.0 (43.8–77.8)	60.0 (44.0–90.0)	0.892
Medication at discharge					

Dual antiplatelet therapy, n	436 (100)	16 (100)	47 (100)	373 (100)	N/A
Statin, n	391 (89.7)	13 (81.3)	37 (78.7)	341 (91.4)	0.082
RAS-inhibitors, n	324 (74.3)	8 (50.0)	29 (61.7)	287 (76.9) †	0.013
β-blocker, n	297 (68.1)	10 (62.5)	26 (55.3)	261 (70.0)	0.113

Values are median (interquartile range) or n (%). *P<0.018 were adjusted by post hoc testing for multiple comparisons among groups. †P<0.01 were adjusted by residual analysis for multiple comparisons among groups. CCP, current cancer patient; HCP, historical cancer patient; LVEF, Left ventricular ejection fraction; MI, myocardial infarction; NCP, non-cancer patient; PCI, percutaneous coronary intervention; RAS, renin angiotensin system; TIMI, thrombolysis in myocardial infarction; uAP, unstable angina pectoris.

Table S4. Details of current and historical cancer patients.

	CCPs (N = 16)	HCPs (N = 47)	*P*-value
Type of cancer, n			0.452
Neck/thyroid	2 (12.5)	5 (10.6)	
Esophageal/gastric/colon/rectum	9 (56.)	14 (29.8)	
Liver/pancreas	2 (12.5)	3 (6.4)	
Lung	1 (6.3)	3 (6.4)	
Skin	0 (0)	2 (4.2)	
Breast	0 (0)	1 (2.1)	
Uterine/ovarian	0 (0)	7 (14.9)	
Renal/bladder/prostate	2 (12.5)	8 (17.0)	
Hematopoietic	0 (0)	0 (0)	
Other	0 (0)	4 (8.6)	
TNM staging category			0.752
Stage I	13 (81.4)	36 (76.6)	
Stage II	1 (6.2)	6 (12.8)	
Stage III	1 (6.2)	4 (8.5)	
Stage IV	1 (6.2)	1 (2.1)	
Metastasis, n	3 (18.8)	3 (6.4)	0.985
Treatment, n			
Surgery	11 (68.8)	34 (72.3)	0.315
Chemotherapy, hormone therapy, or biological therapy	3 (18.8)	3 (6.4)	0.146
Radiation	0 (0)	4 (8.5)	0.228
Recurrence after ACS	1 (6.2)	1 (2.1)	0.746

Values are n (%). ACS, acute coronary syndrome; TNM, tumor, nodes, and metastases.

Table S5. All-cause death and adverse cardiovascular events during the follow-up period according to timing of cancer diagnosis.

Variables	CCPs (N = 16)	HCPs (N = 47)	NCPs (N = 373)	*P*-value
All-cause death, n	2 (12.5)	8 (17.0)*	24 (6.4)	0.030
Cardiac death, n	0 (0.0)	4 (8.5)	18 (4.8)	0.356
Non-fatal MI, n	0 (0.0)	1 (2.1)	7 (1.9)	0.85
TLR, n	3 (18.8)	6 (12.8)	27 (7.2)	0.129
TVR, n	4 (25.0)	7 (14.9)	37 (9.9)	0.112
Non-TVR, n	5 (31.3)	10 (21.3)	49 (13.1)	0.054
Heart failure with admission, n	0 (0.0)	1 (2.1)	5 (1.3)	0.81
Stroke/TIA, n	1 (6.3)	0 (0.0)	7 (1.9)	0.271
MACE, n	9 (56.3)*	18 (38.3)	101 (27.1)	0.016
Coronary ischemic event, n	8 (50.0)*	17 (36.2)	92 (24.7)	0.025

Values are n (%). MACE was composite of cardiac death, non-fatal MI, any revascularization (TLR, TVR, and non-TVR), stroke/TIA, and heart failure with admission. Coronary ischemic event was composite of cardiac death, non-fatal MI, and any revascularization. CCP, current cancer patient; HCP, historical cancer patient; MACE, major adverse cardiovascular event; MI, myocardial infarction; NCP, non-cancer patient; TIA, transient ischemic attack; TLR, target lesion revascularization; TVR, target vessel revascularization.

Table S6. Logistic regression analyses of plaque erosion in ACS culprit lesions.

Variables	Univariate regression			Multivariate regression		
	OR	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Age, yr	0.98	0.96–0.99	0.002	0.97	0.96–0.99	0.002
Cancer history, n	2.65	1.53–4.58	<0.001	3.36	1.88–6.03	<0.001
Non-cancer (ref.)						
Current cancer	2.24	0.82–6.15	0.117	2.76	0.97–7.83	0.057
Historical cancer	2.81	1.50–5.24	0.001	3.81	1.94–7.48	<0.001
Male, n	0.58	0.37–0.93	0.024	0.67	0.39–1.16	0.152
Body mass index, kg/m2	1.04	0.98–1.09	0.212			
<18.5 (ref), n						
18.5–25, n	1.70	0.76–3.80	0.195			
>25, n	2.16	0.93–5.02	0.074			
LVEF <40%, n	1.02	1.00–1.04	0.033	0.69	0.37–1.29	0.248
Family history of coronary artery disease n	0.92	0.54–1.58	0.751			
Current smoking, n	1.43	0.95–2.15	0.084	1.06	0.67–1.69	0.797
Hypertension, n	0.66	0.44–1.00	0.048	0.75	0.48–1.16	0.196
Diabetes mellites, n	1.05	0.71–1.55	0.817			
Dyslipidemia, n	0.81	0.54–1.19	0.282			
Hemodialysis, n	0.33	0.07–1.53	0.156			
Previous MI, n	1.05	0.44–2.50	0.922			
Peripheral artery disease, n	1.11	0.50–2.48	0.797			
ST elevation MI, n	0.90	0.61–1.32	0.584			
Multivessel disease, n	0.86	0.57–1.27	0.438			
Chronic kidney disease, n	0.55	0.35–0.87	0.011	0.65	0.39–1.08	0.095
Statin non-use, n	1.20	0.80–1.81	0.377			
RAS-inhibitor non-use, n	1.29	0.82–2.00	0.268			
β-blocker non-use, n	1.85	0.84–4.08	0.128			

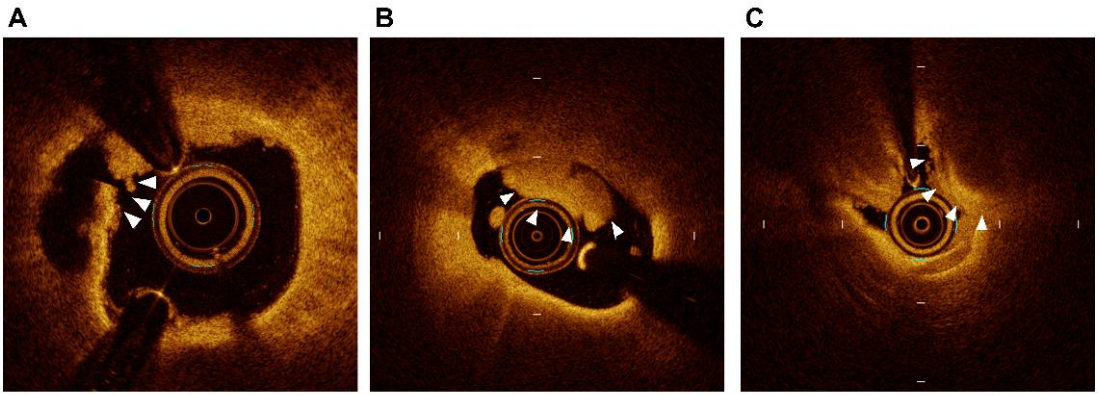
ACS, acute coronary syndrome; CI, confidence interval; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OR, odds ratio; RAS, renin angiotensin system.

Table S7. Logistic regression analyses of calcified nodule in ACS culprit lesions.

Variables	Univariate regression			Multi variate regression		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age, yr	1.07	1.04–1.10	<0.001	1.06	1.03–1.10	<0.001
Cancer history, n	1.98	1.02–3.87	0.045	1.35	0.63–2.89	0.434
Non-cancer (ref.)						
Current cancer	0.99	0.22–4.50	0.991	0.64	0.13–3.26	0.59
Historical cancer	2.38	1.15–4.90	0.019	1.93	0.82–4.57	0.135
Male, n	1.82	1.02–3.25	0.044	1.23	0.64–2.54	0.486
Body mass index, kg/m2	0.93	0.86–1.00	0.06	0.95	0.86–1.04	0.286
<18.5 (ref), n						
18.5–25, n	0.49	0.20–1.16	0.105			
>25, n	0.40	0.15–1.06	0.065			
LVEF <40%, n	0.99	0.96–1.01	0.256			
Family history of coronary artery disease n	0.88	0.40–1.95	0.749			
Current smoking, n	0.65	0.37–1.12	0.117			
Hypertension, n	1.72	0.90–3.29	0.103			
Diabetes mellites, n	2.26	1.31–3.91	0.004	2.61	1.38–4.93	0.003
Dyslipidemia, n	0.95	0.55–1.65	0.857			
Hemodialysis, n	8.07	2.38–27.35	0.001	4.54	1.12–18.44	0.034
Previous MI, n	1.88	0.67–5.30	0.232			
Peripheral artery disease, n	2.43	0.98–6.05	0.057	1.42	0.49–4.12	0.524
ST elevation MI, n	0.51	0.29–0.87	0.013	0.75	0.41–1.39	0.364
Multivessel disease, n	2.17	1.26–3.75	0.005	1.80	0.91–3.10	0.107
Chronic kidney disease, n	1.89	1.07–3.34	0.028	1.00	0.50–2.00	0.998
Statin non-use, n	0.69	0.39–1.19	0.183			
RAS-inhibitor non-use, n	1.55	0.85–2.82	0.15			
β-blocker non-use, n	1.28	0.72–2.28	0.405			

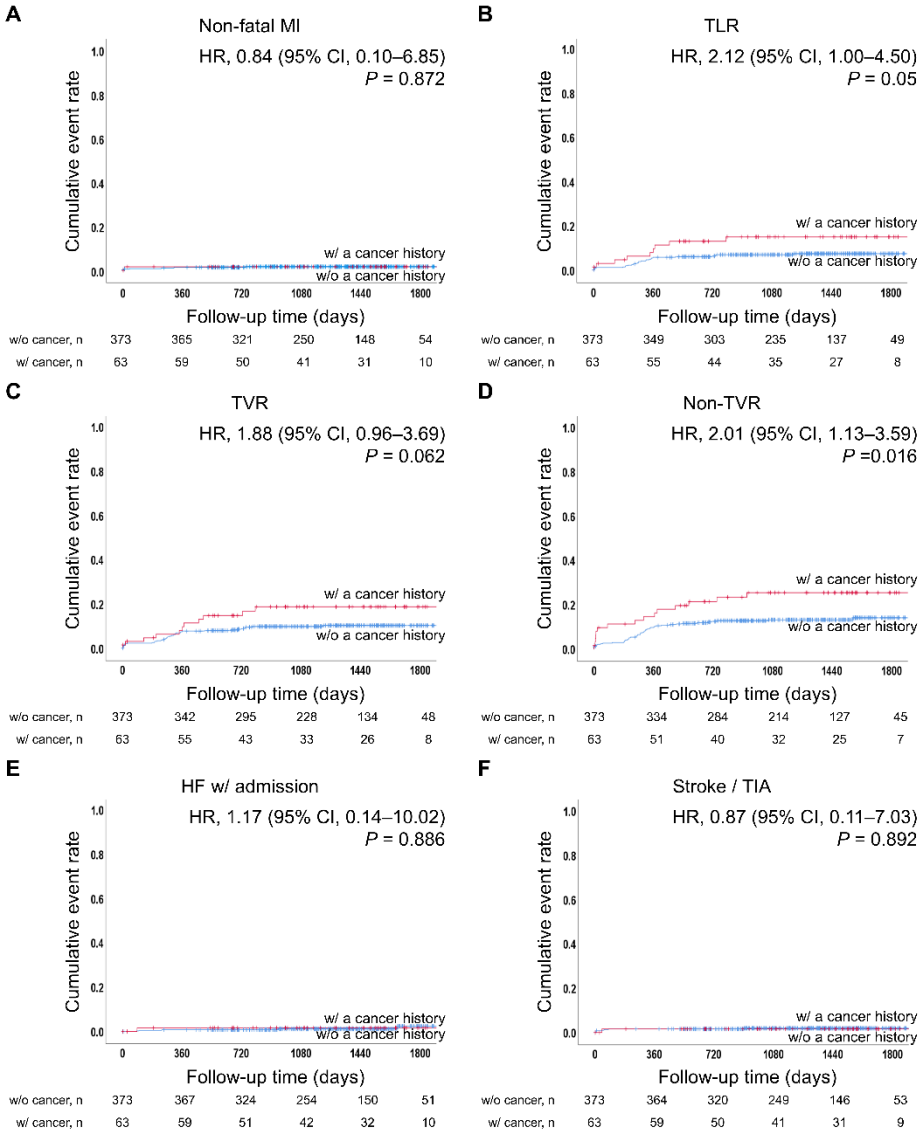
ACS, acute coronary syndrome; CI, confidence interval; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OR, odds ratio; RAS, renin angiotensin system.

Figure S1. Representative optical coherence tomography images.



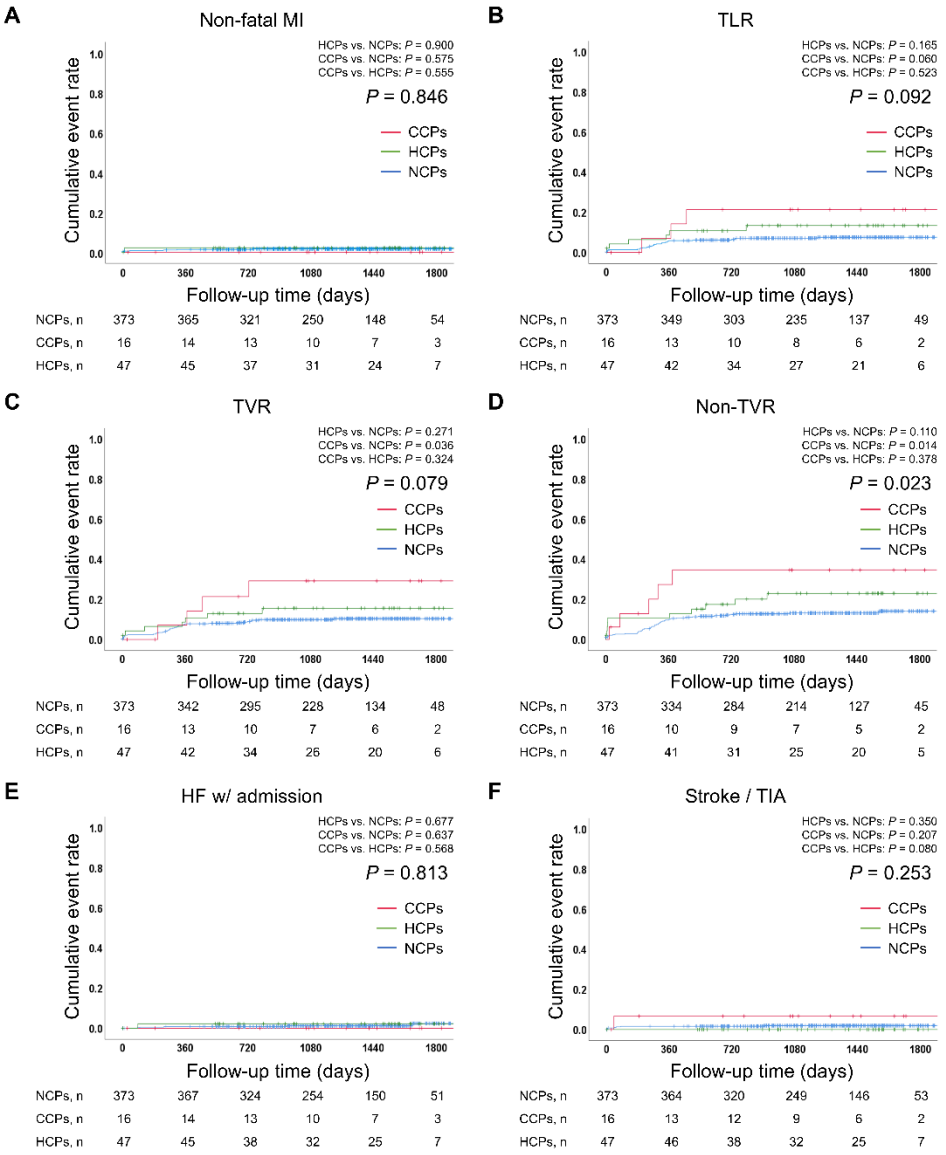
(A) Plaque rupture, (B) Plaque erosion, and (C) Calcified nodule

Figure S2. Kaplan–Meier curves showing the difference in the cumulative incidence of clinical events between patients with and without a cancer history.



(A) Non-fatal MI, (B) TLR, (C), TVR, (D), Non-TVR, (E) Heart failure with admission, and (F) Stroke/TIA. CI, confidence interval; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; TIA, transient ischemic attack; TLR, target lesion revascularization; TVR, target vessel revascularization.

Figure S3. Kaplan–Meier curves showing the difference in the cumulative incidence of clinical events between current, historical, and non-cancer patient groups.



(A) Non-fatal MI, (B) TLR, (C), TVR, (D), Non-TVR, (E) Heart failure with admission, and (F) Stroke/TIA. CCP, current cancer patient; HCP, historical cancer patient; HF, heart failure, MI, myocardial infarction; NCP, non-cancer patient; TIA, transient ischemic attack; TLR, target lesion revascularization; TVR, target vessel revascularization.