ESC European Society of Cardiology

European Heart Journal - Quality of Care and Clinical Outcomes (2018) **4**, 200–207
doi:10.1093/ehjqcco/qcy014

ORIGINAL ARTICLE

Influence of a history of cancer on long-term cardiovascular outcomes after coronary stent implantation (an Observation from Coronary Revascularization Demonstrating Outcome Study-Kyoto Registry Cohort-2)

Kenji Nakatsuma[1], Hiroki Shiomi[2,*], Takeshi Morimoto[3], Hirotoshi Watanabe[2], Yoshihisa Nakagawa[4], Yutaka Furukawa[5], Kazushige Kadota[6], Kenji Ando[7], Koh Ono[2], Satoshi Shizuta[2], and Takeshi Kimura[2]; on behalf of the CREDO-Kyoto PCI/CABG Registry Cohort-2 Investigators

[1]Department of Cardiology, Mitsubishi Kyoto Hospital, 1 Gosho-cho, Nishikyo-ku, Kyoto, 615-8087, Japan; [2]Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan; [3]Department of Clinical Epidemiology, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo, 663-8501, Japan; [4]Division of Cardiology, Tenri Hospital, 200 Mishima-cho, Tenri, Nara, 632-8552, Japan; [5]Division of Cardiology, Kobe City Medical Center General Hospital, 1-1, 2 Minatoshimaminami-cho, Chuou-ku, Kobe, Hyogo, 650-0047, Japan; [6]Division of Cardiology, Kurashiki Central Hospital, 1-1-1 Miwa, Kurashiki, Okayama,710-8602, Japan; and [7]Division of Cardiology, Kokura Memorial Hospital, 2-1, 3 Asano, Kokurakita-ku, Kitakyushu, Fukuoka, 802-8555, Japan

Received 6 February 2018; revised 3 April 2018; editorial decision 5 April 2018; accepted 19 April 2018; online publish-ahead-of-print 20 April 2018

Aims To evaluate the influence of a history of cancer on clinical outcomes in coronary artery disease (CAD) patients who underwent percutaneous coronary intervention (PCI).

Methods and results In the Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) PCI/coronary artery bypass grafting (CABG) Registry Cohort-2, there were 12 180 CAD patients who received PCI with stents. There were 1109 patients with a history of cancer (cancer group) and 11 071 patients without cancer (non-cancer group). The cumulative 5-year incidences of cardiac death and heart failure (HF) hospitalization were significantly higher in the cancer group than in the non-cancer group (12.4% vs. 7.5%, $P < 0.001$ and 12.1% vs. 7.6%, $P < 0.001$, respectively). Even after adjusting for confounders, the excess risk of the cancer group relative to non-cancer group for cardiac death and HF hospitalization remained significant [hazard ratio (HR) 1.27, 95% confidence interval (95% CI) 1.05–1.53; $P = 0.02$, and HR 1.39, 95% CI 1.13–1.68; $P = 0.002$, respectively]. Also, the cancer group had a trend toward higher adjusted risk for definite or probable stent thrombosis as compared with the non-cancer group (HR 1.49, 95% CI 0.99–2.16; $P = 0.055$). The cancer group had significantly higher adjusted risk for all-cause death, non-cardiac death, major bleeding, and non-CABG surgery than the non-cancer group, while the risks for myocardial infarction and stroke were neutral between the two groups.

Conclusion Patients with a history of cancer at the time of PCI had increased risk for cardiac events such as cardiac death and HF hospitalization as well as non-cardiac events such as non-cardiac death, major bleeding, and non-CABG surgery.

Keywords Percutaneous coronary intervention • Coronary artery disease • Cancer

* Corresponding author. Tel: +81-75-751-4255, Fax: +81-75-751-3299, Email: hishiomi@kuhp.kyoto-u.ac.jp

Introduction

Coronary artery disease (CAD) and cancer are the leading causes of mortality and morbidity worldwide.[1] However, long-term mortality in both fields has declined over the past decade owing to better risk factor modification, earlier disease detection, and advances in treatment.[2–6] Risk factors of CAD and cancer have some overlapping features, such as advanced age, smoking, diet, and sedentary lifestyle. Furthermore, several forms of cancer treatments such as radiation or chemotherapy are associated with an increased risk of CAD.[7–10] Therefore, active cancer or history of cancer are present in increasing frequency in CAD patients requiring PCI in real-world clinical practice.[11–13] However, there are limited data with some discordance about the influence of co-existing cancer on cardiovascular outcomes in CAD patients who underwent PCI.[14,15] The purpose of the present study, therefore, was to evaluate the influence of a history of cancer on long-term cardiovascular outcomes in CAD patients who underwent PCI in a large-scale multicentre registry in Japan.

Methods

Study population

The Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) PCI/coronary artery bypass grafting (CABG) Registry Cohort-2 is a physician-initiated non-company-sponsored multicentre registry that enrolled consecutive patients with CAD who underwent their first coronary revascularization between January 2005 and December 2007 at 26 hospitals in Japan (Supplementary material online, *Appendix A*). The relevant review boards or ethics committees at all 26 participating hospitals approved the study protocol. Obtaining written informed consent from the patients was waived because of the retrospective nature of the study; however, we excluded those patients who refused participation in the study when contacted at follow-up. This strategy is concordant with the guidelines of the Japanese Ministry of Health, Labor and Welfare.

The details on the design and patient enrolment of this registry have been described previously.[16] Among 15 939 patients in the registry, 13 058 patients were enrolled in the PCI arm of the registry, excluding 99 patients who refused study participation and 2782 patients who underwent CABG. Further excluding 878 patients without stent implantation, 12 180 patients were subjected to the current analyses, where 1109 patients had a history of cancer (cancer group) and the remaining 11 071 patients did not have a history of cancer (non-cancer group) (Supplementary material online, *Figure S1*).

Experienced clinical research coordinators from the independent clinical research organization (Research Institute for Production Development, Kyoto, Japan; Supplementary material online, *Appendix B*) collected baseline data from the hospital charts or hospital databases according to the pre-specified definitions. Collection of follow-up information was mainly conducted through review of the inpatient and outpatient hospital charts by the clinical research coordinators, and additional follow-up information was collected through contact with patients, relatives and/or referring physicians by sending mail with questions regarding vital status, subsequent hospitalizations, and status of antiplatelet therapy.

Definitions and outcome measures

Cancer group consisted of patients who had any history of cancer at the time of PCI. The outcome measures included all-cause death, cardiac death, non-cardiac death, heart failure (HF) hospitalization, major bleeding, non-CABG surgery, myocardial infarction (MI), definite or probable stent thrombosis (ST), stroke, target-lesion revascularization (TLR), and any coronary revascularization. Death was regarded as cardiac in origin, unless obvious non-cardiac causes could be identified. Any death during the index hospitalization was regarded as cardiac death. Heart failure hospitalization was regarded as present when intravenous drug treatment was administered for worsening HF during hospitalization. Major bleeding was defined according to the global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries (GUSTO) classification.[17] GUSTO moderate or severe bleeding was adjudicated as a major bleeding event. Myocardial infarction was defined according to the definition in the Arterial Revascularization Therapy Study.[18] Stent thrombosis was defined according to the Academic Research Consortium definition.[19] Stroke during follow-up was defined as ischaemic or haemorrhagic stroke requiring hospitalization with symptoms lasting more than 24 h. Target-lesion revascularization was defined as either PCI or CABG due to restenosis or thrombosis of the target lesion that included the proximal and distal edge segments as well as the ostium of the side branches. Clinical events were adjudicated by the clinical event committee (Supplementary material online, *Appendix C*). Persistent discontinuation of either aspirin or thienopyridine was defined as withdrawal lasting at least 2 months. Dual antiplatelet therapy (DAPT) discontinuation was defined as persistent discontinuation of either aspirin or thienopyridine.

Statistical analysis

We present continuous variables as mean ± standard deviation or median with interquartile range (IQR), and categorical variables as numbers and percentages. We compared continuous variables with the Student's *t*-test or the Wilcoxon rank-sum test on the basis of the distributions. We compared categorical variables with the χ^2 test when appropriate; otherwise, we used the Fisher's exact test. We used the Kaplan–Meier method to estimate the cumulative incidences of clinical event rates and assessed the differences with the log-rank test. Cumulative incidence estimators of events accounting for competing risk were also calculated. We estimated the risk of the cancer group relative to the non-cancer group for the individual outcome measures by multivariable Cox proportional hazard models adjusting for 39 clinically relevant factors indicated in *Table 1* according to the previous study.[20] The risks of the cancer group relative to the non-cancer group for the individual outcome measures were expressed as hazard ratios (HR) with 95% confidence intervals (CI). Consistent with our previous reports, continuous variables were dichotomized using clinically meaningful reference values or median values. We also estimated adjusted HRs accounting for the competing risk. We also conducted the subgroup analyses stratified by age (≥75 or <75 years), sex, presentation with acute myocardial infarction (AMI), and drug-eluting stents (DES) use for the endpoints including all-cause death, cardiac death, and HF hospitalization. Statistical analyses were conducted using JMP 10.0 (SAS Institute Inc., Cary, NC, USA). All the statistical analyses were two-tailed. We regarded *P*-values <0.05 as statistically significant.

Results

Baseline characteristics

Baseline clinical characteristics were different between the patients with and without a history of cancer in several important aspects. Patients in the cancer group were older, more often had lower body mass index, severe mitral regurgitation, prior stroke, peripheral

Table 1 Baseline clinical characteristics

Variables	Cancer group ($n = 1109$)	Non-cancer group ($n = 11\,071$)	*P*-value
Age (years)	73.2 ± 8.5	67.8 ± 11.1	<0.001
Age ≥ 75 years[a]	533 (48%)	3270 (30%)	<0.001
Men[a]	825 (74%)	7976 (72%)	0.10
Body mass index (kg/m^2) <25.0[a]	825 (74%)	7507 (68%)	<0.001
Hypertension[a]	904 (82%)	9100 (82%)	0.57
Diabetes mellitus	440 (40%)	4154 (38%)	0.16
On insulin therapy[a]	96 (8.7%)	836 (7.6%)	0.19
Current smoker[a]	230 (21%)	3648 (33%)	<0.001
Heart failure[a]	222 (20%)	2183 (20%)	0.81
Multivessel coronary artery disease[a]	648 (58%)	6165 (56%)	0.08
Mitral regurgitation Grade 3/4[a]	57 (5.1%)	411 (3.7%)	0.02
Prior myocardial infarction[a]	119 (11%)	1141 (10%)	0.66
Prior stroke (symptomatic)[a]	142 (13%)	1149 (10%)	0.01
Peripheral vascular disease[a]	110 (9.9%)	806 (7.3%)	0.002
eGFR (mL/min/1.73 m^2) < 30, without haemodialysis[a]	56 (5.1%)	437 (4.0%)	0.08
Haemodialysis[a]	33 (3.0%)	377 (3.4%)	0.45
Atrial fibrillation[a]	102 (9.2%)	905 (8.2%)	0.24
Anaemia (haemoglobin < 11.0 g/dL)[a]	228 (21%)	1165 (11%)	<0.001
Thrombocytopenia (platelet count <100 × 10^9/L)[a]	36 (3.3%)	137 (1.2%)	<0.001
Chronic obstructive pulmonary disease[a]	50 (4.5%)	388 (3.5%)	0.09
Liver cirrhosis[a]	65 (5.9%)	247 (2.2%)	<0.001
Presentation			
Acute myocardial infarction[a]	317 (29%)	2992 (36%)	<0.001
Cardiogenic shock at presentation[a]	55 (5.0%)	520 (4.7%)	0.69
Angiographic characteristics			
Number of target lesion	1 (1–2)	1 (1–2)	0.80
Target of proximal left anterior descending coronary artery[a]	645 (58%)	6538 (59%)	0.56
Target of unprotected left main coronary artery[a]	71 (6.4%)	392 (3.5%)	<0.001
Target of chronic total occlusion[a]	90 (8.1%)	1232 (11%)	0.002
Target of bifurcation[a]	380 (34%)	3725 (34%)	0.68
Side-branch stenting[a]	56 (5.1%)	558 (5.0%)	0.99
Total number of stents	1 (1–2)	1 (1–2)	0.60
Total stent length >28 mm[a]	542 (49%)	5432 (49%)	0.90
Minimum stent size <3.0 mm[a]	458 (41%)	4886 (44%)	0.07
Drug-eluting stent use[a]	570 (51%)	6218 (56%)	0.002
Medications at discharge			
Thienopyridine	1090 (98%)	10964 (99%)	0.02
Ticlopidine	948 (87%)	9923 (91%)	<0.001
Clopidogrel	136 (13%)	1018 (9.3%)	<0.001
Aspirin	1092 (98%)	10936 (99%)	0.37
Cilostazol[a]	164 (15%)	2212 (20%)	<0.001
Statins[a]	487 (44%)	5816 (53%)	<0.001
Beta-blockers[a]	294 (27%)	3410 (31%)	0.003
ACE-I/ARB[a]	571 (51%)	6573 (59%)	<0.001
Nitrates[a]	397 (36%)	3962 (36%)	0.99
Calcium channel blockers[a]	481 (43%)	4441 (40%)	0.04
Nicorandil[a]	262 (24%)	2625 (24%)	0.95
Warfarin[a]	73 (6.6%)	885 (8.0%)	0.10
Proton pump inhibitors[a]	308 (28%)	2880 (26%)	0.20
H2-blockers[a]	247 (22%)	2911 (26%)	0.004

Categorical variables are expressed as number (%) unless otherwise indicated. Continuous variables are shown as mean ± SD or median (interquartile range).
ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; SD, standard deviation.
[a]Potential independent variables selected in multivariable analyses for the endpoints.

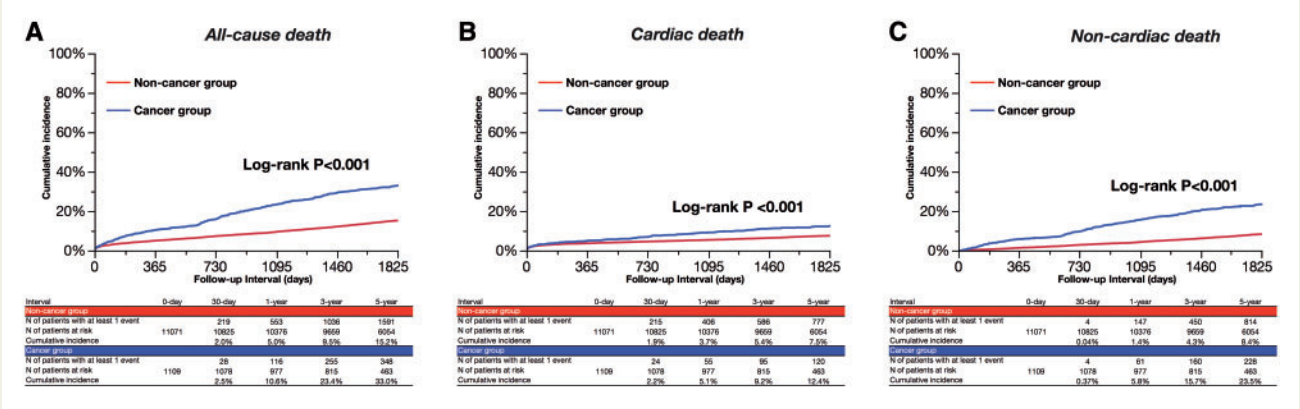


Figure 1 The Kaplan–Meier curves for (*A*) all-cause death, (*B*) cardiac death, and (*C*) non-cardiac death compared between the cancer group (blue line) and the non-cancer group (red line).

Table 2 Clinical outcomes

Outcomes	Cancer group	Non-cancer group	Unadjusted Cancer group			Adjusted Cancer group		
	No. of patients with event (Cumulative 5-year incidence) *n* = 1109	No. of patients with event (Cumulative 5-year incidence) *n* = 11 071	HR	95% CI	*P*-value	HR	95% CI	*P*-value
All-cause death	381 (33.0%)	1817 (15.2%)	2.39	(2.14–2.67)	<0.001	1.80	(1.60–2.01)	<0.001
Cardiac death	129 (12.4%)	868 (7.5%)	1.65	(1.36–1.97)	<0.001	1.27	(1.05–1.53)	0.02
Non-cardiac death	252 (23.5%)	949 (8.4%)	3.11	(2.70–3.57)	<0.001	2.33	(2.01–2.68)	<0.001
Cancer-related death	144 (14.3%)	303 (2.8%)	—	—	—	—	—	—
HF hospitalization	119 (12.1%)	821 (7.6%)	1.64	(1.34–1.98)	<0.001	1.39	(1.13–1.68)	0.002
GUSTO moderate or severe bleeding	164 (15.6%)	1176 (10.6%)	1.56	(1.32–1.83)	<0.001	1.28	(1.08–1.51)	0.005
Non-CABG surgery	456 (45.3%)	3241 (30.2%)	1.77	(1.60–1.95)	<0.001	1.60	(1.45–1.77)	<0.001
Myocardial infarction	50 (4.9%)	541 (4.9%)	1.02	(0.76–1.35)	0.87	0.94	(0.69–1.25)	0.69
Definite or probable ST	30 (2.5%)	242 (1.5%)	1.54	(1.03–2.21)	0.04	1.49	(0.99–2.16)	0.055
Stroke	66 (6.7%)	689 (6.3%)	1.07	(0.83–1.37)	0.59	0.92	(0.71–1.18)	0.54
Target-lesion revascularization	211 (21.5%)	2263 (21.4%)	1.00	(0.87–1.15)	0.96	0.98	(0.84–1.13)	0.76
Any coronary revascularization	338 (34.1%)	3760 (35.4%)	0.97	(0.87–1.09)	0.65	0.96	(0.86–1.08)	0.51

Number of patients with event was counted through the entire follow-up period, while the cumulative incidence was evaluated at 5-year. HR and 95% CI were estimated by the Cox proportional hazard models.
CABG, coronary artery bypass grafting; CI, confidence interval; HF, heart failure; HR, hazard ratio; ST, stent thrombosis; GUSTO, global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries.

vascular disease, anaemia, thrombocytopenia, and liver cirrhosis, and less often had current smoker and AMI presentation than patients in the non-cancer group. Regarding the angiographic characteristics, the cancer group more often had target of unprotected left main coronary artery, and less often had target of chronic total occlusion than the non-cancer group. The prevalence of DES use was significantly lower in the cancer group than in the non-cancer group (*Table 1*). Regarding medical treatment at discharge, the prescription rate of thienopyridines, statins, beta-blockers, angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers, and histamine type-2 (H2) blockers were lower in the cancer group than in the non-cancer group (*Table 1*). During median 5.3 (IQR 4.6–6.1) years follow-up for the surviving patients, the cumulative incidence of DAPT discontinuation after PCI were significantly higher in the cancer group than in the non-cancer group (Supplementary material online, *Figure S2*).

Long-term clinical outcomes

The cumulative 5-year incidences of and the adjusted risk for all-cause death, and non-cardiac death were markedly higher in the cancer group than in the non-cancer group (*Figure 1* and *Table 2*). The cumulative incidences of cardiac events such as cardiac death and HF hospitalization were also significantly higher in the cancer group than in the non-cancer group (*Figures 1* and *2*). Even after adjusting for confounders, the excess risk of the cancer group relative to non-cancer group for cardiac death and HF hospitalization remained

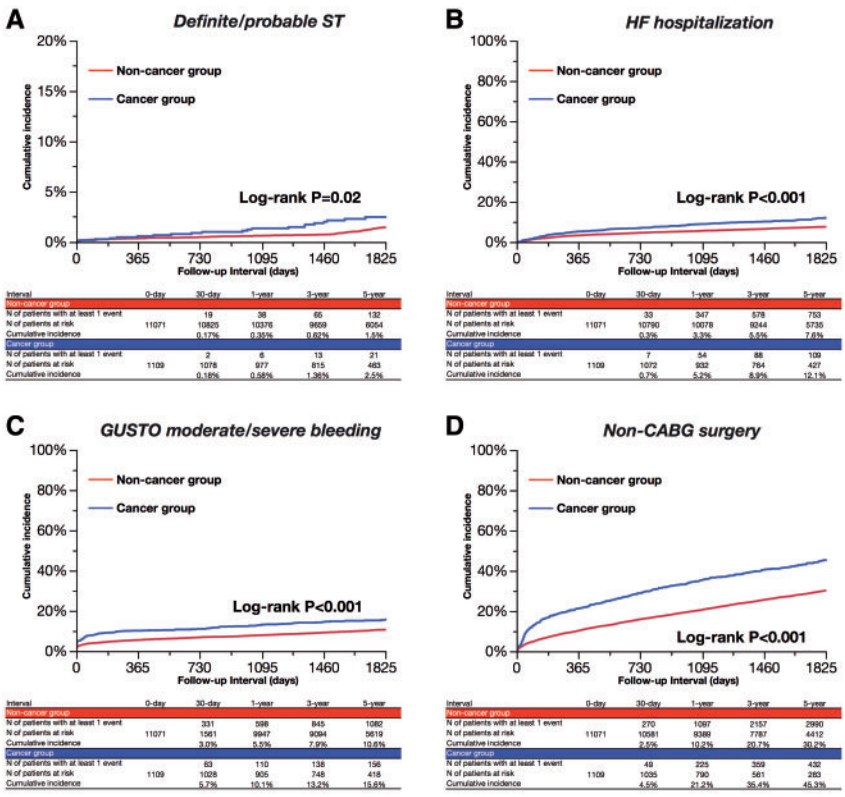


Figure 2 The Kaplan–Meier curves for (*A*) definite or probable stent thrombosis, (*B*) heart failure hospitalization, (*C*) the global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries moderate/severe bleeding, and (*D*) non-coronary artery bypass grafting surgery compared between the cancer group (blue line) and the non-cancer group (red line).

significant (*Table 2*). However, when the competing risk of non-cardiac death was taken into account, the excess risk of the cancer group relative to non-cancer group for cardiac death was no longer significant (Supplementary material online, *Table S1*). The excess risk of the cancer group relative to non-cancer group for HF hospitalization remained significant, even when the competing risk of death was taken into account (Supplementary material online, *Table S1*). Also, the cancer group had a trend toward higher adjusted risk for definite or probable ST as compared with the non-cancer group (*Figure 2* and *Table 2*). The cancer group also had significantly higher adjusted risk for major bleeding, and non-CABG surgery than the non-cancer group, while the risks for MI, stroke, TLR, and any coronary revascularization were neutral between the cancer and non-cancer groups (*Table 2*).

In the subgroup analysis for all-cause death, there were significant interactions between those subgroup factors such as age, sex, and DES use, and the risk of the cancer group relative to non-cancer group. The excess risk of the cancer group relative to non-cancer group was more pronounced in patients <75 years of age, male patients, and patients without DES use (*Figure 3A*). In the subgroup analysis for cardiac death, there was no significant interaction between the subgroup factors and the risk of the cancer group relative to non-cancer group (*Figure 3B*). In the subgroup analysis for HF hospitalization, there was significant interaction between those DES use, and the risk of the cancer group relative to non-cancer group. The excess risk of the cancer group relative to non-cancer group was more pronounced in patients without DES use (*Figure 3C*).

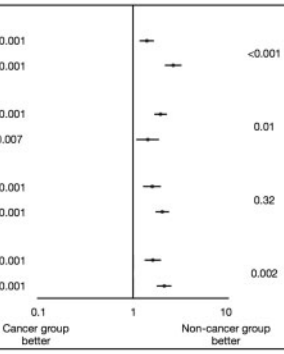
Discussion

The main findings in this study was that patients with a history of cancer at the time of PCI had increased risk for cardiac events such as cardiac death and HF hospitalization as well as non-cardiac events such as non-cardiac death, major bleeding, and non-CABG surgery.

Recent advances in management and treatment for cancer have led to better long-term mortality in cancer patients over the past decade, and a new and important welfare issue of management of CAD in cancer patients has emerged in the rapidly aging society. Actually, more than 60% of all cancer patients have lived 5 years beyond diagnosis in Japan and USA, and cardiac disease reported to be the leading cause of non-cancer related death among cancer survivors.[2,21–24] Therefore, increasing number of patients who have a history of cancer need to receive coronary revascularization in the current clinical practice. However, there are limited data about the influence of co-existing cancer on cardiovascular outcomes in CAD patients undergoing PCI. Hess *et al.*[14] recently reported that patients with a history of cancer (3.3% of the total population) had a similar risk for cardiac death after PCI in a single-centre study which included

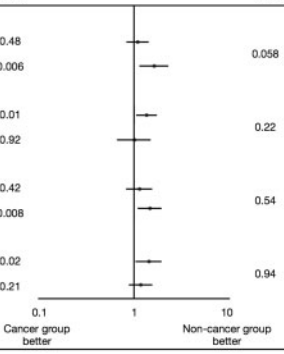
A ***All-cause death***

Subgroups	Cancer group	Non-cancer group	Unadjusted			Adjusted			Interaction
	N of patients with event (Cumulative 5-year incidence)	N of patients with event (Cumulative 5-year incidence)	Cancer group HR	95% CI	P value	Cancer group HR	95% CI	P value	P value
Age									
≥75 years	222 (41.1%)	1018 (29.7%)	1.48	(1.28-1.71)	<0.001	1.40	(1.20-1.62)	<0.001	<0.001
<75 years	159 (25.7%)	799 (9.3%)	3.03	(2.54-3.58)	<0.001	2.58	(2.16-3.08)	<0.001	
Sex									
Male	306 (35.2%)	1236 (14.4%)	2.82	(2.48-3.19)	<0.001	1.92	(1.69-2.19)	<0.001	0.01
Female	75 (26.2%)	581 (17.4%)	1.50	(1.17-1.89)	0.002	1.43	(1.11-1.82)	0.007	
AMI									
Yes	129 (39.3%)	748 (17.7%)	2.50	(2.06-3.00)	<0.001	1.56	(1.28-1.88)	<0.001	0.32
No	252 (30.4%)	1069 (13.9%)	2.43	(2.11-2.78)	<0.001	1.97	(1.71-2.27)	<0.001	
DES use									
Yes	157 (26.6%)	974 (14.4%)	1.94	(1.64-2.29)	<0.001	1.57	(1.32-1.87)	<0.001	0.002
No	224 (39.8%)	843 (16.2%)	2.81	(2.42-3.25)	<0.001	2.05	(1.75-2.38)	<0.001	



B ***Cardiac death***

Subgroups	Cancer group	Non-cancer group	Unadjusted			Adjusted			Interaction
	N of patients with event (Cumulative 5-year incidence)	N of patients with event (Cumulative 5-year incidence)	Cancer group HR	95% CI	P value	Cancer group HR	95% CI	P value	P value
Age									
≥75 years	83 (17.1%)	487 (14.9%)	1.13	(0.89-1.41)	0.33	1.09	(0.85-1.38)	0.48	0.058
<75 years	46 (8.4%)	381 (4.6%)	1.79	(1.30-2.41)	<0.001	1.60	(1.15-2.18)	0.006	
Sex									
Male	98 (12.7%)	536 (6.3%)	2.00	(1.60-2.47)	<0.001	1.33	(1.06-1.66)	0.01	0.22
Female	31 (11.6%)	332 (10.5%)	1.07	(0.73-1.52)	0.72	1.02	(0.69-1.46)	0.92	
AMI									
Yes	57 (19.2%)	435 (10.6%)	1.81	(1.36-2.36)	<0.001	1.13	(0.84-1.49)	0.42	0.54
No	72 (9.7%)	433 (5.7%)	1.69	(1.31-2.16)	<0.001	1.44	(1.10-1.85)	0.008	
DES use									
Yes	57 (10.5%)	424 (6.4%)	1.63	(1.20-2.09)	0.002	1.43	(1.06-1.88)	0.02	0.94
No	72 (14.5%)	444 (9.0%)	1.63	(1.26-2.07)	<0.001	1.18	(0.91-1.52)	0.21	



C ***HF hospitalization***

Subgroups	Cancer group	Non-cancer group	Unadjusted			Adjusted			Interaction
	N of patients with event (Cumulative 5-year incidence)	N of patients with event (Cumulative 5-year incidence)	Cancer group HR	95% CI	P value	Cancer group HR	95% CI	P value	P value
Age									
≥75 years	70 (15.9%)	422 (14.4%)	1.11	(0.86-1.42)	0.41	1.22	(0.93-1.57)	0.15	0.11
<75 years	49 (9.0%)	399 (5.0%)	1.84	(1.35-2.45)	<0.001	1.62	(1.17-2.18)	0.004	
Sex									
Male	86 (12.0%)	523 (6.6%)	1.83	(1.45-2.29)	<0.001	1.42	(1.11-1.78)	0.005	0.43
Female	33 (12.3%)	298 (10.1%)	1.30	(0.89-1.83)	0.17	1.24	(0.84-1.77)	0.28	
AMI									
Yes	37 (14.3%)	286 (7.7%)	1.93	(1.35-2.68)	<0.001	1.28	(0.88-1.80)	0.19	0.77
No	82 (11.2%)	535 (7.5%)	1.53	(1.21-1.92)	<0.001	1.43	(1.12-1.81)	0.01	
DES use									
Yes	53 (10.7%)	498 (8.0%)	1.26	(0.94-1.65)	0.12	1.10	(0.81-1.46)	0.52	0.02
No	66 (13.5%)	323 (7.0%)	2.16	(0.65-2.80)	<0.001	1.72	(1.30-2.25)	<0.001	

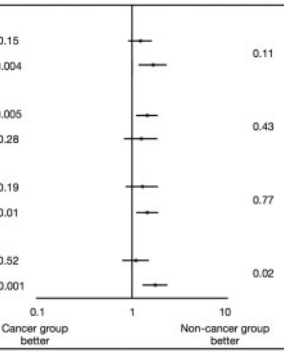


Figure 3 Subgroup analyses for (*A*) all-cause death, (*B*) cardiac death, and (*C*) heart failure hospitalization. Number of patients with event was counted through the entire follow-up period, while the cumulative incidence was evaluated at 5-year. Hazard ratio and 95% confidence interval were estimated by the Cox proportional hazard models. AMI, acute myocardial infarction; CI, confidence interval; DES, drug-eluting stents; HF, heart failure; HR, hazard ratio.

496 cancer patients undergoing PCI at Duke University Medical Center from 1996 to 2010. Velders *et al.*[15] reported that patients with cancer showed greater mortality after ST-segment elevation MI (STEMI) in their multicentre STEMI registry which included 208 cancer patients. There are several possible reasons for the different impact of cancer on cardiovascular mortality between the two previous studies, such as the indication of PCI (both stable CAD and acute coronary syndrome vs. STEMI only), the prevalence of cancer in study population (3.3% vs. 6.0%) and follow-up duration (14- vs. 1-year). Most importantly, small number of cancer patients enrolled precluded drawing any definitive conclusions in all the previous studies. In the present study including more than 1000 patients with a history of cancer, CAD patients with a history of cancer and receiving PCI were associated with significantly higher risk for cardiac death as well as HF hospitalization as compared with those without. The backgrounds for the increased cardiac death in cancer patients would be complex. Cancer patients are considered to be at high risk for HF due to radiotherapy- or chemotherapy-induced cardiac dysfunction and cancer-related anaemia.[7–10] Excess risk for HF might lead to increased risk for cardiac death. Cancer patients are also considered to be at high risk for thrombotic events due to cancer-related hypercoagulative status and interruption of antiplatelet therapy during invasive or surgical procedure.[26] Several case series reported the concern about the high risk for ST in cancer patients after PCI.[27,28] In this study, patients with a history of cancer had a trend toward higher risk for ST after PCI as compared with those without. Furthermore, active cancer patients have higher risk for venous thromboembolism, which might predispose to higher risk for cardiac death.[29] On the other hands, we could not find out any impact of cancer on MI and stroke.

Cancer patients are generally at high risk for bleeding due to bleeding from tumour, more frequent surgical procedures, and cancer-related thrombocytopenia.[25] In this study, actually, two- to three-fold higher prevalence of anaemia and thrombocytopenia was observed in patients with a history of cancer as compared with those without at the time of PCI, and approximately half of patients with a history of cancer received non-CABG surgery during 5 years after PCI. Actually, patients with a history of cancer were associated with significantly higher risk for major bleeding in this study, although the persistent DAPT discontinuation was more common in patients with cancer than those without. Bleeding would lead to increased risk for cardiac death through several postulated mechanisms such as hypovolaemia/hypotension, blood transfusion, and discontinuation of important medications, particularly antithrombotic therapy.[30,31]

Considering the rapidly coming aging society and progress in cancer treatment, appropriate management for those patients with cancer have become an increasingly important issue in clinical practice. Both of DES and optimal medical therapy (ACE-I, angiotensin receptor blockers, beta-blockers, and statins) were underutilized in patients with a history of cancer in this study, despite the increased cardiac risk. Underutilization of evidence-based therapies may partly contribute worse clinical outcomes in cancer patients. Therefore, we have to pay more attention for the clinical history of cancer, and consider appropriate patient-oriented management for cancer patients such as indication of PCI, stent selection, and optimal medical therapy.[32–34]

Study limitations

The current study has several limitations. First and most important, the details of cancer such as active cancer or history of cancer, the duration of cancer before index time, the kind of cancer, clinical stage, and treatment for cancer were not available in this registry of patients undergoing coronary revascularization, which was same as in other previous reported studies. Second, this study, same as other previous studies, had the limitations inherent to observational study design. Unmeasured confounders and selection bias might influence the study results, although we conducted the extensive statistical adjustment for potential confounders. Third, after accounting the competing risk of non-cardiac death, the excess risk of the cancer group relative to the non-cancer group was no longer significant. Fourth, we have no data about number of patients excluded from PCI therapy. Finally, because the practice pattern for CAD and cancer in Japan could be somewhat different from those outside Japan, generalizing these results to populations outside Japan should be done with caution.

Conclusions

Patients with a history of cancer at the time of PCI had increased risk for cardiac events such as cardiac death and HF hospitalization as well as non-cardiac events such as non-cardiac death, major bleeding, and non-CABG surgery.

Supplementary material

Supplementary material is available at *European Heart Journal – Quality of Care and Clinical Outcomes* online.

Acknowledgements

We thank the members of the cardiac catheterization laboratories of the participating centres and the clinical research coordinators.

Funding

Pharmaceuticals and Medical Devices Agency (PMDA) in Japan.

Conflict of interest: None declared.

Ethical approval: The human research ethics committees of the Kyoto University Graduate School of Medicine approved the protocol for the study.

References

1. World Health Organization. WHO Noncommunicable diseases. WHO. 2016 http://www.who.int/topics/noncommunicable_diseases/en/ (24 November 2016).
2. Henley BSJ, Singh SD, King J, Wilson R, Ryerson AB. Invasive cancer incidence and survival in the United States. *Oncol Times* 2011;**64**:75–76.
3. Ito Y, Miyashiro I, Ito H, Hosono S, Chihara D, Nakata-Yamada K, Nakayama M, Matsuzaka M, Hattori M, Sugiyama H, Oze I, Tanaka R, Nomura E, Nishino Y, Matsuda T, Ioka A, Tsukuma H, Nakayama T; J-CANSIS Research Group. Long-term survival and conditional survival of cancer patients in Japan using population-based cancer registry data. *Cancer Sci* 2014;**105**:1480–1486.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics. *CA Cancer J Clin* 2016;**66**:7–30.
5. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe: epidemiological update. *Eur Heart J* 2013;**34**:3028–3034.
6. Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, Allen C, Hansen G, Woodbrook R, Wolfe C, Hamadeh RR, Moore A, Werdecker A, Gessner BD, Te Ao B, McMahon B, Karimkhani C, Yu C, Cooke GS, Schwebel DC, Carpenter DO, Pereira DM, Nash D, Kazi DS, De Leo D,

Plass D, Ukwaja KN, Thurston GD, Yun Jin K, Simard EP, Mills E, Park E-K, Catalá-López F, deVeber G, Gotay C, Khan G, Hosgood HD, Santos IS, Leasher JL, Singh J, Leigh J, Jonas JB, Jonas J, Sanabria J, Beardsley J, Jacobsen KH, Takahashi K, Franklin RC, Ronfani L, Montico M, Naldi L, Tonelli M, Geleijnse J, Petzold M, Shrime MG, Younis M, Yonemoto N, Breitborde N, Yip P, Pourmalek F, Lotufo PA, Esteghamati A, Hankey GJ, Ali R, Lunevicius R, Malekzadeh R, Dellavalle R, Weintraub R, Lucas R, Hay R, Rojas-Rueda D, Westerman R, Sepanlou SG, Nolte S, Patten S, Weichenthal S, Abera SF, Fereshtehnejad S-M, Shiue I, Driscoll T, Vasankari T, Alsharif U, Rahimi-Movaghar V, Vlassov VV, Marcenes WS, Mekonnen W, Melaku YA, Yano Y, Artaman A, Campos I, MacLachlan J, Mueller U, Kim D, Trillini M, Eshrati B, Williams HC, Shibuya K, Dandona R, Murthy K, Cowie B, Amare AT, Antonio CA, Castañeda-Orjuela C, van Gool CH, Violante F, Oh I-H, Deribe K, Soreide K, Knibbs L, Kereselidze M, Green M, Cardenas R, Roy N, Tillmann T, Tillman T, Li Y, Krueger H, Monasta L, Dey S, Sheikhbahaei S, Hafezi-Nejad N, Kumar GA, Sreeramareddy CT, Dandona L, Wang H, Vollset SE, Mokdad A, Salomon JA, Lozano R, Vos T, Forouzanfar M, Lopez A, Murray C, Naghavi M. The global burden of cancer 2013. *JAMA Oncol* 2015;**1**:505–527.

7. Hooning MJ, Botma A, Aleman BMP, Baaijens MHA, Bartelink H, Klijn JGM, Taylor CW, van Leeuwen FE. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst* 2007;**99**:365–375.
8. Nuver J, Smit AJ, Sleijfer DT, van Gessel AI, van Roon AM, van der Meer J, van den Berg MP, Burgerhof JGM, Hoekstra HJ, Sluiter WJ, Gietema JA. Microalbuminuria, decreased fibrinolysis, and inflammation as early signs of atherosclerosis in long-term survivors of disseminated testicular cancer. *Eur J Cancer* 2004;**40**:701–706.
9. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, Correa C, Cutter D, Gagliardi G, Gigante B, Jensen M-B, Nisbet A, Peto R, Rahimi K, Taylor C, Hall P. Risk of ischemic heart disease in women after radiotherapy for breast cancer supplementary information. *N Engl J Med* 2013;**368**:987–998.
10. Yeh ETH, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol* 2009;**53**:2231–2247.
11. Fosså SD, Vassilopoulou-Sellin R, Dahl AA. Long term physical sequelae after adult-onset cancer. *J Cancer Surviv* 2008;**2**:3–11.
12. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, Friedman DL, Marina N, Hobbie W, Kadan-Lottick NS, Schwartz CL, Leisenring W, Robison LL. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006;**355**:1572–1582.
13. Henson KE, Reulen RC, Winter DL, Bright CJ, Fidler MM, Frobisher C, Guha J, Wong KF, Kelly J, Edgar AB, McCabe MG, Whelan J, Cutter DJ, Darby SC, Hawkins MM. Cardiac mortality among 200,000 five-year survivors of cancer diagnosed aged 15-39 years: the Teenage and Young Adult Cancer Survivor Study. *Circulation* 2016;**134**:1519–1531.
14. Hess CN, Roe MT, Clare RM, Chiswell K, Kelly J, Tcheng JE, Hagstrom E, James SK, Khouri MG, Hirsch BR, Kong DF, Abernethy AP, Krucoff MW. Relationship between cancer and cardiovascular outcomes following percutaneous coronary intervention. *J Am Heart Assoc* 2015;**4**:e001779.
15. Velders MA, Boden H, Hofma SH, Osanto S, van der Hoeven BL, Heestermans AACM, Cannegieter SC, Jukema JW, Umans VAWM, Schalij MJ, van Boven AJ. Outcome after ST elevation myocardial infarction in patients with cancer treated with primary percutaneous coronary intervention. *Am J Cardiol* 2013;**112**:1867–1872.
16. Kimura T, Morimoto T, Furukawa Y, Nakagawa Y, Kadota K, Iwabuchi M, Shizuta S, Shiomi H, Tada T, Tazaki J, Kato Y, Hayano M, Abe M, Tamura T, Shirotani M, Miki S, Matsuda M, Takahashi M, Ishii K, Tanaka M, Aoyama T, Doi O, Hattori R, Tatami R, Suwa S, Takizawa A, Takatsu Y, Takahashi M, Kato H, Takeda T, Lee J-D, Nohara R, Ogawa H, Tei C, Horie M, Kambara H, Fujiwara H, Mitsudo K, Nobuyoshi M, Kita T. Long-term safety and efficacy of sirolimus-eluting stents versus bare-metal stents in real world clinical practice in Japan. *Cardiovasc Interv and Ther* 2011;**26**:234–245.
17. GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;**329**:673–682.
18. Marroquin OC, Selzer F, Mulukutla SR, Williams DO, Vlachos HA, Wilensky RL, Tanguay J-F, Holper EM, Abbott JD, Lee JS, Smith C, Anderson WD, Kelsey SF, Kip KE. A comparison of bare-metal and drug-eluting stents for off-label indications. *N Engl J Med* 2008;**358**:342–352.
19. Serruys PW, Ong ATL, van Herwerden LA, Sousa JE, Jatene A, Bonnier JJRM, Schönberger JPMA, Buller N, Bonser R, Disco C, Backx B, Hugenholtz PG, Firth BG, Unger F. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *J Am Coll Cardiol* 2005;**46**:575–581.
20. Natsuaki M, Morimoto T, Furukawa Y, Nakagawa Y, Kadota K, Yamaji K, Ando K, Shizuta S, Shiomi H, Tada T, Tazaki J, Kato Y, Hayano M, Abe M, Tamura T, Shirotani M, Miki S, Matsuda M, Takahashi M, Ishii K, Tanaka M, Aoyama T, Doi O, Hattori R, Kato M, Suwa S, Takizawa A, Takatsu Y, Shinoda E, Eizawa H, Takeda T, Lee J-D, Inoko M, Ogawa H, Hamasaki S, Horie M, Nohara R, Kambara H, Fujiwara H, Mitsudo K, Nobuyoshi M, Kita T, Kimura T. Late adverse events after implantation of sirolimus-eluting stent and bare-metal stent: long-term (5-7 years) follow-up of the Coronary Revascularization Demonstrating Outcome study-Kyoto registry Cohort-2. *Circ Cardiovasc Interv* 2014;**7**:168–179.
21. Cancer Statistics in Japan. http://ganjoho.jp/en/professional/statistics/table_download.html (24 November 2016).
22. Fidler MM, Reulen RC, Winter DL, Kelly J, Jenkinson HC, Skinner R, Frobisher C, Hawkins MM. Long term cause specific mortality among 34 489 five year survivors of childhood cancer in Great Britain: population based cohort study. *BMJ* 2016;**354**:i4351.
23. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;**365**:1687–1717.
24. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, Godwin J, Gray R, Hicks C, James S, MacKinnon E, McGale P, McHugh T, Peto R, Taylor C, Wang Y. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. *Lancet* 2005;**366**:2087–2106.
25. Koskinas KC, Raber L, Zanchin T, Wenaweser P, Stortecky S, Moschovitis A, Khattab AA, Pilgrim T, Blochlinger S, Moro C, Juni P, Meier B, Heg D, Windecker S. Clinical impact of gastrointestinal bleeding in patients undergoing percutaneous coronary interventions. *Circ Cardiovasc Interv* 2015;**8**:e002053–e002053.
26. Caine GJ, Stonelake PS, Lip GYH, Kehoe ST. The hypercoagulable state of malignancy: pathogenesis and current debate. *Neoplasia* 2002;**4**:465–473.
27. Gross CM, Posch MG, Geier C, Olthoff H, Krämer J, Dechend R, Dietz R, Özcelik C. Subacute coronary stent thrombosis in cancer patients. *J Am Coll Cardiol* 2008;**51**:1232–1233.
28. van Werkum JW, Heestermans AA, Zomer AC, Kelder JC, Suttorp M-J, Rensing BJ, Koolen JJ, Brueren BRG, Dambrink J-HE, Hautvast RW, Verheugt FW, ten Berg JM. Predictors of coronary stent thrombosis. *J Am Coll Cardiol* 2009;**53**:1399–1409.
29. Piazza G. Venous thromboembolism and cancer. *Circulation* 2013;**128**:2614–2618.
30. Généreux P, Giustino G, Witzenbichler B, Weisz G, Stuckey TD, Rinaldi MJ, Neumann F-J, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Yadav M, Francese DP, Palmerini T, Kirtane AJ, Litherland C, Mehran R, Stone GW. Incidence, predictors, and impact of postdischarge bleeding after percutaneous coronary intervention. *J Am Coll Cardiol* 2015;**66**:1036–1045.
31. Ndrepepa G, Berger PB, Mehilli J, Seyfarth M, Neumann F-J, Schömig A, Kastrati A. Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions: appropriateness of including bleeding as a component of a quadruple end point. *J Am Coll Cardiol* 2008;**51**:690.
32. Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrié D, Naber C, Lipiecki J, Richardt G, Iñiguez A, Brunel P, Valdes-Chavarri M, Garot P, Talwar S, Berland J, Abdellaoui M, Eberli F, Oldroyd K, Zambahari R, Gregson J, Greene S, Stoll H-P, Morice M-C. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N Engl J Med* 2015;**373**:2038–2047.
33. Garot P, Morice M-C, Tresukosol D, Pocock SJ, Meredith IT, Abizaid A, Carrié D, Naber C, Iñiguez A, Talwar S, Menown IBA, Christiansen EH, Gregson J, Copt S, Hovasse T, Lurz P, Maillard L, Krackhardt F, Ong P, Byrne J, Redwood S, Windhövel U, Greene S, Stoll H-P, Urban P. Two-year outcomes of high bleeding risk patients after polymer-free drug-coated stents. *J Am Coll Cardiol* 2017;**69**:162–171.
34. Palmerini T, Della Riva D, Benedetto U, Bacchi Reggiani L, Feres F, Abizaid A, Gilard M, Morice MC, Valgimigli M, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Colombo A, Chieffo A, Sangiorgi D, Biondi-Zoccai G, Généreux P, Angelini GD, Pufulete M, White J, Bhatt DL, Stone GW. Three, six, or twelve months of dual antiplatelet therapy after DES implantation in patients with or without acute coronary syndromes: an individual patient data pairwise and network meta-analysis of six randomized trials and 11 473 patients. *Eur Heart J* 2017;doi: 10.1093/eurheartj/ehw627.