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Prognosis of acute coronary syndrome stratified by cancer type and status - a nationwide cohort study

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Background To investigated the prognosis of the most prevalent cancers (breast-, gastrointestinal-, and lung cancer), according to cancer status (i.e., active-, non-active-, history of-, and no cancer), following first-time of acute coronary syndrome (ACS).

Methods Danish nationwide registers were used to identify patients with first-time ACS from 2000–2018. Patients were stratified according to cancer type and status. Hazard ratios (HR) estimated by adjusted Cox regression models for 1year all-cause mortality reported. Further absolute risks of 1year cardiovascular versus non-cardiovascular death and 30-day cumulative incidence of coronary angiograms (CAG) was estimated, using the Aalen-Johansen non-parametric method, with competing risk of death.

Results We identified 150,478 (95.7%) with no cancer, 2,370 (1.5%) with history of cancer, 2,712 (1.7%) with non-active cancer and 1,704 (1.1%) with active cancer. Cancer patients were older with more comorbidities than patients with no cancer. When compared with no cancer, we found HRs (95% confidence intervals) of 1.71 (1.44–2.02), 2.47 (2.23–2.73) and 4.22 (3.87–4.60) correspondingly for active breast-, gastrointestinal-, and lung cancer. Increased HRs were also found for non-active cancers, but not for history of cancer. Cardiovascular disease was the leading cause of death in all patients. Among patients with active breast-, gastrointestinal-, and lung cancer 43%, 43%, and 31% underwent CAG, correspondingly, compared with 77% of patients without cancer.

Conclusions Active- and non-active cancers were associated with an increased 1-year all-cause mortality compared with patients with history of cancer and no cancer. Cardiovascular disease was the leading cause of death; notably CAG was less frequently performed in cancer patients. (Am Heart J 2023;256:13–24.)

Cardiovascular disease and cancer are the leading causes of death in developed countries, accounting for two-thirds of disease-related mortality.[1] Survival rates for both major disease groups have risen markedly due to advanced treatments; hence the 2 conditions frequently co-exist in an increasingly aging population.[2] The predicaments that arise with a growing and aging population, calls upon a multidisciplinary approach, often complicated by different perceptions of the prognosis in these patients. The rapidly evolving field of cardio-oncology has been imperative in the clinical setting; however, the scientific community has not been able to keep pace.[3,4] Thus, the prognosis of cardiovascular disease in cancer patients is widely unknown and the lack of guidelines in the field of cardio-oncology makes treatment of these patients physician-dependent, rather than guideline-based.

Cancer has traditionally been viewed as *1* disease entity by cardiologists and only few studies have acknowledged the need to assess cancer types independently.[5–7] Nonetheless, these studies have shown a higher in-hospital mortality, a higher rate of cardiovascular complications, readmissions and bleeding in patients with active cancer.[5,7] Unfortunately, these studies are restricted by database limitations with only in-hospital data and no

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information on cause of death. Moreover, randomized controlled trials typically exclude patients with active cancer, altogether culminating in a poorly documented clinical practice.

We sought to investigate the 1-year prognosis following first-time acute coronary syndrome (ACS), stratified by major cancer types (breast cancer, gastrointestinal cancer, and lung cancer), and cancer status (i.e., active, non-active, and history of cancer).

Methods

Data sources

The Danish population has a unique identification number which enables cross-linkage of information throughout nationwide databases. *The Danish Civil Registration system* provides data on date of birth, sex, and vital status.[8] *The Danish National Patient Registry* holds information on all hospital contacts, including diagnoses and procedural codes.[9] *The National Prescription Register* holds information on date, amount, and dose of all redeemed prescriptions coded per the Anatomical Therapeutic Chemical (ATC) classification system.[10] *The Danish Register of Causes of Death* provides information on date of death and assumed cause of death.[11] Please see supplemental material for ICD-10 and ATC codes used throughout this study (Supplementary Table 1).

Study population

The study is a nationwide cohort study from 2000 through 2018, including individuals aged 18–90 years with first-time ACS (Figure 1). Patients with a cancer diagnosis, other than breast-, gastrointestinal-, or lung cancer, were excluded from the cohort. Patients were followed from the date of ACS until emigration, death, or study end (December 31, 2018), whichever came first.

Cancer type and status

Previous diagnoses of breast-, gastrointestinal-, or lung cancer were identified for all patients with ACS. Cancer status was categorized for each type of cancer, as either "history of cancer", "non-active cancer" or "active cancer". Patients with no medical history of cancer were categorized as "no cancer" (see supplementary Figure 1 for definition of cancer status).

History of cancer was defined as a cancer diagnosis given more than 5 years prior to the admission for ACS *and* no registration of the cancer diagnosis within 5 years of the ACS. Non-active cancer was defined as a cancer diagnosis within 5 years of the ACS, followed by a potentially curative procedure within 6 months of the cancer diagnosis. Active cancer was defined as a cancer diagnosis, within 5 years of the ACS, not followed by a potentially curative procedure within 6 months of the cancer diagnosis (see supplementary Table 1 for the relevant procedure codes). In a limited number of cases (n = 78), patients were diagnosed with 2 or 3 types of cancer. In such instances, the first given cancer diagnosis was registered.

Clinical outcomes

The primary outcomes were 1-year all-cause mortality and 1-year cardiovascular mortality (any cardiovascular diagnosis as primary or underlying cause of death) versus non-cardiovascular mortality. We expected all-cause mortality to be influenced by age, hence we reported an age-stratified 1-year all-cause mortality in addition to our main outcome.

The secondary outcomes were use of guideline-recommended treatments; thus, coronary angiogram (CAG) performed within thirty days and secondary prophylactic pharmacotherapy prescribed within 3 months following ACS.

Characteristics of the cohort

Comorbidities were defined binarily and were considered present if a diagnosis was registered (hospitalization or outpatient visits) up to 5 years prior to baseline. Pharmacotherapy was defined as redeemed prescriptions 6 months prior to the date of ACS for the following medicaments: Oral anticoagulants, ADP-receptor blockers, betablockers, statins, acetylsalicylic acid and renin-angiotensin-system inhibitors. Hypertension and diabetes mellitus were defined from pharmacotherapy, as a combination treatment with at least 2 anti-hypertensive drugs and treatment with a glucose-lowering drug, respectively, as previously done (Supplementary Table 1).[12,13]

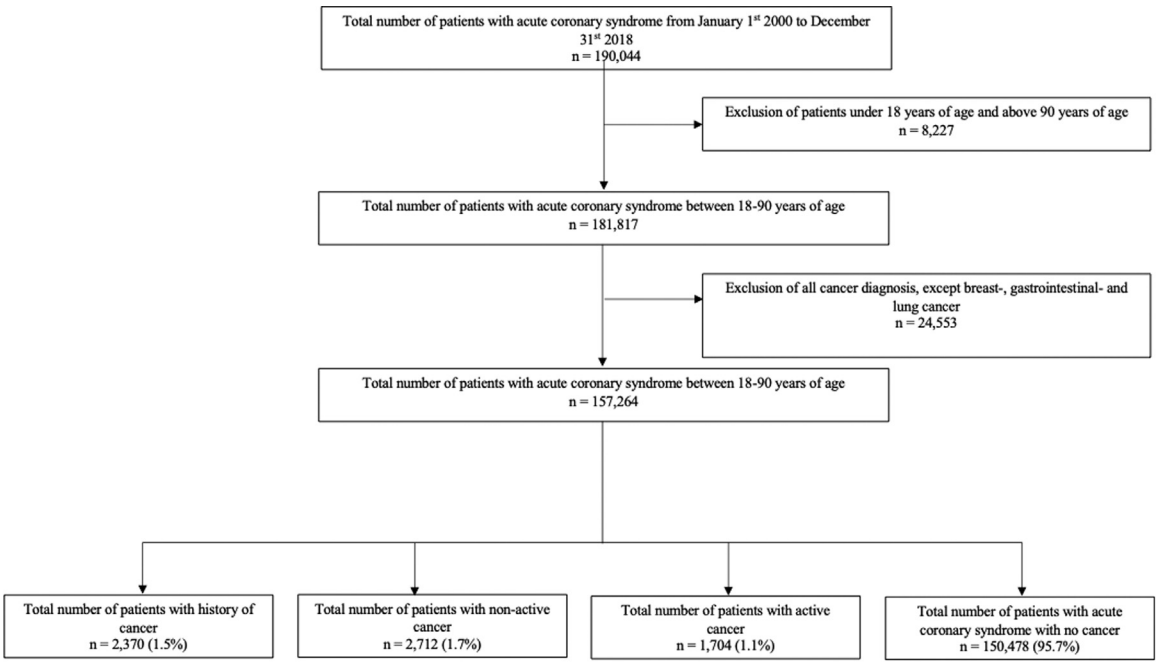
Statistical methods

Baseline characteristics are presented in frequencies and percentages for dichotomous variables and as median with interquartile range for continuous variables. Baseline characteristics were stratified according to cancer type and status.

The Aalen-Johansen non-parametric method was used for generating cumulative incidences for the primary and secondary outcomes. Competing risk of death was accounted for, when investigating cardiovascular mortality, CAG and secondary prophylactic pharmacotherapy.[14,15] The cumulative incidences were stratified according to cancer type and status. Non-cardiovascular mortality was derived from the 1-year all-cause mortality and cardiovascular mortality.

Multivariable Cox proportional hazard analysis was performed to compare hazard ratios of 1-year all-cause mortality according to cancer type and status.[16] Patients with no cancer were defined as the reference group. The models were adjusted for chronic obstructive pulmonary disease, gender, age-groups, calendar year of ACS, hypertension, heart failure, ischemic stroke, chronic kidney

Figure 1



Flowchart of the study cohort. Patients with ACS were included from 2000 through 2018 and ultimately divided into 4 groups; patients with history of cancer, patients with non-active cancer, patients with active cancer and patients with no cancer. ACS, acute coronary syndrome.

disease, diabetes and atherosclerosis. A 95% confidence interval (CI) was reported for all estimates.

Data management, statistics and illustrations were performed using R (version 3.5.0 for Windows, R Foundation for Statistical Computing).[17]

Ethics

This is a cohort study based on anonymous data from the Danish nationwide administrative registers, thus approval from the local ethical committee was not necessary. The study was approved by the data protection organization of Capital Region of Denmark (approval number P-706-130).

Supplementary analyses

We performed several supplementary analyses. In order to provide data on clinical important cardiovascular outcomes we choose to investigate the risk of re-infarction within 1 year of ACS. Reinfarction was defined as an infarction beyond 30-days from the initial event.[18] We used the Aalen-Johansen non-parametric method to estimate cumulative incidences of re-infarction, taking competing risk of death into account.

To address potential temporal trends of cancer status, we performed a time trend analyses. The time period was divided into 5 time periods: 2000–2003, 2004–2007, 2008–2011, 2012–2015, and 2016–2018. For each time period, we specified the number of patients with history of cancer, non-active cancer and active cancer.

We also performed a time-trend analysis to identify temporal trends in 1-year all-cause mortality stratified on cancer type and status. The inclusion period was divided into 5 time periods: 2000–2004, 2005–2009, 2010–2014, and 2015–2018. The 1-year all-cause mortality was investigated using the Aalen-Johansen non-parametric method.[15]

A validation study of the definition of active and non-active cancer in the Danish National Patient Registry is conducted. The validation study is performed by random extraction of 200 patients for each cancer type. Positive predictive values (PPV) are computed using medical records as gold standard and some of these results are presented in this paper.

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Results

Cohort characteristics

We included a total of 157,264 patients with ACS, and 6,786 (4.3%) of these were identified with a cancer di-

Table 1. Baseline characteristics.

	No cancer	Breast cancer			Gastrointestinal cancer			Lung cancer		
		History of cancer	Non-active cancer	Active cancer	History of cancer	Non-active cancer	Active cancer	History of cancer	Non-active cancer	Active cancer
Total no. of patients	150,478	1098	951	305	1054	1463	672	218	298	727
Gender, male, n, (%)	94,679 (62.9)	13 (1.2)	8 (0.8)	<5 (-)	665 (63.1)	950 (64.9)	436 (64.9)	129 (59.2)	179 (60.1)	431 (59.3)
Age, median, Interquartile range (IQR)	68.0(57.5-77.7)	75.8(68.6-81.8)	73.8(66.0-81.0)	78.5(70.8-83.9)	78.8(72.7-83.3)	75.8(72.7-83.3)	76.2(68.2-81.5)	73.8(68.9-79.9)	72.2(66.8-79.9)	73.1(66.8-78.7)
Comorbidities, n, (%)										
Hypertension	43,871 (29.2)	433 (39.4)	385 (40.5)	114 (37.4)	432 (41.0)	525 (35.9)	258 (38.4)	89 (40.8)	101 (33.9)	264 (36.3)
Diabetes mellitus	19,013 (12.6)	149 (13.6)	150 (15.8)	46 (15.1)	173 (16.4)	222 (15.2)	132 (19.6)	30 (13.8)	40 (13.4)	94 (12.9)
Heart failure	9,588 (6.4)	60 (5.5)	83 (8.7)	29 (9.5)	102 (9.7)	131 (9.0)	85 (12.6)	21 (9.6)	29 (9.7)	67 (9.2)
Atrial fibrillation / atrial flutter	9,939 (6.6)	102 (9.3)	102 (10.7)	43 (14.1)	125 (11.9)	178 (12.2)	83 (12.4)	22 (10.1)	40 (13.4)	89 (12.2)
Ischemic stroke	9,034 (6.0)	66 (6.0)	62 (6.5)	33 (10.8)	78 (7.4)	115 (7.9)	72 (10.7)	22 (10.1)	20 (6.7)	55 (7.6)
Chronic obstructive pulmonary disease	10,093 (6.7)	120 (10.9)	86 (9.0)	46 (15.1)	106 (10.1)	153 (10.5)	77 (11.5)	49 (22.5)	93 (31.2)	192 (26.4)
Atherosclerosis	5,888 (3.9)	31 (2.8)	46 (4.8)	22 (7.2)	50 (4.7)	86 (5.9)	49 (7.3)	14 (6.4)	18 (6.0)	46 (6.3)
Chronic kidney disease	4,468 (3.0)	37 (3.4)	44 (4.6)	10 (3.9)	55 (5.2)	77 (5.3)	36 (5.4)	15 (6.9)	14 (4.7)	24 (3.3)
Concomitant medication, n, (%)										
Oral anticoagulants	7,659 (5.1)	81 (7.4)	70 (7.4)	20 (6.6)	86 (8.2)	124 (8.5)	62 (9.2)	25 (11.5)	23 (7.7)	70 (9.6)
Adenosine diphosphate (ADP) receptor blockers	4,971 (3.3)	50 (4.6)	32 (3.4)	10 (3.3)	59 (5.6)	50 (3.4)	32 (4.8)	13 (6.0)	24 (8.1)	19 (2.6)
Betablockers	31,525 (20.9)	294 (26.8)	247 (26.0)	68 (22.3)	289 (27.4)	348 (23.8)	183 (27.2)	54 (24.8)	84 (28.2)	182 (25.0)
Statins	33,961 (22.6)	319 (29.1)	221 (23.2)	63 (20.7)	306 (29.0)	350 (23.9)	165 (24.6)	62 (28.4)	94 (31.5)	176 (24.2)
Acetylsalicylic acid	40,816 (27.1)	327 (29.8)	318 (33.4)	115 (37.7)	368 (34.9)	475 (34.9)	228 (33.9)	82 (37.6)	104 (34.9)	245 (33.7)
Renin-angiotensin system inhibitors	43,954 (29.2)	423 (37.6)	344 (36.2)	89 (29.2)	406 (38.5)	492 (33.6)	233 (34.7)	70 (32.1)	93 (31.2)	228 (31.4)

agnosis. A total of 2,370 (1.5%) patients had a history of cancer, 2,712 (1.7%) had non-active cancer, and 1,704 (1.1%) had active breast-, gastrointestinal-, or lung cancer (Figure 1).

Baseline characteristics are presented in Table 1. Regardless of cancer status, cancer patients were older and suffered more frequently from comorbidities than patients with no cancer. Patients with cancer were also more likely to receive pharmacotherapy at baseline.

One-year absolute risk of all-cause mortality

One-year all-cause mortality, according to cancer type and status, is shown in Figure 2. Overall, incremental incidences (no cancer < history of cancer < non-active cancer < active cancer) were present for all cancer types. The 1-year all-cause mortality for patients with active cancer depended on the type of cancer; lung cancer was associated with the highest 1-year all-cause mortality, whilst breast cancer was associated with lowest risk.

These findings were further investigated in an adjusted Cox proportional hazards model shown in Figure 3. Hazard ratios for history of cancer showed no excess risk of 1-year all-cause mortality compared with no cancer for all cancer types. Hazard ratios of patients with non-active- and active cancer supported the unadjusted analysis of a greater risk of 1-year all-cause mortality, when compared with patients with no cancer.

Age-stratified 1-year all-cause mortality

Age-stratified 1-year all-cause mortality is shown in Figure 4. The 1-year all-cause mortality did not differ for active cancer patients aged 18–69 and 70–79 years. Only a small increase in 1-year all-cause mortality was found for patients >80 years of age with active gastrointestinal cancer and lung cancer (gastrointestinal cancer: 64.4% [95% CI: 58.5 to 70.2] and lung cancer: 84.1% [95% CI: 78.5 to 89.7]), when compared with the youngest group (gastrointestinal cancer: 50.1% [95% CI: 42.6 to 57.5] and lung cancer: 65.1% [95% CI: 59.1 to 71.2]).

Cardiovascular mortality versus non-cardiovascular mortality

One-year mortality stratified according to cardiovascular- and non-cardiovascular mortality is shown in Figure 5. Cardiovascular disease was found to be either the primary or underlying cause of death in the majority of patients following ACS, regardless of cancer type and status. However, 1year non-cardiovascular mortality increased incrementally from history of cancer (breast 4.1%, gastrointestinal 4.2%, lung 6.1%), to non-active cancer (breast 7.0%, gastrointestinal 9.1%, lung 10.2%) to active cancer (breast 12.5, gastrointestinal 23.8%, lung 32.2%) for all cancer types compared to 2.2% of patients with no cancer.

Coronary angiogram and secondary prophylactic pharmacotherapy following ACS

The cumulative incidence of undergoing CAG within 30 days as well as the cumulative incidence of claiming secondary prophylactic pharmacotherapy within 90 days are both shown in Table 2.

Patients with history of breast cancer and history of lung cancer did not have a lower number of CAGs performed when compared with patients with no cancer. On the contrary, patients with history of gastrointestinal cancer had fewer CAGs performed when compared with patients with no cancer.

Patients with non-active cancer had fewer CAGs performed compared with patients with history of cancer and no cancer, regardless of cancer type. Patients with active cancer were least likely to undergo a CAG, regardless of cancer type.

Overall, the proportion of redeemed prescriptions of acetylsalicylic acid-, betablocker-, statin- and renin-angiotensin-system inhibitor prescriptions, was higher for patients with no cancer, when compared with patients with cancer, regardless of type and status. Amid patients with active cancer, we found no difference in the number of claimed prescriptions across cancer types.

Supplementary analyses

In our analyses of re-infarction, we found similar risks of re-infarction, within 1-year of the index event, irrespective of cancer type and status, as shown in supplementary Figure 2.

We found the total number of patients being admitted with ACS and a cancer diagnosis to increase from 2000–2018 as shown in supplementary Figure 3. However, we found a small decline in the proportion of patients admitted with active cancer over time, thus a higher proportion of patients with history of cancer were admitted.

Time trend analyses of the 1year all-cause mortality showed a trend toward decline in mortality over time for all cancer types (supplementary figure 4).

Results from the validation study showed for 200 patients in each cancer category, a PPV for active cancer of 87%, 82% and 91% for correspondingly breast-, gastrointestinal-, and lung cancer and PPV for non-active caner are 95%, 73% and 91% for correspondingly breast-, gastrointestinal-, and lung cancer."

Discussion

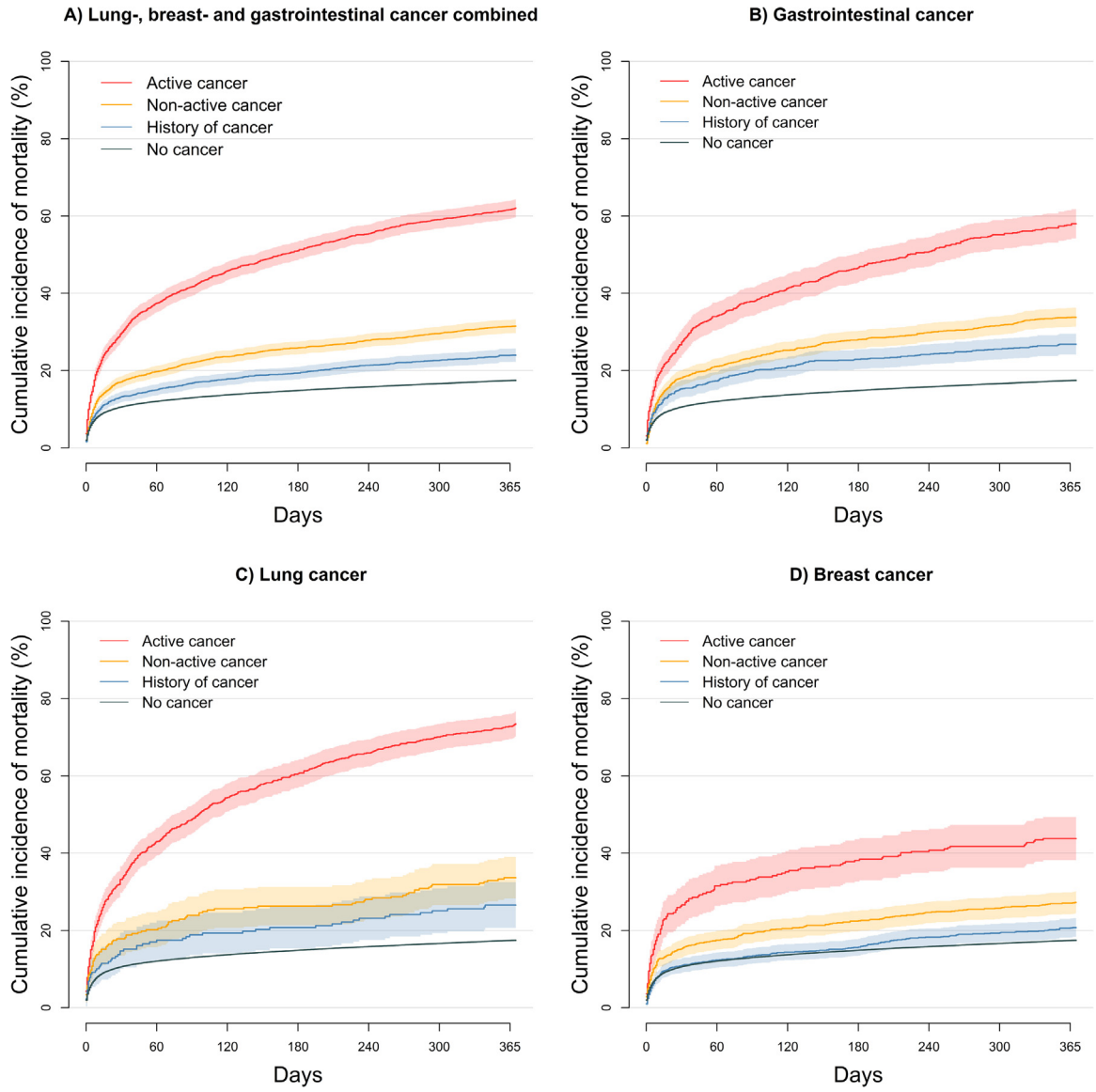
We present the first nationwide large-scale study of 1year follow-up on cancer patients with ACS, stratified on cancer type and status. When investigating approximately 160,000 Danish patients with first-time ACS, we found that the presence of active- or non-active cancer was associated with an increased 1year all-cause mortality in patients with ACS, when compared with patients with history of cancer and no cancer. Perhaps sur-

Table 2. Cumulative incidence of CAG and secondary prophylactic pharmacotherapy within respectively 30 days and 90 days.

	No cancer	Breast cancer			Gastrointestinal cancer			Lung cancer		
		History of cancer	Non-active cancer	Active cancer	History of cancer	Non-active cancer	Active cancer	History of cancer	Non-active cancer	Active cancer
	n = 150,478	n = 1,098	n = 951	n = 305	n = 1,054	n = 1,463	n = 672	n = 218	n = 355	n = 670
CAG, %, (95% CI)	77.1 (76.7 to 77.4)	77.0 (72.9 to 81.1)	61.3 (56.9 to 65.7)	43.3 (35.7 to 50.9)	70.5 (66.4 to 74.6)	57.2 (53.7 to 60.7)	42.6 (37.0 to 48.3)	77.7 (68.2 to 87.1)	58.5 (51.3 to 65.6)	31.2 (27.1 to 35.3)
Acetylsalicylic acid, (%), (95% CI)	69.3 (69.0 to 69.5)	64.1 (61.3 to 67.0)	61.4 (58.3 to 64.5)	50.5 (44.9 to 56.1)	63.9 (61.0 to 66.8)	57.5 (54.9 to 60.0)	46.1 (42.3 to 49.8)	61.4 (54.9 to 67.9)	56.3 (50.7 to 62.0)	45.0 (41.3 to 48.6)
Adenosine-diphosphate receptor antagonists, (%), (95% CI)	56.7 (56.4 to 56.9)	55.9 (52.9 to 58.8)	46.3 (43.2 to 49.5)	31.0 (25.8 to 36.2)	56.0 (53.0 to 59.0)	44.4 (41.9 to 47.0)	34.2 (30.7 to 37.8)	52.5 (45.8 to 59.1)	49.8 (44.1 to 55.5)	34.7 (31.2 to 38.2)
Betablockers, (%), (95% CI)	66.4 (66.1 to 66.6)	61.9 (59.1 to 64.8)	58.2 (55.1 to 61.4)	49.5 (43.9 to 55.1)	60.3 (57.4 to 63.3)	55.5 (53.0 to 58.1)	45.1 (41.3 to 48.9)	59.4 (52.9 to 65.9)	53.9 (48.2 to 59.6)	44.2 (40.6 to 47.9)
Statins, (%), (95% CI)	65.5 (65.3 to 65.7)	61.6 (58.8 to 64.5)	51.9 (48.7 to 55.1)	38.6 (33.1 to 44.1)	60.3 (57.3 to 63.2)	49.3 (46.7 to 51.9)	32.4 (28.8 to 35.9)	56.6 (50.1 to 63.2)	53.6 (47.9 to 59.2)	31.6 (28.3 to 35.0)
Renin-angiotensin system inhibitors, (%), (95% CI)	41.5 (41.3 to 41.8)	43.5 (40.6 to 46.5)	40.0 (36.9 to 43.1)	35.0 (29.6 to 40.4)	43.6 (40.6 to 46.6)	37.7 (35.2 to 40.2)	26.5 (23.1 to 29.8)	43.8 (37.2 to 50.4)	32.2 (26.9 to 37.6)	24.6 (21.4 to 27.7)

CAG, coronary angiogram; CI, confidence interval.

Figure 2

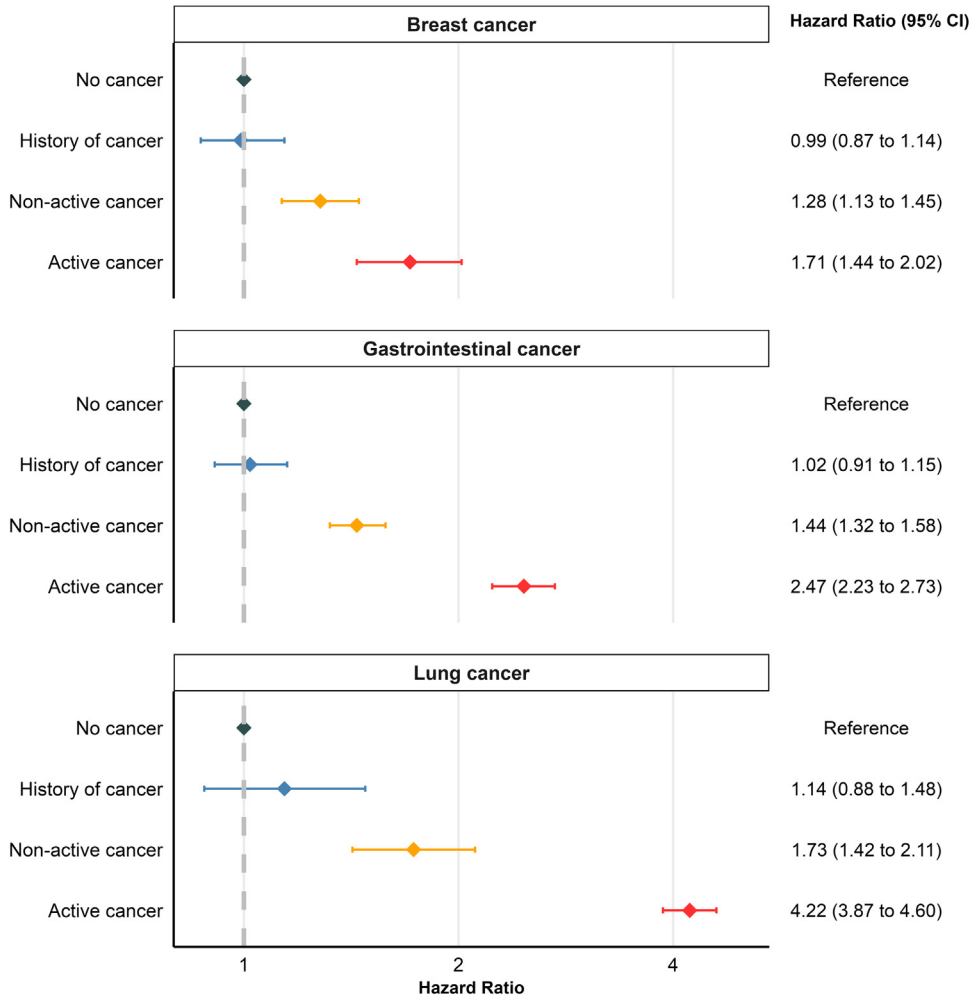


One-year all-cause mortality following ACS. The 1 year all-cause mortality in patients with no cancer (grey), history of cancer (blue), non-active cancer (yellow) and active cancer (red) combined and stratified according to cancer type. Colored areas around the curves represent 95% CI. As shown, there were considerable disparities between cancer types and status, with active cancers and especially lung cancer having the highest 1year all-cause mortality. ACS, acute coronary syndrome; CI, confidence intervals.

prisingly, cardiovascular disease was the leading cause of death which could be interpreted in light of infrequent use of secondary prophylactic pharmacotherapy and CAGs when managing cancer patients.

In an unadjusted analysis, we found a higher 1year all-cause mortality regardless of cancer status, when compared with patients with no cancer. For cancer status, mortality incidences for each cancer type increased incrementally (no cancer < history of cancer < non-active cancer < active cancer), with active lung cancer presenting the highest 1year all-cause mortality. Previous findings by Bharadwaj et al. showed a greater in-hospital mortality for patients with cancer and acute myocardial infarction[6] which supports the findings of this study. Our results extent these findings and suggest that the effect of cancer type and status is not limited to in-hospital events,

Figure 3

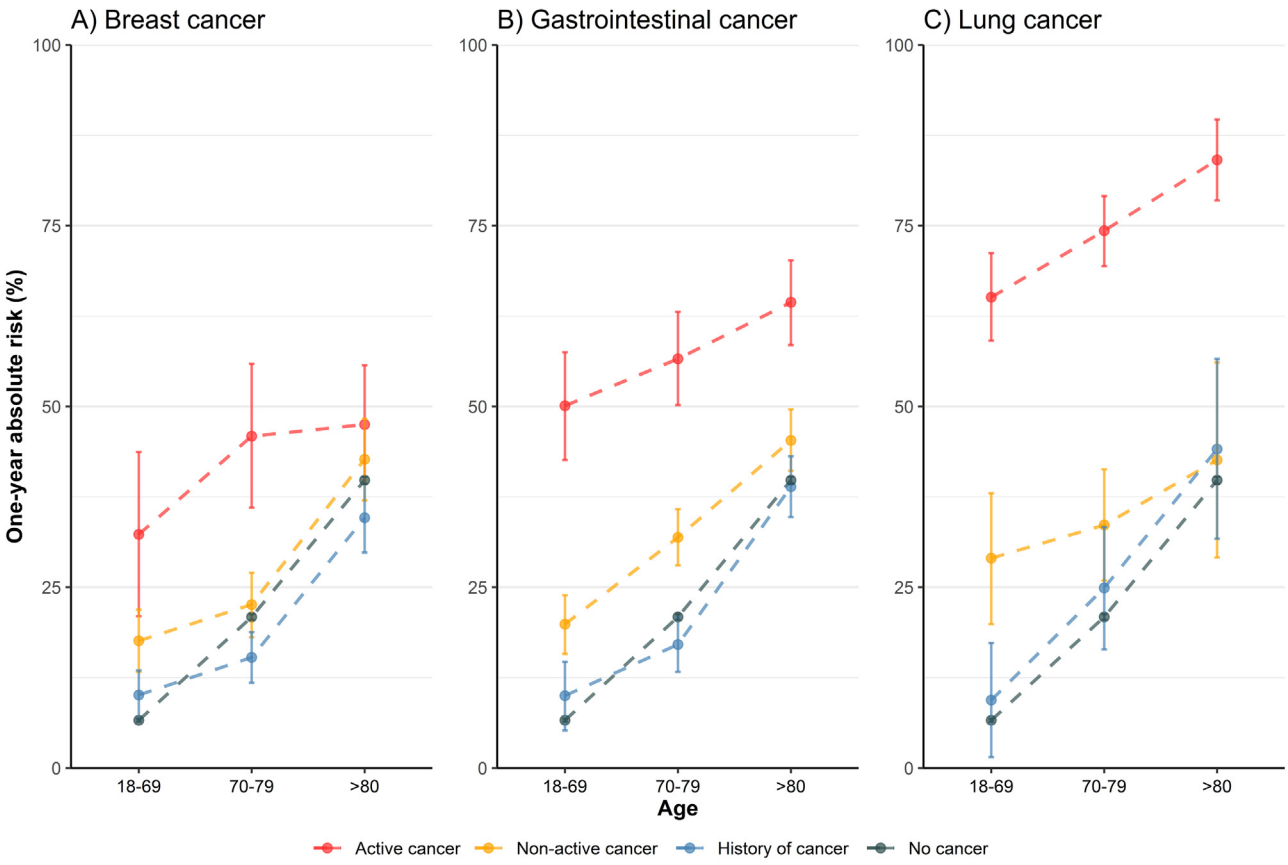


Adjusted hazard ratios of 1year all-cause mortality following ACS. Multivariable Cox proportional hazard analysis was performed to obtain hazard ratios of 1-year all-cause mortality. The models were adjusted for chronic obstructive pulmonary disease, gender, age-groups, calendar year of ACS, hypertension, diabetes and atherosclerosis. As shown, there are increased hazard ratios of 1year all-cause mortality for patients with non-active- and active cancers. ACS, acute coronary syndrome.

and is still substantial at 1year follow-up. This may be explained by a higher degree of frailty in patients with cancer; yet, other factors may be involved. Over the last decades, advanced cancer therapies have resulted in a decline in mortality of patients with cancer.[19] Possibly, bed-side perceptions of the prognosis of patients with ACS and cancer made by cardiologists, may not fully reflect these changes.

When adjusting for relevant confounders, we found no difference in 1year all-cause mortality when comparing patients with history of cancer to patients with no cancer, indicating that a cancer diagnosis given more than 5 years prior to the ACS does not affect the prognosis of these patients. This notion is also supported by Bharadwaj et al. who found no increase of in-hospital mortality when comparing patients with history of cancer to patients with no cancer.[6] Still, our study showed a tendency to diverge from guideline-recommended treatment, i.e., CAG and secondary prophylactic pharmacotherapy, irrespective of cancer type and status. All cancer patients with history of cancer redeemed fewer prescription on acetylsalicylic acid and statins. Further, we found that patients with history of gastrointestinal cancer, were less likely to have a CAG performed, possibly due to the bleeding associations in patients with active gastrointestinal cancer.[7,20] These findings call for attention to the clinical decision-making in patients with history of cancer. Similarly, patients with active cancer, regardless of type,

Figure 4



Age stratified 1year all-cause mortality in patients with ACS. One-year all-cause mortality stratified on 3 age-groups; 18-69 years-old, 70-79 years- old and >80 years old for each cancer type, according to cancer status. Error bars depicting 95% CI. As shown the effect of age is limited in patients with active cancer. Patients with active gastrointestinal cancer >80 exhibit a slightly higher 1-year all-cause mortality. ACS, acute coronary syndrome; CI, confidence intervals.

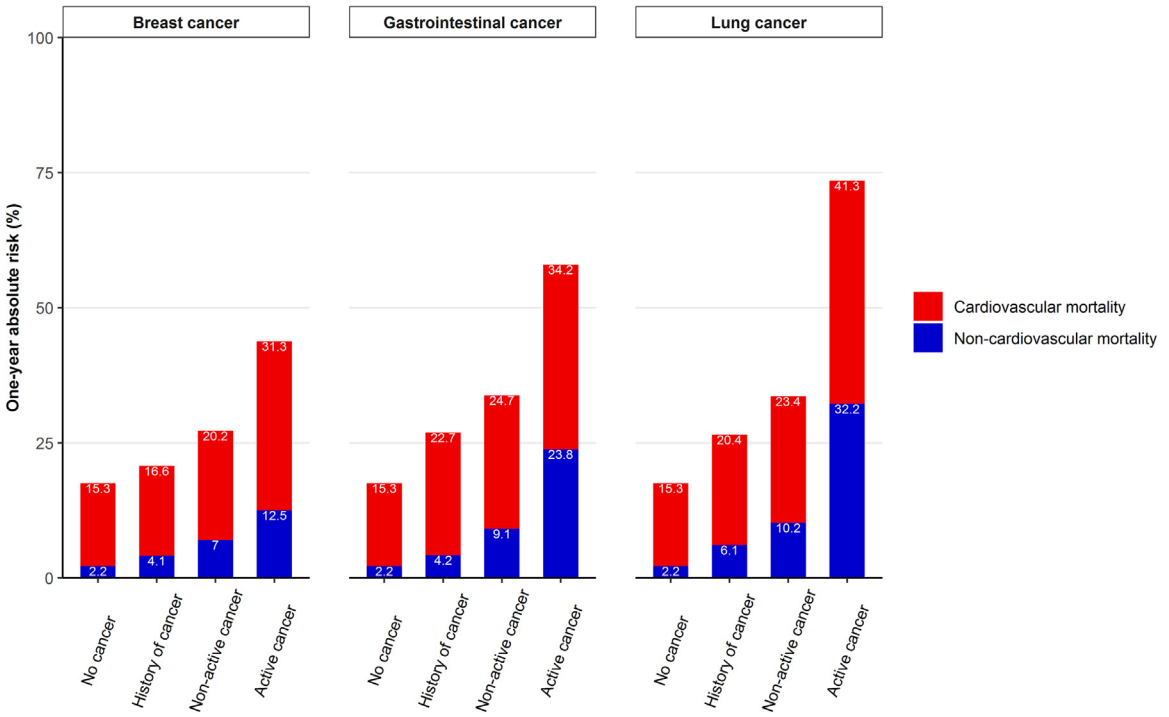
were less likely to receive a CAG. Interestingly, when investigating cardiovascular- and non-cardiovascular mortality, we found a higher 1year cardiovascular mortality, questioning the reluctance for invasive management. Moreover, patients with active breast cancer had the lowest 1-year cumulative incidence of all-cause mortality, but the highest incidence of cardiovascular mortality compared with other cancer types. Still, the number of CAGs performed in these patients did not differ significantly from other cancer types. Hence, some cancer types may benefit from a more aggressive approach, though the hematologic and coagulation abnormalities pose challenges to the use of antithrombotic agents and percutaneous coronary intervention.[21]

The Society of Coronary Angiography and Interventions (SCAI) has put forth an expert consensus statement with emphasis on special considerations regarding CAG and interventions in cancer patients. This work included a revascularization approach, in which platelet count, TIMI risk score and early involvement of a cardio-oncology team was taken into account.[22] This approach may be beneficial in low-risk patients, thereby calling for an individual risk assessment of patients in order to optimize treatment strategies.

Another aspect of our findings is the possibility that patients with active cancer are more likely to experience type 2 myocardial infarction, thereby contributing to excess risk of mortality in patients with active cancer. Type 2 myocardial infarction is known to have a poor prognosis compared to type 1 myocardial infarction.[23] Type 2 myocardial infarctions encompass a variety of conditions with myocardial injury, in which CAG is not always indicated,[24] which could explain the reluctance we find, towards performing CAG in these patients.

Lastly, we found age and comorbidities to have limited impact on the prognosis of patients with active cancer,

Figure 5



One-year cardiovascular mortality and non- cardiovascular mortality following ACS. The 1 year cardiovascular mortality (red) and non-cardiovascular mortality (blue) stratified according to cancer type- and status displays a higher proportion of cardiovascular mortality regardless cancer type and status though there is an incremental increase of non-cardiovascular mortality by cancer status (no cancer < history of cancer < non-active cancer < active cancer). ACS, acute coronary syndrome.

regardless of cancer type, which emphasizes the adverse effects of active cancer. Though, another explanation may be that some cancers e.g., breast- and lung cancer become more indolent with age,[25,26] hence younger patients might experience more aggressive tumors explaining the reduced impact of age on 1year all-cause mortality.

Strengths and limitations

The major strength of this nationwide observational study was the sample size with inclusion of consecutive patients with ACS from 2000 throughout 2018. This approach reduces inclusion and selection bias to a minimal; however, a limitation to this register-based approach was the lack of information on smoking status, TNM-classification, and other important clinical risk factors, which could confound or weaken the associations.

Cancer status (active- and non-active cancer) was identified through a new approach in the Danish registers which is currently being validated; however preliminary results showed high PPVs for both active- and non-active cancer across all cancer types.

A limitation to this study, was our inability to include other major cancer types such as malignant melanoma and prostate cancer. However, validation of cancer status is not performed for these types of cancer, hence we were not able to include them in our analysis.

Furthermore, in order to enhance sample size, we had to expand the inclusion period, which essentially could overestimate the contemporary risk of mortality in cancer patients, since treatment strategies have improved during the inclusion period. A supplementary time-trend analysis was performed in order to address this limitation and found a decreasing 1year mortality over time for all cancers, regardless of status. The results of this study should therefore be interpreted with this limitation in mind.

Clinical perspectives

With lack of data from randomized controlled trials, physicians are often faced with numerous clinical and therapeutic challenges when treating patients with ACS and cancer. Acknowledging the heterogeneity of different cancers and the impact of cancer status could advance the field of cardio-oncology. Results from recent

studies[5–7] accompanied by this study provides a framework for physicians to differentiate between the most prevalent cancer types and status when planning treatment regimens. However, as already proposed by SCAI, this is not an easy task. In patients with ACS there is typically a time frame to consider, which proposes a challenge for thorough examination.[27] Further, the etiology of myocardial injury is difficult to assess in cancer patients, especially in an acute setting.

Moreover, cancer patients with ACS have a higher risk of readmissions and bleeding.[7] This implies, altogether, that a multidisciplinary team, involving cardiologists, oncologists, and palliative physicians would be beneficial when tailoring treatment strategies accordingly; particularly since our data suggest that a more aggressive approach could be beneficial in selected cancer patients.

Conclusions

In conclusion, active- and non-active cancers were associated with an increased 1year all-cause mortality compared with patients with history of cancer and no cancer. Cardiovascular disease was the leading cause of death in all patients. Notably CAG was not performed in the majority of these patients. Likewise, prescription of secondary prophylactic guideline recommended pharmacotherapy was reduced in cancer patients when compared with patients with no cancer. The overall results of this study emphasize that cancer patients should not be regarded and treated as 1 entity. Our data support an individual assessment of patients with ACS and cancer, in which cancer status, cancer type, and expected prognosis should be considered when planning the treatment strategy.

Conflict of interest

None declared.

Authors' contributions

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. NN, MS, and ML conceived the study idea. AH, JS, AH, JT and ML decided on statistical methodology and analyzed the data. All authors contributed to interpretation of the data. NN wrote the first draft of the manuscript. All authors critically revised the manuscript and approved the final version of this manuscript.

Disclosures

All other authors have no relationships relevant to the contents of this paper to disclose.

Data availability statement

It is not allowed by Danish law to share the data used for this study.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2022.11.001.

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