Original article

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Neoplastic disease after acute coronary syndrome: incidence, duration, and features: the ABC-4* Study on Heart Disease

Giuseppe Berton[a], Rocco Cordiano[b], Fiorella Cavuto[c], Francesco Bagato[b], Beatrice Segafredo[c] and Mattia Pasquinucci[a]

Aim **To investigate the clinical features and incidence of malignant neoplasia during 17 years of follow-up in an unselected sample of patients with acute coronary syndrome (ACS).**

Methods **The Adria, Bassano, Conegliano, and Padova Hospital-4 Study on Heart Disease is an ongoing, prospective study of an unbiased population of patients with ACS. Baseline clinical and laboratory data were obtained during the first 7 days of hospitalization at three different intensive coronary care units. The current study included data from 589 patients with ACS.**

Results **At enrollment, 19 patients had confirmed neoplasia. During follow-up, 99 additional patients developed malignant neoplastic disease. The incidence rate was 17.8 cases per 1000 person-years, which was about three times higher than that observed in the general population. Patients had a shorter duration of neoplasia when they developed it after enrollment compared with those with preexisting neoplasia [hazard ratio = 2.0 (1.5–2.6), $P = 0.001$]. Patients with neoplasia who died during follow-up had an earlier onset of neoplasia [hazard ratio = 1.8 (1.1–2.9), $P = 0.01$] and shorter duration than survivors [hazard ratio = 4.1 (2.4–7.0), $P < 0.0001$]. The estimated time to diagnosis of neoplasia indicated elderly patients had a significantly higher risk than younger people during the 17 years of follow-up. After the onset of neoplasia, survival time declined more sharply in the elderly than younger people.**

Conclusion **The long-term prospective study showed that patients with ACS have a higher incidence of malignancy than the general population. Those who develop neoplasm after being diagnosed with ACS have a worse prognosis than patients with a preexisting neoplasia.**

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Keywords: acute coronary syndrome, long-term follow-up, neoplasia, outcomes, survival analysis

[a]Department of Cardiology, Conegliano General Hospital, Conegliano, [b]Department of Internal Medicine and Cardiology, Adria General Hospital, Adria and [c]Department of Cardiology, Bassano del Grappa General Hospital, Bassano del Grappa, Italy

Correspondence to Dr Giuseppe Berton, MD, FESC, Department of Cardiology, Conegliano General Hospital, Via Brigata Bisagno, 31015 Conegliano, TV, Italy
Tel: +39 0438663613; fax: +39 0438663360; e-mail: giube.s@alice.it

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Introduction

Several studies have improved our understanding of the factors that predict adverse outcomes after acute coronary syndrome (ACS).[1–3] Most of these studies reported on predictions over a short time period, namely during the index hospitalization or the first year after ACS, and few studies examined long-term mortality.[1,4] In addition, most studies evaluated selected samples of patients with little data on the cause of death in real-world patients.[1,5–7] Knowledge of long-term outcomes, including causes of death, is important for implementing new strategies and designing secondary prevention programs with the goal of further reducing mortality.[2,4,5,8] At first glance, cardiovascular disease and cancer seem to have little in common. Yet, either cardiovascular disease and/or its treatment may affect the cancer incidence, and cancer and cardiovascular disease have common underlying mechanisms.[9–18] The reduction in mortality from primary percutaneous coronary intervention (PCI) may be short lived and other causes of mortality may come into play over time.[2,12] Thus, we need to recognize the factors, both cardiac and noncardiac, that pose the greatest risk to patients who survive ACS and initiate treatment and behavior changes that will reduce their risk of mortality later.[2,19] The aim of the current study was to describe the presence, incidence, time to onset, duration, and mortality related to malignant neoplasia in an unselected sample of patients, who were discharged alive after an index hospitalization for ACS and followed for over 17 years. For comparison, the incidence rates from general population registries were also examined.

Methods

Patients and baseline evaluation

The Adria, Bassano, Conegliano, and Padova Hospital Study on Heart Disease (the ABC Study on Heart Disease) is an ongoing, prospective investigation designed to reflect, as closely as possible, an unbiased population of patients with ACS. The sample includes white patients with definite ACS [ST elevation myocardial infarction

* ABC is the acronym for Adria, Bassano, Conegliano, and Padova Hospitals.

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(STEMI)], non-STEMI, and unstable angina who were admitted to the ICUs of the Adria, Bassano, and Conegliano hospitals between June 1995 and January 1998. The original aim of the ABC study was to follow the natural, long-term history of these patients and to evaluate the prognostic value of clinical variables. The criteria for the diagnosis of ACS included the clinical presentation, ECG findings, and the identification of serum biochemical markers of necrosis.[20–22]

Each patient received an anonymous code, and no personal data or identifiers were included in the baseline or follow-up database. Written informed consent was obtained from all enrolled patients, and the study was approved through the hospital ethics committee. At enrollment, a thorough patient history was collected from medical records and patient interviews. All baseline clinical and laboratory data reported in the current study were obtained during the first 7 days of hospitalization in the intensive coronary care unit. Details of the variables accrued have been published elsewhere.[21–24]

Follow-up and outcome

At 1, 3, 5, 7, 10, 12, 15, and 17 years after recruitment, each patient underwent a clinical check-up. At each recruitment hospital, two cardiologists followed the cohort of patients for 17 years. All data were obtained from scheduled examinations, public administrations, hospital records, family doctors, postmortem examinations, and death certificates. For the current study, the following data were recorded: presence of malignant neoplastic disease at the index admission; time of onset of the neoplastic disease (onset time was considered the first documented clinical diagnosis of the disease); duration of the neoplasia (time from diagnosis up to 17 years of follow-up or until the time of death); and site of the malignancy. All patients were followed for 17 years or until the time of death. All data after enrollment were prospectively recorded according to the protocol of the ABC Study on Heart Disease.

Statistical analysis

The accrued variables were analyzed as continuous variables or proportions. Log transformations were used to correct for positive-skewed distributions, when appropriate. Unpaired Student's *t* test and Pearson's Chi-square test were used to analyze measured and categorical variables, respectively. If a patient dropped out before completing 17 years of follow-up, her/his data were censored at that time. Survival curves were constructed by the Kaplan–Meier method and compared by log-rank test. The time to onset and the duration of malignant neoplastic disease were compared with the Cox proportional hazard regression analysis.[25] Scaled Schoenfeld residuals were used to test the proportionality assumption with 95% confidence intervals.[26] The baseline features were summarized using median values and interquartile ranges for continuous variables and numbers and percentages for categorical variables. The incidence rate was expressed as the number of cases per 1000 person-years. The International System of Units was used throughout the text. Unless otherwise indicated, two-tailed *P* values less than 0.05 were considered significant. The statistical analyses were performed using STATA 14 (College Station, Texas, USA).

Results

Baseline features

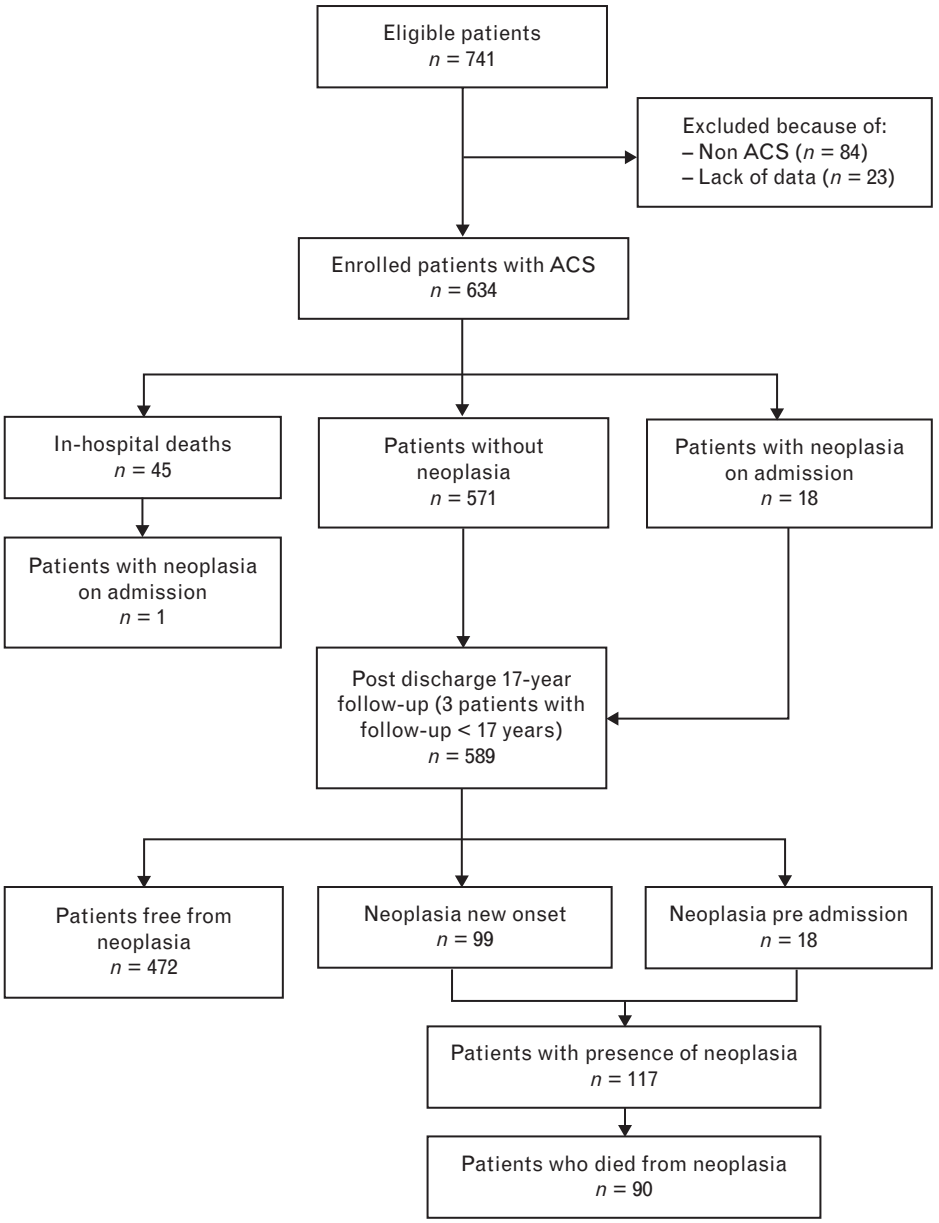
A total of 741 patients were considered eligible upon admission (Fig. 1). Among these, 84 patients had diseases other than ACS and 23 lacked baseline data; these patients were excluded from the study. Among the 634 patients with ACS enrolled, 19 had a confirmed malignant neoplasia at the time of enrollment. Forty-five patients died during the index hospitalization (one who had neoplasia at enrollment), and were excluded from the present analysis. Hence, the postdischarge follow-up study included 589 patients (Fig. 1). The survival time was censored in three patients before 17 years (two withdrew consent and one moved overseas). All other patients completed the follow-up unless preempted by death. At enrollment, 19 patients had malignancies (one died during the index hospitalization and was excluded from the present analysis). During the follow-up, 99 patients developed malignant neoplastic disease (Fig. 1).

The age at enrollment did not differ between patients who developed neoplasia during follow-up and those who did not, but the prevalence of neoplasia was higher among men (Table 1). Patients with neoplasia were more frequently smokers and less frequently had diabetes, whereas there were no differences regarding their history of hypertension or coffee and alcohol use. Patients with neoplasia less frequently had baseline signs of heart failure. As for humoral characteristics, patients with neoplasia had lower plasma levels of total cholesterol, lactate dehydrogenase-1 isoenzyme peak, and uric acid (Table 1). The main sites of neoplasia in the overall sample of patients are shown in Figure 2 and the most frequent sites were the respiratory and digestive systems. Prostatic and breast sites were the most frequent malignancies of the genitourinary system among men and women, respectively. Thirteen (11%) of the patients with neoplasms experienced a second malignancy (Fig. 2).

Incidence, onset time, and duration of neoplasia

During follow-up, we calculated the time between enrolling in the ABC study and the clinical onset of neoplasia, and the duration of the neoplasia. Nineteen patients had malignancies prior to enrollment. Their times to diagnosis are reported as negative values in Table 2, starting from enrollment. The incidence rate for all neoplasms after ACS was 17.8 per 1000 person-years. The risk of early onset of neoplasia was higher for hematologic and

Fig. 1



Flow diagram of patients' progress during follow-up. ACS, acute coronary syndrome.

respiratory sites (NS in our analysis), whereas it was lower for urinary and upper digestive sites (Table 2). The duration of malignancy was much shorter in patients who developed a neoplasia after enrollment than in those with preexisting malignancies (Table 2), even when only the duration after enrollment (fixing the time at enrollment as 0) was considered (Table 2). The incidence rate of death due to all site neoplasia was 14.9 per 1000 person-years. Neoplastic patients who died during follow-up had an earlier onset of neoplasia and, consequently, a shorter duration than survivors with neoplasia (Table 2). The shortest duration of neoplasia was observed for hematologic, upper digestive tract, and respiratory sites. The longest duration was for breast and prostatic sites (Table 2).

Kaplan–Meier curves of the estimated time to diagnosis indicated that the risk of developing a neoplasia was not different between men and women (Fig. 3a), whereas elderly patients had a significantly higher risk than younger people during the 17 years of follow-up (Fig. 3b). After the onset of neoplasia (fixing the time at neoplasia

Table 1 Baseline characteristics of patients with acute coronary syndrome by developing neoplastic disease during follow-up

Variable	Overall sample[a], $n=571$	Non-neoplastic, $n=472$	Neoplastic, $n=99$	P values
Median age (years)	67 (58–74)	67 (58–75)	67 (61–74)	0.71
Sex (female)	30	31	21	0.04
Education (above primary school)	26	26	26	0.93
Median BMI (kg/m^2)	26 (24–28)	26 (24–28)	25 (24–29)	0.66
Smoking habit[b]	67	65	80	0.003
Alcohol use	74	74	74	0.99
Hypertension	48	48	46	0.66
Diabetes mellitus	23	25	13	0.01
Median SBP (mmHg)	120 (110–130)	120 (110–130)	120 (110–130)	0.62
Median DBP (mmHg)	80 (70–80)	76 (70–80)	80 (70–80)	0.1
Median heart rate (bpm)	71(60–82)	72 (63–82)	70 (60–80)	0.07
Non-ST elevation ACS	38	37	46	0.09
Killip class >1	66	36	22	0.008
LVEF, $n=500$	52 (45–60)	52 (45–60)	56 (46–61)	0.06
Hb (g/l)	137 (125–147)	137 (126–147)	137 (126–147)	0.88
Blood glucose level (mmol/l)	6.7(5.6–8.8)	6.8 (5.7–9.3)	6.2 (5.4–7.7)	0.05
Blood cholesterol level (mmol/l)	5.4 (4.6–6.3)	5.5 (4.7–6.3)	5.2 (4.4–6.1)	0.02
GFR (ml/min/1.73 m^2)[c]	75.3 (55.8–105.5)	72.7 (55.0–105.2)	85.5 (60.2–114.6)	0.002
Serum creatinine level (μmol/l)	84.0 (74.3–97.2)	86.6 (75.1–79.2)	82.2 (72.5–94.6)	0.06
Uric acid level (mmol/l)	0.33 (0.27–0.40)	0.34 (0.28–0.40)	0.31(0.24–0.40)	0.02
CK-MB peak (U/l)[c]	103 (43–205)	106 (43–207)	78 (34–186)	0.15
LDH peak (U/l)[c]	848 (517–1380)	874 (538–1418)	701 (454–1200)	0.003

The values are presented as medians and interquartile ranges or percentages. CK-MB, creatine kinase-MB isoenzyme; GFR, glomerular filtration rate; Hb, hemoglobin; LDH, lactate dehydrogenase-1 isoenzyme; LVEF, left ventricular ejection fraction. [a] Excluding 19 patients with preexisting malignancy. [b] Previous smokers and currently smoking patients. [c] P values were calculated on log-transformed data.

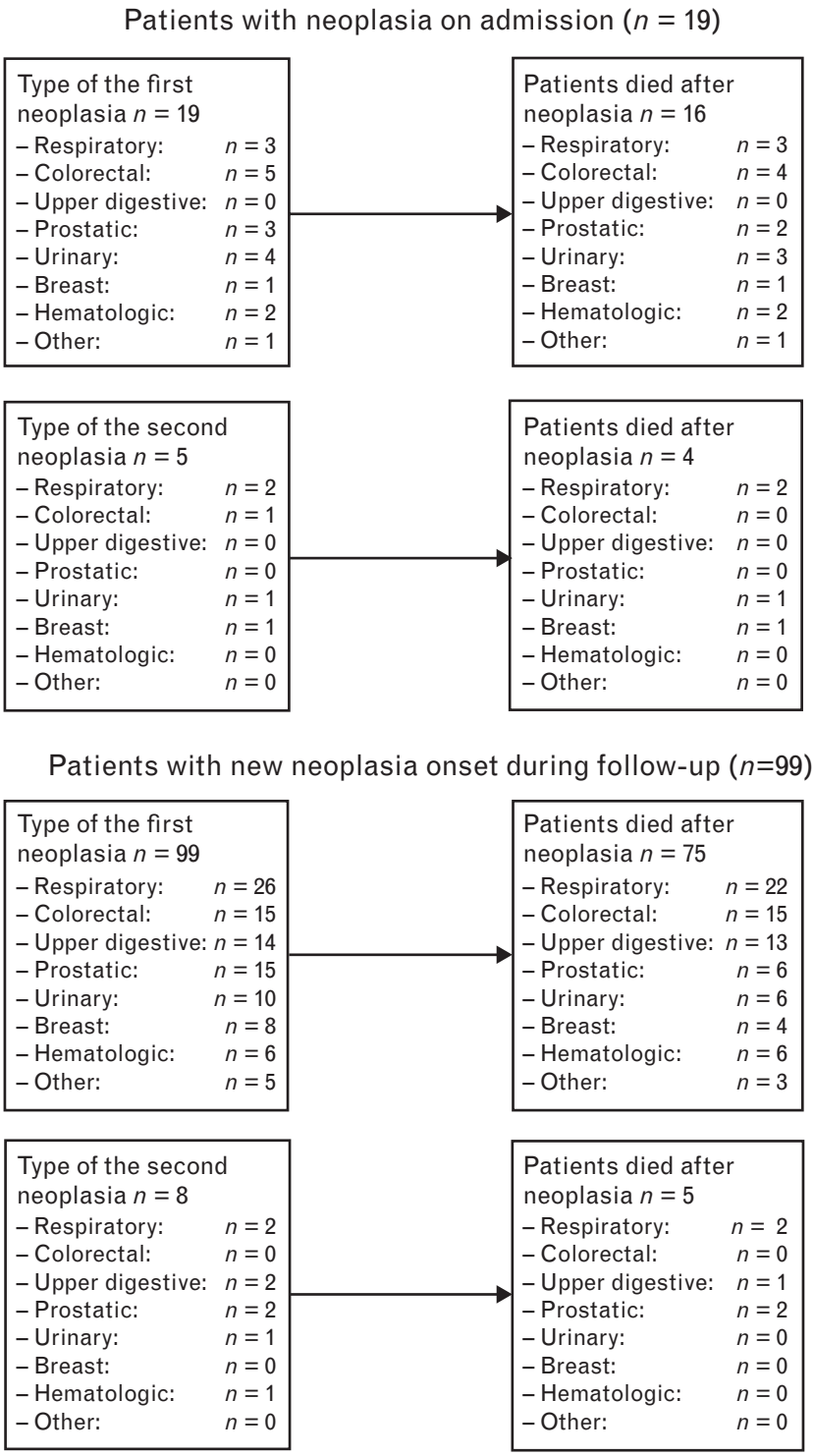
onset to 0), survival time showed a sharp decline in both men and women, but was not significantly different between them (Fig. 3c). The survival time decline was significantly sharper in the elderly versus younger people (Fig. 3d).

Discussion

The current prospective, long-term study showed an increase in the risk of malignant neoplasia in patients who survived ACS. Such a trend was already observed in other samples of patients after ACS when they were followed for about 5 years.[27,28] In our patients, the risk of neoplasia demonstrated an increasing trend for up to 17 years of observation. Furthermore, patients with a neoplasia onset after ACS had a dramatically worse prognosis when compared with patients who had a pre-existing neoplasia at the time of ACS. To the best of our knowledge, this is the first study examining the incidence rate of malignancy long after the diagnosis of ACS. The risk of malignancy after ACS found in the current study appears higher than that of the general population. In fact, we observed an incidence rate of approximately 17.8 cases per 1000 person-years, whereas the general population male and female incidence rate estimates from the United States, Denmark, Italy, and Veneto Region were 5.0 and 4.2; 6.3 and 4.5 (age standardized rate 3.0); and 4.0 and 7.0 (age standardized rate 3.2) cases per 1000 person-years, respectively.[29–32]

The reason for an increased cancer risk in ischemic patients after ACS is unclear. However, inflammation is an established component of carcinogenesis. As coronary disease is characterized by chronic inflammation, this may play a role in the increased risk of developing cancer in these patients.[9–18] Furthermore, cardiovascular disease and cancer are the two leading causes of death worldwide. Although commonly thought of as two separate disease entities, cardiovascular disease and cancer possess various similarities, including a number of risk factors (e.g. obesity, diabetes mellitus), suggesting that they have a shared biology.[9] In the current study, the incidence of cancer was similar in men and women, and higher in older patients than in younger people. The duration of neoplasia was similar in men and women, and shorter in older versus younger people. Accordingly, Kvakkestad *et al.*[33] found there were no significant sex differences in the risk of cancer death after an observation period of 7 years. The shorter duration of neoplasia in the elderly patients is likely due to shorter survival times than for younger patients.[4] Noncardiac causes are responsible for the majority of later deaths in patients affected by cardiovascular disease.[3,4,8,12] Due to the age of the population in developed countries and the common occurrence of risk factors, it is increasingly likely that a patient may develop both cancer and cardiovascular disease.[4] The rates of death from cardiovascular and cerebrovascular disease have been steadily declining over the past few decades, with improvements observed across most age groups and for both sexes.[5] The improvements in prognosis for cardiovascular patients are largely due to the decrease in traditional risk factors and to new medical diagnostic and therapeutic procedures such as coronary angiography and PCI for ACS.[6,7] At the same time, these types of exams expose patients to ionizing radiation, which can elevate a person's lifetime risk of developing cancer. A recent retrospective cohort study on patients

Fig. 2



Description of the types of malignancies in patients with acute coronary syndrome (including first and second neoplasia).

with cardiac problems without cancer who were followed for a median of 10 years showed that noncardiovascular causes of death were responsible for almost half of the later deaths. These authors found that the radiological exposure from medical imaging procedures is predictive of cancer risk and cancer death.[34]

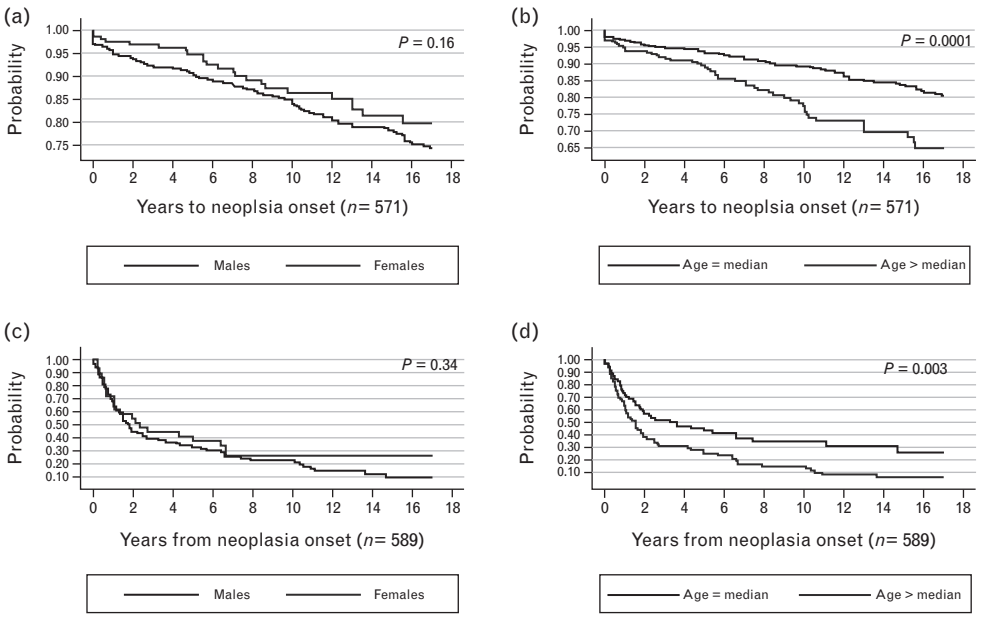
Table 2 Time to the onset and duration of the neoplastic disease after acute coronary syndrome through 17 years of follow-up

Patients with neoplasia	*n*	Time to neoplasia onset[a] median (I.Q.)	Hazard ratios (95% CI)[b]	Duration of neoplasia[c] median (I.Q.)	Hazard ratios (95% CI)[b]
Preexisting neoplasia	19	−1.1 (−5.0, −0.9)		10.0 (5.9, 17.1) After enrollment: 6.6 (2.7, 11.1)	2.0 (1.5, 2.6)[d] After enrollment: 1.5 (1.2, 2.0)[e]
New onset neoplasia	99	7.1 (3.0, 11.5)	1.8 (1.1, 2.9)	1.4 (0.6, 5.0)	4.1 (2.4, 7.0)
Alive	24	8.5 (5.5, 12.0)		8.4 (4.7, 11.3)	
Dead	75	6.2 (2.6, 10.4)		1.0 (0.6, 2.2)	
Site of neoplasia[f]					
Respiratory[b]	26	5.0 (1.5, 9.6)	1.4 (0.9, 2.2)	0.9 (0.5, 2.5)	1.3 (0.8, 2.1)
Colorectal[b]	15	8.3 (2.1, 13.0)	1.0 (0.6, 1.7)	2.2 (0.6, 3.6)	1.3 (0.7, 2.3)
Prostatic[b]	15	8.1 (4.9, 11.1)	1.1 (0.6, 1.9)	6.2 (1.8, 10.0)	0.5 (0.3, 0.9)
Upper digestive[b]	14	10.2 (5.0, 13.0)	0.8 (0.5, 1.5)	0.8 (0.5, 1.3)	2.3 (1.3, 4.2)
Urinary[b]	10	10.0 (6.5, 15.6)	0.4 (0.2, 0.8)	1.3 (0.9, 1.9)	1.1 (0.6, 2.2)
Breast[b]	8	5.7 (4.7, 8.6)	1.5 (0.7, 3.1)	5.0 (4.3, 8.4)	0.4 (0.2, 0.9)
Hematologic[b]	6	3.0 (3.0, 9.0)	1.4 (0.6, 3.2)	0.7 (0.5, 1.3)	1.9 (0.8, 4.4)
Other[b]	5	7.1 (7.0, 7.7)	1.0 (0.4, 2.5)	1.4 (1.1, 1.4)	1.1 (0.5, 2.8)

CI, confidence interval. [a] Time of onset of the neoplastic disease is the time from enrolment to the first documented clinical diagnosis of the neoplastic disease in years. [b] Cox regression-based test for equality of survival curves. [c] Duration of the neoplasia is the time from diagnosis up to 17 years of follow-up or to time of death in years. [d] Preexisting versus new onset neoplasia. [e] Only time after enrollment versus new onset neoplasia. [f] Hazard ratio for each malignancy site was calculated versus all the other sites.I.Q., Interquartile ranges.

Recently, Pedersen *et al.*[12] observed that noncardiac causes of death, which are rare in the early phase after STEMI treated with primary PCI, become considerably more frequent with time and that late noncardiac causes of death were mainly due to malignancies and lung diseases, including pneumonia. In the Pedersen study, the median time to death for patients with malignancies was approximately 3 years; however, there was no mention of the time of onset of the neoplasia. Most likely, some patients had neoplasia at the time of enrollment and some developed the disease after. This may strongly affect time estimates. In the present report, we divided enrolled patients into two groups: one with patients who had a diagnosis of malignancy prior to enrollment and one including those in whom malignancy was diagnosed after enrollment. We observed that patients with cancer at enrollment had a much longer duration of their oncologic disease (median of approximately 10 years, with 6.6 years

Fig. 3



Kaplan–Meier estimates of the probability of onset and duration of malignant neoplasia after acute coronary syndrome by sex and by age (equal, above, and below the median value). Panel (a) comparison of time from enrollment to diagnosis of neoplasia by sex; panel (b) comparison of time from enrollment to onset of neoplasia by age; panel (c) comparison of the duration of neoplasia, from neoplasia onset to death or the end of follow-up, by sex; panel (d) comparison of the duration of neoplasia, from neoplasia onset to death or the end of follow-up, by age. The *P* values are calculated using the log-rank test.

after enrollment) than those diagnosed with neoplasia after enrollment (median duration approximately 1.4 years). There are two explanations for this observation. First, neoplasia that developed before enrollment was less severe than malignancies that developed after enrollment, or that the shorter duration in the latter was influenced by the patient's clinical condition after ACS, or both. It is also possible that patients with more aggressive malignancies had a shorter survival time that precluded the manifestation of ACS.

The concurrence of cancer and cardiovascular disease is a controversial topic given the competing risks for mortality and similar risk factors for both disease states.[11,19] However, considering the dramatic prognostic severity of these clinical conditions, further assessment of this relationship appears to be remarkably relevant.[2,11,16] The MASS II study, conducted in patients with coronary artery disease (CAD), excluded patients with preexisting cancer. This study showed that different treatment options for multivessel CAD had similar overall mortality rates.[10] Indeed, patients with coronary artery bypass grafting had the lowest incidence of cardiac death but the highest incidence of noncardiac causes of death and, specifically, a higher tendency toward cancer-related deaths.

A retrospective study on patients who underwent PCI found a marked temporal switch from predominantly cardiac to predominantly noncardiac causes of death after PCI over 2 decades of follow-up.[4,12] The decline in cardiac mortality was independent of changes in baseline clinical characteristics. Similar trends were observed regardless of age, the extent of coronary disease, or PCI indication. After adjustment for baseline variables, there was no temporal decline in noncardiac mortality. The decline in cardiac mortality was driven by fewer deaths from myocardial infarction/sudden death, but not from heart failure.[8,35] The increase in noncardiac mortality was primarily attributable to cancer and chronic diseases.[4,8,12] Improved awareness of the symptoms of common cancers and participation in evidence-based cancer screening and management programs is important.[19,36] Further understanding of the delicate interaction between cardiovascular disease and cancer may lead to better prevention, earlier detection, and safer treatment strategies.

Limitation of the study

A major limitation of the ABC study on ACS was that at the time of patient enrollment, percutaneous coronary angioplasty was not currently used for reopening coronary arteries in patients with STEMI. Thus, it remains uncertain whether early mechanical reperfusion would have modified the results. In addition, the patients in this study were all whites; therefore, we cannot generalize these findings to other populations and ethnic groups.

Conclusion

The long-term prospective study showed that patients with ACS have a higher incidence of malignancy than the general population. Furthermore, patients who develop a neoplasm have a dramatically worse prognosis than patients with a preexisting neoplasia at the time of ACS.

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Conflicts of interest

There are no conflicts of interest.

The article represents valid work and neither this article nor one with substantially similar content under our authorship has been published or is being considered for publication elsewhere.

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