ORIGINAL RESEARCH

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Stress Echocardiography Positivity Predicts Cancer Death

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***Background*—**Stress echocardiography (SE) predicts cardiac death, but an increasing share of cardiac patients eventually die of cancer. The aim of the study was to assess whether SE positivity predicts cancer death.

***Methods and Results*—**In a retrospective analysis of prospectively acquired single-center, observational data, we evaluated 4673 consecutive patients who underwent SE from 1983 to 2009. All patients were cancer-free at index SE and were followed up for a median of 131 months (interquartile range 134). We separately analyzed predetermined end points: cardiovascular, cancer, and noncardiovascular, noncancer death, with and without competing risk. SE was positive in 1757 and negative in 2916 patients; 869 cardiovascular, 418 cancer, and 625 noncardiovascular, noncancer deaths were registered. The 25-year mortality was higher in SE-positive than in SE-negative patients, considering cardiovascular (40% versus 31%; $P<0.001$) and cancer mortality (26% versus 17%; $P<0.01$). SE positivity was a strong predictor of cancer (cause-specific hazard ratio 1.19; 95% confidence interval, 1.16–1.73; $P=0.05$) and cardiovascular mortality (1.18; 95% confidence interval, 1.03–1.35; $P=0.02$). Fine–Gray analysis to account for competing risk gave similar results. Cancer risk diverged after 15 years, whereas differences were already significant at 5 years for cardiovascular risk.

***Conclusions*—**SE results predict cardiovascular and cancer mortality. SE may act as a proxy of the shared risk factor milieu for cancer or cardiovascular death. **(*J Am Heart Assoc*. 2017;6:e007104. DOI: 10.1161/JAHA.117.007104.)**

Key Words: cancer and stroke • coronary artery disease • prognosis • stress echocardiography

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Stress echocardiography (SE) is an established and cost-effective option for diagnosis and risk stratification in patients with known or suspected coronary artery disease (CAD).[1–4] The prognostic value of SE was shown initially for cumulative end points, mainly consisting of soft end points such as recurrence of angina or coronary revascularization,[5–8] later for hard end points such as myocardial infarction (MI)[9,10] and—as data matured—for all-cause death and cardiac death.[11–13] The clinical meaning of the prognostic stratification is based not only on statistical but also on biological plausibility.[14] From the pathophysiological viewpoint, it is consistent with our current knowledge of ischemic heart disease that SE positivity mirrors the functional impact of underlying CAD, which is the strongest predictor of future cardiovascular events.[15] With longer follow-up times of expanding cohorts becoming available, now additional, more refined analyses also can be made. Death is the hardest and methodologically strongest of all end points,[16] but there is little apparent rationale for linking the SE results to cancer death (for instance, because of lung cancer or leukemia) and to noncancer death (such as Alzheimer's or pneumonia). Therefore, it seems statistically and biologically plausible to explore the link between SE results and different types of death, specifically separating cardiovascular, cancer, and noncardiovascular, noncancer death. The study of predictors of different cause-specific death in individuals referred to SE in a cohort study is an example of competing risk analysis, since the death because of the primary cause of interest such as cardiac disease could be precluded by a death because of another cause such as cancer. A comprehensive view of the cumulative mortality dynamics can be provided with the use of 2 regression approaches used to assess mortality risk without competing risk (cause-specific hazard) or with competing risk (proportional subdistribution hazard).[17] In an epidemiological, retrospective, single-center, cohort study we enrolled 4673 in-hospital patients evaluated with SE at the time of admission from 1983 up to 2009 and enrolled in a follow-up program, with the aim of assessing the association between SE results and different broad classifications of causes of death (cardiovascular, cancer, and

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Clinical Perspective

What Is New?

- A positive echocardiogram stress test predicts not only cardiac death but also cancer death.
- Long-term follow-up data of patients with coronary artery disease demonstrate an increasing incidence of cancer.

What Are the Clinical Implications?

- These results suggest shared risk factors for cancer or cardiovascular death.
- In patients with stable, low-risk coronary artery disease, it may be advantageous to minimize exposure to known oncogenic risk factors.

noncardiovascular noncancer), with and without competing risks (proportional subdistribution hazard and cause-specific hazard methods, respectively).

Methods

Study Population

The study included 4673 patients consecutively hospitalized at the Institute of Clinical Physiology, National Research Council of Italy, Pisa, Italy over a 27-year period (1983–2009) who underwent at least 1 SE as a screening test for CAD. SE was performed in all patients with an exercise electrocardiography test that was unfeasible, submaximal, or nondiagnostic, or patients in whom it was necessary to have a geographic stratification of ischemia or risk stratification after acute MI or revascularization procedure with angioplasty or coronary artery bypass surgery (Table 1). Patients were referred to the hospital for coronary angiography, often performed independently of test results.

At discharge, all demographic, history, clinical, and instrumental data were collected in the Institute's dedicated cardiovascular database. For this study, data on risk factors, type of symptoms, diagnosis, and SE results were considered.

Table 1. Indications for Testing

Indication	Patients, N
Asymptomatic	599
Stable angina	2408
Nonspecific chest pain	1021
After ACS	379
After revascularization	266

ACS indicates acute coronary syndrome.

Patients referred to SE were excluded if they met one of the following criteria: current evidence or recent history of cancer, diagnosed in the 5 years before index-SE (n=111); or patients lost to follow-up (n=200; Figure 1).

Current smoking status was defined as having smoked cigarettes within the past 6 months, and a former smoker was defined as having smoked in the past but quit >6 months ago. A history of high cholesterol was defined as having a total cholesterol value >240 mg/dL or on drug therapy. Diabetes mellitus was defined as a documented diagnosis requiring treatment with medication or diet. Hypertension was defined as a documented history or treatment with medication. Coronary artery disease was defined as ≥1 major coronary artery with at least 50% stenosis.

SE Protocol

Each patient performed at least 1 SE. A second SE using different stressor was performed when the diagnostic end point for the detection of myocardial ischemia (ie, the induction of a transient change in regional function during stress) was not induced. Out of 4673 patients, 280 (6%) performed more than 1 SE test; in these cases, we considered the second one with diagnostic results (up to wall motion positivity or maximal drug dose or maximal predetermined heart rate during exercise). In Table 2, for the sake of clarity we report the result of only 1 SE for each patient (number of SE=number of patients).

Exercise SE was conducted using a semisupine bicycle ergometer with 25W incremental loading every 2 minutes. Dipyridamole (up to 0.84 mg/kg over 10 min with coadministration of atropine up to 1 mg, or up to 0.84 mg/kg over

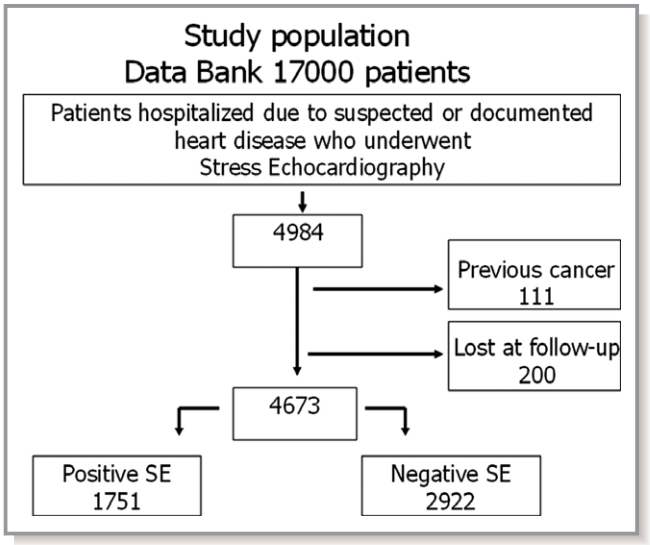

Figure 1. Study selection process. SE indicates stress echocardiography.

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Table 2. Clinical Characteristics of Population Stratified by SE Results

	Total	Positive		Negative		*P* Value
Patients, N (%)	4673	1751 (37)		2922 (63)		
Age, y (mean±SD)	62±11	63±12		61±11		<0.001
Male sex, N (%)	3394 (73)	1241 (71)		2153 (74)		0.018
History of MI, N (%)	2010 (43)	991 (56)		1019 (35)		<0.001
Risk factors, N (%)						
Family history	2161 (46)	836 (48)		1325 (46)		0.173
Diabetes mellitus	855 (18)	344 (20)		511 (18)		0.086
Hypertension	2284 (49)	786 (45)		1498 (52)		<0.001
Hypercholesterolemia	2266 (49)	897 (51)		1369 (47)		0.008
LDL cholesterol, mg/dL		120		116		0.09
Hypertriglyceridemia	1097 (24)	477 (27)		620 (21)		<0.001
Smoking	2408 (52)	1033 (59)		1375 (47)		<0.001
Obesity	1351 (29)	528 (30)		823 (28)		0.183
Angiography	3384 (72)	1651 (94)		1733 (59)		<0.001
No. of vessels, mean±SD		1.81±1.012		0.99±1.018		<0.001
Normal vessels		8		38		<0.001
1 vessel		33		34		0.07
2 vessels		32		18		<0.001
3 vessels		27		10		<0.001
SE results		1813		3140		
Follow-up PCI		760 (55)		616 (45)		<0.001
Follow-up CABG		641 (66)		326 (34)		<0.001
Medications, N %						
Statins	1108 (39)	416	48	692	35	<0.001
β-Blockers	1416 (30)	503	29	913	31	0.05
ACE inhibitors	999 (21)	295	17	704	24	<0.001
Nitrates	2662 (57)	1314	75	1348	46	<0.001
Calcium-channel blockers	1993 (43)	1066	61	927	32	<0.001
Antiplatelet agents	3249 (70)	1390	79	1859	64	<0.001

ACE indicates angiotensin converting enzyme; CABG, coronary artery bypass graft; LDL, low-density lipoprotein; MI, myocardial infarction; PCI, percutaneous coronary intervention; SE, stress echocardiography.

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6 minutes) and dobutamine (up to 40 μg/kg per minute with coadministration of atropine up to 1 mg) SE were performed according to well-established protocols.[1,2]

Echocardiographic images were semiquantitatively assessed using a 17-segment, 4-point score model of the left ventricle (from 1=normal/hyperkinetic, to 4=dyskinetic). A wall motion score index was derived by dividing the sum of individual segment scores by the number of interpretable segments. Ischemia was defined as stress-induced new or worsening of pore-existing wall motion abnormality or biphasic response (ie, low-dose improvement followed by high-dose deterioration). A test was considered positive when at least 2 adjacent segments of the same vascular territory showed a regional wall motion abnormality (absent or of a lesser degree at rest) at peak stress.[1,2] Subjects gave informed consent.

Follow-Up

For each patient, follow-up began at discharge and was planned for a maximum period of 40 years. It was concluded in December 2013. In total 200 patients were lost to follow-up. Follow-up data were obtained routinely every year in at least one of the following ways: from the patient's hospital record; by contacting the patient's physician; by telephone

interview conducted by trained personnel; and during periodic scheduled visits at the outpatient clinic. The end points considered were death that included all-cause, primary cancer onset, and new MI. Cause of death was based on medical records or death certificates. The cause of death was classified as cardiovascular or noncardiovascular cause. Cardiovascular death was classified as either cardiac or noncardiac. The diagnosis of cardiac death required documented life-threatening arrhythmias, cardiac arrest, and death attributable to congestive heart failure or MI in the absence of any other precipitating factor. Sudden unexpected death was classified as a cardiac death when an obvious noncardiac explanation was excluded. Cardiovascular noncardiac death included the following: hemorrhagic stroke, ischemic or undefined stroke, abdominal aortic aneurysm rupture, pulmonary embolus, and other vascular. Noncardiac death included cancer, infectious, chronic diseases such as neurological, pulmonary, renal failure, liver/multiorgan failure, noncardiac surgery, trauma (accident/trauma, suicide), other noncardiac; and unknown or unobtainable. When the only information was the death certificate and when primary cause was stated as ischemic heart disease, this was classified as other cardiac death. Fatal valvular heart disease was classified as congestive heart failure. When there were competing noncardiac and cardiac causes of death, we favored cardiac classification. The diagnosis of cancer was based on medical records or death certificates. Cancer diagnosis was identified also on the basis of codes from the *International Classification of Diseases 9th and 10th revisions* reported as first or secondary diagnosis.

Statistical Analysis

Continuous variables were summarized as mean±SD and were compared using the unpaired 2-tailed Student *t* test. Categorical variables were expressed as percentages and were compared using χ^2 test with Yates correction. Kaplan–Meier estimates were used to summarize event rates for all-cause, cancer, and cardiac mortality, with the log-rank test used for group comparisons. The mortality risk with competing risk (proportional subdistribution hazard) was used to estimate the cumulative incidence of cause-specific modes of death and was assessed by the Fine–Gray regressions. It considers as a single cause of death both the association of SE with a single cause of death and the contribution of another competing event by actively maintaining individuals in the risk sets (ie, divides the probability of death into the probability corresponding to each competing event). The Cox proportional hazards model was used to explore the cause-specific hazard, and the possible association between SE results and risk of deaths of various origins (cancer, cardiovascular, or other causes). Deaths from cardiovascular and other causes were considered censored at the time of death when the cancer death was analyzed. The regression model included known potential confounders such as baseline age, sex, diabetes mellitus, smoking habit, history of MI, and rest and peak wall motion score index. Only the variables predictive at univariate analysis were included in the multivariable model. SE result was included in the regression models as categorized variable. Hazards ratios (HR) and their 95% confidence intervals (CI) were calculated on the entire population for cancer death after adjusting for the same confounders listed above. Two-sided *P* values 0.05 were considered statistically significant. Analyses were performed with the following statistical packages: SPSS (version 20) and the "cmprsk" R package.[17]

Ethical Committee

The study was approved by the Pisa Ethical Committee on November 11, 2014 (Study Protocol n. 335/2014).

Results

Population

The characteristics of the population at study entry stratified by SE results are shown in Table 2. Positive SE patients were slightly older, with prevalence of atherosclerotic risk factors except hypertension. In 56% of SE-positive patients, a history of MI was reported. About 72% of patients underwent the angiographic procedure, and SE-positive patients showed a significant prevalence of coronary stenosis.

SE Results

A pharmacological stress SE was performed in 3741 (80%) patients (dipyridamole in 3337, dobutamine in 404), and exercise SE in 932 (20%) patients. The percentages of SE positivity in dipyridamole, dobutamine, and exercise SE groups were 38%, 32%, and 33%, respectively (Table 3).

Prognostic Data

We observed 1912 deaths (41%), including 869 cardiovascular deaths (761 cardiac and 108 vascular deaths) (40%) and 418 cancer deaths, with an average follow-up time of 12±7 years. The remaining 625 deaths occurred because of noncardiovascular, noncancer causes (sepsis, dementia, chronic obstructive pulmonary disease, renal disease, accident, suicide, surgery, etc). Major causes of cardiac deaths were 47% heart failure, 28% myocardial infarction, 10% sudden, and 4% cardiac arrest.

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Table 3. SE Results and Events

SE Modality	Dipyridamole	Dobutamine	Exercise
Number of tests	3337	404	932
Number of patients	3337	404	932
Positive/negative (%)	1315/2022 (38/62)	110/294 (32/68)	326/606 (33/67)
Median follow-up, mo	164±89	112±70	83±41
% Cancer deaths			
Positive/negative SE	12/10	11/8	5/3
% Cardiovascular deaths			
Positive/negative SE	28/17	26/25	4/7
% Noncancer, non-Cardiovascular			
Positive/negative SE	16/14	24/18	6/6

SE indicates stress echocardiography.

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The top cancer sites were lung (24% of all cancer deaths), prostate (12% in men), colon (11%), leukemia and lymphoma (10%), breast (8% in women), and liver (7%). Site of cancer with a frequency of at least 3% is reported in Table 4.

Patients who died of other causes were older (67±10 versus 64±11 years, cardiovascular death, and 64±9 years, cancer death, $P \leq 0.001$) with more females in the group (28%, versus 21% cardiovascular death, 19% cancer death, $P \leq 0.001$).

The mortality was significantly higher in subjects with SE positivity than in those with SE negativity, considering the overall mortality (70% versus 60%; $P=0.003$), cardiovascular mortality (40% versus 31%; $P<0.001$), and cancer mortality (26% versus 17%; $P<0.01$). Noncancer, noncardiovascular mortality was not significantly associated with SE result (32 versus 30%, $P=0.399$). The cumulative mortality function was obtained (Figure 2) and a major long-term appearance of cancer death was observed over the 25 years of follow-up. At multivariable cause-specific hazard approach, SE positivity was a predictor of cancer (HR 1.19; 95% CI, 1.16–1.73; $P=0.05$), and cardiovascular mortality (HR 1.18, 95% CI, 1.03–1.35; $P=0.02$) after adjusting for age, smoking status, diabetes mellitus, and sex but it was not a predictor of noncancer, noncardiovascular death (Table 5).

The interaction term between smoking and SE result added to the model was not statistically significant ($P=0.93$), showing that the relationship between SE and cancer was

Table 4. Site of Cancer With a Frequency of at Least 3%

Type	N (%)
Lung	101 (24)
Colon	46 (11)
Bone marrow	42 (10)
Prostate	49 (12)
Breast	34 (8)
Liver	33 (7)
Stomach	30 (7)
Pancreas	30 (7)
Bladder	18 (4)
Kidney	11 (3)
Brain	13 (3)

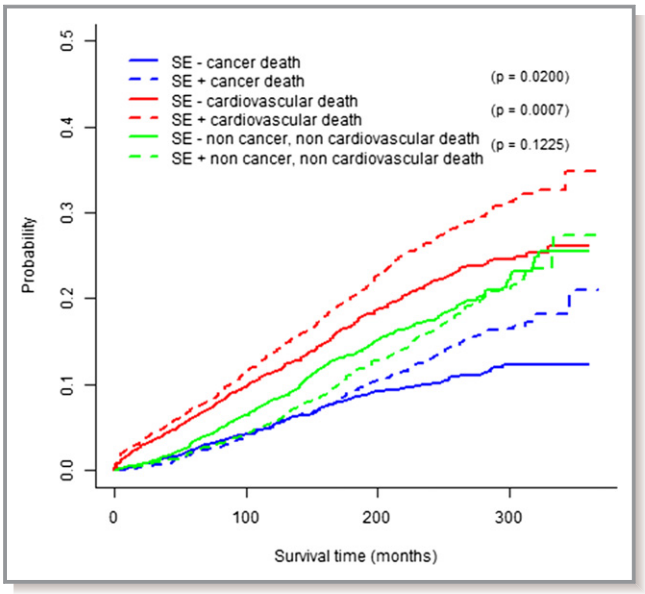

Figure 2. The cumulative mortality functions for the 3 types of deaths, attributable to cardiovascular (red lines), cancer (blue lines), and noncardiovascular, noncancer causes (green lines). Dotted lines: events in negative stress echocardiography test; solid lines: events in positive stress echocardiography test. SE indicates stress echocardiography.

Table 5. HR for Deaths Estimated by Cox and Fine–Gray Regression Model, After Adjustment for the Potential Risk Factors

	Fine–Gray Regression Multivariable Model		Cox Regression Multivariable Model	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Cancer death				
Sex	1.40 (1.06–1.84)	0.02	1.57 (1.21–2.04)	<0.001
SE positivity	1.28 (1.05–1.55)	0.01	1.19 (1.16–1.73)	0.05
Smoking habit	1.36 (1.08–1.70)	0.007	1.37 (1.10–1.73)	0.004
Age	1.04 (1.06–1.84)	<0.001	1.07 (1.06–1.08)	<0.001
Diabetes mellitus	0.76 (0.58–1.01)	0.63	1.01 (0.80–1.33)	0.93
Cardiovascular death				
Diabetes mellitus	1.56 (1.33–1.84)	<0.001	1.78 (1.52–2.09)	<0.001
Sex	1.47 (1.24–1.75)	<0.001	1.60 (1.34–1.91)	<0.001
SE positive	1.28 (1.11–1.46)	0.0004	1.18 (1.03–1.35)	0.02
Age	1.04 (1.03–1.04)	<0.001	1.06 (1.05–1.07)	<0.001
Smoking habit	1.06 (0.92–1.23)	0.41	1.09 (0.94–1.26)	0.26
Noncancer–noncardiovascular death				
Diabetes mellitus	1.38 (1.14–1.68)	0.001	1.91 (1.58–2.31)	<0.001
SE positive	1.01 (0.86–1.20)	0.82	0.89 (0.76–1.05)	0.19
Age	1.07 (1.06–1.08)	<0.001	1.12 (1.11–1.13)	<0.001
Sex	0.9 (0.82–1.02)	0.94	1.23 (1.01–1.49)	0.03
Smoking habit	1.06 (0.89–1.27)	0.47	1.12 (0.94–1.33)	0.18

CI indicates confidence interval; HR, hazard ratio; SE, stress echocardiography.

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significant both in nonsmoker and in smoker patients. However, the limited number of never smokers did not allow a significant analysis (*P*=0.14, HR 1.26, 95% CI, 0.15–1.46).

At univariate analysis, peak wall motion score index predicted cardiovascular (HR 3.44, CI, 2.90–4.06, *P*<0.001), cancer (HR 1.44, CI, 1.08–1.92, *P*=0.01), and noncardiac, noncancer death (HR 1.79, CI, 1.42–2.25, *P*<0.001). At multivariate analysis, peak wall motion score index predicted only cardiovascular (HR 2.91, CI, 2.46–3.43, *P*<0.001) and noncardiac, noncancer death (HR 1.54, CI, 1.22–1.93, *P*<0.001). Angiographically assessed CAD and history of MI were not predictive of cancer death at univariate analysis. They predicted cardiovascular death at univariate, but only history of MI was predictive of cardiovascular death at multivariable model (HR 1.73, CI, 1.51–1.98, *P*<0.001). History of MI also predicted noncardiac, noncancer death (HR 1.30, CI, 1.11–1.51, *P*=0.001).

The estimates performed with the Fine–Gray method gave similar results (Table 5).

Discussion

SE results predict overall mortality, cardiovascular death, and also cancer death whereas they are unable to predict noncardiovascular, noncancer death. This might reflect common epidemiological and biological roots between atherosclerosis and cancer and/or the possibility of competing risk with a death attributable to the primary cause of interest such as cardiovascular disease precluded by a death attributable to another cause such as cancer. We cannot exclude an asymmetric effect of therapeutic or diagnostic interventions, which may limit chances of cardiac death and simultaneously favor the chances of cancer death, for instance, with lifesaving diagnostic and therapeutic cardiologic interventions based on ionizing radiation.

Elusive Pathogenetic Link Between SE Results and Cancer Death

As shown in the past by several groups with physical and pharmacological stresses, functional testing with SE predicts all-cause death and in particular, cardiac death.[11–14] A less expected and less obvious finding of the present study is that SE results also predict cancer death, but with a different temporal trend compared with cardiovascular death. SE results and cancer death overlap at 5, 10, and 15 years; they significantly diverge at 20 years and even more clearly, at 25 years of follow-up. On the contrary, SE results and cardiovascular death probability already diverge at 5 years of

follow-up. This finding is apparently counterintuitive but not totally unexpected for several reasons. Cancer and ischemic heart disease share many risk factors (eg, obesity and diabetes mellitus),[18] underlying biology (eg, chronic inflammation, somatic DNA instability),[19,20] and possibly iatrogenic links (since radiation widely used in CAD diagnosis and treatment is also a risk factor for cancer, in the same way—conceptually—as radiation and drugs used for diagnosis and treatment of cancer are an established risk factor for ischemic heart disease).[21–23] The interaction analysis established that the relationship between SE result and cancer risk was valid both in smokers and in nonsmoker patients, which ruled out the smoking history influence on the relation between SE result and cancer.

Whether it is the efficacy of preventive and curative measures in ischemic heart disease, and/or the vulnerability to potential long-term effects of oncogenic or cardiological interventions, as a result, the initially cardiological patient is increasingly at risk to die of cancer as time goes by.

A possible interpretation of our findings is that with index-SE, we are indirectly measuring the common risk factor milieu of degenerative diseases such as cardiovascular disease and cancer. This vulnerability is mirrored in the functional significance of an epicardial coronary artery stenosis in SE, but affects a variety of different degenerative diseases, which will eventually produce either cancer or cardiovascular death, the latter more likely to be slowed—and the former more likely to be unaffected or perhaps accelerated—by the cascade of interventions triggered by (or associated with) SE positivity.

Comparison With Previous Studies

To our knowledge, there are no studies evaluating the changing trends in causes of death after SE testing, although emerging data from coronary angiography[24] or myocardial perfusion stress imaging[25] data suggest that the coronary atherosclerotic burden assessed by functional (stress-induced perfusion defects) or anatomical (CAD by coronary angiography) proxies predict noncardiac and especially cancer death more than cardiac death. Recently, Poulin et al have shown that the use of adenosine stress for perfusion imaging is associated with higher risk of death than exercise testing, and this difference in mortality is mainly driven by noncardiac death. The positivity for perfusion criteria was predictive of noncardiac death at univariable, but not multivariable analysis.[24] This is different from our findings but can be explained by different patient selection criteria and sample sizes. First, for decades in our population, pharmacological SE has been the only, and is still in many cases the preferred, mode of stress imaging since pharmacological SE has similar accuracy but provides substantially better image quality, lower technical difficulty, and higher potential for dual imaging (wall motion and coronary flow velocity reserve) than exercise SE imaging. Second, the lack of independent predictive value of inducible ischemia by perfusion imaging in the study by Poulin et al may be because of sample size limitations. With a sample size of 1511 patients and a follow-up of 4.0 years, only 50 noncardiac and 18 cardiac deaths occurred, with a high risk of collinearity (between stress mode and perfusion defect presence) and overfitting of the Cox model, leading to a significant type II (not seeing an existing difference) error.[24] Third, the study clustered together all causes of noncardiac death, whereas we could separate cancer causes, where most of the difference was found. Previous studies have evaluated the changing trends in causes of death after percutaneous coronary interventions (PCIs), which is a more direct index of anatomic coronary artery disease, of which SE results are only a proxy. In a retrospective analysis of >19 000 patients surviving an index PCI, Spoon et al found a 33% decline in cardiac death at 5 years after PCI, but a 57% increase in noncardiac death, primary attributable to cancer, which accounted for 26.2% of deaths (4.3% from hematologic malignancies) during 5 years of follow-up after PCI.[24] For men and women aged at least 60 years at the time of the first PCI, excess risk of potentially fatal cancers attributable to radiation ranged from 0.4% to 4%.[26,27] The number of PCIs is a risk factor for subsequent development of lung cancer[28] and leukemia,[23] and contributes to the majority of the significant radiological exposure of the adult cardiology patient.[29] In a previous study in a much larger population of 16 311 in-hospital cardiac patients admitted to our institution over the past 40 years, we showed that the cumulative estimated effective radiation dose from cardiologic testing was a significant predictor of cancer death and for (fatal and nonfatal) cancer onset.[28]

Clinical Implications

As expected and in keeping with previous extensive evidences,[6–13] a negative SE was associated with a significantly lower death rate compared with patients with positive SE. However, the 25-year mortality difference between patients with SE positive versus those with SE negative results, albeit significant because of the large sample size, was modest: 70% versus 60% for all-cause death and 40% versus 31% for cardiovascular death. This finding may recognize several different explanations. First, the snapshot assessment with a cardiac stress testing of any kind has a limited warranty period, and coverage usually expires within a few years. Second, the difference in natural history is diluted by effective interventions changing, hopefully for the better, the outcome in positive SE patients. Third, the conventional SE testing is based on regional wall motion analysis and detection of

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ischemia-producing coronary artery stenosis, but other variables (from coronary microcirculation to coronary vasospasm to neural and blood vulnerability) may contribute to cardiac events and are in the blind spot of any form of cardiac stress testing.

What we can say from our data is that a negative SE test is associated with a low cardiovascular and cancer risk, which can be a clinically relevant information. What we cannot say is that we can reassure a cancer patient with negative SE that they will do fine, since a previous history or current evidence of cancer were exclusion criteria in our study. Nevertheless, cardiovascular complications are often the limiting prognostic problem in patients effectively cured of cancer, because of the efficacy of anticancer cures and of the known cardiotoxic effects of radiotherapy and chemotherapy, and a systematic assessment of SE in known cancer patients at low risk of recurrence might be a rational method for early detection and risk stratification in cancer patients, especially considering that the new generation of SE allows integrated testing of coronary arteries, left ventricular contractile reserve, coronary microcirculation, and valvular and diastolic function, all of which are targets of effective anticancer treatment.[30]

Study Limitations

Medical therapy could not be controlled in our study, but only recorded, since it was left to the clinical judgment of the referring physician-cardiologist. Patients with positive SE compared with those with negative SE received more therapy with statins (48% versus 35%, $P<0.001$) and antiplatelet agents (79% versus 64%, $P<0.001$), and also much more nitrates (75% versus 46%, $P<0.001$) and calcium-channel blockers (61% versus 32%, $P<0.001$). They received less angiotensin converting enzyme inhibitors (17% versus 24%, $P<0.001$) and slightly less β-blockers (29 versus 31%, $P=0.05$) possibly because of lower incidence of arterial hypertension (45 versus 52%, $P<0.001$). The observed differences in medical therapy might have introduced a bias both in the acute determination of SE result and in the long-term outcome data. At the time of testing, ongoing therapy with calcium antagonists, β-blockers, and nitrates can substantially reduce the positivity rate of SE performed off-therapy.[31,32] In addition, some long-term medical therapy might be associated with a reduced risk of specific types of cancer, such as aspirin for colorectal cancer[33] or statins for gastric cancer.[34] Immediate-release calcium antagonists (now abandoned for sustained-release forms) have been possibly associated with slightly increased risk of breast cancer.[35] The long-term use of β-blockers and angiotensin-converting enzyme inhibitors has shown a neutral effect on liver cancer risk.[36] In general, the effects of cardiovascular drugs, if any, are likely to be of small size and limited to specific cancer types, and the medical therapy asymmetry observed in our population between SE-positive and SE-negative population is unlikely to affect the observed results.

Lifestyle information (physical activity, nutrition, psychosocial aspects) comprises the most important etiopathogenetic factors on both CAD and cancer, but they are also the most difficult to identify and quantify, and were not available in our database, which was structured in the 1980s.

Although we have adjusted the model for classes of age, age might have affected asymmetrically the different causes of death, because of the known greater cancer mortality in the elderly and the lower effect on some of the causes of noncardiovascular, noncancer death. However, the HR of age was similar for the 3 causes of death at univariate and multivariate analysis (HR =1.07 for cancer; 1.06 for cardiovascular; 1.12 for noncancer, noncardiovascular death).

We did not use time-dependent covariates in the Cox model and we cannot exclude the effect of changes in lifestyle, such as smoking cessation, on mortality curves.

The data were prospectively collected by different teams of scientists for SE and prognostic data, with causes of death collected by a dedicated team, unaware of SE results and study hypothesis, through scheduled surveillance. The cause of death was usually verified by multiple sources: direct perusal of in-hospital records, interview of the closest relative, report of the family physician. Nevertheless, there are limitations inherent to the retrospective design, single-center approach with possibility of referral bias, and the unavoidable inaccuracy of classifying the mode of death, especially in patients with multiple morbidities evaluated many years after the initial study enrollment, with potential of some misclassification.[16]

We lost 200 patients to follow-up. This is 4% of the initially considered cohort and is a very reasonable percentage in a longitudinal study performed in a tertiary care referral center with patients coming from across the entire nation, at least until the year 2000. The patients lost to follow-up also included foreign, non-Italian patients admitted on an emergency basis during their Tuscany visit. In general, it is considered that a follow-up study can have a significant bias when the dropout rate exceeds 20%, and our 4% for a large-scale study with a median follow-up of 131 months is of little concern as a possible source of bias, since loss to follow-up is unavoidable, and increases with time.[37]

Conclusion

Although a confounding effect of age (acting asymmetrically in the long term on cancer, cardiovascular, and noncardiac, noncardiovascular causes of death) cannot be ruled out, we found that in the long term, SE results predict not only—as

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known and expected—cardiovascular death, but also, as less expected and less known, cancer death. Since both cancer and CAD have common risk factors, this might imply that our preventive strategies for CAD have an even stronger drive in high-risk patients, in whom effective treatment on shared risk factors can help to achieve 2 goals (cancer and CAD prevention) with 1 method. In patients with stable CAD, our diagnostic and therapeutic strategies in low-risk CAD patients should probably also be planned in order to minimize the exposure to known oncogenic risk factors, for instance, avoiding inappropriate, unjustified, or unoptimized testing or therapies with ionizing radiation.[38]

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Disclosures

None.

References

1. Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG. American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. *J Am Soc Echocardiogr*. 2007;20:1021–1041.
2. Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D, Voigt JU, Zamorano JL. European Association of Echocardiography Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur J Echocardiogr*. 2008;9:415–437.
3. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabaté M, Senior R, Taggart DP, van der Wall EE, Vrints CJ; ESC Committee for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S; Document Reviewers, Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, Hamilos M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Rydén L, Simoons ML, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirir A, Zamorano JL. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013; 34:2949–3003.
4. Wolk MJ, Bailey SR, Doherty JU, Douglas PS, Hendel RC, Kramer CM, Min JK, Patel MR, Rosenbaum L, Shaw LJ, Stainback RF, Allen JM; American College of Cardiology Foundation Appropriate Use Criteria Task Force. ACCF/AHA/ASE/ASNC /HFSA/HRS/SCAI/ SCCT/ SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014; 63:380–406.
5. Picano E, Severi S, Michelassi C, Lattanzi F, Masini M, Orsini E, Distante A, L'Abbate A. Prognostic importance of dipyridamole-echocardiography test in coronary artery disease. *Circulation*. 1989;80:450–457.
6. Picano E, Landi P, Bolognese L, Chiarandà G, Chiarella F, Seveso G, Sclavo MG, Gandolfo N, Previtali M, Orlandini A, Margaria F, Pirelli S, Magaja O, Minardi G, Bianchi F, Marini C, Raciti M, Michelassi C, Severi S, Distante A; on behalf of the EPIC study group. Prognostic value of dipyridamole echocardiography early after uncomplicated myocardial infarction: a large-scale, multicenter trial. The EPIC Study Group. *Am J Med*. 1993;95:608–618.
7. Severi S, Picano E, Michelassi C, Lattanzi F, Landi P, Distante A, L'Abbate A. Diagnostic and prognostic value of dipyridamole echocardiography in patients with suspected coronary artery disease. Comparison with exercise electrocardiography. *Circulation*. 1994;89:1160–1173.
8. Picano E, Pingitore A, Sicari R, Minardi G, Gandolfo N, Seveso G, Chiarella F, Bolognese L, Chiaranda G, Sclavo MG, Previtali M, Margaria F, Magaja O, Bianchi F, Pirelli S, Severi S, Raciti M, Landi P, Vassalle C, de Bento Sousa MJ, De Moura Duarte LF; on behalf of Echo Persantine International Cooperative (EPIC) Study Group. Stress echocardiographic results predict risk of reinfarction early after uncomplicated acute myocardial infarction: large-scale multicenter study. *J Am Coll Cardiol*. 1995;26:908–913.
9. Varga A, Picano E, Cortigiani L, Petix N, Margaria F, Magaia O, Heyman J, Bigi R, Mathias W Jr, Gigli G, Landi P, Raciti M, Pingitore A, Sicari R. Does stress echocardiography predict the site of future myocardial infarction? A large-scale multicenter study. EPIC (Echo Persantine International Cooperative) and EDIC (Echo Dobutamine International Cooperative) study groups. *J Am Coll Cardiol*. 1996;28:45–51.
10. Arruda AM, Das MK, Roger VL, Klarich KW, Mahoney DW, Pellikka PA. Prognostic value of exercise echocardiography in 2,632 patients > or = 65 years of age. *J Am Coll Cardiol*. 2001;37:1036–1041.
11. Marwick TH, Case C, Sawada S, Rimmerman C, Brenneman P, Kovacs R, Short L, Lauer M. Prediction of mortality using dobutamine echocardiography. *J Am Coll Cardiol*. 2001;37:754–760.
12. Sicari R, Pasanisi E, Venneri L, Landi P, Cortigiani L, Picano E; Echo Persantine International Cooperative (EPIC) Study Group; Echo Dobutamine International Cooperative (EDIC) Study Group. Stress echo results predict mortality: a large-scale multicenter prospective international study. *J Am Coll Cardiol*. 2003;41:589–595.
13. Cortigiani L, Rigo F, Gherardi S, Bovenzi F, Molinaro S, Picano E, Sicari R. Coronary flow reserve during dipyridamole stress echocardiography predicts mortality. *JACC Cardiovasc Imaging*. 2012;5:1079–1085.
14. Sleight P. Debate: subgroup analysis in clinical trials: fun to look at—but don't believe them!. *Curr Controls Trials Cardiovasc Med*. 2000;1:25–27.
15. Shaw LJ, Berman DS, Picard MH, Friedrich MG, Kwong RY, Stone GW, Senior R, Min JK, Hachamovitch R, Scherrer-Crosbie M, Mieres JH, Marwick TH, Phillips LM, Chaudhry FA, Pellikka PA, Slomka P, Arai AE, Iskandrian AE, Bateman TM, Heller GV, Miller TD, Nagel E, Goyal A, Borges-Neto S, Boden WE, Reynolds HR, Hochman JS, Maron DJ, Douglas PS; National Institutes of Health/National Heart, Lung, and Blood Institute-Sponsored ISCHEMIA Trial Investigators. Comparative definitions for moderate-severe ischemia in stress nuclear, echocardiography, and magnetic resonance imaging. . *JACC Cardiovasc Imaging*. 2014;7:593–604.
16. Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: time for a reassessment? *J Am Coll Cardiol*. 1999;34:618–620.
17. Wolbers M, Koller MT, Stel VS, Schaer B, Jager KJ, Leffondré K, Heinze G. Competing risks analyses: objectives and approaches. *Eur Heart J*. 2014;35:2936–2941.
18. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. *Circulation*. 2016;133:1104–1114.
19. Ross JS, Stagliano NE, Donovan MJ, Breitbart RE, Ginsburg GS. Atherosclerosis: a cancer of the blood vessels? *Am J Clin Pathol* 2001;116(suppl):S97–S107.
20. De Flora S, Izzotti A. Mutagenesis and cardiovascular diseases. Molecular mechanisms, risk factors, and protective factors. *Mutat Res*. 2007;621:95–105.
21. Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. *JAMA*. 2007;298:317–323.
22. Gonzalez de Berrington A, Kim KP, Smith-Bindman R, Mc Areavey D. Myocardial perfusion scans: projected population cancer risks from current levels of use in the United States. *Circulation*. 2010;122:2403–2410.
23. Wei KC, Lin HY, Hung SK, Huang YT, Lee MS, Wang WH, Wu CS, Su YC, Shen BJ, Tsai SJ, Tsai WT, Chen LC, Li CY, Chiou WY. Leukemia risk after cardiac fluoroscopic interventions stratified by procedure number, exposure latent time, and sex. A Nationwide Population-Based Case-Control Study. *Medicine (Baltimore)*. 95:e2953.
24. Spoon DB, Psaltis PJ, Singh M, Holmes DR Jr, Gersh BJ, Rihal CS, Lennon RJ, Moussa ID, Simari RD, Gulati R. Trends in cause of death after percutaneous coronary intervention. *Circulation*. 2014;129:1286–1294.
25. Poulin MF, Alexander S, Doukky R. Prognostic implications of stress modality on mortality risk and cause of death in patients undergoing office-based SPECT myocardial perfusion imaging. *J Nucl Cardiol*. 2016;23:202–211.

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26. Eisenberg MJ, Afilalo J, Lawler PR, Abrahamowicz M, Richard H, Pilote L. Cancer risk related to low-dose ionizing radiation from cardiac imaging in patients after acute myocardial infarction. *CMAJ*. 2011;183:430–436.

27. Jacob P, Stram DO. Late health effects of radiation exposure: new statistical, epidemiological, and biological approaches. *Int J Radiat Biol*. 2013;89:673–683.

28. Carpeggiani C, Rossi G, Landi P, Michelassi C, Brambilla M, Cortigiani L, Picano E. Long-term outcome and medical radiation exposure in patients hospitalized for cardiovascular disease. *Int J Cardiol*. 2015;195:30–36.

29. Bedetti G, Botto N, Andreassi MG, Traino C, Vano E, Picano E. Cumulative patient effective dose in cardiology. *Br J Radiol*. 2008;81:699–705.

30. Lancellotti P, Pellikka PA, Budts W, Chaudhry FA, Donal E, Dulgheru R, Edvardsen T, Garbi M, Ha JW, Kane GC, Kreeger J, Mertens L, Pibarot P, Picano E, Ryan T, Tsutsui JM, Varga A. The Clinical Use of Stress Echocardiographycardiography in Non-Ischaemic Heart Disease: Recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2017;30:101–138.

31. Lattanzi F, Picano E, Bolognese L, Piccinino C, Sarasso G, Orlandini A, L'Abbate A. Inhibition of dipyridamole-induced ischemia by antianginal therapy in humans. Correlation with exercise electrocardiography. *Circulation*. 1991;83:1256–1262.

32. Ferrara N, Coltorti F, Leosco D, Sederino S, Abete P, Caccese P, Landing P, Longobardi G, Verde R, Rengo F. Protective effect of beta-blockade on dipyridamole-induced myocardial ischemia. Role of heart rate. *Eur Heart J*. 1995;16:903–908.

33. Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, Meade TW. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet*. 2010;376:1741–1750.

34. Singh PP, Singh S. Statins are associated with reduced risk of gastric cancer: a systematic review and meta-analysis. *Ann Oncol*. 2013;24:1721–1730.

35. Chen Q, Zhang Q, Zhong F, Guo S, Jin Z, Shi W, Chen C, He J. Association between calcium channel blockers and breast cancer: a meta-analysis of observational studies. *Pharmacoepidemiol Drug Saf*. 2014;23:711–718.

36. Hagberg KW, Sahasrabuddhe VV, McGlynn KA, Jick SS. Does Angiotensin-Converting Enzyme Inhibitor and β-Blocker Use Reduce the Risk of Primary Liver Cancer? A Case-Control Study Using the U.K. Clinical Practice Research Datalink. *Pharmacotherapy*. 2016;36:187–195.

37. Kristman V, Manno M, Côté P. Loss to follow-up in cohort studies: how much is too much? *Eur J Epidemiol*. 2004;19:751–760.

38. Picano E, Vañó E, Rehani MM, Cuocolo A, Mont L, Bodi V, Bar O, Maccia C, Pierard L, Sicari R, Plein S, Mahrholdt H, Lancellotti P, Knuuti J, Heidbuchel H, Di Mario C, Badano LP. The appropriate and justified use of medical radiation in cardiovascular imaging: a position document of the ESC Associations of Cardiovascular Imaging, Percutaneous Cardiovascular Interventions and Electrophysiology. *Eur Heart J*. 2014;35:665–672.

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