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Pericarditis as a Marker of Occult Cancer and a Prognostic Factor for Cancer Mortality

Running Title: *Søgaard et al.; Pericarditis and Cancer Risk*

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Abstract

Background—Pericarditis may be a serious complication of malignancy. Its significance as a first symptom of occult cancer and as a prognostic factor for cancer survival is unknown.
Methods—Using Danish medical databases, we conducted a nationwide cohort study of all patients with a first-time diagnosis of pericarditis during 1994–2013. We excluded patients with previous cancer and followed the remaining patients for subsequent cancer diagnosis until November 30, 2013. We calculated risks and standardized incidence ratios (SIRs) of cancer for patients with pericarditis compared with the general population. We assessed whether pericarditis predicts cancer survival by the Kaplan-Meier method and Cox regression, using a matched comparison cohort of cancer patients without pericarditis.
Results—Among 13,759 patients with acute pericarditis, 1,550 subsequently were diagnosed with cancer during follow-up. The overall cancer SIR was 1.5 (95% confidence interval [CI]: 1.4-1.5), driven predominantly by increased rates of lung, kidney, and bladder cancer, lymphoma, leukemia, and unspecified metastatic cancer. The <3-month cancer risk among patients with pericarditis was 2.7% and the SIR was 12.4 (95% CI: 11.2-13.7). The 3-<12-month SIR of cancer was 1.5 (95% CI: 1.2-1.7), subsequently decreasing to 1.1 (95% CI: 1.0-1.2). Three-month survival following cancer diagnosis was 80% and 86% among those with and without pericarditis, and the hazard ratio (HR) was 1.5 (95% CI: 1.3-1.8). One-year survival was 65% and 70%, respectively, corresponding to a 3-<12 month HR of 1.3 (95% CI: 1.1-1.5).
Conclusions—Pericarditis may be a marker of occult cancer and augurs increased mortality following a cancer diagnosis.

Key Words: pericarditis, pericardial effusion, epidemiology, cancer

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Clinical Perspective

What is new?

- Patients with newly diagnosed pericarditis had higher risks than age- and sex-matched members of the general population of being diagnosed with lung cancer, non-Hodgkin lymphoma, and myeloid leukemia during the first 3 months following a pericarditis diagnosis.
- The increased risk for lung cancer, non-Hodgkin lymphoma, and bladder cancer persisted beyond 1 year following a pericarditis diagnosis.
- The increased cancer risk was not restricted to patients with pericardial effusion.
- Pericarditis was a prognostic factor for survival after lung cancer, breast, and bladder cancer.

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What are the clinical implications?

- Patients with pericarditis, particularly when complicated by pericardial effusion, may need to be considered for work-up targeted at diagnosing or ruling out cancer.

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Pericarditis, the most common disease of the pericardium, is a relatively benign and self-limiting disease[1], with an annual incidence rate of approximately 30 per 100,000 persons[2]. While its etiology remains elusive in many patients, up to two-thirds of the cases are attributable to infection, predominantly with viral pathogens[3,4]. Other known risk factors are recent cardiothoracic surgery, recent myocardial infarction, recent bacterial infection, autoimmune disease, and cancer[4,5]. In unselected cohorts of pericarditis patients, around 5% are attributed to cancer etiology[4,6,7]. However, in patients with pericarditis and pericardial effusion, malignancy is more prevalent, ranging between 12% and 23%[8-11].

Cancer-related pericarditis may develop via direct infiltration by malignant cancer cells from adjacent structures, pericardial hemorrhage, or hematogenous dissemination of cancer cells[12]. In addition, pericarditis may occur as part of the paraneoplastic syndrome[13]. Among patients with acute pericarditis or pericardial effusions, cancers of the lung and breast and hematological malignancies are diagnosed most frequently[14-16]. Case reports describe pericarditis as an early manifestation of lymphoma, gastric cancer, or ovarian cancer[17-20]. However, the magnitude of cancer risk in pericarditis patients remains unknown.

In this Danish cohort study, we examined the risk of subsequent cancer among patients with a first-time diagnosis of pericarditis with or without pericardial effusion, compared with the general population. As pericarditis may predict an advanced cancer stage, it may also predict poorer cancer survival. We investigated this hypothesis by comparing survival in matched cohorts of cancer patients with and without pericarditis.

Methods

Study design and setting

This cohort study was based on the cumulative source population of 7,107,948 persons in Denmark, between 1994 and 2013. The Danish healthcare system provides tax-supported medical care to all Danish residents, including access to hospitals and outpatient clinics[21]. In the current study, we used data from the Danish National Patient Registry (DNPR)[22], in which diagnoses are coded according to the *International Classification of Diseases*, *Eighth* and *Tenth Revisions* (ICD-8 and ICD-10). In the DNPR, the main condition prompting a hospital contact is recorded in the 'primary diagnosis' field, and other relevant diagnoses are recorded in 'secondary diagnosis' fields.

We obtained information on cancer from the Danish Cancer Registry (DCR), which has recorded incident primary cancers in Denmark since 1943[23], classified according to the ICD-10. The DCR is virtually complete and its diagnoses are highly valid[24].

Information on mortality was derived from the Danish Civil Registration System (CRS), which has monitored changes in vital status and migration on a daily basis for the entire Danish population since 1968.

Patients with acute pericarditis

We identified all patients (hospital inpatients, hospital outpatients, and emergency room encounters) with a primary or secondary diagnosis of acute pericarditis (including unspecified pericarditis, infectious pericarditis, pericardial effusion, and pericarditis with underlying autoimmune disease) using ICD-10 diagnosis codes between January 1, 1994 and November 30, 2013. We excluded patients diagnosed with pericarditis recorded before 1994.

We retrieved information from the DNPR starting in 1977 on comorbidities, including tuberculosis, connective tissue disease, and chronic obstructive pulmonary disease as a proxy for heavy smoking. We also obtained information on the following diagnoses registered during or within 30 days before the hospital contact for pericarditis: cardiothoracic surgery, cardiac catheterization, pneumonia/empyema, sepsis, and acute myocardial infarction. We documented the number of patients who underwent echocardiography or other relevant imaging of the chest in connection with their hospital contact for pericarditis (within 30 days before or after this contact).

Cancer outcomes

We linked data from the members of the pericarditis cohort to the DCR to identify previous and subsequent cancer diagnoses (other than non-melanoma skin cancer) and restricted the pericarditis cohort to patients without a previous cancer diagnosis.

For the analysis of cancer survival, we selected all patients in the pericarditis cohort who subsequently developed cancer, and matched them to up to five cancer patients identified in DCR without a pericarditis diagnosis preceding cancer diagnosis, by sex, age (5-year intervals), year of pericarditis diagnosis (5-year intervals), and cancer site. For the most frequent cancer types (non-Hodgkin lymphoma, lung, breast, bladder, colon, and prostate cancer), we also matched by cancer stage (Ann Arbor staging for non-Hodgkin lymphoma, and TNM staging for other cancers) and repeated the cancer-specific analysis.

Statistical analysis

Each patient with pericarditis was followed for cancer occurrence from the date of the first hospital contact with a discharge diagnosis of pericarditis until the date of death, emigration, or November 30, 2013, whichever came first. The cumulative incidence (or risk) of cancer in

patients with pericarditis was computed while treating death (without cancer) as a competing risk[25]. We tested equality of the cumulative incidence functions by sex, age group, pericarditis type, type of hospitalization, and type of diagnosis, using Gray´s tests[26].

We used indirect standardized incidence ratios (SIRs) as a measure of relative risk, comparing the cancer incidence observed among patients with pericarditis with that expected in the general Danish population (the observed number of a specific cancer subtype was compared to the expected number of that specific subtype)[27].

We computed the expected numbers of cancer cases based on national cancer incidence rates by age (+/-1 year), sex, and the calendar year (+/-1 year) of the pericarditis diagnosis. We computed 95% confidence intervals (CIs) for the SIRs based on the assumption that the observed number of cases followed a Poisson distribution, using the Byar's approximation[28]. SIRs were computed for all cancers combined and for each cancer type separately. We split the follow-up time into three periods: <3 months, 3-≤12 months, and 12+ months, determined a priori. The aim was detecting occurrence of occult cancer related to the acute event (*i.e.,* <3 months), long-term cancer risk (*i.e.,* 12+ months), and any potential compensatory deficit indicating detection bias (*i.e.,* 3-≤12 months). We used a single Cox model to obtain the estimates for the various time intervals using an interaction between time interval and exposure. We stratified our analyses by sex, age group (<30, 30-49, 50-69, ≥70 years), primary vs. secondary diagnosis, type of pericarditis, and the covariates. In a post-hoc analysis prompted by large differences in risk by pericardial effusion status in our main set of stratified analyses, we computed SIRs for all cancer types and by time period for patients with pericardial effusion, and for other pericarditis patients without a record of pericardial effusion, to investigate whether any increased risk of cancer depended on the presence of pericardial effusion. In the analysis pericarditis as a potential

prognostic factor, we constructed Kaplan-Meier survival curves to describe survival of cancer patients with and without a pre-cancer pericarditis. We then used Cox proportional-hazards regression to compare risks of death between the two cohorts at 3 months, 1 year, and 5 years after cancer diagnosis. We calculated hazard ratios (HRs) and associated 95% CIs, adjusting for sex, age, calendar year of diagnosis, and cancer type and stage (accounting for the matching by forming strata for the baseline hazard for the matched patients). All codes are included in the Supplemental Appendix 1.

The study was approved by the Danish Data Protection Agency, record number 1-16-02-1-08. Danish registry data are generally available to researchers, and in accordance with Danish law, use of this data does not require informed consent. All statistical analyses were conducted using SAS statistical software, v. 9.4 (SAS Institute, Cary, NC, USA).

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Results

Patient characteristics

We identified 13,759 patients with pericarditis during a 20-year period, corresponding to an incidence rate of 168 cases per 100,000 persons per year. Median age at pericarditis diagnosis was 49 years (interquartile range [IQR]: 34-64 years), and 72% of the patients were male. Among the pericarditis patients, 9,758 (71%) had unclassified acute pericarditis, 1,401 (10%) had acute infectious pericarditis, 2,221 (16%) had pericardial effusion, and the remaining 379 (3%) had an autoimmune disease. Prevalent risk factors included recent thoracic surgery (11%), pneumonia/empyema (8%), myocardial infarction (6%), heart failure (6%), connective tissue disease (4%), implanted pacemaker (4%), tuberculosis (0.5%), and sepsis (1%) (Table 1). Prevalence of chronic obstructive pulmonary disease and alcohol-related diagnoses was each 4%.

Most patients (79%) had pericarditis recorded as their primary discharge diagnosis. The remaining patients had the following conditions as the most frequent primary reason for their contact: other cardiovascular conditions (myocardial infarction, cardiac insufficiency, and atrial fibrillation), pneumonia, and empyema. There were differences in patients´ characteristics according to type of hospital contact: patients with emergency room diagnoses tended to be younger (median age 34 years) and to have unclassified or infectious pericarditis. These patients also had a lower burden of underlying disease than patients with an inpatient or hospital outpatient diagnosis of pericarditis. (Supplemental Figure 1)

Overall cancer risk

Overall, there were 1,550 observed new cancer diagnoses among the pericarditis patients vs. 1,070 expected, during median follow-up of 6.4 years (IQR: 2.5-11.5 years), corresponding to an overall SIR of 1.5 (95% CI: 1.4-1.5).

While all types of pericarditis were associated with an increased risk of subsequent cancer, patients with pericardial effusion had the highest incidence rate ratio [SIR = 2.1 (95% CI: 1.9-2.3)]. For patients with unclassified pericarditis, the SIR was 1.3 (95% CI: 1.2-1.4); for patients with acute infectious pericarditis, the SIR was 1.3 (95% CI: 1.0-1.5); and for patients with underlying autoimmune disease, the SIR was 1.7 (95% CI: 1.2-2.3). The types of cancer underlying this increased cancer risk were cancers of oral cavity, lung, heart, colon, kidney, prostate, and bladder, as well as lymphoma, leukemia, and unspecified metastatic cancer (Table 2).

Cancer risk during the first year of follow-up

Within the first <3 months following an incident pericarditis diagnosis, 376 cancers were diagnosed among the 13,759 pericarditis patients, corresponding to an absolute risk of 2.7%.

More than half of the cases were lung cancers (n=210, 56%). Lymphoma accounted for 36 cases, leukemia for 16 cases, and unspecified metastatic cancers for 17 cases. The other cancer sites had 10 events or fewer each (Table 2). Among cancers diagnosed during the same hospital contact as the qualifying pericarditis episode (N = 123), lung cancer accounted for 52% (n = 64), non-Hodgkin lymphoma for 9% (n = 11), and 7% (n = 9) had unspecified metastatic cancer.

The 3-month SIR was 12.4 (95% CI: 11.2-13.7), mainly driven by lung cancer [SIR = 65.0 (95% CI: 56.5-74.4)]. The risk of hematological cancers also was markedly increased during first 3 months of follow-up: 30-fold for non-Hodgkin lymphoma and up to 49-fold for myeloid leukemia (Table 2). Other sites with excess cancer risks were the heart and thoracic cavity, pancreas, ovary, kidney, and bladder. However, the associated estimates were imprecise. The risk of breast cancer, albeit based on few cases, was increased threefold during this period.

During the 3 to <12 months following an incident pericarditis diagnosis, 123 cancers were registered, corresponding to a 1-year absolute cancer risk of 3.7% and a SIR of 1.5 (95% CI: 1.2-1.7) (Table 2) for any cancer. The observed number of cases was greater than expected for lung and bladder cancer, non-Hodgkin lymphoma, and myeloid leukemia.

Cancer risk one year or more following pericarditis

One year or more following pericarditis, 1,051 cancers were diagnosed, compared with 954 expected. This corresponded to a SIR of 1.1 (95% CI: 1.0-1.2). Increased SIRs were observed for cancer of the oral cavity, colon, lung, and bladder, and for non-Hodgkin lymphoma. In contrast, one or more years following a pericarditis diagnosis, no association was found between pericarditis and breast, or unspecified metastatic cancers.

Subgroup analysis by patient characteristics

Several patient characteristics modified the association between pericarditis and overall cancer risk. Both absolute and relative risks were higher in women than men. Absolute cancer risks rose with increasing age (Table 3). However, relative risks were higher among patients aged under 30 years than for older patients, compared with the expected risk in the general population (as expected given age-dependent increase in cancer risk) (Figure 1). P-values for equality of the cumulative incidence functions were <0.0001 (i.e. non-overlapping CIs) in all strata (of sex, age groups, different pericarditis types, type of hospitalization and diagnosis). We examined the SIRs for the different age groups and follow-up periods, and found that all age groups had elevated 3-months SIRs, whereas only patients aged 50-69 years had elevated SIRs beyond three months of follow-up (Supplemental Table 1).

In particular, pericarditis patients with pericardial effusion had a high 3-month cancer risk (9.4%), followed by pericarditis patients with autoimmune disease (4.5%). In contrast, patients with infectious pericarditis and unclassified pericarditis had cancer risks of 1.4% (Table 3).

While patients with an outpatient or inpatient diagnosis of pericarditis had almost the same increase in cancer risk (SIR = 1.5), there was no evidence of an elevated cancer risk associated with pericarditis diagnosed only in the emergency room (SIR = 1.0) (not presented in a table). Patients with a secondary pericarditis diagnosis had higher absolute cancer risks and a higher SIR than did patients with pericarditis as their primary diagnosis (Table 3).

Patients with pericarditis following recent thoracic surgery or recent myocardial infarction had a lower SIR for cancer than other pericarditis patients (Figure 1). Patients with

chronic obstructive pulmonary disease, alcoholism-related diagnoses, or recent pneumonia had a higher SIR for cancer than patients without these diseases.

Characteristics and cancer risks in patients with and without pericardial effusion

We noted important differences within the groups of pericarditis patients (Supplemental Table 2). Compared with patients who did not have pericardial effusion, patients who had this complication were older (median age, 63 vs. 46 years); had a shorter median follow-up time (4.0 years vs. 6.9 years); and were more likely to have their diagnosis entered in a secondary diagnosis field (34% vs. 19%). The latter difference was consistent with greater prevalence of chronic and acute diseases, and recent interventions. Specifically, patients with pericardial effusion had a higher prevalence than the remaining pericarditis patients of heart failure (15% vs. 4%), pacemaker implant (10% vs. 2%), chronic obstructive pulmonary disease (8% vs. 3%), pneumonia or empyema (10% vs. 7%), and recent thoracic surgery (42% vs. 5%). Almost all (93%) patients with pericardial effusion had an echocardiography-confirmed diagnosis (Supplemental Table 2).

Results from the supplemental analyses, estimating SIRs for pericarditis patients with and without pericardial effusion, revealed higher cancer risks in patients with than in patients without pericardial effusion within the first year after diagnosis. The <3-months SIRs were 26-fold increased among patients with and 8-fold among those without pericardial effusion (Supplemental Tables 3-4). Cancer-specific SIRs were higher among patients with than among those without effusion for lung cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, and unspecified metastatic cancer. While the SIRs of breast and kidney cancers remained elevated among patients with pericardial effusion during the first <3 months, we found no association for these cancers among other pericarditis patients during the first <3 months of follow-up

(Supplemental Tables 3-4). By contrast, the SIRs for prostate and pancreas cancers were elevated among patients without pericardial effusion, but not among patients with pericardial effusion (Supplemental Tables 3-4). During the 3-<12 months follow-up period, patients with pericardial effusion continued to have higher than expected risks of lung cancer and non-Hodgkin lymphoma, whereas there was no convincing association for patients without pericardial effusion. By contrast, we found a persistently increased SIR for myeloid leukemia only among pericarditis patients without pericardial effusion.

Beyond one year of follow-up, the SIRs of cancer for pericarditis patients with and without pericardial effusion were overall in agreement with the main analysis. In particular, the risk of lung cancer remained elevated in patients both with and without pericardial effusion. Patients without pericardial effusion had an elevated SIR of cancers of the oral cavity, whereas no cases of this cancer type were observed among those with pericardial effusion. Only patients without pericardial effusion remained at an increased risk of colon cancer (Supplemental Tables 3-4).

Pericarditis as prognostic factor for cancer patients

The survival analyses included 1,550 patients with pericarditis preceding their cancer diagnosis, and a matched cohort of 7,664 cancer patients without antecedent pericarditis. Reflecting successful matching, median age was 67 years (IQR: 59-75 years) and 67% patients were male in both cohorts. Among the pericarditis patients, 40% had localized cancer, 36% had metastatic cancer and 24% had unknown or missing cancer stage. The corresponding proportions for patients without pericarditis were 42%, 37%, and 22%.

Regardless of presence of pericarditis before a cancer diagnosis, the cancer patients had poor outcomes (Figure 2). Three-month survival after any cancer was 80% for patients with and

86% for patients without pericarditis, corresponding to an adjusted HR of 1.5 (95% CI: 1.3-1.8) for cancer overall. For specific malignancies, the adjusted three-month HR was 1.7 (95% CI: 1.4-2.0) for lung cancer, 2.0 (95% CI: 0.4-10.3) for breast cancer, and 0.8 (95% CI: 0.3-2.5) for non-Hodgkin lymphoma (Table 4). Survival at one year was 65% for patients with and 70% patients without pericarditis, and the 3-12 month HR was 1.3 (95% CI: 1.1-1.5).

Over time, pericarditis remained a prognostic factor for impaired cancer survival; after five years of follow-up, survival was 44% among cancer patients with previous pericarditis and 48% among patients without previous pericarditis (Figure 2). HRs 1-<5 years after a cancer diagnosis preceded by pericarditis indicated persistent increased mortality for bladder cancer (HR = 2.4 [95% CI: 1.3-4.2]) and breast cancer (HR = 2.2 [95% CI: 1.1-4.8]) (Table 4).

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Discussion

In this population-based nationwide cohort study, pericarditis was a marker for occult cancer. In particular, we observed a higher than expected rate of lung cancer, non-Hodgkin lymphoma, and myeloid leukemia during the first 3 months after an incident pericarditis diagnosis. While the excess risk decreased for several cancers after the first 3 months for, it nevertheless persisted for lung cancer, non-Hodgkin lymphoma, and bladder cancer diagnoses up to several years after a pericarditis diagnosis. Importantly, we observed an increased cancer risk both in patients with and without pericardial effusion. No previous study has compared the prognostic impact of pericarditis preceding cancer diagnosis. We found that pericarditis was a prognostic factor for both short-term cancer survival after lung cancer, and long-term cancer survival after bladder and breast cancer.

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Primary tumors of the heart are rare, and the majority of cancer-related pericarditis cases are caused by metastatic tumors of remote origin[29]. The most common cancers with a known potential to spread to the pericardium include lung and breast cancer, lymphoma, and leukemia[12]. Other cancers leading to pericarditis through hematogenous spread include thymic, esophageal, bladder, kidney, and ovarian cancers[7,29]. Moreover, pericarditis may occur as a part of the paraneoplastic syndrome[13]. In our unselected cohort of previously "cancer free" patients, we corroborated some associations that earlier were described only as case reports [17-20] or in small cohort studies (maximum of 453 patients) without comparison cohorts[4,6,7].

Most previous studies of pericarditis have sought to characterize its underlying causes and to examine prognostic factors for mortality [4,15,30]. The prognosis among patients with pericarditis is usually good,[31] but some characteristics are associated with a less favorable course. Co-infections (pneumonia and sepsis) and heart failure in patients with pericarditis increase in-hospital mortality[15], while fever > 38˚C, large effusions/tamponade, and NSAID treatment failure are associated with poor 6-12 month survival[4]. Bacterial pericarditis, especially purulent pericarditis, is fatal if untreated, and mortality is high even in patients receiving proper treatment[32]. Among patients with known cancer, purulent pericarditis and pericardial effusion have serious implications for prognosis[5,33,34].

All Danish residents have tax-supported universal access to medical care, including hospital admission and treatment, which minimizes the risk of selection bias. Data in the DNPR are recorded by treating clinicians and registered mainly for administrative use. As it is mandatory to report incident cancers to the DCR, we had complete cancer ascertainment (used both for exclusion of previous cancers and for cancer diagnosed during follow-up). The registry diagnoses included in our study generally are of high quality[22,23], and the positive predictive

value of hospital-based pericarditis is 92% (95% CI: 85-96%) overall, and 97% (95% CI: 91-99%) for inpatient diagnoses[35]. Because pericarditis is a serious disease, it is likely to lead to hospitalization, with diagnoses made mainly at highly specialized centers. Thus, validity and completeness of our pericarditis definition are likely high.

However, our findings reflected outcome of pericarditis in patients with symptoms sufficiently severe to necessitate hospital referral by general practitioners or the prehospital emergency service and may differ from the outcome in patients with trivial symptoms of pericarditis.

Data on the incidence of pericarditis are sparse. One study reported an annual incidence of 30 per 100,000 persons, based on 274 patients diagnosed with pericarditis at two general hospitals (covering an urban area of 220.000 inhabitants)[2]. In comparison, we included a nationwide cohort capturing persons from the entire population of Denmark (approx. 7 million people alive between 1994 and 2013) diagnosed with pericarditis at both general hospitals and university hospitals. The difference may thus be explained by our population-based setting.

A number of limitations must also be considered. There were some limitations in the clinical details available at patient level in our register-based data. We had no information on the clinical presentation, and therefore could not examine potential differences in cancer risk according to the clinical presentation.

Though the overall PPV for pericarditis diagnosis is high, there may have been misclassification between the subtypes of pericarditis, potentially diluting differences in the associations of different subtypes with cancer.

We adjusted for age and sex by indirect standardization; whereas we did not adjust for other factors. While life style factors are not strong risk factors for pericarditis, they may have

modified the cancer risk. Unfortunately, we lacked data to sufficiently examine potential effect modification by smoking and alcohol use.

Patients with pericarditis as a secondary diagnosis of had a higher risk of cancer than patients with pericarditis as the primary reason for their hospital contact. Pericarditis in a secondary position is indicative of additional or more severe morbidities at the time of the pericarditis diagnosis, which could explain the findings. Potentially, symptoms suggestive of cancer could have led to more thorough examination of these patients.

A few clinical factors may signal neoplastic origin of pericarditis, e.g. unremitting course or recurrent episodes, pericardial effusion, or inefficient recovery after NSAIDs treatment[14]. We confirmed that pericardial effusion is associated with high cancer risk; in fact, almost every tenth patient with pericardial effusion had a cancer diagnosis within the first 3 months after the pericarditis diagnosis.

We found especially high risks of lung cancer and non-Hodgkin lymphoma in patients with pericardial effusion, but also a higher short-term risk of lung cancer, breast cancer, non-Hodgkin lymphoma, and unspecific metastatic cancer. Patients without pericardial effusion had higher short-term risks of myeloid leukemia and prostate cancer, and long-term risks of colon cancer and cancer of the oral cavity.

Patients with pericardial effusion were older, and had higher prevalence of heart failure, pacemaker implants, chronic obstructive pulmonary disease, and recent thoracic surgery than patients without pericardial effusion.

The overall stratified analyses showed that presence of heart failure, chronic obstructive pulmonary disease, alcohol-related diagnoses, tuberculosis, and recent pneumonia or empyema, was associated with elevated cancer SIRs among pericarditis patients. While these conditions are

known to be associated with increased cancer risk [36-38], they are not considered important confounders in the relation between pericarditis and cancer. However, they could potentially be modifiers of the cancer risk among pericarditis patients. Accordingly, patients with these conditions may have an increased risk of cancer and should thus be classified as high-risk patients. By contrast, patients with recent thoracic surgery or recent myocardial infarction had a lower SIR than patients without this history. This finding accord with a lower a priori cancer risk among patients with underlying diseases not strongly related to cancer. However, the lower SIR for patients who underwent thoracic surgery may also indicate that patients with obvious signs of cancer were deemed unsuitable for surgery.

In agreement with the previous guidelines for diagnostic work-up in patients with pericarditis, the work-up conducted in patients in our cohort may have been targeted mainly at excluding myocardial infarction (i.e., ECG, echocardiography, examination of biomarkers for acute cardiac ischemia, chest x-ray). However, the updated guidelines recommend additional assessment of markers of inflammation (i.e., CRP and/or erythrocyte sedimentation rate [ESR]), white blood cell count with differential count, renal function, liver tests, and tests indicating myocardial lesion (creatine kinase and troponin) in all cases of suspected pericarditis[1]. In addition, further testing (e.g. CT scan) is indicated in high-risk patients according to clinical indicators (fever >38˚C, subacute course, large pericardial effusion, cardiac tamponade, and/or failure of aspirin or NSAIDs)[1].

The clinical value of the different diagnostic tests was summarized in a review, showing that malignancy as etiology shares several features with other causes[8]. Clinical examination with auscultation, ECG, echocardiography, and markers of inflammation does not discriminate between etiologies, whereas more specific tumor makers and CT or CMR could lead to

diagnosis[8]. In a study examining 55 patients with effusion, CT revealed pathological findings in all patients with malignancy, whereas clinical and biochemical data were not able to differentiate between malignant or non-malignant causes[39]. The final diagnostic of neoplastic pericarditis requires isolation of neoplastic cells from pericardial fluid by pericardiocentesis and histological examination of pericardial biopsies[5].

The frequent use of x-ray or other imaging examinations in our cohort could have revealed lung cancer or lymphoma, or led to a more thorough investigation that identified cancers, which may or may not have been related to pericarditis. Accordingly, our results for the initial 3-month follow-up period are likely influenced by heightened diagnostic effort to some degree. We observed an increased risk of most cancers during that period, but no clear compensatory drop in incidence ratios in the later follow-up period. Without access to patients' medical records, it is difficult to differentiate patients whose pericarditis was the first manifestation of advanced cancer, from those coincidentally occurring with cancer. In contrast, cancers diagnosed more than one year after a pericarditis diagnosis are unlikely to be subject to detection bias, although some may have been present at the time of pericarditis diagnosis.

Clinically it is important to know whether patients presenting with first-time pericarditis should be investigated more thoroughly to rule-out specific cancers. An x-ray examination potentially could lead to detection of lung cancer, metastatic cancer, or lymphoma. We speculate that if the standard work-up in our cohort of patients had included such tests as a complete blood count, liver enzyme level, and CT scan, then additional cancers might have been detected earlier. Patients, both with and without effusion had elevated relative risks of several cancers but the absolute risks were low. Accordingly, the 'number needed to examine' to detect additional cancers would be high. Thus, economic and patient-related costs, including exposure to

radiation and anxiety associated with the diagnostic work-up may outweigh the clinical utility of an extended screening such as whole body scans. Nevertheless, our results may raise awareness for lung cancer and non-Hodgkin lymphoma in patients presenting with pericardial effusion.

In conclusion, pericarditis may be a marker of occult lung and breast cancer, as well as hematological and unspecified metastatic cancers. The increased diagnosis rate of cancers of the heart and thoracic cavity, pancreas, kidney, and bladder, which may represent metastatic spread of such cancers to the pericardium. While cancer risk was increased in patients both with and without pericardial effusion, pericardial effusion was associated with particular high cancer incidence, specifically lung cancer, lymphoma, and unspecified metastatic cancer. Even though pericarditis is associated with a worse survival among patients with certain cancers, it is unclear whether an earlier detection of cancer improves survival.

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Disclosures

None.

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Table 1. Characteristics of 13,759 patients with acute pericarditis, Denmark, 1994-2013.

	N (%)
Men	9,865 (72)
Age groups, years	
<30	2,663 (19)
30-49	4,386 (32)
50-69	4,544 (33)
70+	2,166 (16)
Type of diagnosis	
Primary	10,869 (79)
Secondary	2,890 (21)
Type of hospital contact	
Inpatient	11,247 (82)
Outpatient	1,037 (7)
Emergency room	1,475 (11)
Recent procedure*	
Thoracic surgery	1,499 (11)
Cardiac catheterization	109 (1)
Recent diagnosis*	
Myocardial infarction	764 (6)
Pneumonia or empyema	1,046 (8)
Sepsis	152 (1)
Previous diagnosis†	
Tuberculosis	71 (0.5)
Connective tissue disease	557 (4)
Chronic obstructive pulmonary disease	537 (4)
Alcoholism-related diagnosis	538 (4)
Heart failure	814 (6)
Pacemaker	494 (4)
Recent imaging‡	
Echocardiography	6,537 (72)
Chest x-ray, CT or MR	7,628 (84)

* During the same hospital contact or within 30 days before a hospital contact for pericarditis.
† Since 1977
‡30 days prior to or after diagnosis (only available for patients diagnosed after 2002).

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Table 2. Standardized incidence ratios for cancer in 13,759 patients with acute pericarditis.

	Observed cancers, standardized incidence ratios (95% confidence interval), and 3-month risk (%)								
Cancer site	**0 to <3 months**			**3 to <12 months**		**12+ months**		**Overall**	
Any	376	12.4 (11.2–13.7)	2.7	123	1.5 (1.2–1.7)	1,051	1.1 (1.0–1.2)	1,550	1.5 (1.4–1.5)
Oral cavity	0	–	0.0	1	2.0 (0.1–11.3)	12	2.3 (1.2–4.0)	13	2.2 (1.2–3.7)
Esophagus	1	2.7 (0.1 –15.0)	0.0	3	2.9 (0.6–8.4)	10	0.8 (0.4–1.6)	14	1.1 (0.6–1.8)
Stomach	1	2.2 (0.1–12.0)	0.0	0	–	13	0.9 (0.5–1.6)	14	0.9 (0.5–1.5)
Colon	9	4.5 (2.1–8.5)	0.1	6	1.1 (0.4–2.3)	78	1.3 (1.0–1.6)	93	1.4 (1.1–1.7)
Rectum	1	0.9 (0.0–4.9)	0.0	2	0.6 (0.1–2.3)	37	1.1 (0.8–1.5)	40	1.0 (0.7–1.4)
Pancreas	4	6.1 (1.7–15.7)	0.0	4	2.2 (0.6–5.6)	19	0.9 (0.6–1.5)	27	1.2 (0.8–1.7)
Lung, bronchi, or trachea	210	65.0 (56.5–74.4)	1.5	19	2.1 (1.3–3.3)	132	1.4 (1.2–1.6)	361	3.3 (3.0–3.7)
Heart and thoracic cavity	4	337 (92–862)	0.0	1	31.5 (0.8–175)	2	6.4 (0.8–23.1)	7	19.7(7.9–40.5)
Breast	6	2.8 (1.0–6.2)	0.0	6	1.0 (0.4–2.2)	48	0.9 (0.6–1.1)	60	0.9 (0.7–1.2)
Ovary	5	17.2 (5.6–40.0)	0.0	1	1.2 (0.0–6.9)	8	1.1 (0.5–2.2)	14	1.7 (0.9–2.9)
Prostate	10	2.9 (1.4–5.3)	0.1	11	1.1 (0.6–2.0)	141	1.1 (0.9–1.3)	162	1.2 (1.0–1.4)
Kidney	6	12.1 (4.5–26.4)	0.0	4	2.9 (0.8–7.4)	20	1.3 (0.8–2.0)	30	1.7 (1.2–2.4)
Bladder	3	1.9 (0.4–5.5)	0.0	11	2.5 (1.2–4.4)	73	1.5 (1.2–1.9)	87	1.6 (1.3–2.0)
Brain	4	6.0 (1.6–15.3)	0.0	5	2.6 (0.9–6.2)	16	0.8 (0.5–1.3)	25	1.1 (0.7–1.6)
Hodgkin malignant lymphoma	6	64.7 (23.8–141)	0.0	0	–	2	0.8 (0.1–2.9)	8	2.8 (1.2–5.5)
Non-Hodgkin malignant lymphoma	30	29.9 (20.2–42.7)	0.2	8	2.9 (1.2–5.6)	44	1.4 (1.0–1.9)	82	2.3 (1.9–2.9)
Lymphoid leukemia	4	11.5 (3.1–29.3)	0.0	0	–	10	0.9 (0.5–1.7)	14	1.2 (0.6–2.0)
Myeloid leukemia	11	48.9 (24.4–87.5)	0.1	5	8.0 (2.6–18.7)	7	1.1 (0.4–2.2)	23	3.1 (2.0–4.6)
Unspecified metastatic cancer	17	30.5 (17.8–48.9)	0.1	1	0.6 (0.0–3.6)	12	0.8 (0.4–1.3)	30	1.7 (1.1–2.4)
Malignant melanoma	2	2.2 (0.3–7.9)	0.0	1	0.4 (0.0–2.1)	26	0.9 (0.6–1.3)	29	0.9 (0.6–1.2)
Basal cell carcinoma	4	0.7 (0.2–1.7)	0.0	15	0.9 (0.5–1.5)	205	1.0 (0.9–1.2)	224	1.0 (0.9–1.1)

Table 3. Three-month and one-year risks of any new cancer diagnosis in 13,759 patients with acute pericarditis.

	Risk in % (95% CI)	
Characteristics	**3 months**	**1 year**
Overall	2.7 (2.5-3.0)	3.7 (3.4-4.0)
Women	4.8 (4.2-5.5)	6.2 (5.4-6.9)
Men	1.9 (1.7-2.2)	2.7 (2.4-3.0)
Age groups, yr		
<30	0.6 (0.4-1.0)	0.7 (0.4-1.1)
30-49	1.1 (0.8-1.5)	1.4 (1.1-1.8)
50-69	4.6 (4.0-5.2)	5.9 (5.2-6.6)
70+	4.8 (4.0-5.8)	7.3 (6.3-8.5)
Type of pericarditis		
Unclassified	1.4 (1.1-1.6)	2.2 (1.9-2.5)
Pericardial effusion	9.4 (8.3-10.7)	11.1 (9.8-12.4)
Infectious pericarditis	1.4 (0.9-2.1)	1.9 (1.3-2.7)
Autoimmune disease	4.5 (2.7-6.9)	5.0 (3.1-7.6)
Type of hospital contact		
Inpatient	3.1 (2.8-3.4)	4.0 (3.7-4.4)
Outpatient	2.7 (1.9-3.9)	4.1 (3.0-5.5)
Emergency room	0.3 (0.1-0.8)	0.7 (0.4-1.2)
Type of diagnosis		
Primary	2.5 (2.2-2.8)	3.3 (3.0-3.7)
Secondary	3.7 (3.0-4.4)	4.9 (4.1-5.7)

P-values for equality of the cumulative incidence functions were <0.0001 in all strata (within gender, within age groups, within different pericarditis types, within type of hospitalization and diagnosis).

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Table 4. Adjusted hazard ratios (HRs) of mortality among 1,550 patients with cancer and prior pericarditis and a matched cohort of 7,664 patients with cancer and no prior pericarditis.

Cancers	Pericarditis*		No pericarditis*		Adjusted HR and 95% confidence interval†		
	N	Deaths, n‡	N	Deaths, n‡	0-<3 months	3-<12 months	1-<5 years
Any cancer	1,550	824	7,664	3757	1.5 (1.3-1.8)	1.3 (1.1-1.5)	1.2 (1.0-1.3)
Lung	326	296	1,630	1435	1.7 (1.4-2.0)	1.1 (0.8-1.4)	1.0 (0.7-1.6)
Breast	51	17	255	48	2.0 (0.4-10.3)	1.2 (0.3-4.3)	2.2 (1.1-4.8)
Non-Hodgkin lymphoma	39	12	183	69	0.8 (0.3-2.5)	0.8 (0.3-2.6)	0.7 (0.2-2.0)
Bladder	45	30	225	110	1.6 (0.5-4.9)	1.4 (0.6-3.7)	2.4 (1.3-4.2)
Colon	78	40	390	213	0.8 (0.4-1.6)	0.8 (0.4-1.7)	1.1 (0.6-2.0)
Prostate	90	26	450	137	0.2 (0.0-1.7)	3.3 (1.4-7.4)	0.7 (0.4-1.3)

*Patients were matched by age, sex, and type cancer.

† In the overall analyses (any cancer), the HRs were adjusted for cancer stage. For the specific cancer types, we matched by cancer stage.

‡ Total number of deaths five years after cancer diagnosis.

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Figure Legends

Figure 1. Standardized incidence ratios for cancer in 13,759 patients with acute pericarditis, stratified according to patient characteristics.

Figure 2. Survival among cancer patients with and without a prior pericarditis diagnosis.

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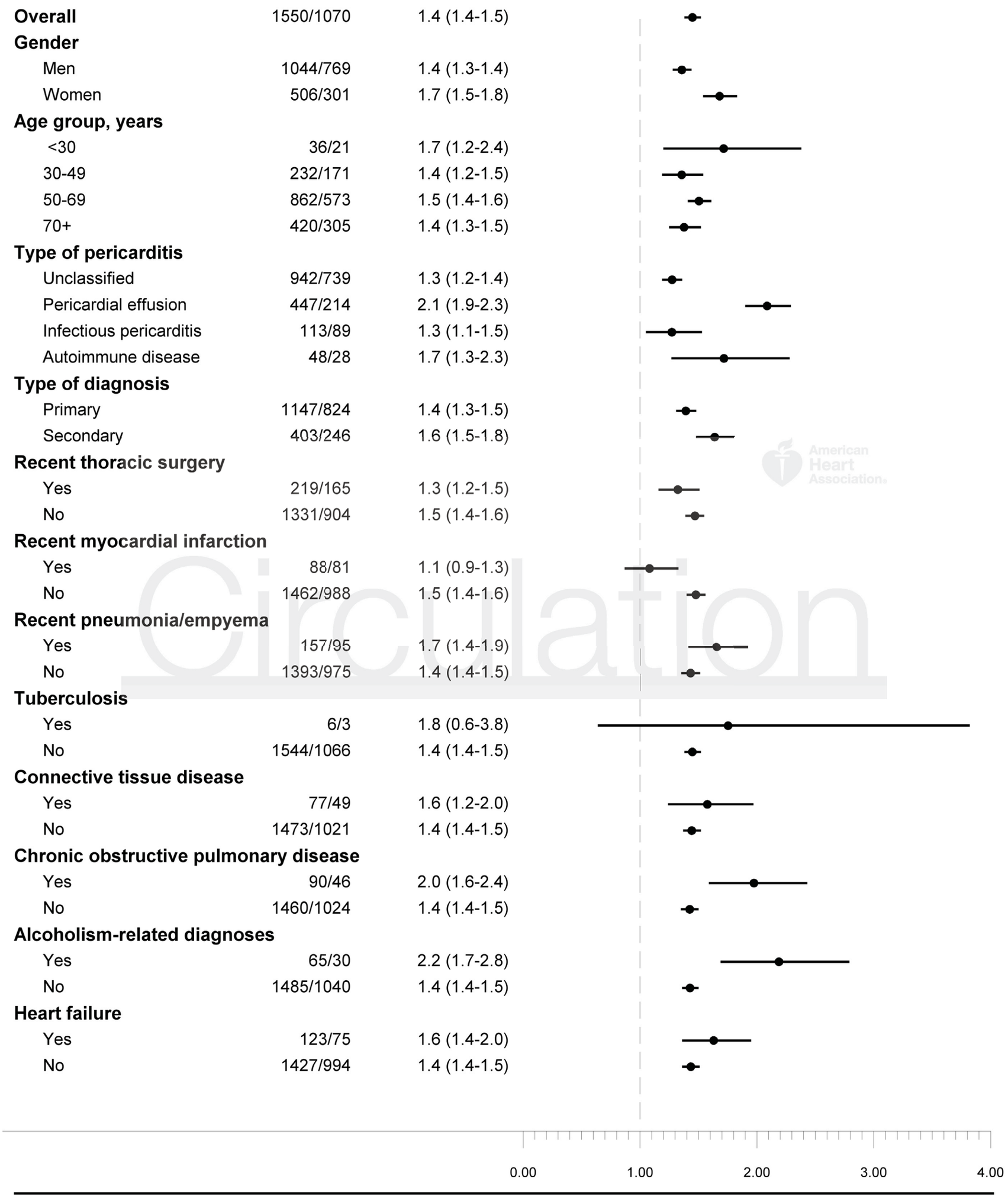
Group	O/E	SIR (95% CI)
Overall	1550/1070	1.4 (1.4-1.5)
Gender		
Men	1044/769	1.4 (1.3-1.4)
Women	506/301	1.7 (1.5-1.8)
Age group, years		
<30	36/21	1.7 (1.2-2.4)
30-49	232/171	1.4 (1.2-1.5)
50-69	862/573	1.5 (1.4-1.6)
70+	420/305	1.4 (1.3-1.5)
Type of pericarditis		
Unclassified	942/739	1.3 (1.2-1.4)
Pericardial effusion	447/214	2.1 (1.9-2.3)
Infectious pericarditis	113/89	1.3 (1.1-1.5)
Autoimmune disease	48/28	1.7 (1.3-2.3)
Type of diagnosis		
Primary	1147/824	1.4 (1.3-1.5)
Secondary	403/246	1.6 (1.5-1.8)
Recent thoracic surgery		
Yes	219/165	1.3 (1.2-1.5)
No	1331/904	1.5 (1.4-1.6)
Recent myocardial infarction		
Yes	88/81	1.1 (0.9-1.3)
No	1462/988	1.5 (1.4-1.6)
Recent pneumonia/empyema		
Yes	157/95	1.7 (1.4-1.9)
No	1393/975	1.4 (1.4-1.5)
Tuberculosis		
Yes	6/3	1.8 (0.6-3.8)
No	1544/1066	1.4 (1.4-1.5)
Connective tissue disease		
Yes	77/49	1.6 (1.2-2.0)
No	1473/1021	1.4 (1.4-1.5)
Chronic obstructive pulmonary disease		
Yes	90/46	2.0 (1.6-2.4)
No	1460/1024	1.4 (1.4-1.5)
Alcoholism-related diagnoses		
Yes	65/30	2.2 (1.7-2.8)
No	1485/1040	1.4 (1.4-1.5)
Heart failure		
Yes	123/75	1.6 (1.4-2.0)
No	1427/994	1.4 (1.4-1.5)



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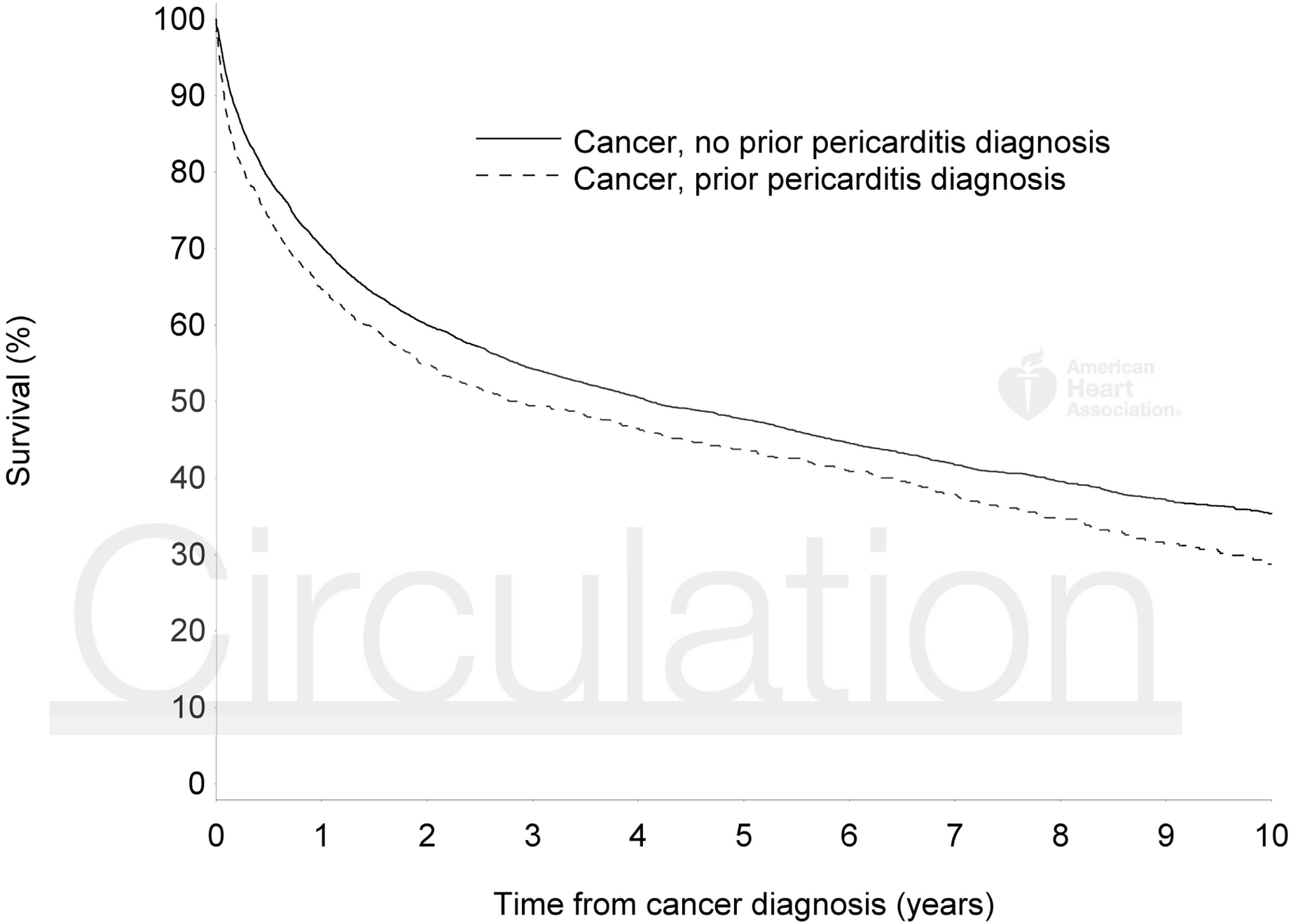

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Number at risk:

No prior pericarditis:	7664	5382	4153	3289	2640	2114	1699	1340	1055	829	617
Prior pericarditis:	1550	1002	752	593	484	373	303	226	181	132	99