


Heart failure is associated with an increased incidence of cancer diagnoses

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Abstract

Aims The prognosis and quality of life of heart failure patients is determined to a significant extent by co-morbidities. New data suggest that heart failure may be associated with an increased incidence of cancer. The present retrospective study investigates this association in a large collective of outpatients with heart failure.

Methods and results This retrospective cohort study assessed the incidence of cancer in patients with an initial diagnosis of heart failure and a matched non-heart failure cohort in 1274 general practices in Germany between January 2000 and December 2018. The study is based on the Disease Analyser database (IQVIA), which contains drug prescriptions, diagnoses, and basic medical and demographic data. Hazard regression models were used to study the association between heart failure and the incidences of different cancers. A total of 100 124 patients with heart failure and 100 124 patients without heart failure were included in the analysis. Patients were matched individually by sex, age, diabetes, obesity, and yearly consultation frequency. Within the 10 year observation period, 25.7% of patients with heart failure and 16.2% of patients without heart failure had been diagnosed with cancer (log-rank $P < 0.001$). These proportions were 28.6% vs. 18.8% in female and 23.2% vs. 13.8% in male patients. Heart failure was significantly associated with the incidence of cancer [hazard ratio (HR), 95% confidence interval: 1.76, 1.71–1.81; $P < 0.001$ in total; HR: 1.85, 1.77–1.92, $P < 0.001$ in women; HR: 1.69, 1.63–1.76, $P < 0.001$ in men]. A significant association was found between heart failure and all cancer sites assessed. The strongest association was observed for cancer of lip, oral cavity, and pharynx (HR: 2.10, 95% confidence interval: 1.66–2.17; $P < 0.001$), followed by respiratory organs (HR: 1.91, 1.74–2.10; $P < 0.001$) and genital organs of female patients (HR: 1.86, 1.56–2.17; $P < 0.001$). The association for skin tumours was 1.83 (1.72–1.94; $P < 0.001$), for cancer of lymphoid and haematopoietic tissue 1.77 (1.63–1.91; $P < 0.001$), for cancer of the digestive tract 1.75 (1.64–1.87; $P < 0.001$), for breast cancer 1.67 (1.52–1.84; $P < 0.001$), for cancer of the genitourinary tract 1.64 (1.48–1.81; $P < 0.001$), and for male genital organ cancer 1.52 (1.40–1.66; $P < 0.001$).

Conclusions Our study indicates that heart failure patients experience a significantly higher incidence of cancer during the course of the disease.

Keywords Heart failure; Co-morbidities; Cancer

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Background

Despite innovative therapeutic approaches, the mortality rate of heart failure patients remains unacceptably high. The prognosis and quality of life of heart failure patients is

affected to a significant extent by additional multiple co-morbidities.^{1–3} In Western Europe, patients already have an average of five co-morbidities at the time of diagnosis.⁴ In this context, special attention has recently been paid to the co-morbidity of cancer (cardio-oncology). It should be noted

that the term cardio-oncology is not limited explicitly to the cardiac side effects of antitumour therapies.⁵ Rather, a recent theory suggests that there may also be an increased incidence of cancer in heart failure patients.⁶ Further epidemiological data are needed to clarify this relationship, especially with regard to individual tumour types.

Aims

The aim of this study was to record the incidence of cancers in heart failure patients. Cancers in general (ICD10:C00–C99) as well as malignancies of individual organ systems such as the lips, oral cavity, and pharynx (ICD10:C00–C14), digestive organs (ICD10: C15–C26), skin (ICD10:C15–C26), breast (ICD10: C50), genital organs (ICD10:C51–C58;C60–C63), urinary tract

Table 1 Basic characteristics of the study sample (after 1:1 matching by sex, age, index year, obesity, diabetes, and yearly consultation frequency)

Variable	Proportion affected among patients with heart failure (%) N = 100 124	Proportion affected among patients without heart failure (%) N = 100 124	P-value
Age (mean, SD)	72.6 (12.2)	72.6 (12.2)	1.000
Age ≤ 60	16.5	16.9	1.000
Age 61–70	20.3	20.6	
Age 71–80	34.9	35.1	
Age > 80	28.3	27.4	
Women	54.0	54.0	1.000
Men	46.0	46.0	1.000
Diabetes	37.4	37.4	1.000
Obesity	15.9	15.9	1.000
Yearly consultation frequency	6.0 (5.7)	6.0 (5.7)	1.000

SD, standard deviation.

Proportions of patients in % given, unless otherwise indicated.

Figure 1 Selection of study patients. ICD-10, International Statistical Classification of Diseases and Related Health Problems, Version 10.

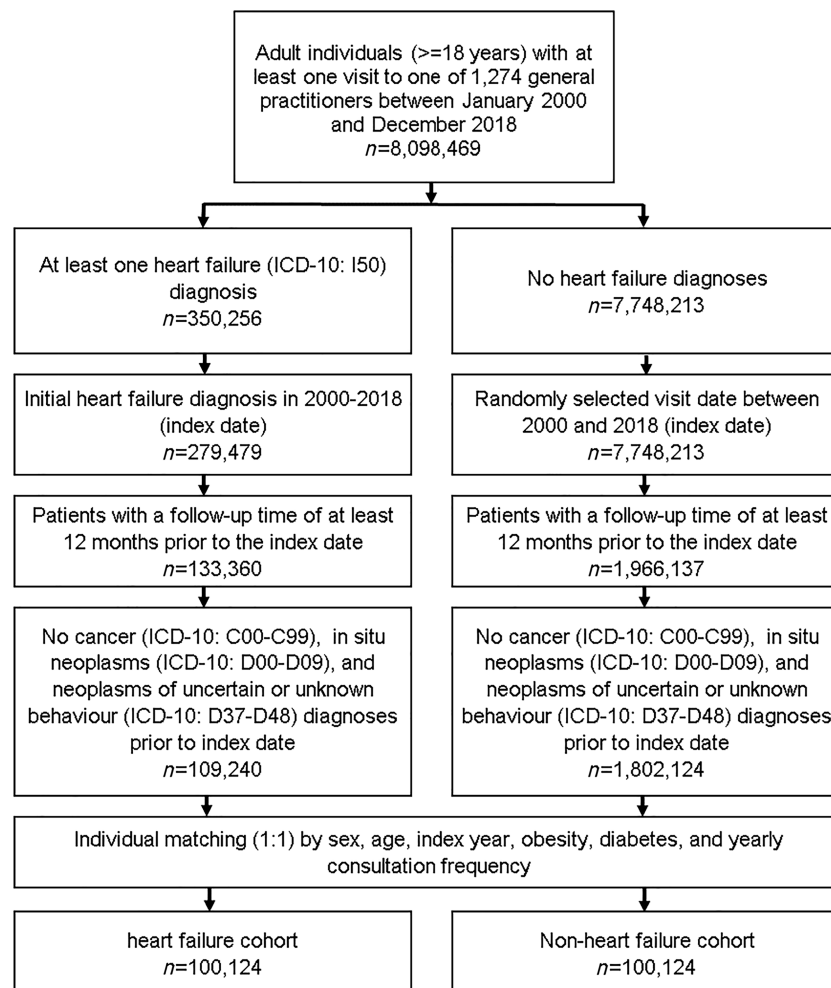
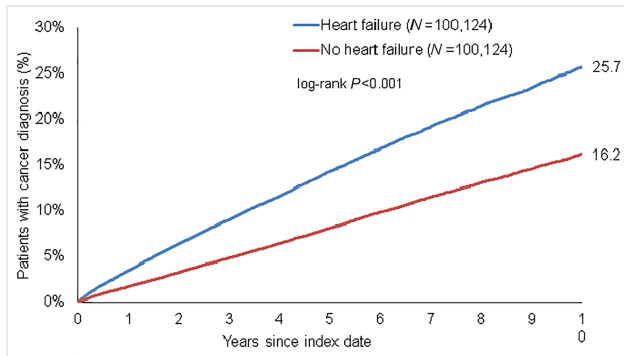


Figure 2 Kaplan–Meier curves for time to cancer diagnosis in patients with and without heart failure.



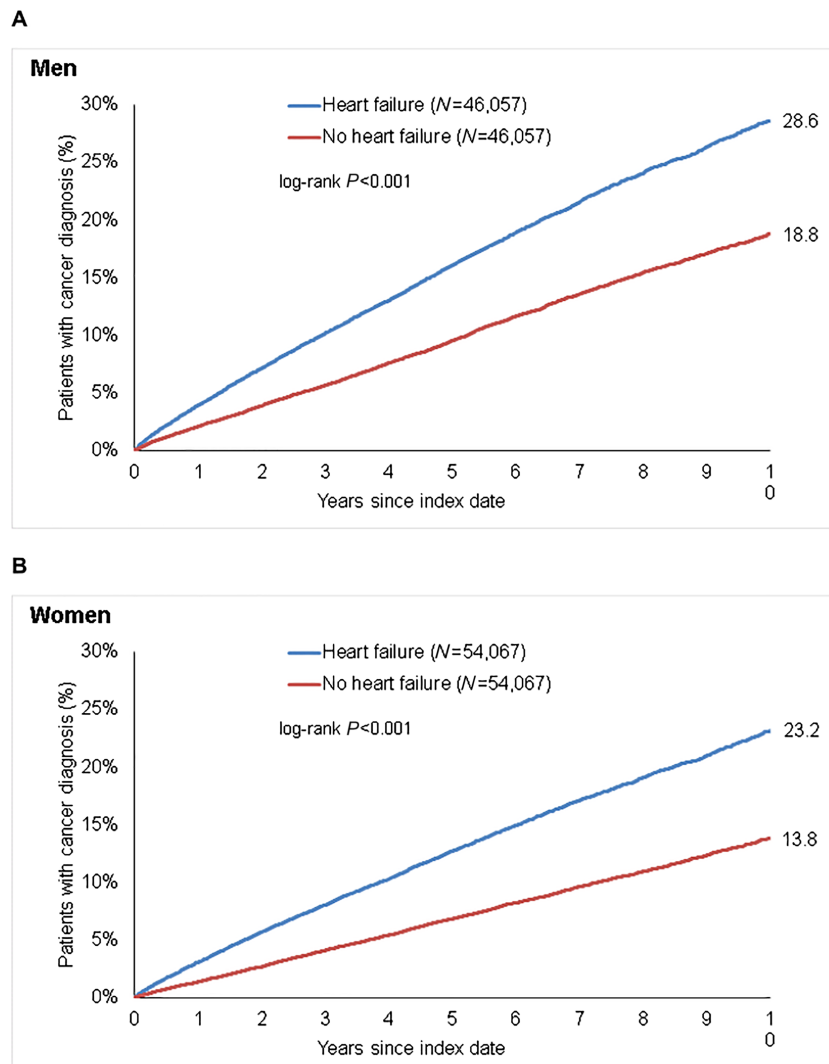
(ICD10:C64–C68), and lymphatic and haematopoietic tissue (ICD10:C81–C96) were recorded.

Methods

Database and study population

This study was based on the Disease Analyser database (IQVIA), which contains drug prescriptions, diagnoses [according to the International Classification of Diseases, 10th revision (ICD-10)], and basic medical and demographic data obtained in anonymous format from the practices of general practitioners and specialists.⁷ This retrospective

Figure 3 Kaplan–Meier curves for time to cancer diagnosis in women (A) and men (B) with and without heart failure.



cohort study included patients (≥ 18 years) with an initial diagnosis of heart failure (ICD-10: I50) treated in 1274 general practices in Germany between January 2000 and December 2018 (index date; *Figure 1*). The observation time was ≥ 12 months prior to the index date. Patients already diagnosed with cancer at the time of their heart failure diagnosis were excluded. Further explicit methodological details can be found in the Supporting Information, Methods section.

Results

Basic characteristics of the study sample

The present study included 100 124 patients with heart failure and 100 124 patients without heart failure. The basic characteristics of study patients are displayed in *Table 1*. The mean age [standard deviation] was 72.6 [12.2] years; 54.0% of patients were women. Diabetes mellitus and obesity were present in 37.4% and 15.9% of patients without any significant difference in both subgroups. On average, patients visited their general practitioner 6.0 [standard deviation: 5.7] times per year during the follow-up time.

Association between heart failure and incidence of cancer

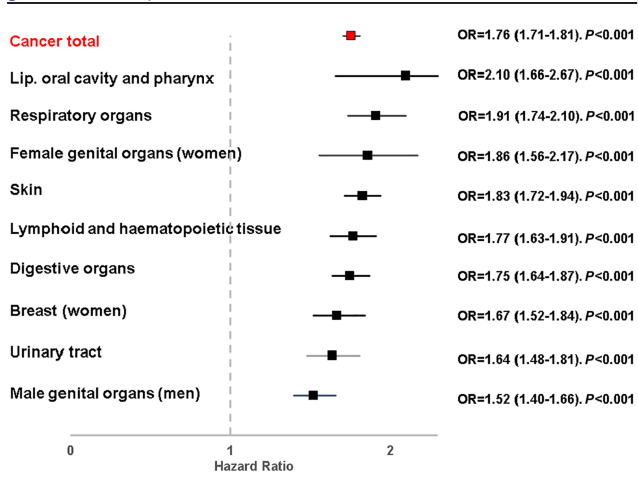
We first compared incidence rates of cancer in patients with and those without heart failure within 10 years after the index date. Interestingly, 25.7% of patients with heart failure but only 16.2% of patients without heart failure were diagnosed with cancer (log-rank $P < 0.001$) (*Figure 2*). These

proportions were 28.6% vs. 18.8% in female and 23.2% vs. 13.8% in male patients (*Figure 3*). In the regression analyses, heart failure was significantly associated with the incidence of cancer [hazard ratio (HR): 1.76, $P < 0.001$ in total; HR: 1.85, $P < 0.001$ in women; HR: 1.69, $P < 0.001$ in men]. Notably, a significant association was found between heart failure and all cancer sites (*Figure 4*). The strongest association was observed for cancer of lip, oral cavity, and pharynx (HR: 2.10, 1.66–2.17; $P < 0.001$) followed by respiratory organs (HR: 1.91, 1.74–2.10; $P < 0.001$) and genital organs of female patients (HR: 1.86, 1.56–2.17; $P < 0.001$). The weakest association was detected for male genital organ cancer (1.52, 1.40–1.66; $P < 0.001$), but the result was still highly significant.

Conclusions

Our study demonstrates that heart failure patients have a significantly increased incidence of cancer in general and of each individual cancer type studied. The data—based on a collective of over 100 000 heart failure patients—confirm the results of previous evaluations in smaller study populations.^{8,9} The data do not prove a causal relationship but instead show a statistical relationship between heart failure and cancer. Nevertheless, these results allow us to speculate that there may be a causal relationship between heart failure and an increased cancer rate. The particularly high incidence of oropharyngeal carcinoma in heart failure patients suggests that common extrinsic risk factors such as nicotine are a possible trigger of the co-morbidity. In this regard, one limiting factor of our study is that our database does not provide data on nicotine use or alcohol consumption. In addition to these external risk factors, cancer in general and cardiovascular diseases share common risk factors such as obesity and diabetes.¹⁰ As our data are adjusted for these risk factors, our highly significant results cannot be explained by these factors alone. One possible explanation could be the occurrence of certain pathomechanisms such as chronic inflammation or increased free radical formation, which may interact with a certain genetic background to connect both heart failure and cancer.¹⁰ Another interesting hypothesis suggests that heart failure is an oncogenic condition. This means that the failing heart may promote tumourigenesis or tumour growth.¹⁰ New data from animal studies suggest that the secretion of certain proteins may be up-regulated in failing hearts, promoting the secretion of certain tumour growth factors. SerpinA3 and A1, fibronectin, ceruloplasmin, and paraoxonase 1 have been identified as such proteins.¹¹ As another example, the cardiac stretch marker affixin activates the oncogene STAT3.¹² Serpin A3 has been shown to directly induce growth of human colon cancer (HT-29) cells.¹¹ The authors of the same study also showed that elevated

Figure 4 Association between heart failure and the incidence of cancer diagnoses in patients followed in general practices in Germany (Cox regression models). OR, odds ratio.



cardiac and inflammation biomarkers in apparently healthy humans were predictive of new-onset cancer.¹¹ Supporting evidence comes from a study demonstrating that serum levels of heart failure markers such as N-terminal pro-brain natriuretic peptide and troponin T were elevated in cancer patients even before the application of cardiotoxic anticancer therapy, suggesting that subclinical myocardial injury exists in cancer patients.¹³ The specific interaction of cardiac stress-induced proteins with oncogenic signalling pathways is a relatively new branch of research with great potential. Some of these potential heart failure/oncogenic pathway interactions may be organ specific. In this context, studies such as ours that link large collectives of heart failure patients not only to cancer development in general but also to individual organ systems may be helpful.

Our study is subject to several limitations that are due to the study design and cannot be avoided. First, the use of the ICD-10 coding system might lead to misclassification and undercoding of certain diagnoses. For example, we cannot distinguish between heart failure with reduced pump function and heart failure with preserved pump function in our database. Because heart failure with preserved pump function in particular is virtually defined by co-morbidities, such a distinction would have been desirable. Similarly, data on socio-economic status (e.g. education and income) and lifestyle-related risk factors (e.g. smoking, alcohol consumption, and physical activity) are also lacking. These possible confounders could not be matched in our analysis, which would have been desirable.

It should be noted that our report is not the first to show an increased rate of cancer in heart failure patients. This main finding has previously been reported in other studies on smaller patient collectives.^{8,9} However, we would like to emphasize that our data are based on a very large cohort of >200 000 patients, which ensures the high scientific reliability of our results. This enabled us to

provide a broad correlative picture of the association between heart failure and several tumour entities, while other studies have concentrated on single tumour entities only.

Further clinical and experimental studies are needed to clarify this relationship. In the future, these studies could help to better protect heart failure patients and improve their prognosis, for example, by establishing intensified tumour screening specifically for heart failure patients.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting Information.

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