



ORIGINAL ARTICLE

The association between pre-existing heart failure and cancer incidence: A systematic review and meta-analysis

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KEYWORDS

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Abstract

Introduction and objectives: Cardiovascular diseases (CVD) and cancer are some of the most recognized causes of mortality and morbidity worldwide. Cancer is the second leading cause of death in heart failure (HF) populations. Recent studies have hypothesized that HF might promote the development and progression of cancer. We aim to analyze and discuss the most recent evidence on the relationship between HF and cancer development.

Methods: From inception to November 2022, we searched PubMed, Web of Science and ClinicalTrials.gov for relevant articles on patients with HF and a subsequent cancer diagnosis that reported outcomes of overall and site-specific cancer incidence, or mortality.

Results: Of 2401 articles identified in our original search, 13 articles met our criteria. Studies reporting risk rate estimates were summarized qualitatively. Studies reporting hazard ratios (HRs), or relative risks were combined in a meta-analysis and revealed that HF was associated with an increased overall cancer incidence with a HR=1.30 (95% CI: 1.04–1.62) compared with individuals without HF. Subgroup analyses by cancer type revealed increased risk for lung cancer (HR=1.87; 95% CI: 1.28–2.73), gastrointestinal cancer (HR=1.22; 95% CI: 1.03–1.45), hematologic cancer (HR=1.60; 95% CI: 1.23–2.08) and female reproductive cancer (HR=1.67; 95% CI: 1.27–2.21). Mortality from cancer was higher in HF patients compared with non-HF subjects with a HR=2.17 (95% CI: 1.23–3.84).

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Conclusions: Our systematic review and meta-analysis revealed that HF may result in a subsequent increase in cancer incidence as well as in cancer-related mortality. The most common cancer subtypes in HF patients were lung, female reproductive system, and hematologic cancers. Further research is needed to understand this association better and to provide the best cardiological and oncological care.

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PALAVRAS-CHAVE

Insuficiência cardíaca;
Cancro;
Incidência;
Mortalidade;
Cardio-oncologia

Incidência de cancro em doentes com insuficiência cardíaca: revisão sistemática e meta-análise

Resumo

Introdução e objetivos: As doenças cardiovasculares (DCV) e o cancro representam algumas das mais reconhecidas causas de morbimortalidade a nível mundial, sendo o cancro a segunda principal causa de morte nos doentes com insuficiência cardíaca (IC). Estudos recentes admitem a hipótese de que a IC poderia promover o desenvolvimento e a progressão da doença maligna. O nosso objetivo com este estudo é analisar e discutir a evidência mais recente que relacione a insuficiência cardíaca com o desenvolvimento do cancro.

Métodos: Procedemos a uma pesquisa na PubMed, WebofScience e ClinicalTrials.gov de artigos publicados até novembro de 2022 que incluíam doentes com história de IC que tenham sido posteriormente diagnosticados com cancro, tendo como resultado incidência global ou específica de cada tipo cancro ou mortalidade por cancro.

Resultados: Dos 2401 artigos identificados na pesquisa original, 13 artigos cumpriram os nossos critérios. Os estudos que descreviam algum tipo de estimativa de risco foram resumidos qualitativamente. Os estudos com resultados relativos a *hazard ratios* (HR), ou riscos relativos foram combinados numa meta-análise, mostrando um aumento da incidência global do cancro dos doentes com IC em comparação com indivíduos sem IC, com um HR = 1,30 (95%CI:1,04-1,62). A análise de subgrupos por tipo de cancro revelou um risco aumentado no cancro do pulmão (HR = 1,87;95%CI:1,28-2,73), nos cancros gastrointestinais (HR = 1,22;95%CI:1,03-1,45), nos cancros hematológicos (HR = 1,60;95%CI:1,23-2,08) e nos cancros do sistema reprodutivo feminino (HR = 1,67;95%CI:1,27-2,21). A mortalidade por cancro foi mais elevada em doentes com IC em comparação aos indivíduos sem IC com um HR = 2,17 (95%CI:1,23-3,84).

Conclusões: Esta revisão sistemática e meta-análise revelou que em doentes com IC verifica-se um aumento da incidência e mortalidade por cancro. Os subtipos de cancro mais incidentes nos doentes com IC foram os cancros do pulmão, sistema reprodutor feminino e hematológicos. São necessários estudos mais aprofundados nesta área de modo a melhor compreender esta associação e para poder prestar o melhor cuidado a esta população do ponto de vista cardíaco e oncológico.

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Introduction

Cardiovascular diseases (CVD) and cancer are some of the most recognized causes of mortality and morbidity worldwide.¹ Heart failure (HF) coupled with cancer contribute to almost 50% of deaths in the middle-age population.² Despite recent advances in treatment, HF mortality rate remains high.³ The 10-year survival rate stands at only 35%.⁴ Cancer is the second leading cause of death in the HF population after CVD, accounting for over 15% of all mortality.^{5,6}

Heart failure and cancer have been the subject of much debate in the scientific community. Recent epidemiological and experimental studies have supported the link between

these two conditions, suggesting that the relationship between HF and cancer relation may be a two-way street.

In one direction, a vast amount of evidence suggests that cancer patients have a higher risk of developing HF. In fact, the cardio-oncology field has recognized the negative impact of oncological treatment on the heart, demonstrating the cytotoxic contribution of these therapies to the development of HF.⁷ In the other direction, recent studies have suggested that a diseased heart may promote cancer development and progression.⁸⁻¹⁶ These two apparently distinct clinical entities share similar risk factors, symptoms, and pathophysiological mechanisms – inflammation, metabolic disturbances, neurohormonal and immune system activation, and endothelial dysfunction.

tion and may explain the coexistence of these two diseases.^{1,7}

Further research into this topic is essential and could have a significant impact on clinical practice. The diagnosis of new cancers worsens HF prognosis, impairing patients' already weak homeostasis. In addition, the incidence of cardiotoxicity caused by oncological treatments is higher, limiting the therapeutic options that can be offered, which contributes to higher mortality.¹⁷ Improved acknowledgment of this topic may enable risk stratification in predisposed patients promoting early prevention and optimal management in the era of increasingly personalized medicine. A one size-fits-all treatment approach is ineffective for these patients.¹⁸

In recent years, epidemiological studies have been conducted to identify whether patients with HF have an increased risk of incident cancer and its impact on mortality.^{8,19,20} Additionally, they have investigated the difference in incidence between multiple subtypes of cancer, as well as factors that may influence this relationship, such as age, sex, or number of hospitalizations. Even though there is a previous systematic review²¹ on the topic, it reports on only four studies and since then, larger, and more detailed studies have been published, some of them with conflicting results. Furthermore, to the best of our knowledge, our review is the first one that gives a site-specific cancer quantitative analysis to understand better which types of cancer may be more involved in this possible association.

Objectives

In this systematic review and meta-analysis, we aim to analyze and discuss the most recent epidemiological and clinical evidence on new-onset cancer in HF population, exploring cancer incidence and mortality in this population, comparing it with non-HF subjects. We also aim to ascertain whether some types of cancer are more sensitive than others to this possible association, such as lung, breast, prostate, hematologic, skin, gastrointestinal and female reproductive system diseases.

Methods

Data sources and searches

The present review was produced according to the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines.²² We searched MEDLINE, Web of Science and ClinicalTrials.gov from inception to November 2022. We searched terms such as "heart failure", "cancer", "neoplasm", "incidence", "mortality", "cohort"; "case control"; "cross section", "RCT" (randomized controlled trial). The queries used for each database are described in more detail in [Table S1 \(supplementary material\)](#).

Study selection

Regarding primary study selection, the process involved two phases: the screening phase, in which all records identi-

fied by searching the databases were selected by title and abstract; and in second, the inclusion phase that consisted in reading the full text of eligible articles. Two reviewers independently assessed all records in all phases of the study search, selection, data extraction, methodological quality assessment and risk of bias analysis. Differences were resolved by consensus ([Figure 1](#)).

The inclusion criteria were as follows: (1) observational studies (cohort, case-control, or cross section studies) or randomized controlled trials; (2) population of patients with diagnosis of HF and cancer; (3) any type of cancer incidence or mortality as a result outcome; (4) Any new cancer diagnosis in patient with HF history. The exclusion criteria were as follows: active cancer at time of enrolment, acutely ill patients, pediatric age.

Additionally, to be included in our meta-analysis, articles had to meet both of the following criteria: they reported a risk estimate (e.g., hazard ratio (HR) or equivalent estimate relating pre-existing HF to subsequent cancer diagnosis or mortality) and they reported an estimate of precision, such as a standard error or 95% confidence interval (CI). Moreover, to be included in meta-analysis studies, they needed a defined non-HF control group.

Data extraction and quality assessment

A data extraction sheet based on the Cochrane Consumers and Communication Review Group's data extraction template was created and adapted to collect all relevant data from each study that met the criteria. Data were collected by two independent reviewers and disagreements between reviewers were resolved by consensus. In the event of persisting disagreement, a third reviewer was consulted. For each study, we extracted the following information: publication characteristics (authors and publication year), study design, duration of follow-up, mean age, gender proportion, number of patients, intervention, and outcome classification, analyzed outcomes, subtypes of cancer, adjusted variables and exclusion criteria ([Table 1](#)).

The main outcomes of interest were incidence of all type of cancer, incidence of cancer subtypes, with at least four risk-estimates of incidence, or cancer mortality.

All included studies were evaluated for their methodological quality following the National Institutes of Science Quality Assessment Tool. The overall risk of bias was independently assigned to each study and classified as "good", "fair", or "poor", as detailed in [Figure S1 \(supplementary material\)](#).

Data synthesis and statistical analysis

Hazard ratios reported with 95% confidence interval were extracted from each individual study and used as the effect measure. All analyses were conducted using Review Manager version 5.4.1. For all outcomes considered, the Generic Inverse Variance method was used along with a random effects analysis model. For each individual study and outcome considered, the lnHR was calculated to estimate the intervention effect; additionally, standard error (SE) with 95% CI was calculated.

Table 1 Baseline characteristics of included studies.

Study (year) Country	Study type	Follow-up (years±SD)	Mean age (years±SD)	Male (%)	HF (No.)	Control (No.)	Intervention classifica- tion	Outcome classifica- tion	Analyzed outcomes	Subgroup analysis	Subtypes of cancer	Adjusted variables	Exclusion criteria
Bertero et al. ¹⁰ (2022) Italy	Retrospective cohort	≥5	76±10	46.8	104020	104020	HDR with a diagnosis of HF or received a HFW for HF within the previous 12 months	ICD-9-CM or ATC codes assigned in outpatient visits, HDRs, and HFWs	Cancer incidence and cancer mortality	Age; sex; diuretic dose; hospi- talizations	Upper digestive system, colorectal cancer, liver, pancreas, others of digestive system, lung, others of respiratory system, melanoma, others of skin, soft tissues or bones, breast, urinary system, male reproductive system, female reproductive system, head and neck, nervous system, endocrine system, lymphoma, multiple myeloma, leukemia	Age, sex, drug-derived complexity index, Charlson comorbidity index, and follow-up duration	3 years prior cancer diagnosis
Sagastagoitia- Fornie et al. ¹⁵ (2022) Spain	Prospective cohort	4.07	66.9±8.2	81.8	1909	General Spanish popula- tion	Clinical registry and case by case review by a clinical cardiologist	Clinical records, case by case review by a clinical car- diologist, autopsy reports, medical certificates of dead	Cancer incidence and cancer mortality	Age, sex, risk factors, cancer type	Lung; skin; prostate; urinary bladder; kidney; suprarenal; colorectal; stomach; pancreas; liver; small bowel; esophagus; breast; ovary; thyroid; pharynx; larynx; tongue; oral mucosa; maxillary sinus; salivary gland; lymphoma; leukemia; central nervous system; unknow primary site	Age, gender, history of smoking, history of alcohol abuse, diabetes mellitus, body mass index, hypertension, dyslipidaemia, coronary artery disease, chronic obstructive pulmonary disease, previous history of malignancy, chronic renal failure (glomerular filtration rate <60 ml/min), anemia, NYHA class III, serum NTproBNP, LVEF, diuretic use, ACE inhibitor use, ARB use, sacubitril-valsartan use, beta-blocker use, mineralocorticoid receptor antagonist use, ivabradine use and digoxin use	Nonmelanoma skin cancer

Table 1 (Continued)

Study (year) Country	Study type	Follow-up (years±SD)	Mean age (years±SD)	Male (%)	HF (No.)	Control (No.)	Intervention classifica- tion	Outcome classifica- tion	Analyzed outcomes	Subgroup analysis	Subtypes of cancer	Adjusted variables	Exclusion criteria
Kwak et al. ¹³ (2021) Republic of Korea	Retrospective cohort	4.06	67.1±12.4	51.9	101924	578266	ICD-10-CM with at least one hospital admission attributed to HF diagnosis	ICD-10-CM codes of cancer, and new registration of the patient to the NHIS enhanced benefits coverage registry by the cancer diagnosis	Cancer incidence	Re- hospitali- zations; cancer type	Gastrointestinal; liver/biliary; lung; prostate; hematology; genitourinary; thyroid; breast; female reproductive; head and neck; skin	Age, sex, income, diabetes mellitus, smoking, alcohol consumption, body mass index; hypertension and dyslipidaemia	Prior cancer
Leedy et al. ⁸ (2021) Denmark	Prospective cohort	8.4	63.07±7.2	0	3272	146817	Medical records cohort and self-report cohort	Self- reported cancers were docu- mented with medical records, and centrally reviewed and coded	Cancer incidence	Age; ejection fraction; cancer type	Obesity-related; tabaco-related; lung; breast; colorectal	BMI, diabetes, smoking, age at enrollment, baseline PCP visit within 1-year, physical activity, alcohol, ethnicity, education, income, hormone use ever, hypertension, cardiac medication use, family history of cancer, history of CVD and high cholesterol	No follow-up time. Self-reported HF or cancer at enrollment
Roderburg et al. (2021) ⁹ Germany	Retrospective cohort	10	72.6±12.2	46	100124	100124	ICD-10 codes	ICD-10 codes	Cancer incidence	Sex; cancer type	Lips, oral cavity, and pharynx; digestive organs; skin; breast; genital organs; urinary tract; lymphatic and hematopoietic tissue	Sex, age, index year, obesity, diabetes, consultation frequency	No follow-up time of at least 12 months prior index date. Prior cancer
Schwartz et al. ²⁰ (2020) Denmark	Retrospective cohort	3 (HF) 6.8 (control)	70.9±13.3	45	167633	837126	ICD-10 codes	ICD-10 codes	Cancer incidence	Previous ischemic disease; cancer type	Lung, liver/gall bladder; gastric; colon; rectal; prostate; bladder; renal; testicular; ovarian; breast; hematologic; melanoma; non-melanoma skin cancer	Age, sex, baseline prevalence of ischemic heart disease (including prior MI), diabetes, COPD, liver disease, and chronic kidney disease as present at baseline, baseline use of aldosterone antagonists, beta-blockers, ACE inhibitors, oral anticoagulation, antiplatelet therapy	3 months prior cancer diagnosis

Table 1 (Continued)

Study (year) Country	Study type	Follow-up (years±SD)	Mean age (years±SD)	Male (%)	HF (No.)	Control (No.)	Intervention classifica- tion	Outcome classifica- tion	Analyzed outcomes	Subgroup analysis	Subtypes of cancer	Adjusted variables	Exclusion criteria
Lam et al. ²³ (2020) USA	Retrospective and prospective cohort	14 (incidence) 7 (mortality)	63±7.0	0	665	673	Self- reported by patients	Centralized review and coded by trained cancer epi- demiologist and physician	Cancer incidence and cancer mortality	-	Female breast	Age; race; BMI; WHR; diabetes mellitus; hypertension; myocardial infarction; coronary artery disease; atrial fibrillation; pulse; systolic blood pressure; smoking; alcohol use; total physical activity (metabolic equivalent-hours per week) hemoglobin; menopausal hormone therapy trial participation and menopausal hormone therapy trial arm; age at menarche; parity; oophorectomy; and hysterectomy	Prior breast cancer
Oikawa et al. ¹⁹ (2019) Japan	Prospective cohort	6.5	67.7±11.7	69.4	3064	3064	Medical chart review Framingham criteria	Case reports, death certificates and medical records provided by the investi- gators	Cancer mortality	Age, sex, BMI, smoking, hyperten- sion, diabetes mellitus, MI, CRP, pharmaco- logical treatment; cancer type	Lung; gastric; colorectal; pancreas; bile duct; blood; liver; esophagus; prostate; bladder; kidney; head and neck; brain; gall bladder; ureter; mammary; uterine Others	Age, sex, BMI, smoking, hypertension, diabetes mellitus, dyslipidaemia, stroke, myocardial infarction, ACE-I or ARB, β blocker, antiplatelet, and statin	<20 years, prior cancer
Selvaraj et al. (2018) USA	Retrospective cohort	19.9	55±10	100	1420 (men)	26921	Self-report, validated by Framingham criteria	Self-report confirmed by pathology or cytology reports	Cancer incidence and cancer- specific mortality	Age, smoking, aspirin use	Hematologic cancer; smoking related cancer; obesity-related cancer; lung cancer; prostate; melanoma; colorectal cancer	Sex, age, Charlson comorbidity index	Nonmelanoma skin cancer
Sakamoto et al. ¹⁶ (2017) Japan	Retrospective cohort	14	64±12	59.9	106	-	Framingham criteria	Medical records	Cancer incidence Time of onset of HF and cancer	-	Stomach; lung; prostate; breast; colon	Age and sex	

Table 1 (Continued)

Study (year) Country	Study type	Follow-up (years±SD)	Mean age (years±SD)	Male (%)	HF (No.)	Control (No.)	Intervention classifica- tion	Outcome classifica- tion	Analyzed outcomes	Subgroup analysis	Subtypes of cancer	Adjusted variables	Exclusion criteria
Banke et al. ¹¹ (2016) Denmark	Retrospective cohort	4.5±2.3	67.8±2.2	72.6	9307	4959275	Clinical evaluation and echocardi- graphy	ICD-10 codes without cancer confirma- tion	Cancer incidence and all-cause mortality	Comorbidity; pharmaco- logical treatment; type of cancer	Colon; liver system; lung; melanoma; breast; prostate; kidney; lymphoma	Sex, age, date, follow-up time	Prior cancer
Hasin et al. ¹² (2016) USA	Prospective cohort	4.9±3	64±15	60	228	853	Medical chart review (Framing- ham criteria)	Anatomic and system primary involvement	Cancer incidence and multiple sources mortality	Age, sex, time from MI, type of cancer	Digestive system cancer; male reproductive; hematologic; breast; respiratory; urinary; female reproductive; skin; other cancers	Initial adjustment was made for age, sex, and Charlson comorbidity index. Additional adjustment was made for hypertension, smoking, BMI, anterior MI, peak cTnT, Killip class, reperfu- sion/revascularization, and treatment with aspirin at hospital discharge	Prior cancer, non-melanoma skin cancer
Hasin et al. ¹⁴ (2013) USA	Case-control and cohort	7.7±6.4	73±14	47	596	596	Medical chart review (Framing- ham criteria)	Medical chart review without specific cancer confirma- tion	Cancer incidence and multiple sources mortality	-	Digestive; respiratory; hematologic; male reproductive	Sex, age, index year, body mass index, smoking, comorbidity	Prior cancer

ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; ATC: anatomical therapeutic chemical; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; cTnT: cardiac troponin T; HDR: hospital discharge record; HF: heart failure; HFW: health care cost related fee waiver; ICD-CM: International Classification of Diseases – Clinical Modification; MI: myocardial infarction; NHF: no heart failure; NHIS: National Institute of Health Science; NTproBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; PCP: primary care provider; SD: standard deviation; SEER: surveillance, epidemiology, and end results; USA: United States of America; WHR: waist-hip ratio.

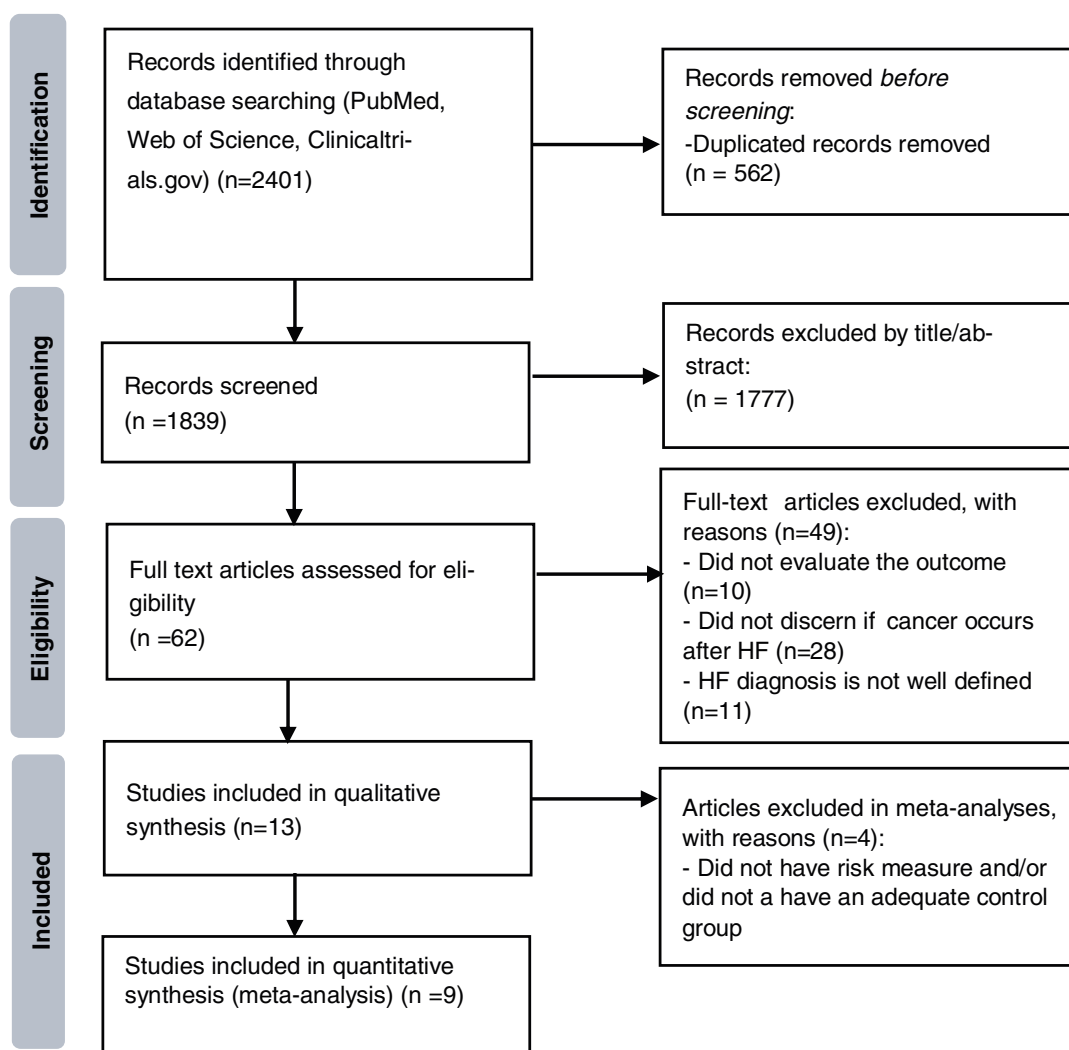


Figure 1 Flow diagram of the studies selection according to PRISMA guidelines.

To estimate heterogeneity, the I^2 statistic was used. If several estimates were reported in the same article, we chose the most fully adjusted estimate (i.e., multivariate regression was selected over univariate regression). If an article gave site-specific as well as overall estimates, the overall estimate was used in the primary meta-analysis and site-specific estimates were used in meta-analyses by cancer site. If an article reported multiple estimates by subgroup, these estimates were entered separately into our meta-analysis. If a study gave more than one estimate for the same result, for example, if one of the estimates exclude the cancer diagnosed in the first years, we used that one. Then, sensitivity analyses were conducted by excluding the studies that only include men or women, the studies that include patients with cancer history in the past and by omitting each estimate one at a time (Figure S2 – supplementary material).

Results

A total of 2401 studies were retrieved using the above methodology. After removing 562 duplicates, 1839 records

were assessed for eligibility. Concerning the screening phase, 1777 articles were not eligible for not meeting our inclusion criteria. Therefore, 62 eligible studies were selected for full reading and assessment.

Thirteen observational studies, published between 2013 and 2022, were included in the qualitative analysis and their results were reviewed and discussed (Figure 1). Of these 13 studies, seven assessed cancer incidence and mortality, five assessed only cancer incidence, while one assessed exclusively mortality. The main characteristics and outcomes of these studies have been summarized in Tables 1 and 2.

In general, studies included in the qualitative analysis demonstrated an overall bias of low risk according to National Institutes of Health quality assessment tool. Nine studies were ≥ 11 in a total of 14 questions and were considered to be good quality, whereas the remaining studies pointed between 8 and 10 in 14 and were considered to be fair quality. The major concerns were related with short timeframe for follow-up, the assessment of outcome of interest more than once or by different methods and the investigator's blindness was not reported in most of the studies (Figure S1 – supplementary material).

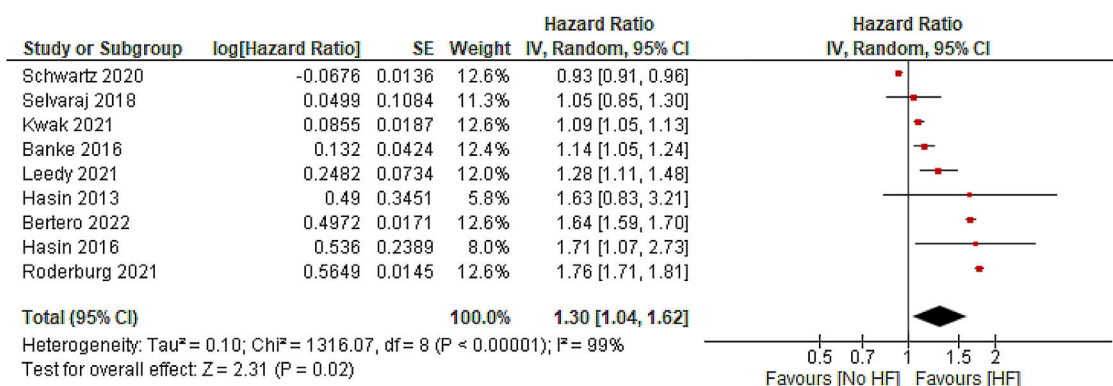


Figure 2 Forest plot of the random effect models for estimating the pooled overall cancer incidence in patients with HF compared with patients without HF. The diamond represents the combined effect and the respective confidence interval.

Incidence of all-cancer types

Accounting the 12 studies that report a risk estimate for all-cancer type incidence, 8 found a significantly association favoring a higher all-cancer type incidence in the group of patients with prior HF diagnosis, while four suggest no significant association (Table 2).

Of the studies reporting incidence of cancer, nine provided adjusted Cox or Poisson models (HRs or IRRs (incidence risk ratios)) of the risk of developing cancer in HF group comparing with the group of patients without HF. These studies were included in the quantitative analysis, that took in consideration data availability (Table S2 – supplementary material). The studies included in this analysis assessed a total of 7238 643 patients (487 931 in the HF group and 6750 718 in control group).

Of these nine estimates, six reported that HF was associated with significantly increased risk of all-cancer patients, two indicates that HF was associated with non-significantly increased cancer risk and 1 that HF was associated with non-significantly decreased cancer incidence.

The pooled HR for risk of overall cancers in patients with prior HF diagnosis compared with those without HF was 1.30 (95% CI: 1.04–1.62, p=0.02; I²=99%, p<0.001) (Figure 2).

Sensitivity analyses

Sensitivity analyses were conducted first by excluding the studies that only include men or women, with a HR=1.34 (95% CI: 1.04–1.13, p=0.02). The percentage of men versus women subjects was not similar between the studies, therefore, to explore in depth the impact of gender on results, we made a subgroup analysis by gender including the studies that provide this data (Tables S3 and S4 – supplementary material), observing an outstanding association in the women subgroup (HR: 1.55 (95%: 1.20–2.00, p<0.001)) than in men (HR: 1.38 (95% CI: 1.11–1.73, p=0.005)).

Second, we conducted sensitivity analyses by excluding the studies that include patients with cancer history in the past, obtaining a HR of 1.39 (95% CI: 1.02–1.89, p=0.04).

Finally, we evaluated the influence of each study on the overall estimate by calculating a pooled HR, omitting each estimate 1 at a time. The omission of any one study did not appreciably change the pooled HR, and the estimates

in each case were well within the confidence limits of the overall estimate (Figure S2 – supplementary material).

Incidence by cancer site

Lung cancer

Seven cohorts reported results for incidence of lung cancer. All studies showed higher lung cancer incidence in the group of patients with prior HF diagnosis. The pooled HR was 1.87 (95% CI: 1.28–2.73, p<0.001; I²=99%, p<0.001) indicating a significantly increased risk of lung cancer diagnosis in HF patients compared with the group without HF (Figure 3A).

Female breast cancer

For incidence of female breast cancer, seven cohorts reported results. Three of the studies indicate a significantly increased risk and four of them reported no significant association. Lam²³ did not report an HR estimate, and therefore was only included in the qualitative analyses (Table 2). The pooled HR of the six remaining studies was 1.23 (95% CI: 0.97–1.55, p=0.08; I²=97%, p<0.001) showing that there is no significantly increased risk of breast cancer diagnosis in HF patients compared with the group without HF (Figure 3B).

Gastrointestinal cancers

Seven cohorts reported results for incidence of gastrointestinal system cancer. Five of the studies indicate a significant increased risk and four of them reported no significant association. The pooled HR was 1.22 (95% CI: 1.03–1.45, p=0.02; I²=97%, p<0.001) indicating significantly increased risk of gastrointestinal cancer diagnosis in HF patients compared with the group without HF (Figure 3C).

Hematologic cancers

Six cohorts reported results for incidence of hematologic cancer (leukemia, lymphoma, or multiple myeloma). Five of the studies indicate a significantly increased risk, and two of them reported no significant association. The pooled HR was 1.60 (95% CI: 1.23–2.08, p<0.001; I²=98%, p<0.001) indicating a significantly increased risk of hematologic cancer diagnosis in HF patients compared with the group without HF (Figure 3D).

Table 2 Study aims and general results of included studies in the qualitative review.

Study	Aim	Main outcomes
Bertero et al. ¹⁰	“Assess cancer incidence and mortality according with pre-existing HF in a community-based cohort.”	<ul style="list-style-type: none"> - The cancer incidence rate was higher in patients with HF compared with control subjects, the association maintains after excluding the cancer diagnosis in the first year. While the incidence of all types of cancer increased with age, HF-related excess risk was consistent across all age groups. The overall and type-specific risks of cancer were similar in men and in women. The increased risk of incident cancer in HF patents applied to most malignancies. The risk of melanoma, breast cancer, and neoplasms of the endocrine system did not differ between cases and control. - HF patients died secondary to cancer more frequently than control subjects. The excess risk of cancer death applied to all age groups but declined with age. Increased risk of death caused by cancer was detected for all types of malignancies. The increased risk of cancer mortality was seen both in men and in women. - HF patients with a high consumption of loop diuretic agents also had higher cancer incidence and mortality.
Sagastagoitia-Fornie et al. ¹⁵	“Assess the incidence of new cancer diagnoses and cancer-related mortality in patients with HF, and to compare them with those estimated for the general Spanish population. Additionally, they aim to identify specific risk factors for cancer in the HF population, as well as to assess the prognostic impact of pre-existing HF.”	<ul style="list-style-type: none"> - Crude incidence rates of malignancy observed in the study population were significantly higher than those expected for the general Spanish population, both in women and in men. Age, a history of smoking and the prescription of ACE inhibitors at baseline were associated with statistically increased risk of incident malignancies. - New malignant disease during follow-up were associated with statistically significant higher risk of any death cause, as compared with the absence of malignancy, both in women and in men. Crude incidence rate of malignancy was higher among patients with LVEF \leq40% than patients with LVEF >40%.
Kwak et al. ¹³	“Evaluate the association between HF and cancer using data from Korean National Health Insurance Service claims database.”	<ul style="list-style-type: none"> - HF group demonstrated a significantly increased risk of overall cancers with a smaller HR in the 2 years lag analysis compared to that of no lag analysis. Among the site-specific cancers, in the 2 years lag analyses the risk remained higher for liver/biliary/pancreas, lung and hematologic malignancies, while the statistical difference was lost for the other site-specific cancers. - Regarding the subgroups by MI history, the risk of overall cancers remained significant for HF patients without MI history while it was not in those with MI history. - The incidence for all cancers were higher for patients with more re-hospitalization compared to those without.

Table 2 (Continued)

Study	Aim	Main outcomes
Leedy et al. ⁸	“Investigate the association of HF with incident cancer among a large cohort of post-menopausal women.”	<ul style="list-style-type: none"> - HF was significantly associated with subsequent risk of cancer. Increased risk was observed for obesity-related, lung, and colorectal cancers, but not for breast or tobacco-related cancer. - After stratifying by LVEF, HFpEF appeared to be more strongly associated with total cancer as well as site-specific lung and colorectal cancers than HFrEF.
Roderburg et al. ⁹	“Record the incidence of cancers in heart failure patients in general as well as malignancies of individual organ system.”	<ul style="list-style-type: none"> - HF was significantly associated with the incidence of cancer. - A significant association was found between HF and all cancer sites assessed. - The strongest association was observed for cancer of lip, oral cavity, and pharynx, followed by respiratory organs and genital organs of female patients.
Schwartz et al. ²⁰	“Examine the hypothesis that HF may increase the overall risk of malignancy.”	<ul style="list-style-type: none"> - Patients with HF had higher cancer incidence, however, after adjustment for comorbidities the increased risk of malignancy was greatly attenuated for incident all-cause cancer and dissipated altogether after additional adjustment for medications. Although it remains higher in lung cancer and hematologic cancer. - In patients with ischemic heart disease, the increased risk of all-cause cancer was only marginally increased after adjustment for baseline comorbidities.
Lam et al. ²³	“Examine the temporal association between HF and breast cancer.”	<ul style="list-style-type: none"> - There was no difference in the incidence of invasive or all breast cancer between women with or without prevalent HF. - Women with prevalent HF or prevalent and interim HF had a higher risk of mortality after incident invasive breast cancer compared with women without HF. The association of incident breast cancer by prevalent HF with all-cause mortality was unaffected by the competing risk of death.
Oikawa et al. ¹⁹	“Examined whether HF increases cancer death, especially with a reference to inflammation using CHART- 2 (Chronic HF Registry and Analysis in the Tohoku district-2 cohort.)”	<ul style="list-style-type: none"> - HF patients had significantly higher cancer mortality than those without HF.
Selvaraj et al. ²⁴	“Determine whether HF is associated with cancer incidence and cancer-specific mortality.”	<ul style="list-style-type: none"> - HF was not associated with cancer incidence. - No association was found between HF and site-specific cancer incidence or cancer-specific mortality after multivariable adjustment.
Sakamoto et al. ¹⁶	“Investigate the time of onset of each cancer and HF and examined the prevalence of HF preceding cancer onset.”	<ul style="list-style-type: none"> - When we omitted the patients whose cancer diagnosis occurred prior to their diagnosis of chronic HF, we observed a significantly higher incidence of cancer in patients with HF than in controls.

Table 2 (Continued)

Study	Aim	Main outcomes
Banke et al. ¹¹	“Assess the incidence of risk of cancer and all-cause mortality in a Danish HF cohort.”	<ul style="list-style-type: none"> - Risk of any type of cancer was increased in the HF group. Type-specific analysis demonstrated an increased hazard ratio for all major types of cancer except for prostate cancer. When stratified by age, incidence rates were increased in all age groups in the HF cohort. - All-cause mortality was higher in HF patients with cancer compared with cancer patients from the background population. - Analysis of comorbidity within the HF cohort revealed previous myocardial infarction and ACE inhibitors pharmacological treatment as associated with an increased risk of cancer.
Hasin et al. ¹²	“Examine whether HF was associated with an increased risk of subsequent cancer among population of first myocardial infarction survivors.”	<ul style="list-style-type: none"> - HF patients had a higher risk of developing cancer. - The mortality associated with cancer were higher for HF patients compared with patients without HF. - Both HF and cancer were independently associated with increased mortality after MI. - The risk was higher in women compared with men. And higher in the group of patients with >75 years. - Among patients with HF, the most common types of cancer were respiratory, digestive, and hematologic. - Patients with HFpEF had an increased risk of cancer compared with patients with HFrEF.
Hasin et al. ¹⁴	“Evaluate the risk of cancer in patients with HF compared with community controls and to determine the impact of cancer post-HF on outcomes.”	<ul style="list-style-type: none"> - HF patients had a higher risk of developing cancer. The risk was similar for men and women. - Incident cancer was associated with a large increased risk of death. - Cancer was not associated with preserved versus reduced ejection fraction.

ACE: angiotensin-converting enzyme; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HR: hazard ratio; LVEF: left ventricular ejection fraction; MI: myocardial infarction.

Female reproductive system cancers

Four cohorts reported results for incidence of female reproductive system cancer (including ovarian and uterus). Three of the studies indicate a significantly increased risk and 1 of them reported no significant association. The pooled HR was 1.67 (95% CI: 1.27–2.21, $p < 0.001$; $I^2 = 92\%$, $p < 0.001$) indicating a significantly increased risk of female reproductive system cancer diagnosis in HF patients compared with the group without HF (Figure 3E).

Prostate cancer

Five cohorts reported results for incidence of prostate cancer. Only one of the studies indicate a significantly increased risk, three reported a significant decrease in cancer incidence and one indicated no significant association. The pooled HR was 0.97 (95% CI: 0.67–1.20, $p < 0.001$; $I^2 = 97\%$, $p = 0.46$) indicating no significantly decreased risk of prostate

cancer diagnosis in HF patients compared with the group without HF (Figure 3F).

Skin cancers

Six cohorts reported results for incidence of skin cancer. Four of the studies indicate a significantly increased risk and three of them reported no significant association. The pooled HR was 1.19 (95% CI: 0.83–1.72, $p = 0.34$; $I^2 = 99\%$, $p < 0.001$) suggesting no significantly increased risk of skin cancer diagnosis in HF patients compared with the group without HF (Figure 3G).

Cancer mortality

Five cohorts reported results for cancer-specific mortality in HF patients compared with patients without HF. All studies found a significant increase in cancer death when these two diseases coexist, except for the Selvaraj²⁴ where the

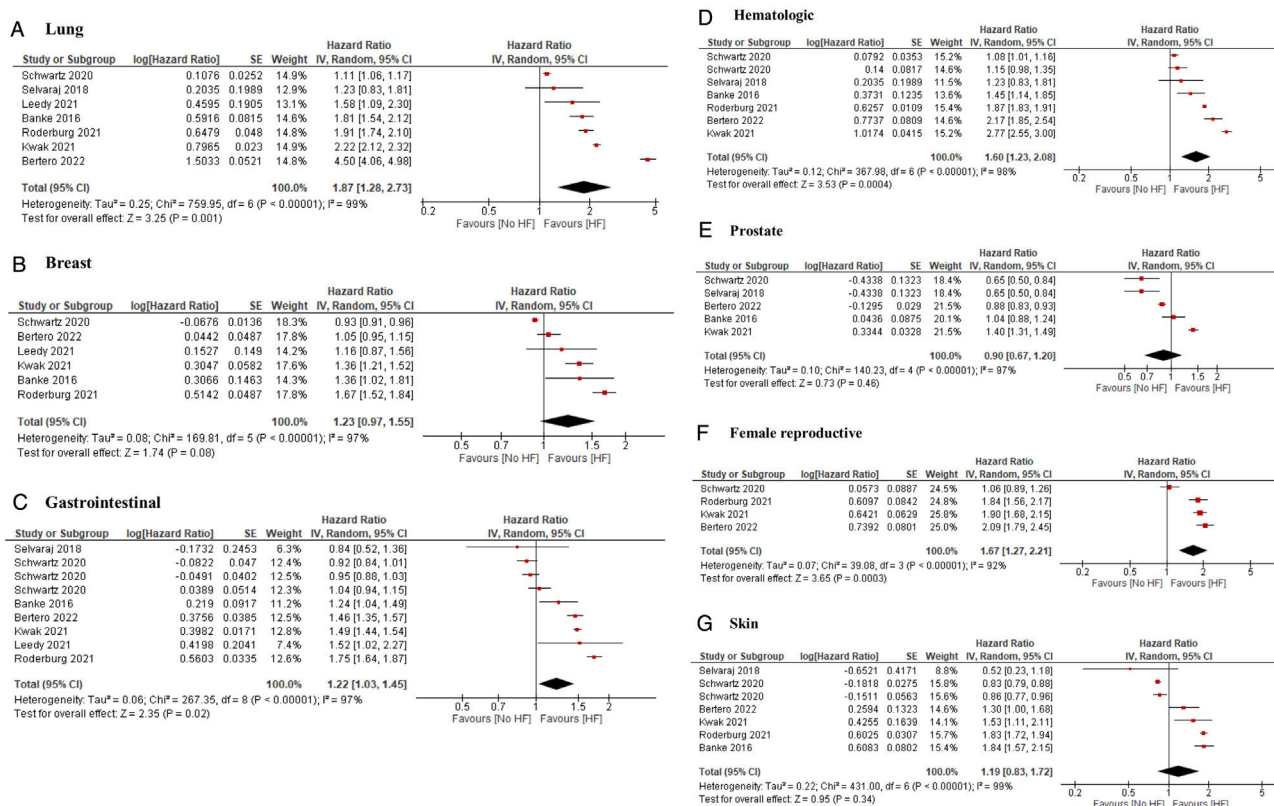


Figure 3 Forest plot of the random effect models for estimating the pooled cancer incidence by cancer site (A. Lung cancer; B. Women breast cancer; C. Gastrointestinal system cancer (including gastric and colorectal cancers); D. Haematologic cancers (leukaemia, lymphoma, and multiple myeloma); E. Prostate cancer; F. Female reproductive system cancers (ovarian and uterine cancers); G. Skin cancer (melanoma and non-melanoma skin cancers)) in patients with HF compared with patients without HF. The diamond represents the combined effect and the respective confidence interval.

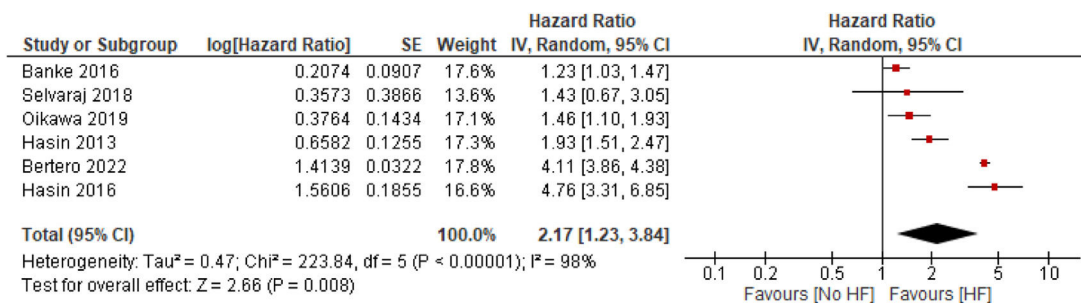


Figure 4 Forest plot of the random effect models for estimating the pooled cancer mortality in patients with HF compared with patients without HF. The diamond represents the combined effect and the respective confidence interval.

result was not statistically significant (Table S5 – supplementary material). The pooled HR was 2.17 (95% CI: 1.23–3.84, p=0.008; I²=98%, p<0.001) (Figure 4). Additionally, some of the studies found an increased all-cause mortality in HF group.^{10,12}

Discussion

This systematic review and meta-analysis summarize all cohort studies presently available and suggests that there is a significantly increased risk of incident cancer among HF patients. The pooled HR across the nine studies was 1.30 (95% CI: 1.04–1.62, p=0.02), showing that HF patients are

at 30% greater risk of being diagnosed with a new malignancy. This estimate was robust across sensitivity analyses performed. We observed that this association increases with age, as expected, and seems to be higher in women.

The association of HF and site-specific cancer risk reached statistical significance for lung, gastrointestinal, hematologic and female reproductive system cancers. However, no significant association was found in breast, prostate, and skin cancers. The cancer types associated with higher risk were lung and female reproductive system, followed by hematologic cancer. This consistent association suggests the shared biological link between HF and certain site-specific cancers.

In sum, there are several potential explanations for the observed association between increased incidence of cancer in patients with pre-existing chronic HF.

First, it is acknowledged that HF and cancer share common risk factors (smoking, aging, genetic predisposition, obesity, and diabetes mellitus), which can explain, at least in part, the co-occurrence of these two conditions, and combating the modifiable factors will inevitably reduce both HF and cancer.^{7,25,26} Although, even after the adjustment made for some of these factors by the several studies included (Table 2) the correlation seems to persist and might be further explained by other mechanisms.

Second, some common pathophysiological mechanisms are involved in both diseases. It is known that inflammation plays an important role in these two conditions.^{27,28} Maladaptive chronic inflammation leads to progressive myocardial injury, development of vascular dysfunction and reduces cardiac tissue survival. In fact, independent of its etiology, HF is associated with an increase in circulating proinflammatory cytokines, such as tumor necrosis factor- α interleukin-1, and interleukin-6.²⁹ On the other hand, chronic inflammation predisposes to development of cancer and affects the tumorigenesis and tumor-permissive state by promoting the same proinflammatory cytokines and chemokines.² In line with this, the CANTOS trial (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) demonstrated that canakinumab, an interleukin-1-targeting antibody, reduces cardiovascular events in patients with a history of myocardial infarction (MI) with a moderate increase in C-reactive protein levels, as well as a reduction in lung cancer incidence in these patients.^{7,30}

Moreover, the metabolic changes caused by toxic intermediate accumulation and the use of unbalanced substrates can disrupt cardiac cell homeostasis and promote cancer growth. In response to pathophysiological insult and stress, metabolic reprogramming occurs as an adaptive event in both cancer and cardiac cells indicating that both cells share the same metabolic pathways.^{2,31}

Angiogenesis adaptations are another common mechanism favoring this linkage. Cardiomyocyte hypertrophy causes a mismatch between capillary density and increased oxygen demand during the early stages of chronic pressure overload, stimulating microvascular expansion by inducing angiogenic factor secretion, such as vascular endothelial growth factor.³² Angiogenesis is critical for tumor growth and dissemination in cancer using dysfunctional tumor vessels to spread throughout the body.¹⁸

Also, there is the hypothesis that neurohormonal activation may also account for the increased risk of cancer observed in HF. This is supported by a large body of experimental data demonstrating that sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system activation promote cancer progression and dissemination via multiple mechanisms. The SNS's pro-oncogenic effects are primarily mediated by β -AR (beta arrestin), which is expressed by both cancer cells and, more importantly, non-malignant cells in the tumor microenvironment.³³

Third, HF may promote oncogenesis through release of cardiac circulating factors. Relevant preclinical models of CVD, including surgical models of MI and subsequent HF, as well as aortic stenosis, identifying several candidate systemic factors including cardiac-specific circulating factors

(e.g., serpinA3, periostin), that drive CVD-induced acceleration of colon, breast, and lung cancer.^{31,34}

Finally, mutual pathogenic gene variants may also predispose individuals to both cancer and HF. Clonal hematopoiesis of indeterminate potential (CHIP), as mentioned above, is an emerging entity in which somatic blood mutations are present in individuals without established hematologic abnormalities. Studies have demonstrated that the presence of CHIP is associated with increased risk of hematologic cancer, CVD, disease progression and mortality in HF.³⁵ Moreover, several genes associated with familial cardiomyopathies appear to be relevant genetic variants in somatic cancer cells. Interestingly, somatic mutations in titin, dystrophin, and desmoglein2 have been associated with different stages of the carcinogenesis.^{2,36,37}

Furthermore, the diagnosis of cancer in HF patients seems to have a strong impact in these patient's prognosis. Most studies reported an increase in cancer-specific death in HF patients (HR 2.17 (95% CI: 1.23–3.84)), as well as an increase in overall mortality, suggesting that cancer is more lethal in HF patients. This rise in mortality can be explained by various factors. On one hand, the impact of the tumor itself on the already weak homeostasis of HF patients can make them prone to the development of more cardiotoxicities during or after antineoplastic therapies and reduce chances to survive oncological surgery, therefore less intensive oncological therapy is applied limiting therapeutic choices. On the other hand, optimization and up-titration of cardiological therapy may be compromised by cancer diagnosis and sometimes represent a significant problem in maintaining an optimal medical therapy for these patients.^{17,38,39} Also, end-stage cancer patients are often excluded from therapies that would improve their life expectancy, such as devices implantation.³⁸

Even though we think that this phenomenon might be in part attributable to heightened surveillance, it also suggests that patients with HF tend to have hidden diseases of various forms, which could be identified under a close re-evaluation. These results found in the most recent studies suggest that doctors should be more encouraged to consider the possibility of coexisting disease throughout the follow-up. In individuals with HF, prompt diagnosis of de novo cancer can therefore be crucial. In HF patients, clinicians frequently focus on the cardiovascular consequences. Patients with HF have worse outcomes from superimposed cancer than cancer patients or patients with HF alone. The clinical decision can be modified in the presence of the concurrent disease and the decision to invest in some invasive procedures can be rejected in patients diagnosed with cancer at a more advanced stage.

Therefore, HF populations may need greater attention in cancer screening since early cancer detection could lead to better clinical outcomes. Given the various risks associated with each form of site-specific disease, the monitoring may focus particularly on certain types of disease (such as lung cancer). Further research is needed to determine whether an active, focused cancer surveillance program can improve the prognosis for HF, although we must emphasize that the improved prognosis that might be attributable to cancer screening in patients with HF would not help in reducing the social burden, because cancer screenings are not generally recommended at present, and they may not be

cost-effective.¹⁶ Instead, we suggest that clinicians should always consider the possibility of cancer when examining HF patients; and oncologists should assess baseline cardiovascular risk in patients before starting a cancer therapy that might be related with cardiovascular toxicity.⁴⁰

The overlap between HF and cancer is considerable and complex. Future research in these fields will likely clarify this relationship, which we believe will help to understand and treat these both lethal diseases better.

Strengths and limitations

We used a broad search strategy to capture all relevant information. However, the evidence in literature about this topic is still limited and we found few studies that met our inclusion criteria.

Although we observed an association between HF and incident cancer, the following aspects should be considered when interpreting the outcomes, and several limitations of the literature, as well as our systematic review and meta-analysis, deserve comment.

Biases, such as surveillance and self-selection, cannot be prevented when data are obtained from observational studies and causation cannot be established because of the study's design. Despite this, we were able to account for many potential confounding factors related to both HF and cancer that were not available in earlier research. However, the possibility of residual confounding still remains. Some of these studies lack data on associated diseases and risk factors (e.g., smoking, alcohol consumption, obesity). In these epidemiological studies, the socioeconomic situation should also be taken into consideration. The differences in follow-up period may also limit the interpretation of the results.

The fact that HF patients carry a risk of hospitalization and undergo more medical exams may result in an overdiagnosis of disease, which is another significant concern in this research. Some studies, such Kwak,¹³ Banke,¹¹ Bertero¹⁰ and Hasin¹⁴ exclude all diagnosis of cancer within the first years of follow-up after HF diagnosis, and Leedy⁸ and Roderburg⁹ adjusted for consultation frequency and medical appointments.

Moreover, most of the included studies did not provide sufficient data to understand the clear impact of the different types of HF, stratified by ventricular ejection fraction, on cancer diagnosis and prognosis. Further research in this field would be interesting since HF with preserved ejection fraction and HF with reduced ejection fraction have potential distinct clinical characteristics and disease processes.^{41,42}

Another important concern is heterogeneity in terms of population demographics, as the measurement and adjustment for the many confounders showed between the studies. Despite the use of appropriate meta-analytic techniques with random effect models, we are unable to account for these differences. However, multiple sensitivity analyses found the risk estimate was robust across various quality components and the consistency of results across studies, cancer sites, follow-up time and continents support the main findings.

Conclusion

In conclusion, our systematic review and meta-analysis revealed that HF may result in a subsequent increase in cancer incidence. These findings support previous studies published in the literature. The cancer types that had a higher incidence in HF patients were lung, female reproductive system, and hematologic cancers. Furthermore, we conclude that having a diagnosis of HF at baseline carries an increased risk of death from cancer, underlining the importance of noncardiac morbidity and of cancer surveillance in the management of HF patients.

However, because of the significant degree of heterogeneity in the studies, the results should be evaluated carefully. More research in this area is required to clarify the contradictory clinical data and identify the underlying mechanisms.

Nevertheless, all things considered, each HF patient who develops cancer has their own unique characteristics, and the clinical and therapeutic management should be personalized to provide the best cardiological and oncological care and to improve their prognosis.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.repc.2023.10.015](https://doi.org/10.1016/j.repc.2023.10.015).

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