Cancer in patients with heart failure: incidence, risk factors and prognostic impact

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Abstract

Aims. To assess the incidence of cancer diagnosis and cancer-related mortality in patients with heart failure (HF).

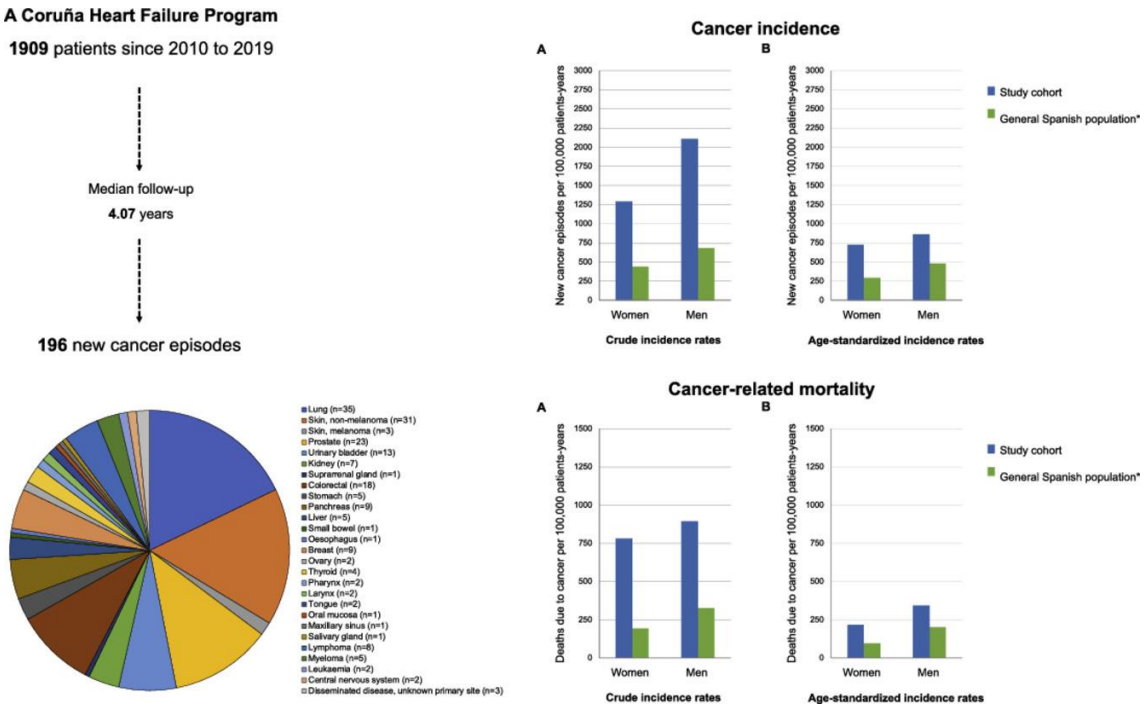
Methods. Observational study based in a prospective cohort of patients with HF referred to a specialized Spanish clinic between 2010 and 2019. The observed incidence of malignancies (excluding non-melanoma skin cancer) was compared to that expected for the general Spanish population according to the Global Cancer Observatory.

Results. We studied 1909 consecutive patients with HF. Over a median follow-up of 4.07 years, 165 new cases of malignancy were diagnosed. Observed age-standardized incidence rates of cancer were 861 (95% CI 618.4–2159.4) cases per 100,000 patients-years in men and 728.5 (95% CI 451.1–4308.7) cases per 100,000 patients-years in women; while age-standardized incidence rates of cancer expected for the general Spanish population were 479.4 cases per 100,000 patients-years in men (risk ratio = 1.80) and 295.5 cases per 100,000 patients-years in women (risk ratio

= 2.46). Both a history of pre-existing malignancy at baseline and the development of new malignancies during follow-up were associated with reduced survival. Observed age-standardized cancer-related mortality was 344.1 (95% CI 202.1–1675) deaths per 100,000 patient-years in men and 217.0 (95% CI 32.8–3949.3) deaths per 100,000 patient-years in women; while age-standardized cancer-related mortality expected for the general Spanish population was 201.4 deaths per 100,000 patients-years in men (risk ratio = 1.71) and 96.2 deaths per 100,000 patients-years in women (risk ratio = 2.26).

Conclusión. Patients with HF showed higher incidence rates of cancer diagnosis and cancer-related mortality than those expected for the general population.

Graphical abstract



Abbreviations

ACE, Angiotensin converter enzyme; CI, Confidence Interval; HF, Heart Failure; HR, Hazard-Ratio; IR, Incidence Rate; LVEF, Left Ventricular Ejection Fraction; NYHA, New York Heart Association

1. Introduction

Heart Failure (HF) and cancer are the main causes of morbidity and mortality in developed countries [1], and their prevalence is increasing due to ageing of the population. Therefore, patients with both pathologies represent a challenge in our daily clinical practice [2]. Several cancer therapies have cardio-toxic effects and may increase de risk of developing HF in patients with malignancies [3]. Furthermore, a few recent studies have suggested that there could also be a relation between HF and cancer in the opposite direction, in other words, that patients with HF might be exposed to an increased risk of incident malignancies [4],[5],[6],[7],[8],[9]. Many pathophysiological hypotheses tried to explain this possible association between pre-existing HF and increased cancer risk, although they are at the time weak and not yet consolidated, with controversial published evidence. In addition, HF patients who develop cancer may not be offered standard oncological treatments because of concerns of tolerability, and this could affect their prognosis negatively [10].

The main objective of this study was to 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 population. Additionally, we aimed to identify specific risk factors for cancer in the HF population, as well as to assess the prognostic impact of pre-existing and incident malignancies in these individuals.

2. Methods

2.1. Study description

We conducted an observational single-center study based on the prospective clinical registry of ambulatory patients with chronic HF who were referred to the specialized HF external clinic of the Cardiology Department of the Complejo Hospitalario Universitario de A Coruña (A Coruña, Spain) since January 1st, 2010 to December 31st, 2019.

Most of the data presented in this study were extracted from the *Sistema Inteligente de Monitorización (SiMon®)*, an electronical manager of clinical records developed by our own institution. This application contains a database in which comprehensive information regarding the baseline clinical characteristics and long-term follow-up of all HF patients

referred to our department is collected prospectively since their first medical visit. Several previous publications from our group were based in this source of clinical information [11],[12],[13]. Additionally, a clinical cardiologist from our institution (M. S-F.) conducted an individual, case-by-case review of the clinical records of all patients with HF included in the registry, to collect specific data about every cancer case diagnosed in these subjects.

The study protocol was approved by the Committee for Ethics in Clinical Investigation of the Autonomous Community of Galicia (Spain). Informed consent was collected from study participants.

2.2. Study variables

The incidence of newly diagnosed malignancies during follow-up was the primary endpoint of the study. Non-melanoma skin cancer was specifically excluded from the definition of the primary endpoint, with the purpose to compare our results with those estimated for the general Spanish population by the Global Cancer Observatory *(*https://gco.iarc.fr/overtime/en*).*

Repeated episodes of cancer in a same patient were counted as >1 malignant event only in the case that they affected different body sites and were not justified by dissemination from a single primary site. Therefore, episodes of cancer with multiple relapses or distant metastases affecting more than one body site were counted only as one malignant event.

Patients were followed since the date of study enrolment until the date of death or until the date of heart transplantation, if performed. Otherwise, follow-up was completed on July 31st, 2021.

2.3. Causes of death

Causes of death were collected from clinical records, autopsy reports or medical certificates of death. Cardiovascular deaths were those caused by refractory HF, arrhythmias, acute coronary syndrome, cerebrovascular disease, arterial or venous thromboembolism, peripheral artery disease or complications of a cardiovascular procedure, as well as unexplained sudden deaths.

In patients who died after having a diagnosis of malignant disease, cancer-related death was assumed unless other evident primary cause of death could be identified.

2.4. Statistical analyses

In this study, qualitative variables are expressed by means of proportions, while quantitative variables are expressed by means (standard deviation) or median (rank), as appropriate.

Crude incidence rates of cancer diagnosis and cancer-related death in the study cohort were calculated separately in women and in men, and across different segments of age (15–49, 50–59, 60–69, 70–79 and ≥80 years). Individuals in the paediatric age (<15 years) were not represented in our cohort, as they are not seen in our specialized HF clinic. Ninety-five% confidence intervals (CI) of incidence rates were estimated by means of the normal approximation. Age-standardized incidence rates of cancer diagnosis and cancer-related death were adjusted by means of the direct method, taking the modified world standard population proposed by Doll et al. [14] as a reference. These assumptions were made to compare our findings with the estimations published by the Global Cancer Observatory *(*https://gco.iarc.fr/overtime/en*)*.

Crude incidence rates of cancer diagnosis and cancer-related death observed in the study cohort were compared by means of the normal approximation with those reported for the general Spanish population aged ≥15 years by the Global Cancer Observatory (all sites, excluding non-melanoma skin cancer). Given that the incidence of cancer diagnosis and cancer-related death decreased in the general Spanish population along the recruitment period of our study (2010–2019), we decided to use the Global Cancer Observatory estimations for the year 2010 as the reference for comparison. This approach, therefore, was a conservative evaluation of the potential role of HF as a risk factor for cancer and cancer-related mortality.

Fine-Gray´s competing risks regression was used to identify independent risk factors for incident malignancy (excluding non-melanoma skin cancer) in the study population. Both death from any cause and heart transplantation were considered as competing events for incident malignancy. Initially, we evaluated the univariate associations of all relevant baseline clinical variables and the risk of incident malignancy (excluding non-melanoma skin cancer) during follow-up. Variables which showed a univariate p-value <0.10 in this

first analysis entered a multivariable backward stepwise process with a p-removal criterion of <0.10. The variables that remained in the final model were considered as independent risk factors for incident malignancy.

Candidate variables explored as potential risk factors for malignancy in the first step of the competing risks analysis were 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 (other than non-melanoma skin cancer), chronic renal failure (glomerular filtration rate <60 ml/min), anaemia, New York Heart Association (NYHA) class III or IV (vs. I or II), serum NTproBNP, left ventricular ejection fraction (LVEF), diuretic use, angiotensin converter enzyme (ACE) inhibitor use, angiotensin 2 receptor blocker use, sacubitril-valsartan use, beta-blocker use, mineralocorticoid receptor antagonist use, ivabradine use and digoxin use. Among them, only 6 variables showed a univariate p-value <0.10 and, so, entered the backward stepwise process –age, history of smoking, ACE inhibitor use, coronary artery disease, female gender and chronic obstructive pulmonary disease–. Given that the number of patients who developed newly diagnosed malignancies during follow-up was 156, the variable-to-event ratio of the backward stepwise multivariable model was 26.

The Kaplan-Meier method was used to depict the long-term survival curves of study participants after study enrolment, as well as after a new subsequent diagnosis of cancer. Multivariable Cox´s regression models were used to evaluate the impact of a previous diagnosis of malignancy at baseline and of a new diagnosis of malignancy during follow-up on the long-term survival of HF patients. For this purpose, incident malignancy was treated as a time-dependent co-variable.

Statistical significance was set as a p-value <0.05 for all contrasts. Statistical analyses were performed with Epidat 4.2, SPSS 25 and Stata 14.

3. Results

3.1. Study population

The study population was formed by 1909 ambulatory patients with HF, which were referred to our clinic since January 1st, 2010 to December 31st, 2019.
The median age of studied patients was 64.4 years (range 15.9 to 94.2 years), and 537 (28.1%) were women. An antecedent of coronary artery disease was noted in 791 (41.4%) patients and left ventricular ejection fraction was <= 40% in 1431 (75%) cases.

3.2. Previous history of cancer at baseline

A previous history of cancer was present in 285 (15%) patients at baseline, with a total number of 309 cancer sites. Among them, 43 (2.3%) patients had exclusively an antecedent of non-melanoma skin cancer, while an antecedent of other types of cancer was present in the remaining 242 (12.7%) patients. Fig. 1 (panel A) shows the specific sites of cancer in patients who presented a history of pre-existing neoplasms at baseline.
Treatment of previous cancer episodes included surgery in 212 (68.6%) cases, chemotherapy in 116 (37.5%) cases, radiotherapy in 80 (25.9%) cases and hormonotherapy in 36 (11.7%) cases.

3.3. Newly diagnosed cancer during follow-up

Patients were followed over a median period of 4.07 years (range 0.1 to 11.5 years), which corresponded to an overall follow-up of 8814.1 patients-years. Over this period, 196 new cases of cancer were diagnosed in 186 (9.7%) patients. Thirty-one (15.8%) cases corresponded to new diagnoses of non-melanoma skin cancer, while 165 (84.2%) cases, which occurred in 156 patients, corresponded to new diagnoses of other types of cancer. Among this latter group, 21 cases were second malignant tumours in patients with a previous story of non-melanoma skin cancer.
Fig. 1 (panel B) shows the specific sites of newly diagnosed cancer cases during long-term follow-up in the study population.

3.4. Baseline clinical characteristics according to cancer history

Table 1 shows the baseline clinical characteristics of patients with a history of previous malignant disease (excluded non-melanoma skin cancer) at baseline (*n* = 242), patients with a new diagnosis of malignancy (excluded non-melanoma skin cancer) during follow-up (*n* = 132), and patients with no malignancy (*n* = 1535).

3.5. Incidence of malignancy

In the whole study cohort, crude incidence rate of malignancy (all sites, excluding non-melanoma skin cancer) during long-term follow-up was 1872 (95% CI 1586.4–2157.6) episodes per 100,000 patients-years. Crude incidence rate of all types of cancer in the whole study cohort reached 2223.7 episodes per 100,000 patients-years (95% confidence interval (CI) 1912.4–2535) when incident cases of non-melanoma skin cancer were also counted as events.

Crude incidence rate of malignancy (all sites, excluding non-melanoma skin cancer) was 1873.9 (95% CI 1545.4–2202.4) episodes per 100,000 patients-years among patients with LVEF <= 40% (*n* = 1431) and 1866 (95% CI 1287.8–2444.3) episodes per 100,000 patients-years among patients with LVEF >40% (*n* = 478).

If patients with a previous history of non-melanoma skin cancer were excluded from the analysis, the estimated crude incidence rate of malignancy (all sites, excluding non-melanoma skin cancer) during long-term follow-up in the whole study cohort was 1802.1 (95% CI 1504.6–2099.5) episodes per 100,000 patients-years.

3.6. Comparison with the general Spanish population

Table 2 shows the specific crude incidence rates of malignancy (all sites, excluding non-melanoma skin cancer) observed in the study cohort, as well as those estimated by the Global Cancer Observatory for the general Spanish population aged ≥15 years, across different age and gender subgroups.

Crude incidence rates of malignancy observed in the study population were significantly higher than those expected for the general Spanish population, both in women (observed = 1291.7 (95% CI 850.9–1732.4) cases per 100,000 patients-years; expected = 441.2 cases per 100,000 patients-years; $p<0.001$; crude risk ratio = 2.93) and in men (observed = 2108.8 (95% CI 1749.1–2468.6) cases per 100,000 patients-years; expected = 681.6 cases per 100,000 patients-years; $p<0.01$; crude risk ratio = 3.09) (Fig. 2).

Age-standardized incidence rates of malignancy (excluding non-melanoma skin cancer) observed in the study population were 861 (95% CI 618.4–2159.4) cases per 100,000 patients-years in men and 728.5 (95% CI 451.1–4308.7) cases per 100,000 patients-years in women. According to the Global Cancer Observatory, the age-standardized incidence rates of malignancy expected for the general Spanish population aged ≥15 years were 479.4 cases per 100,000 patients-years in men (age-standardized risk ratio = 1.80) and 295.5 cases per 100,000 patients-years in women (age-standardized risk ratio = 2.46) (Fig. 2).

Supplemental Table 1 shows crude and age-standardized incidence rates of the most frequent specific types of cancer in the study population, as compared with those expected in the general Spanish population aged ≥15 years, according to the Global Cancer Observatory.

3.7. Risk factors associated with cancer

Univariate competing risks regression identified 6 baseline clinical variables that showed a statistically significant ($p<0.05$) or near-significant ($p<0.10$) association with the risk of developing incident malignancies (excluded non-melanoma skin cancer) during follow-up. However, only 3 of them remained as independent predictors of this event of interest after backward stepwise multivariate analyses (Table 3). Univariate HR of all clinical variables for which their statistical association with incident malignancies were explored are presented in *Supplemental Table 2*.

Age (adjusted HR per 1 year = 1.04; 95% CI 1.03–1.05; $p<0.01$), a history of smoking (adjusted HR = 1.69; 95% CI 1.19–2.38; $p<0.01$) and the prescription of ACE inhibitors at baseline (adjusted HR = 1.56; 95% CI 1.11–2.19; $p = 0.01$) were associated with statistically increased risk of incident malignancies (excluding non-melanoma skin cancer) during long-term follow-up.

3.8. Treatment and outcomes after a new diagnosis of cancer

Treatment of newly diagnosed cancer episodes (*n* = 196) involved surgery in 95 (48.5%) cases, chemotherapy in 44 (22.4%) cases, radiotherapy in 43 (21.9%) cases and hormonotherapy in 16 (13.3%) cases. No specific therapy was delivered in 40 (20.4%) cases of cancer.

Curation or complete remission was achieved after treatment in 108 (55.1%) cancer episodes; subsequent relapses of the disease were observed in 11 (10.2%) of these cases. Curation or complete remission was observed in 77 out of 165 episodes (46.7%) of malignant disease different than non-melanoma skin cancer.

Fig. 3 shows the Kaplan-Meier cumulative estimates of survival following a new diagnosis of cancer in the study population. Overall survival was significantly higher after a new diagnosis of non-melanoma skin cancer as compared to survival following a new diagnosis of other malignant diseases (p log rank <0.01).

Estimated cumulative survival rates after a new diagnosis of malignancy (excluding non-melanoma skin cancer) were 56.4% at 1 year, 47% at 3 years and 36.1% at 5 years.

3.9. Prognostic impact of malignancy in heart failure patients

Fig. 4 shows the cumulative estimates of long-term survival after study enrolment of patients with a previous history of malignancy (excluded non-melanoma skin cancer) at baseline (*n* = 242), patients with a new diagnosis of malignancy (excluded non-melanoma skin cancer) during follow-up (*n* = 132), and patients with no malignancy (*n* = 1535).

In multivariable Cox´s regression, both a previous history of malignancy (adjusted HR = 1.34; 95% CI 1.07–1.69; *p* = 0.01), as well as the diagnosis of a new malignant disease during follow-up (adjusted HR = 6.19, 95% CI 3.1–10.3; <0.01) were associated with statistically significant higher risk of death from any cause, as compared with the absence of malignancy. Newly diagnosed malignancy was treated as a time-varying co-variable in survival analyses.

3.10. Cancer-related mortality in heart failure patients

Over long-term follow-up, 536 deaths were registered in the study population, whose specific causes are presented in *Supplemental Table 3*. Globally, 74 (13.8%) deaths were directly attributable to cancer –22 patients with a previous history of malignancy at baseline and 52 patients with newly diagnosed malignancies during follow-up–.

Table 4 shows the crude and age-standardized incidence rates of cancer-related mortality observed in the study population, as well as those expected for the general Spanish population aged ≥ 15 years according to the Global Cancer Observatory.

Observed crude incidence rates of cancer-related mortality were higher than expected, both in women (observed = 782.8 (95% CI 439.7–1129.5) deaths per 100,000 patients-years; expected = 192.9 deaths per 100,000 patients-years; $p<0.01$; crude risk ratio = 4.06) and in men (observed = 894.7 (95% CI 660.3–1125.9) deaths per 100,000 patients-years; expected = 325.9 deaths per 100,000 patients-years; $p<0.01$; crude risk ratio = 2.74) (Fig. 5).

Observed age-standardized incidence rates of cancer-related mortality were 344.1 (95% CI 202.1–1675) deaths per 100,000 patients-years in men and 217.0 (95% CI 32.8–3949.3) deaths per 100,000 patients-years in women. Meanwhile, expected age-standardized rates of cancer-related mortality were 201.4 deaths per 100,000 patients-years in men (age-standardized risk ratio = 1.71) and 96.2 deaths per 100,000 patients-years in women (age-standardized risk ratio = 2.26) (Fig. 5).

4. Discussion

In this research, we reviewed all previous and new diagnoses of cancer in a large single-center Spanish cohort of patients with HF who were referred to a dedicated HF clinic and followed in the long term. The most important finding of the study was an increased incidence of malignancy and cancer-related mortality in our cohort of HF patients as compared to those expected in the general Spanish population, according to the estimations published by the Global Cancer Observatory. Both a history of pre-existing malignancy and, more markedly, the development of newly diagnosed malignancies during follow-up, had a negative impact in the long-term survival of HF patients.

Some previous epidemiological evidence supports the hypothesis that HF might be a risk factor for developing malignant disease. In their case-control study conducted in Olmsted County, Minnesota (United States), Hasin et al. [4] observed an increased incidence of newly diagnosed cancer among community patients with HF, as compared to matched controls. These authors confirmed their initial findings in a subsequent cohort-based study that focused on patients with acute myocardial infarction with or without coexistent HF [5]. More recently, Kwak S et al. [8] observed a 1.6-fold increased risk of incident cancer in Korean patients with HF, as compared to matched controls. Similar results were found in retrospective cohort study conducted in 1274 general practices in Germany [9], in a multi-institutional Danish cohort study that involved 26 specialized HF clinics[6] and in a community-based study in the region of Puglia, Italy [15]. However, another Danish nationwide study suggested that the association between HF and the risk of incident cancer might be explained by associated co-morbidities and medications, rather than being independent [16].

The major strength of our study is the methodology used to collect and confirm cancer diagnoses in HF patients, which was based on a case-by-case review by an expert clinician of the individual medical records of every patient with HF enrolled in our prospective cohort. In previous studies, cancer diagnoses were mainly collected from pre-existing population-based clinical registries [[4],[5]] or administrative databases [[6],[8],[9],[15],[16]] (*Supplemental Table 4*).

Heart failure and cancer share common risk factors like smoking, alcohol consumption, obesity, inactivity, or dietary habits. However, there is also a biological rationale that suggest that chronic HF itself induces several pathophysiological changes that may favour the development of malignant diseases. Increased sympathetic activity [17], renin-angiotensin-aldosterone system activation [18], chronic inflammation and increased oxidative stress are well-known components of the pathophysiology of chronic HF, which have been related with an increased risk of malignancy [19],[20],[21],[22],[23],[24].

Our multivariable competing-risk analyses identified three baseline clinical variables associated independently with a higher risk of newly diagnosed cancer. Not surprisingly, the risk of malignancy was higher in patients with a history of smoking, as well as in older subjects. However, the excess incidence of cancer observed in patients with HF as compared with the general population was more evident in the youngest strata of age,

while the incidence of cancer of elderly patients with HF tended to be comparable to the one estimated for the general population of similar age and gender. Therefore, this finding suggests that the impact of HF as a risk factor for malignancy might be more important in younger than in older individuals, in the line of what has been observed by other authors [4,15].

In our cohort, patients who received ACE inhibitors showed an increased incidence of malignancies in the long-term, a statistical association that persisted even after multivariable adjustments. This is an intriguing finding, as previous literature in this topic is conflicting. In one multi-center cohort-based study [6], the prescription of ACE inhibitors was associated with an increased incidence of cancer of any type in patients with HF; other studies suggested that ACE inhibitors might be associated more specifically with a higher risk of lung cancer, because of a chronic local increase of bradykinin levels in the lung tissue [25],[26],[27],[28]. However, one meta-analysis of randomized controlled trials [29] and another one of observational studies [30] did not demonstrate any significant impact of ACE inhibitors on the global risk of malignancy, and a recent systematic review specifically found no association between the use of these drugs and the incidence of lung cancer [31]. Moreover, the prescription of ACE inhibitors in patients with a previous diagnosis of cancer does not increase the risk of progression of the malignant disease [32]. The discrepancy of the results reported by different studies probably reflects the presence of significant statistical bias derived from competing risks and confounding factors. Therefore, until now there is no consistent evidence to affirm that ACE inhibitors are pro-cancerous drugs.

In our cohort, both a previous history of malignancy at baseline and the development of incident malignancies during follow-up were associated with reduced survival in patients with HF. Prognosis was especially ominous for patients who developed cancer during follow-up, with 1-year mortality rates after the diagnosis of the neoplasm that exceed 40%. Previous literature shows that comorbid cancer is associated with impaired prognosis in patients with HF [33,34]; and viceversa, that comorbid HF is associated with worse outcomes in patients with cancer [35]. Clinical management of patients who suffer from both HF and cancer is challenging [2]. Optimal oncologic therapy may be limited by the probability of cardiac toxicity, that may impair the clinical course of HF. Concurrent HF is associated with increased surgical risk and may prevent some patients

with cancer to be offered an invasive therapeutic management of their disease. In the other hand, patients with cancer and HF are usually frail, so HF medications may be more difficult to be tolerated and up titrated. Finally, the presence of cancer may reduce the chance of patients with HF to be eligible for invasive cardiovascular therapies like implantable devices or heart transplantation.

The present study has a few limitations. First, as an observational one, it may be affected by inherent selection, information, and confusion bias. Second, given the single-center scope of the investigation, the external validity of our conclusions is not ensured. Third, the study lacks a control group of patients without HF to make a direct comparison of the incidence of cancer during follow-up; instead of this, we decided to make an indirect comparison with the incidence of cancer estimated for the Spanish general population by the Global Observatory of Cancer. Fourth, our analysis is based in a clinical registry of real-world practice; so, the diagnosis and management of the cases of cancer was led to the discretion of the attending physicians, rather than driven by a pre-specified protocol. Finally, we cannot exclude the presence of a surveillance bias derived from the close clinical follow-up of the study cohort, which was managed in a single specialized HF unit.

In conclusion, the observed incidence of newly diagnosed malignancies in our single-center cohort of patients with HF was higher than the one expected for the general Spanish population, both in women and in men; moreover, observed cancer-related mortality was also higher than expected. Increasing age, a history of smoking and the prescription of ACE inhibitors at baseline were independently associated with an increased risk of malignancies during follow-up. The outcomes of HF patients who developed malignancies were poor. Further research is needed to elucidate the complex mechanisms underlying the pathophysiological relation between HF and cancer to improve the challenging clinical management of these high-risk individuals.

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Declaration of Competing Interest

There are no conflicts of interest regarding this publication.

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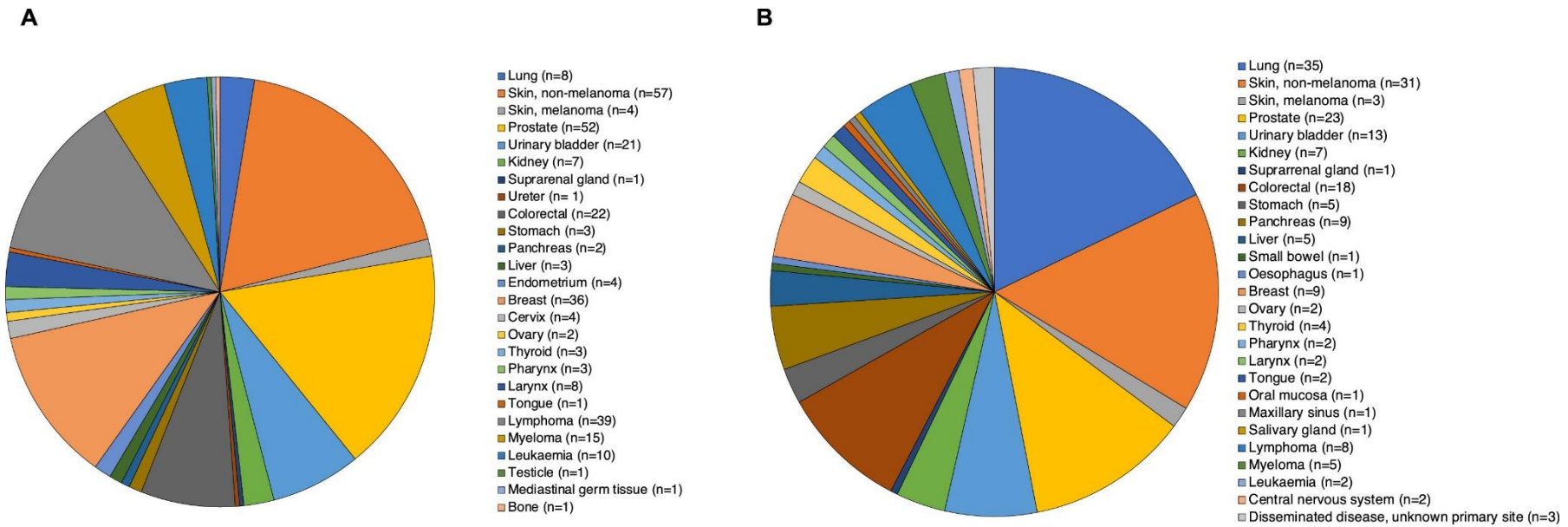

Fig. 1. Cancer sites in patients with a history of previous cancer at baseline (panel A) and in patients with newly diagnosed tumours during long-term follow-up (panel B).

Table 1. Baseline clinical characteristics of study patients classified according to the presence or absence of malignancy (excluding non-melanoma skin cancer), either as a previous diagnosis or newly diagnosed during follow-up. NYHA, New York Heart Association.

	No malignancy (*N* = 1535)	Previous history of malignancy* (*N* = 242)	Newly diagnosed malignancy (*N* = 132)	P value
Age (years)	62.3 ± 12.5	67.5 ± 11.7	66.9 ± 8.2	<0.01
Women	421 (27.4%)	92 (38%)	24 (18.2%)	<0.01
Hypertension	798 (52%)	148 (61.2%)	76 (57.6%)	0.02
Diabetes mellitus	452 (29.4%)	86 (35.5%)	45 (34.1%)	0.10
Obesity	547 (35.6%)	64 (26.4%)	44 (33.3%)	0.02
Dyslipidaemia	818 (53.3%)	131 (54.1%)	74 (56.1%)	0.81
History of smoking	898 (58.5%)	112 (46.3%)	88 (66.7%)	<0.01
History of alcohol abuse	416 (27.1%)	53 (21.9%)	44 (33.3%)	0.05
Coronary heart disease	646 (42.1%)	79 (32.6%)	66 (50%)	<0.01
Atrial fibrillation	377 (24.6%)	64 (26.4%)	40 (30.3%)	0.31
Chronic obstructive pulmonary disease	150 (9.8%)	32 (13.2%)	20 (15.2%)	0.06
Peripheral artery disease	106 (6.9%)	17 (7%)	16 (12.1%)	0.08
History of stroke	137 (8.9%)	32 (13.2%)	10 (7.6%)	0.08
NYHA class III or IV	516 (33.6%)	101 (41.7%)	35 (26.5%)	<0.01
Left ventricular ejection fraction (%)	34.3 ± 13.7	36.3 ± 14.5	33.9 ± 12.9	0.08
left ventricular ejection fraction <= 40%	1154 (75.2%)	173 (71.5%)	104 (78.8%)	0.27
hemoglobin (g/dl)	13.7 ± 1.9	13 ± 1.8	13.7 ± 1.9	<0.01
Creatinine (mg/dl)	1.24 ± 0.83	1.39 ± 1.1	1.19 ± 0.38	0.02
NTproBNP (pg/dl)	3031.2 ± 4763.1	4447 ± 6696.7	2790.7 ± 4187.6	<0.01
Glomerular filtration rate (ml/min/m^2)	77.9 ± 34.6	62.5 ± 27.3	72.3 ± 29.5	<0.01
Diuretic	1239 (80.7%)	214 (88.4%)	104 (78.8%)	0.01

Table 1. Baseline clinical characteristics of study patients classified according to the presence or absence of malignancy (excluding non-melanoma skin cancer), either as a previous diagnosis or newly diagnosed during follow-up. NYHA, New York Heart Association.

	No malignancy (*N* = 1535)	Previous history of malignancy* (*N* = 242)	Newly diagnosed malignancy (*N* = 132)	P value
Mineralocorticoid receptor antagonist	1000 (65.1%)	155 (64%)	76 (57.6%)	0.22
Beta-blocker	1359 (88.5%)	204 (84.3%)	120 (90.9%)	0.10
Angiotensin converter enzyme inhibitor	871 (56.7%)	120 (49.6%)	90 (68.2%)	<0.01
Angiotensin 2 receptor blocker	228 (14.9%)	36 (14.9%)	16 (12.1%)	0.69
Sacubitril-valsartan	144 (9.4%)	22 (9.1%)	5 (3.8%)	0.10
Digoxin	133 (8.7%)	20 (8.3%)	15 (11.4%)	0.55
Ivabradine	91 (5.9%)	19 (7.9%)	6 (4.5%)	0.38
Implantable defibrillator	242 (15.8%)	28 (11.6%)	19 (14.4%)	0.23

∗ The definition of malignancy excluded non-melanoma skin cancer.

Table 2. Crude incidence rates of cancer (excluding non-melanoma skin cancer) in the study population and in the general Spanish population, according to age and gender. CI, Confidence Interval. IR, Incidence Rate.

	Women						Men					
	Patients	Cases of cancer	Patients-years of follow-up	Crude IR (95% CI)	Crude IR General Spanish population*	P value for comparison	Patients	Cases of cancer	Patients-years of follow-up	Crude IR (95% CI)	Crude IR General Spanish population**	P value for comparison
15–49 years	69	2	374.9	533.5 (64.6–1927.0)	140.5	0.04	185	3	1181.2	254.0 (52.4–742.2)	92.4	0.07
50–59 years	113	4	583.9	685.0 (13.7–1356.4)	551.3	0.66	339	30	1795.6	1670.7 (1072.9–2268.6)	711.9	<0.01
60–69 years	156	11	747.2	1472.2 (602.2–2342.1)	778.2	0.03	446	52	1999.6	2600.5 (1893.7–3307.3)	1739.1	<0.01
70–79 years	156	13	710.1	1830.7 (835.5–2825.9.)	1039.6	0.04	307	39	1105.1	3529.0 (2421.5–4636.7)	2690.4	0.09
≥80 years	43	3	138.6	2164.5 (446.3–6325.6)	1355	0.41	95	8	255.1	3136.0 (962.9–5309.1)	2868.4	0.80
All	537	33	2554.8	1291.7 (851–1732.4)	442.4	<0.01	1372	132	6259.3	2108.8 (1749.1–2468.6)	681.6	<0.01

∗ Crude incidence rate of cancer (all sites, excluding non-melanoma skin cancer) expected for the general Spanish population of women aged ≥15 years in the year 2010, according to the Global Cancer Observatory. Source: https://gco.iarc.fr/overtime/en.

∗∗ Crude incidence rate of cancer (all sites, excluding non-melanoma skin cancer) expected for the general Spanish population of men aged ≥15 years in the year 2010, according to the Global Cancer Observatory. Source: https://gco.iarc.fr/overtime/en.

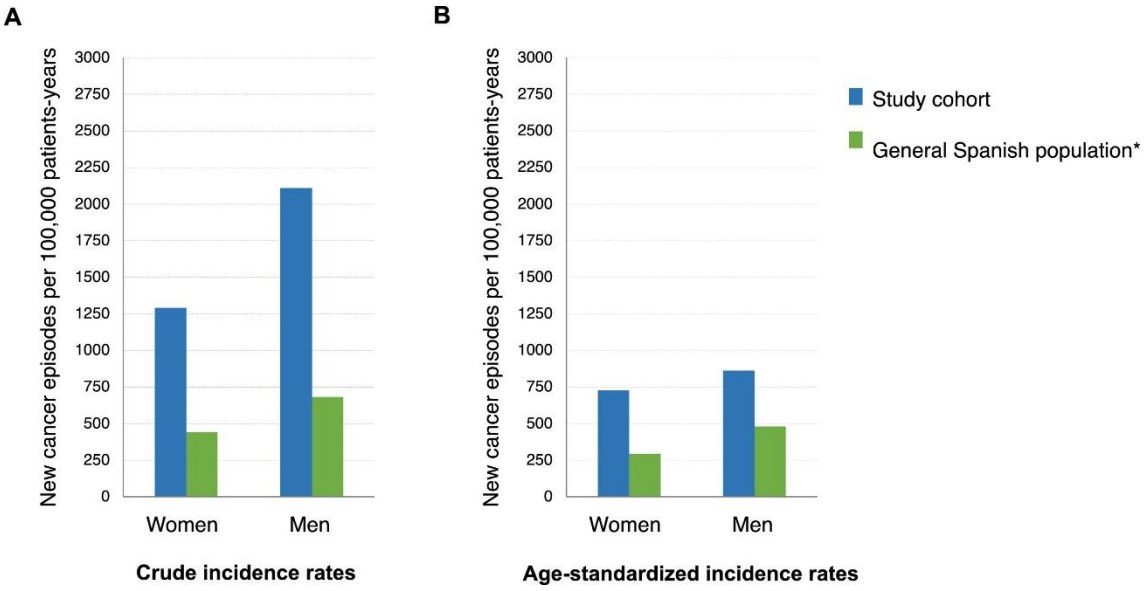

Fig. 2. Crude (panel A) and age-standardized incidence rates (panel B) of newly diagnosed malignancies (all sites, excluding non-melanoma skin cancer) observed in the study cohort and estimated for the general Spanish population according to the Global Cancer Observatory. *Crude and age-standardized incidence rates of cancer (all sites, excluding non-melanoma skin cancer) expected for the general Spanish population of women or men aged ≥15 years in the year 2010, according to the Global Cancer Observatory. Source: https://gco.iarc.fr/overtime/en. Age-standardized rates were calculated by the direct method, taking the modified world standard population proposed by Doll et al. as a reference. Doll R, Payne P, Waterhouse J. Cancer incidence in five countries: a technical report. Berlin: Springer-Verlag Berlin Heidelberg; 1966. Available in https://www.springer.com/gp/book/97835400347.

Table 3. Risk factors for incident cancer (excluding non-melanoma skin cancer) in patients with heart failure: univariate and multivariate competing risks regression.

	Univariate analysis*			Multivariate análisis		
	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
Age (years)	1.03	1.02–1.04	<0.01	1.04	1.03–1.05	<0.01
Female gender	0.68	0.46–1.01	0.05	–	–	–
History of smoking	1.45	1.04–2.03	0.03	1.69	1.19–2.38	<0.01
Coronary artery disease	1.31	0.95–1.79	0.09	–	–	–
Chronic obstructive pulmonary disease	1.71	1.12–2.61	0.01	–	–	–
Angiotensin enzyme converter inhibitor use	1.40	1.00–1.95	0.05	1.56	1.11–2.19	0.01

CI, 95% Confidence Interval

∗ Variables explored in univariate analyses: Age, gender, previous history of malignancy (other than non-melanoma skin cancer), history of smoking, history of alcohol abuse, diabetes mellitus, body mass index, hypertension, dyslipidaemia, coronary artery disease, chronic obstructive pulmonary disease, chronic renal failure (glomerular filtration rate <60 ml/min), anemia, NYHA class III or IV (vs. I or II), serum NTproBNP, left ventricular ejection fraction, angiotensin converter enzyme inhibitor use, angiotensin 2 receptor blocker use, sacubitril-valsartan use, beta-blocker use, mineralocorticoid receptor antagonist use, ivabradine use, digoxin use. The clinical variables shown in the Table 3 are only those that showed a univariate association with the risk of malignancies with a p-value <0.10. Univariate coefficients of all explored baseline variables are shown in *Supplementary Table 2*.

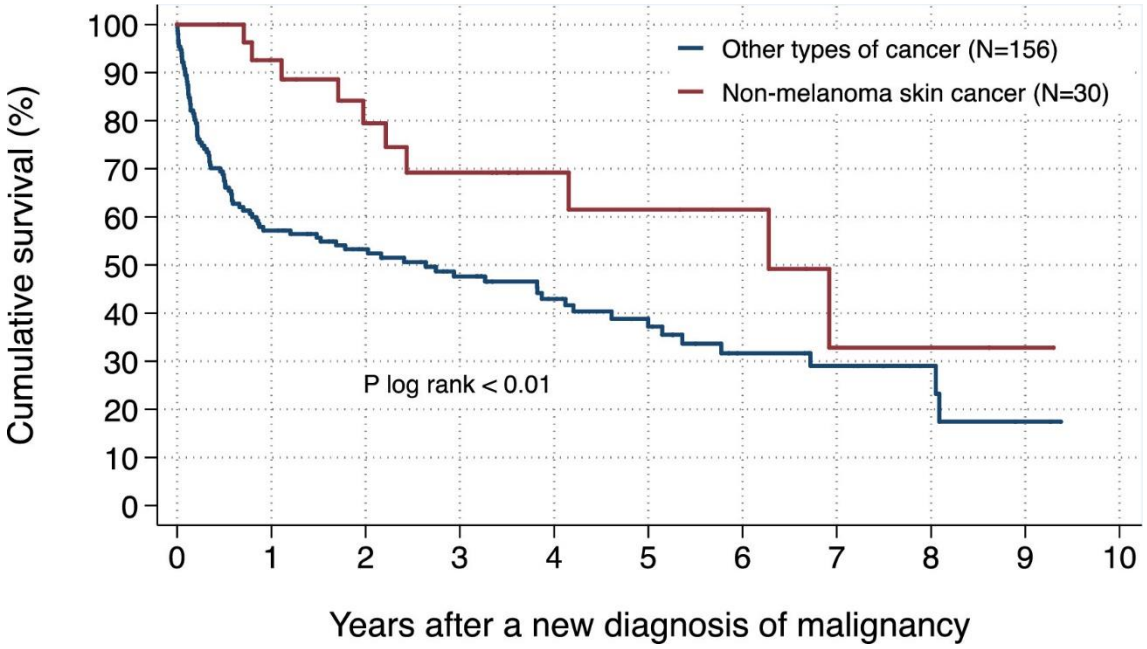

Fig. 3. Kaplan-Meier cumulative estimates of survival after a new diagnosis of non-melanoma skin cancer vs. other types of cancer in patients with heart failure.

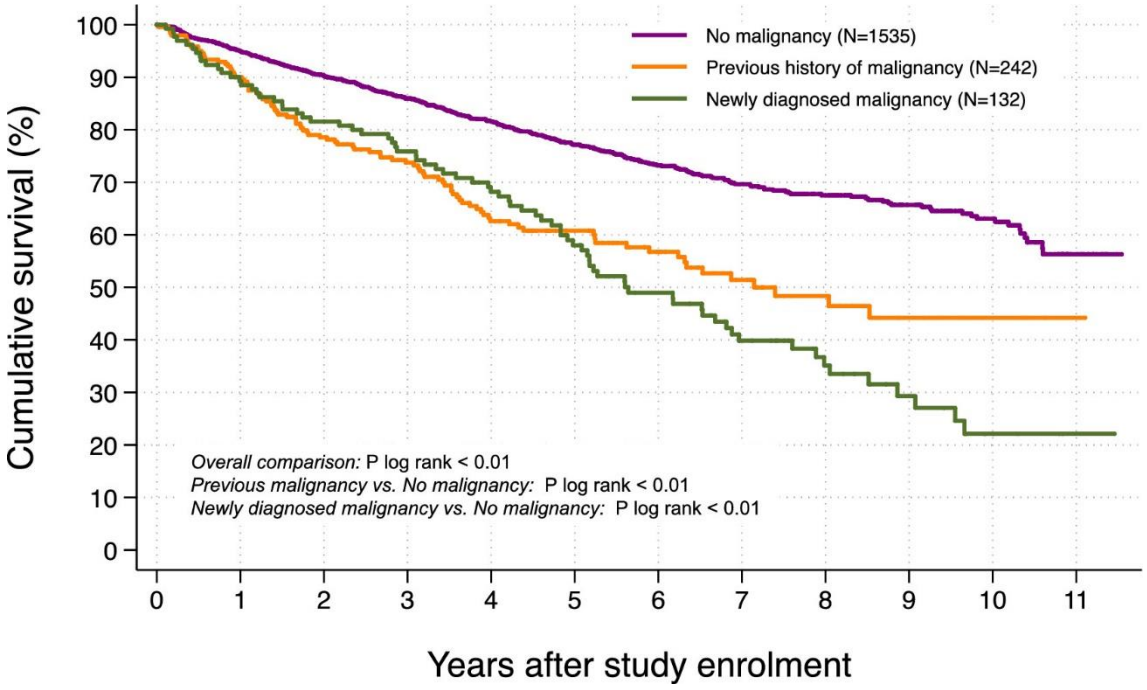

Fig. 4. Kaplan-Meier cumulative estimates of survival from baseline in patients with heart failure and a history of pre-existing malignancy, newly diagnosed malignancies during follow-up or no malignancy. The definition of malignancy excluded non-melanoma skin cancer.

Table 4. Incidence rate of cancer-related mortality in the study population, as compared to those estimated for the general Spanish population. Incidence rates of cancer-related mortality are expressed in deaths due to cancer per 100,000 patients-years

	Women					Men				
	Patients	Cancer-related deaths	Crude cancer-related mortality (95% CI)	Crude cancer-related mortality General Spanish population*	P value	Patients	Cancer-related deaths	Crude cancer-related mortality (95% CI)	Crude cancer-related mortality General Spanish population∗∗	P value
15–49 years	69	0	0	23.9	–	185	1	84.7 (2.1–471.7)	20.0	0.12
50–59 years	113	3	513.8 (105.9–1501.5)	150.3	0.02	339	11	612.6 (250.6–974.6)	267.9	<0.01
60–69 years	156	5	669.2 (82.6–1255.7)	258.2	0.03	446	21	1050.2 (601–1499.4)	626.6	0.02
70–79 years	156	10	1408.2 (535.4–2281.1)	519.8	<0.01	307	19	1719.3 (946.2–2492.4)	1273.4	0.19
≥80 years	43	2	1443 (174.7–5212.6)	1052.3	0.65	95	4	1568 (31.4–3104.6)	2363.5	0.41
All	537	20	782.8 (439.7–1125.9)	192.9	<0.01	1372	56	894.7 (660.3–1129)	325.9	<0.01

CI, Confidence Interval

∗ Crude incidence of cancer-related mortality expected for the general Spanish population of women aged ≥15 years in the year 2010, according to the Global Cancer Observatory. Source: https://gco.iarc.fr/overtime/en.

∗∗ Crude incidence of cancer-related mortality expected for the general Spanish population of men aged ≥15 years in the year 2010, according to the Global Cancer Observatory. Source: https://gco.iarc.fr/overtime/en.

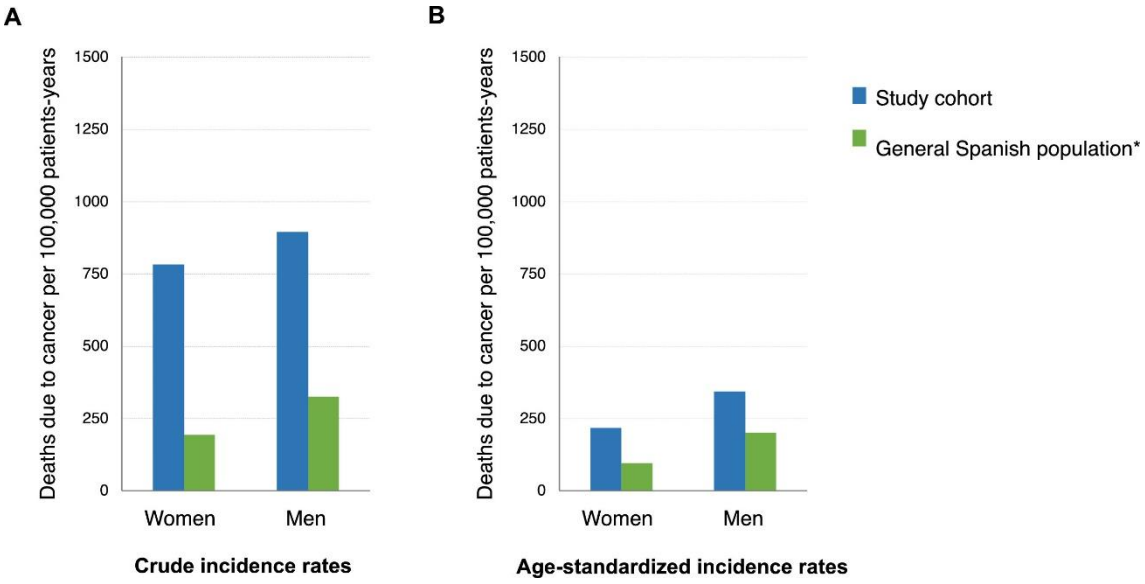

Fig. 5. Crude (panel A) and age-standardized (panel B) incidence rates of cancer related mortality observed in the study cohort and estimated for the general Spanish population according to the Global Cancer Observatory. *Crude and age-standardized incidence rates of cancer-related death expected for the general Spanish population of women or men aged ≥15 years in the year 2010, according to the Global Cancer Observatory. Source: https://gco.iarc.fr/overtime/en. Age-standardized rates were calculated by the direct method, taking the modified world standard population proposed by Doll et al. as a reference. *Doll R, Payne P, Waterhouse J. Cancer incidence in five countries: a technical report. Berlin: Springer-Verlag Berlin Heidelberg; 1966. Available in* https://www.springer.com/gp/book/97835400347.