Title: Characteristics of haematologic and breast cancer patients (1996-2009) who died of heart failure-related causes after cancer therapy

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Total word count: 4713 (including References, Figure Legends and Tables)

ABSTRACT

Aims: To describe the characteristics and time to death of patients with breast or haematologic cancer who died of heart failure (HF) after cancer therapy. Patients with an index admission for HF who died of HF-related causes (IAHF) and those with no index admission for HF who died of HF-related causes (NIAHF) were compared.

Methods and Results: We performed a linked data analysis of Cancer Registry, Death Registry and Hospital Administration records (n=15,987). Index HF admission must have occurred after cancer diagnosis. Of the 4894 patients who were deceased (30.6% of cohort), 734 died of HF-related causes (50.1% female) of which 279 (38.0%) had at least one IAHF (41.9% female) post-cancer diagnosis. Median age was 71 years (IQR 62-78) for IAHF and 66 years (IQR 56-74) for NIAHF. There were fewer chemotherapy separations for IAHF patients (median=4, IQR 2-9) compared to NIAHF patients (median=6, IQR 2-12). Of the IAHF patients, 71% had died within one year of the index HF admission. There was no significant difference in HF-related mortality in IAHF patients compared to NIAHF (HR, 1.10, 95%CI, 0.94-1.29, p=0.225)

Conclusion: The profile of IAHF patients who died of HF-related causes after cancer treatment matched the current profile of heart failure in the general population (over half were aged ≥70 years). However, NIAHF were younger (62% were aged ≤69 years), female breast cancer patients that died of HF-related causes before hospital admission for HF-related causes – a group that may have been undiagnosed or undertreated until death.

KEYWORDS: cardiotoxicity; mortality; haematologic; breast; cancer; heart failure

INTRODUCTION

Anticancer therapies have increased recurrence-free survival for many cancer patients. However associated comorbidities and treatment-related toxicity have limited overall survival gains. (1) Cardiotoxicity is one of the most significant side-effects of some anticancer agents, so that any gain in life expectancy is potentially diminished by increased mortality due to cardiotoxic sequelae such as heart failure (HF), myocardial ischaemia, arrhythmias, hypertension, and thromboembolism. (1)

The incidence and outcomes of cardiotoxicity depend on different factors related to oncological therapies including the type of drug, the mode of administration (i.e. bolus or continuous), dose administered during each cycle, cumulative dose, combinations (or prior treatment) with other cardiotoxic drugs or radiotherapy of the cardiac region and patient age, mediastinal radiation, female sex, presence of cardiovascular (CV) risk factors and previous cardiovascular disease (CVD). (2,3)

Cardiotoxicity related to anthracyclines is well documented, with early studies reporting variable rates, often based upon retrospective identification in cancer-survivor cohorts. A recent large, prospective study, which included regular monitoring of cardiac function, reported an incident rate of cardiotoxicity following anthracycline therapy of 9% over a median 5-year follow-up period, (3) with 98% of these cases occurring in the first 12 months. High mortality rates have also been reported in patients with anthracycline-mediated cardiotoxicity identified through historical longitudinal cohorts (4). More recent studies have suggested better cardiac-related survival of chemotherapy patients, especially in patients identified with pre-symptomatic left ventricular dysfunction (5). This is likely to be a result of routine baseline and ongoing monitoring being implemented as standard practice where known cardiotoxic drugs are considered. (5) Cardinale et al. (2015) recently reported that left ventricular function either partially or completely recovered following early detection and treatment in 82% of patients with anthracycline-mediated cardiotoxicity. (3) Torti and colleagues, (6) based on histologic evidence of anthracycline cardiotoxicity, showed that only higher doses and frequency of anthracycline administration and previous cardiac irradiation were independent risk factors. Cumulative doxorubicin dose was also recently confirmed to be an independent risk factor by Cardinale et al. (2015), in addition to end-chemotherapy left ventricular ejection fraction. Nonetheless, there is wide variation in individual sensitivity to anthracyclines, with some patients developing cardiotoxicity at doses as low as 300 mg/m^2 body surface area. (3)

Previous work from our research group, using a linked dataset, demonstrated that in those individuals with breast or haematologic cancer (leukaemias, lymphomas and related blood disorders), 7% of patients previously treated with chemotherapy had an index hospital admission for heart failure (HF) (1,062/15,987) within the 14-year study period (Figure 1). (7) Of these patients who had an index admission for HF, 68% (728/1062) died within the study period, with 38% (279/728) of deaths attributed to HF-related causes. Approximately 93% (14,925/15,987) of individuals did not have an index admission for HF following chemotherapy.

INSERT FIGURE 1

Of these patients, 28% (4166/14925) had died, with approximately 11% (455/4166) of deaths attributed to HF-related causes. Individuals who had no previous index heart failure admission were significantly younger and comprised a greater proportion of females compared with patients admitted with heart failure. (7) This group was the focus of this study.

The aim of this sub-analysis was to further explore the characteristics of those patients who died of HF-related causes after chemotherapy. As 11% of the cohort described above died of HF-related causes without an index hospital admission for heart failure, the objectives of this study were to:

1) Identify differences in demographic characteristics between those who died of HF-related causes after an index admission for HF (IAHF), compared to those who died of HF-related causes without an index admission for HF (NIAHF) and

2) Identify whether there were differences in HF-related mortality risk between the two patient groups.

METHODS

Study design and setting

This is a retrospective cohort study of patients linked using health data between January 1996 and December 2009 from Queensland, Australia. Queensland is Australia's third most populous state with an estimated residential population of four million people during the study period. (8) This timeframe enabled linkage and analysis of uniform data across the three data sources relating to morbidity, hospitalisation, and mortality.

Ethics approval was granted by the Metro South Service District Human Research Ethics Committee on behalf of the Queensland Government (HREC/11/QPAH/600).

Assumptions of this analysis

The purpose of this analysis was to review the characteristics of patients who died of heart failure after cancer treatment. We used "real world" data from clinical administration datasets using data linkage techniques. Data for cardiovascular risk factors, previous disease and details on specific dose and chemotherapy agents were not available or obtainable during the process of data abstraction and linkage. Therefore, as a surrogate variable to control for confounders (such as a previous diagnosis of heart failure) we examined the outcomes of patients who had their first heart failure admission after chemotherapy. An index heart failure admission is a first ever recorded admission as coded on discharge using ICD9 of ICD10 codes for the classification of heart failure. This is regarded as an acceptable criterion for diagnostic confirmation of heart failure. (9) The comparison group may have contained patients with existing heart failure.

The second assumption of this analysis is that patients with breast or haematologic cancers were more likely than patients with other cancers to be treated with cardiotoxic drugs, particularly anthracyclines. (3)

Thirdly while chemotherapy is usually delivered in the outpatient setting, ambulatory care of this nature is often recorded as an admission for chemotherapy, which we have used as a surrogate for the number of chemotherapy cycles. The assumption of this variable is that all patients in the cohort received chemotherapy for haematologic and breast cancer from 1996 to 2009 but that not all chemotherapy cycles have been captured. Outpatient and pharmacotherapy data were not available for linkage at the time of our data request.

Participants

Primary cancer diagnosis was used to identify the cancer site/morphology using the International Classification of Diseases and Tenth Revision Australian Modification (ICD 10-AM) and ICD-O (oncology) site codes in the original linked dataset. Cancer sites were defined as breast (ICD 10-AM: C50) or haematologic (leukemia, lymphoma and related disorders) (ICD10-AM: C42, C77 and ICD-O: M9590/3-M9989/3) henceforth referred to as 'haematologic cancers'. No age exclusions were applied. In this analysis, only patients who had died of HF-related causes were included and these patients were then stratified into two groups – those who had their first admission / diagnosis for HF as identified by an index admission for HF (IAHF) and those who did not have an index HF admission (NIAHF), following commencement of chemotherapy.

Data sources and linkage

Data were accessed from the Queensland Cancer Registry, the Hospital Admitted Patient Data Collection, and the Queensland Births, Deaths and Marriages database.

The Queensland Cancer Registry was used to access data on age, sex, marital status, residence (rural or metropolitan), country of birth, and Aboriginal or Torres Strait islander status. Primary cancer diagnosis was used to identify the cancer type, and the cancer site/morphology was identified by applying the relevant site codes from ICD 9 and ICD 10.

Patients receiving chemotherapy were identified by using chemotherapy-related procedure codes from the Hospital Patient Data Collection and linked to the primary cancer diagnoses records from the Queensland Cancer Registry. The procedure codes were defined according to ICD-9CM (Clinical Modification) and ICD-10-AM (Australian Modification). Cancer morphology codes were defined in accordance with uniform ICD-O. Radiotherapy was not considered in this study due to the unknown proportion of patients receiving concomitant treatment in an outpatient setting.

Selection of patients with an index HF hospitalisation was based upon hospital records with patients flagged if they had an admission to hospital for the first time with heart failure coded as the principle diagnosis (i.e. ICD-9-CM and ICD-10-AM diagnostic codes). This first admission or "index event" must have occurred after the diagnosis of cancer and the commencement of chemotherapy.

The third database involved in the linkage process was the Queensland Birth, Deaths and Marriages database – a complete repository of all registered deaths in the state of Queensland. All causes of death underwent a manual recoding from the text entries – a process that underwent quality assurance by three independent investigators. The end date of data for study purposes was December 31, 2009. Deaths after this date were not accounted for and the patients alive at the specified end date were considered alive for the purposes of calculating survival times and mortality analyses. Data extraction and coding were undertaken using STATA 13.0. Linkage Wiz software was used to undertake probabilistic record matching. Quality control undertaken during the linkage process included a 20-step manual clerical review to identify false positives – a method that quantified the false positive rate at 0.3%. (9)

Statistical analyses

Based upon the stratification of patients as 1) an index heart failure admission (IAHF) and 2) no admission for heart failure (NIAHF), admission groups were compared using χ^2-contingency table testing for categorical variables (age group, sex marital status, country of birth, Indigenous status, residence, cancer morphology/site). Age in years was categorised as <20, 20-29, 30-30, 40-49, 50-59, 60-69, and ≥70 to describe the demographics of the study population and is also presented as a continuous variable. Due to the non-normal distribution of the continuous variables (age, hospitalisations, chemotherapy treatments), they are presented as medians with IQR and compared using the non-parametric Mann-Whitey U test. The effect of an index admission for HF on the risk of HF mortality was assessed adjusted for age, sex, marital status, country of birth, cancer site and chemotherapy along with other confounders using a time-varying Cox proportional hazards regression model. Multivariate adjustment was undertaken for the covariates of age group in years [<20, 20-29, 30-30, 40-49, 50-59, 60-69, and ≥70], sex, marital status, country of birth, cancer site, and number of chemotherapy separations categorised as quintiles [Q1: 1-3; Q2: 4-6; Q3: 7-9; Q4: 10-16; Q5: ≥17]. To examine associations between admission groups, an adjusted Kaplan-Meier survival analysis was used with a log-rank test. All statistical tests were conducted at the 5% significance level and were performed using IBM SPSS 22.0.

RESULTS

Participants

A STrengthening the Reporting of Observational studies in Epidemiology (STROBE) flowchart describes the allocation of patients to the respective groups for the subsequent analyses (Figure 1). (10) A total of 73,158 patients from the Cancer Registry were able to be record-matched with hospital administration records and mortality data.

Of these, 918 were diagnosed with multiple cancers. To avoid duplicating patients in the analyses the primary cancer diagnosis was chosen and the remaining registrations of subsequent cancers in this group were excluded (n=927). A further 15,750 were excluded as they fell outside the study time period, and another 40,494 were excluded as they did not receive chemotherapy. The remaining 15,987 patients were then identified as those who had an index HF admission (n=1,062), or those who did not have an index HF admission (n=14,925).

Within each of these groups, those with HF-related death within the study period were identified, resulting in the two groups analysed in this study: those with a diagnosed index HF admission who died of HF related causes (IAHF, n=279) and those with no index HF admission but who died of HF related causes (NIAHF, n=455).

Demographics and Characteristics

Within the deceased group the median age at cancer diagnosis was 71 and 66 years for the IAHF and NIAHF patients respectively (Table 1, p<0.001). There was a significant association between age group and HF admission status between these two groups, with the majority of HF patients being ≥70 years, while the NIAHF were more evenly spread across the younger age groups (χ^2=32.05, df=6, p<0.001). Gender (χ^2=12.11, df=1, p=0.001) and cancer morphology/site (χ^2=25.57, df=1, p<0.001) were also significantly different between the two groups, as were the median number of overall hospitalisations for heart failure or chemotherapy (p<0.001) and median number of chemotherapy admissions (p<0.001). All other comparisons were non-significant.

INSERT TABLE 1

Outcomes

There was no significant difference in HF-related mortality in IAHF patients compared to NIAHF (HR, 1.10, 95%CI, 0.94-1.29, p=0.225) (Figure 2) when adjusted for age, sex, marital status, country of birth, cancer site, and number of chemotherapy treatments.

In the NIAHF group, individuals diagnosed with haematologic cancer were almost 1.5 times more likely to die of heart-failure related causes than breast cancer patients (p=0.006) (Table 2). A similar odds ratio was evident in the IAHF patients, but was non-significant. The only other significant difference was that those in the IAHF group received 4-6 admissions for chemotherapy compared to those who had 1-3 admissions (Table 2). All other covariates were non-significant in the adjusted models.

Of those who died of HF-related causes, 31% of IAHF and 33% of NIAHF patients died within the first year after the cancer diagnosis and 60% of IAHF and 62% of NIAHF patients had died of HF-related causes within three years of cancer registration.

Of note, of the IAHF patients, 70.6% of patients had died of HF-related causes within the first year following their HF diagnosis.

INSERT FIGURE 2

INSERT TABLE 2

DISCUSSION

In this analysis of linked hospital administration data we have examined the patient journey through cancer diagnosis, chemotherapy and the onset of heart failure and ultimately heart failure-related death. We have described and compared individuals who had an index heart failure hospital admission (IAHF) with those who did not have an index -heart failure hospital admission (NIAHF) following chemotherapy. All of the patients included in the analyses died of HF-related causes. Specifically, we were interested in those patients who died of HF-related causes but were not newly diagnosed (index admission) or already had a HF diagnosis. When comparing characteristics of the IAHF and NIAHF patients, the median age, gender differences for the IAHF patients had similar demographical characteristic to heart failure in the non-cancer population. (11). That is, the study group had a similar median age and a greater proportion of men. (11) In contrast, NIAHF patients were younger and had a greater proportion of female patients than males. In addition there was a greater proportion of patients with breast cancer in the NIAHF patients compared to the IAHF group. Collectively our results indicated that younger, female breast cancer patients died of HF-related causes before hospital admission for heart failure related causes.

The first year following an index HF admission saw the highest mortality, with 71% of individuals dying of HF-related causes in that period. The first year after cancer diagnosis showed very similar proportions of patients in both groups dying from HF related causes (30.5% and 33.4% in the IAHF and NIAHF respectively). Without supplementary information (see *Strengths and Limitations* below) it is difficult to further explore this finding in more depth. It may be that IAHF patients are symptomatic and mortality is high shortly after admission. A possible explanation of similar mortality in NIAHF (typically younger patients) is a higher tolerance of HF symptoms and as such were not admitted to hospital and sudden death followed due to arrhythmia. Nonetheless, our results are comparable with other studies that have demonstrated that 38% of patients with a HF diagnosis had died within 12 months. (12) Although not statistically significant, the risk of crude HF mortality was about 10% higher for individuals not admitted to hospital with HF compared with those admitted with HF. Whilst it may seem counterintuitive, and one might expect the NIAHF group to have a lower proportion of mortality due to HF, a possible explanation could be that those diagnosed with HF received some intensive cardiac interventions that reduced their mortality risk in the first year. It is possible that extra cardiac treatment is also responsible for comparable proportions of mortality due to HF at the end of three years also (60% and 62% in the IAHF and NIAHF respectively). These mortality rates are all substantially higher, within all age groups within this cohort, than those reported in the most recent epidemiological studies for heart failure in the general population where, although survival has improved, the absolute mortality rates for HF remain approximately 50% within 5 years of diagnosis. (13, 14) In the ARIC study, the 30-day, 1-year, and 5-year case fatality rates after hospitalization for HF were 10.4%, 22%, and 42.3%, respectively. (15)

Over the course of their treatment, IAHF patients received significantly fewer chemotherapy treatments than the NIAHF group. This trend could be attributed to clinical adherence to cardiotoxicity treatment guidelines, with a commensurate reduction in cumulative chemotherapy dose or complete cessation of treatment after HF was identified. (5) However, in the context of a retrospective observational study, there are numerous confounders that were beyond our control that would need to be accounted for to definitively conclude if this was the case. In addition we may need to consider that current available therapies for HF administered earlier in the chemotherapy treatment phase are of limited efficacy. Also, our outcomes may be indicating that the admission index was a poor surrogate for efficacy of early introduction of effective therapies.

Strengths and Limitations

The strengths of this study are the large sample size and the inclusion of virtually all cancer patients who underwent chemotherapy over a 14 year period. The ability to link administrative datasets allows for the integration of multiple databases to provide a comprehensive picture of patient outcomes. However, potential limitations should be considered.

The nature of this type of study method means that what is gained in overall numbers of patients comes at the expense of detailed case information. The direct implication of this is numerous confounding factors cannot be accounted for. For example, the absence of information regarding the cancer treatment, including the precise chemotherapy drugs used and the site and extent of irradiation, plus radiotherapy and the lack of information about pre-existing cardiovascular risk factors or established heart disease prevents us from understanding the association of specific treatments and the subsequent development of HF. Furthermore, in the absence of supplementary data we are unable to elucidate the causes of HF-related deaths (e.g. was death due to advanced cardiomyopathy, cardiogenic shock, arrhythmia, or electrolytes imbalance due to diuretics?) or the severity of HF status. These limitations were due to only being able to access datasets with custodian approval, and in an idealised situation more relevant data would have been incorporated in the analysis framework (e.g. whether patients were administered appropriate and optimal HF medications). In the absence of this data we included chemotherapy separations as a surrogate for drug information. The gender balance in our study is not representative of the general population with 31% of the sample being male and 69% female. The inclusion of breast cancer patients has resulted in an over-representation of female patients.

Clinical Implications

Current Clinical Practice Guidelines for cardiovascular toxicity after chemotherapy and radiotherapy from the European Society of Medical Oncology (ESMO) recommend that patients are frequently monitored for cardiovascular risk before, during and after treatment. (5) These guidelines state that both cardiovascular risk factor screening and heart structure and function monitoring, including appropriate cardiovascular intervention, should occur prior to cancer treatment. In addition cardiac monitoring should continue at baseline, three, six and nine months during treatment and further monitoring should be undertaken at 12 and 18 months and followed up at four and ten years. In the present study we have identified that HF-related death can occur rapidly after cancer treatment in individuals diagnosed with cancers in which cardiotoxic drugs are often prescribed. This finding is consistent with the ESMO recommendations of ongoing cardiac monitoring and it is likely with on-going frequent monitoring appropriate intervention can be implemented to decrease HF-related mortality after cancer therapy.

Conclusion

The profile of patients who died of HF-related causes who had an index admission for HF after cancer treatment matched the current profile of heart failure in the general population (over half were aged ≥70 years). However, the group that did not have an index admission for heart failure were younger (62% were aged ≤69 years), females with breast cancer. In this group Heart Failure after cancer therapy may have been under-diagnosed or undertreated until death and the heart failure caused by the chemotherapy may manifest long after discharge from cancer care.

ACKNOWLEDGEMENTS

The research work was supported by the Institute of Health and Biomedical Innovation of Queensland University of Technology under Collaborative Research Development Grant Scheme 2011 and a Flinders University Faculty of Health Sciences Seeding grant 2013.

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Figures

1. Figure 1: Population selection flow diagram. This diagram displays the initial study population through to the final study population.
2. Figure 2: Time to HF-related death after diagnosis in cancer registry between those who had an index admission for HF (IAHF, n=279) compared to those who did not (NIAHF, n=455)

Table 1: Demographics, Hospitalisation and Chemotherapy Rates for Patients who died of HF-related causes by index admission for HF

Characteristics	**Patient with index HF admission** **N=279 (38.0)**	**Patient with no admission for HF** **N=455 (62.0)**	***P*** *
Median Age (at cancer diagnosis)	71.0 year	66.0 year	<0.001
IQR	62 – 78	56 – 74	
Age Group			
< 20 years	1 (0.4)	3 (0.7)	<0.001
20-29 years	1 (0.4)	5 (1.1)	
30-39 years	3 (1.1)	17 (3.7)	
40-49 years	11 (3.9)	49 (10.8)	
50-59 years	31 (11.1)	80 (17.6)	
60-69 years	78 (28.0)	128 (28.1)	
≥ 70 years	154 (55.2)	173 (38.0)	
Sex			
Female	117 (41.9)	251 (55.2)	0.001
Male	162 (58.1)	204 (44.8)	
Marital Status			
Married/De Facto	160 (57.3)	273 (60.0)	0.487
Single/divorced/widowed	119 (42.7)	182 (40.0)	
Country of Birth			
Australia	195 (69.9)	337 (74.1)	0.234
All Other Countries	84 (30.1)	118 (25.9)	
Indigenous Status			
Indigenous	3 (1.1)	10 (2.2)	0.389
Non-indigenous	276 (98.9)	445 (97.8)	
Residence (Postcode)			
Metropolitan	244 (87.5)	379 (83.3)	0.138
Rural/Remote	35 (12.5)	76 (16.7)	
Cancer Morphology/Site			
Breast	34 (12.2)	128 (28.1)	<0.001
Haematologic	245 (87.8)	327 (71.9)	
Median No of hospitalisation (IQR)	7 (3 – 13)	6 (2 – 12)	<0.001
Median no of chemotherapy separations (IQR)	4 (2 – 9)	6 (2 – 12)	<0.001

IQR indicates interquartile range (25th-75th percentile); SMR, standardised mortality ratio
* Data were considered significantly different at p≤0.05

Table 2: Adjusted time-varying Cox Proportion Hazards Model for HF-related mortality of Chemotherapy receiving haematologic and breast cancer patients by index admission for HF. Data were adjusted for age, sex, marital status, country of birth, cancer site and time dependent number of chemotherapy treatment

	Patient with index HF admission		**Patient with no HF admission**	
Parameter	**HR (95% CI)**	***P****	**HR (95% CI)**	***P****
Age				
< 20 years †				
20-29 years	0.30 (0.02-5.08)	0.408	0.56 (0.13-2.38)	0.435
30-39 years	0.26 (0.03-2.56)	0.246	0.47 (0.14-1.67)	0.245
40-49 years	0.33 (0.04-2.66)	0.295	0.49 (0.15-1.61)	0.240
50-59 years	0.35 (0.05-2.64)	0.307	0.57 (0.18-1.83)	0.343
60-69 years	0.46 (0.06-3.40)	0.447	0.44 (0.14-1.40)	0.165
≥ 70 years	0.44 (0.06-3.19)	0.413	0.50 (0.16-1.58)	0.237
Sex				
Female vs male	1.22 (0.89-1.68)	0.221	0.96 (0.75-1.23)	0.754
Marital status				
Married/de facto vs all other	0.96 (0.72-1.29)	0.802	0.98 (0.80-1.21)	0.869
Country of birth				
Australia vs all other	0.86 (0.65-1.14)	0.303	1.15 (0.92-1.44)	0.214
Cancer Site				
Breast vs Haematologic	1.47 (0.97-2.23)	0.068	1.48 (1.11-1.95)	0.006
Chemotherapy separations (quintiles)				
1-3 †				
4-6	0.91 (0.83-0.99)	0.027	0.97 (0.90-1.05)	0.420
7-9	0.93 (0.83-1.02)	0.152	0.94 (0.87-1.01)	0.102
10-16	0.92 (0.84-1.02)	0.108	0.98 (0.91-1.06)	0.684
≥ 17	0.95 (0.86-1.06)	0.364	0.97 (0.90-1.05)	0.479

HF indicates heart failure; HR, hazard ratio.
* Statistically significant at $p \leq 0.05$
† Reference category

Figure 1: Population selection flow diagram. This diagram displays the initial study population through to the final study population.

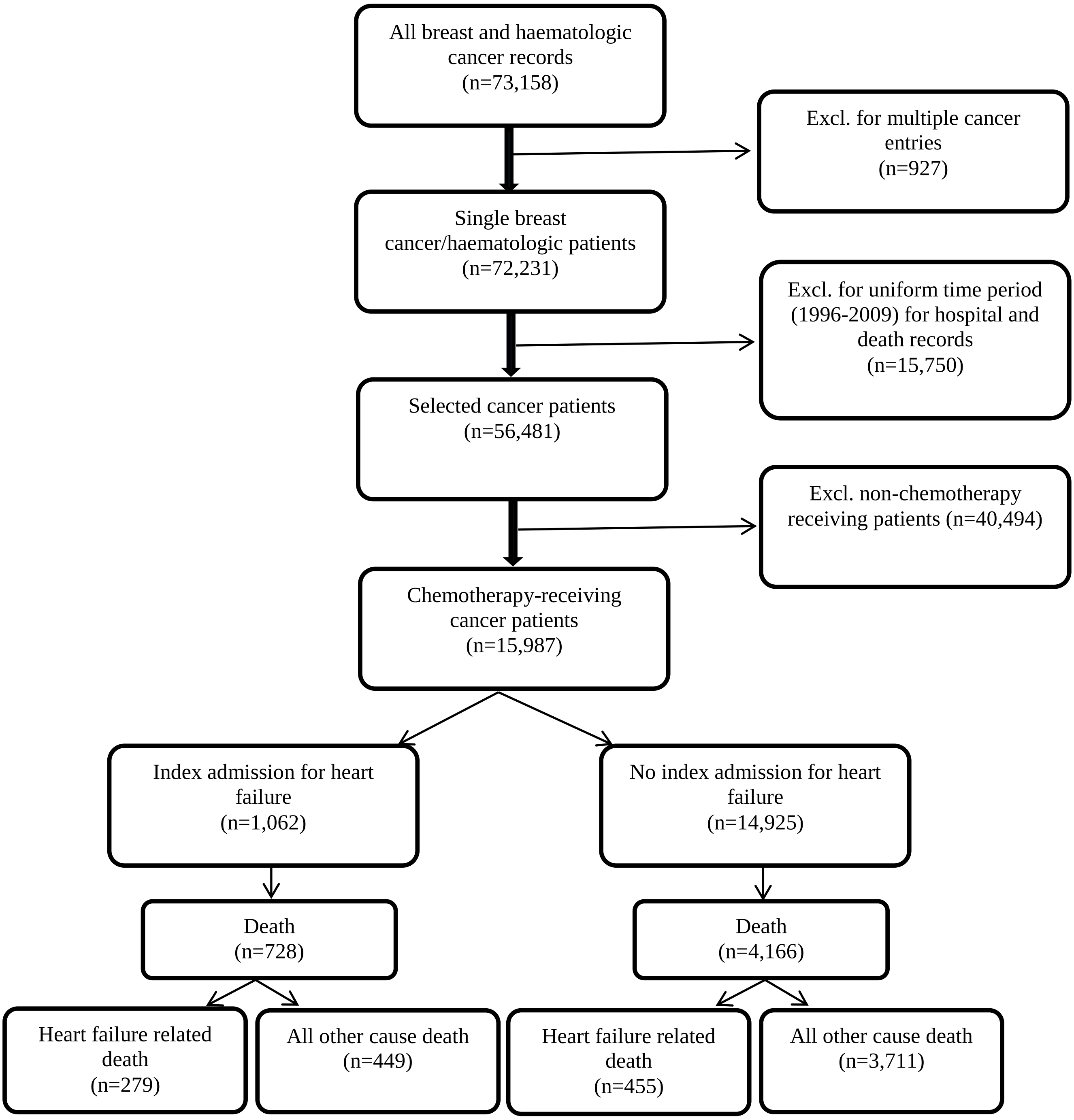
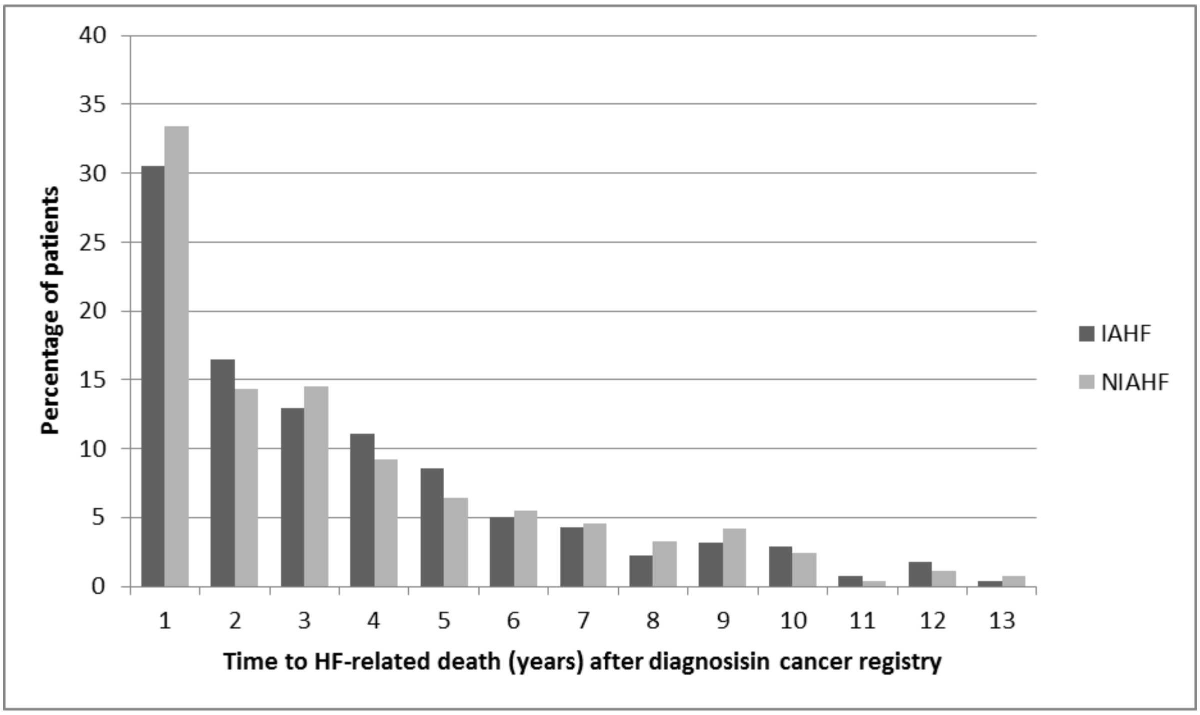


Figure 2. Time to HF-related death after cancer diagnosis between those who had an index admission for HF (IAHF, n=279) compared to those who did not (NIAHF, n=455)



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