Title page

Journal: Internal Medicine Journal

Title: Heart Failure Following Cancer Treatment: Characteristics, Survival and Mortality of a Linked Health Data Analysis.

Robyn A. Clark PhD[1], Narelle M Berry PhD[1], Munir H. Chowdhury MSc[1], Alexandra L. McCarthy PhD[2], Shahid Ullah PhD[3], Vincent L. Versace PhD[4], John J. Atherton MBBS[5], Bogda Koczwara BMBS[6], David Roder DDSc.[7]

Affiliations:

1. School of Nursing & Midwifery, Flinders University, Adelaide, SA, Australia
2. School of Nursing, Queensland University of Technology (QUT), Brisbane, Australia
3. Flinders Centre for Epidemiology and Biostatistics, Flinders University, Adelaide, SA, Australia
4. Greater Green Triangle University Department of Rural Health, Flinders University and Deakin University, Warrnambool, VIC, Australia
5. Royal Brisbane and Women's Hospital, Herston, QLD, Australia 4029,
6. Flinders Centre for Innovation in Cancer, Flinders University, Adelaide, SA, Australia
7. School of Health Sciences, University of South Australia, Adelaide, SA, Australia

Corresponding author

Professor Robyn A. Clark PhD, FAHA
School of Nursing & Midwifery, Flinders University
GPO Box 2100
Adelaide, South Australia 5001
Phone: +61 8 8201 3266
Email: robyn.clark@flinders.edu.au

Author Contributions:

RC, AM and JA Contributed to conception and design of the work, funding applications, data analysis and interpretation and manuscript preparation

MC, SU, NB VV, BK and DR contributed to data analysis and interpretation and manuscript preparation and revising for intellectual content.

Acknowledgements: This research 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.

Abstract Word Count: 208

Manuscript word count: 3000

Short Running Title: Heart Failure after chemotherapy

Abstract

Background: Cardiotoxicity resulting in heart failure is a devastating complication of cancer therapy. A patient may survive cancer only to develop heart failure (HF) which is more deadly than cancer.

Aim: This project aimed to describe the characteristics and outcomes of HF in patients with blood or breast cancer after chemotherapy treatment.

Methods Queensland Cancer Registry, Death Registry and Hospital Administration records were linked (1996-2009). Patients were categorised as those with an index HF admission (that occurred after cancer diagnosis) and those without an index HF admission (non-HF).

Results: 15,987 patients were included, 1,062 (6.6%) had an index HF admission. Median age of HF patients was 67 years (IQR 58-75) vs. 54 years (IQR 44-64) non-HF. More men than women developed HF (48.6% vs. 29.5%) and a greater proportion in the HF group had haematologic cancer (83.1%) compared with breast cancer (16.9%). After covariate adjustment, HF patients had increased mortality risk compared with non-HF patients (HR 1.67 [95% CI, 1.54-1.81]), 47% of the index HF admission occurred within 1 year from cancer diagnosis; 70% within 3 years.

Conclusion: Cancer treatment may place patients at a greater risk of developing HF. The onset of HF occurred soon after chemotherapy, and those who developed HF had a greater mortality risk.

Keywords: Cardiotoxicity; Heart Failure; Chemotherapy; Cardiology; Oncology

Introduction

Cardiotoxicity resulting in left ventricular failure is a potential outcome of cancer therapy. Patients may survive cancer only to develop heart failure (HF), which has a higher mortality rate than cancer.[1] Current guidelines recommend that the development of cardiotoxicity should lead to reconsideration of further chemotherapy and thus limits cancer treatment options and potentially affect cancer outcomes.[2] Treatment-induced cardiotoxicity is well established and may occur in one-third of cancer patients,[1] although current figures are probably underestimates [3] as patients with underlying predisposition to cardiotoxicity are often excluded from cancer trials.[4] Adult survivors of childhood cancers have been shown to have an eightfold risk of cardiac-related mortality.[5] Cardiotoxicity, can occur up to 20 years after cancer therapy and maybe identified as a lifelong risk as new data emerges,[3, 6] and may become more prevalent as survivorship from childhood cancer improves.

The incidence of cardiotoxicity following chemotherapy varies based on the type of agent, with the cardiotoxicity incidence of anthracyclines between 1 and 26%, high-dose cyclophosphamide between 7 and 28%, trastuzumab between 2 and 28%, and tyrosine kinase inhibitors between 0.05 and 11%.[1, 5] These drugs are commonly used to treat breast or haematologic cancers; therefore these cancers are the focus of this study.

Treatment-related risk factors in cancer patients include specific chemotherapy agent(s) (with reversible and irreversible cardiotoxicity),[1] dose exposure [7] and concomitant therapies (including anaesthetic procedures and radiation therapy).[8, 9] In fact, treatment-induced cardiotoxicity should not be considered the result of a single treatment, but rather as the result of additive or supra-additive toxicities, in conjunction with risks such stress, history of cardiac disease, genetic profile, and body mass index.[10] Cardiotoxicity is likely to become more prevalent as chemotherapy is administered to an ageing population.

Vigilant initial monitoring and early intervention during cancer treatment, with continued surveillance after treatment could prevent or ameliorate cardiotoxicity.[1, 6, 10-14] A limited number of the possible risk factors associated with this toxicity (such as high cumulative doses of anthracyclines in the context of pre-existing heart disease) are well-understood.[1, 5, 6, 10-14] Before intervention studies are undertaken, the precise nature of the problem needs to be investigated.

This study aimed to gain greater understanding of the development of HF in patients after exposure to chemotherapy for breast or haematologic (leukemias, lymphomas and related disorders) cancer. The focus of this paper is on the development of HF, acknowledging that other cardiovascular conditions may develop after cancer treatment.[5] The objectives were to describe patient characteristics, duration of outset, mortality and survival between those who developed HF after chemotherapy compared to those who did not. The long term aim of this research is to better understand the profile of these patients so that appropriate inventions for prevention and potential reversal can be designed.

Materials and Methods

Study design

This study was a retrospective audit of linked health administration data from Queensland, Australia. The Queensland Cancer Registry (QCR), the Hospital Admitted Patient Data Collection and Birth, Deaths and Marriages from January 1996 to December 2009 were accessed. Approval was granted by the Metro South Health Service District Human Research Ethics Committee (HREC/11/QPAH/600).

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 (leukemias, lymphomas and related disorders) (ICD10-AM: C42, C77 and ICD-O: M9590/3-M9989/3) henceforth referred to as 'haematologic cancers'.

Patients who did not undergo chemotherapy were excluded. Participants were categorised as: Those that had an index HF admission after cancer diagnosis (HF group) compared with those that did not (non-HF group).

Variables

QCR, Death Registry and Hospital Administration records were linked (1996-2009). Index HF must have occurred after the date of cancer registry entry.

Demographic information was extracted from the QCR (Table 1). Age was categorised as <20 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years and ≥70 years for the Cox proportional hazard modelling. Age groupings for the Kaplan-Meier survival

curve analysis were based on the median and were categorized as <50 years, 50–59 years, 60–69 years and ≥70 years.

Chemotherapy-receiving patients were identified from the relevant codes in hospital records, defined by ICD-9-CM (clinical modification) (99.25) and ICD-10-AM (Australian Modification) (96196-00, 96199-00, 96209-00, 96207-00, 96208-00, 96204-00, 13942-00, 13915-00, 13918-00, 13921-00, 13927-00, 13939-00, 13942-00, Z51.1, Z51.2).

Chemotherapy admissions were categorised as quintiles (Table 1). Details of radiotherapy treatment of patients were not included as data were not available for linkage.

An index HF admission was defined as a patient's first hospitalisation coded for HF. HF diagnosis was based on the ICD-9-CM (428.0. 428.1 and 428.9) and ICD-10-AM (I50.0, I50.1 and I50.9) codes. HF included Congestive HF, Left Ventricular failure and other unspecified cardiomyopathies.

All-cause mortality data were extracted from the Queensland Birth, Deaths and Marriages database – a repository for all registered deaths in Queensland. Patients who died after the end of the study period (December 31 2009) were considered to be alive for the calculation of survival time and mortality.

Data sources and data linkage

The QCR has been collecting data since 1982 was used to identify patients with a primary diagnosis of breast or haematologic cancers. [15]

The QCR facility and Unit Record numbers were match-merged with Hospital Admitted Patient Data Collection episodes to identify those who had chemotherapy and those with an index HF admission following QCR registration. Details of pre-existing cardiovascular risk factors were not available in this administrative dataset. Death records were obtained from

Birth, Deaths and Marriages and were linked to QCR records. LinkageWiz software was used for probabilistic matching.[16]

Bias

To reduce false and mismatched linkages,[17] a 20-step review process to identify false positives was undertaken within a broader quality control framework. The false positive rate for this methodology has been shown to be 0.3%.[18]

Statistical methods

Linked Health Data were extracted and coded using STATA 13.0 (STATA, Texas, USA) and analysed using IBM SPSS for Windows version 22.0 (IBM, Armonk, NY, USA). Differences in demographics, cancer treatment history and morphology/site were analysed for between-group differences using Fisher's exact test and chi-square. Where continuous data were non-normally distributed, the data are presented as median (IQR) and compared using appropriate non-parametric tests. Differences were considered significant at $p \leq 0.05$.

Standardized mortality ratios (SMRs) for all-cause mortality were derived using an indirect standardization methodology by calculating the age-specific, all-cause death rates of the Australian population for each year within the study period (1996–2009) relative to observed deaths in our study population. Data are presented as the mean of the yearly SMR calculations.

Kaplan-Meier survival curves were derived to compare the time to death from cancer diagnosis between groups, and by sex and age using a log-rank test.

Time-varying Cox proportional hazards regression models were used to evaluate factors associated with mortality risk during follow up within groups adjusted by demographic variables, cancer treatment history and morphology/site (Table 2). Hazard ratios (HR) were

used to describe the probability of survival after chemotherapy treatment. The proportional hazard assumptions and goodness of fit of the models were also tested.

Results

Participants

A total of 73,158 breast or haematologic cancer records were linked to hospital admissions and death records. Within the QCR there were 918 patients registered with multiple cancers (1 patient with four, 7 patients with three and 910 patients with two types of cancers). In order to count each patient once, the primary cancer diagnosis was selected and all other registrations were excluded (n=927).

N=15,750 records were excluded that fell outside the study timeframe and 40,494 records were excluded as these patients did not receive chemotherapy. The final sample was n=15,987 patients, of these, n=1,062 had at least one index HF admission following their cancer diagnosis and n=14,925 had no HF admission. The Median follow up time was 3.34 years (IQR, 1.34-7.25, range: 0-13.9 years) (Figure 1).

Demographics and clinical characteristics

The Median age at cancer diagnosis was 55.0 years (IQR, 44–65). 5.3% (n=852) were aged ≤20 years and 34.8% (n=5,564) were aged over 60 years. There was a greater proportion of females (69.3%, n=11,074) than males (30.7%, n= 4,913). 52.2% (n=8,339) had a primary diagnosis of haematologic cancer and 47.8% (n=7,648) had a primary diagnosis of breast cancer. The overall SMR for the sample was 5.08 – a fivefold greater mortality rate than the Australian population.

Compared to the non-HF group, HF patients were significantly older ($p<0.001$), there were a lower proportion of female patients ($p<0.001$) and a greater proportion of patients with haematologic cancers ($p<0.001$) (Table 1). There were differences in the number of chemotherapy admissions between groups ($p<0.001$). Non-HF patients were more likely to be Australian-born and in a Married/De Facto relationship (Table 1).

Outcome data

All-cause mortality was 2.45 times higher in HF than in non-HF patients ($p<0.001$), and HF-related mortality was 5.80 times higher in the HF group compared to the non-HF group ($p<0.001$). SMR for all-cause mortality for the non-HF and HF groups were 5.27 and 4.19 times greater than the comparable Australian population respectively, most likely due to the age differences between these groups.

In the first 12 months after cancer diagnosis 47.1% of patients developed HF and 69.6% of patients developed HF within the first three years (Figure 2). All-cause mortality (adjusted for age, sex, marital status, country of birth, cancer site and chemotherapy admissions) differed between groups with the HF group having a greater risk of mortality relative to the non-HF group (HR 1.67 (95% CI, 1.54–1.81), $p<0.001$) (Figure 3).

Mean survival times from cancer diagnosis were 9.57 years (95% CI 9.46-9.86, n=4166) and 5.30 years (95% CI 4.99-5.62, n=728) for the non-HF and HF groups respectively.

The time-varying Cox Proportional Hazard modelling showed non-HF patients had an increased risk of mortality with increasing age (Table 2). This was not observed in the HF patients with no difference in mortality with increasing age, excepting those aged over 70 years (Table 2). Males had a higher and similar risk of mortality in both the HF and non-HF groups compared with females. Patients who were not Married/De Facto had increased risk of mortality in the non-HF group, but no difference was evident in the HF group. Patients born in a country other than Australia had a lower risk of mortality among HF patients and there was a higher risk of mortality in haematologic cancers relative to breast cancer in both groups.

In the non-HF group relative to those who had 1–3 chemotherapy admissions, there was a decrease in mortality risk for each quintile of chemotherapy admissions, until ≥17 admissions

where there was a small but significant increase in mortality risk. However, there were no significant differences in mortality risk across quintiles of chemotherapy admissions in the HF group (Table 2).

Kaplan-Meier survival curves of all-cause mortality by age, and sex in HF patients indicate similar survival rates between the younger patients (<50 years compared to 50–59 years); however, there was a steeper decline in mortality in older age-groups (log-rank $p<0.001$) (Figure 4). Survival rates were higher in female patients than in males (log-rank $p<0.001$).

Discussion

In the context of well-established evidence for causality between chemotherapy, radiotherapy and cardiotoxicity, this study aimed to determine differences in characteristics and clinical outcomes of cancer patients who received chemotherapy that has the highest incidence of cardiotoxicity and who subsequently developed HF relative to those who did not. We have shown that 6.6% of breast or haematologic cancer patients who received chemotherapy subsequently developed HF. Results from the USA,[19] Australia [8, 20] and Europe [21] have shown HF rates ranging from 1.3-4% of the population. Our study suggests that cancer treatment could increase the risk of developing HF by approximately 2-3 times.

In the HF group, 47.7% of patients had an index HF admission within 12 months following cancer diagnosis and 69.6% within three years. This is of concern, especially for patients who develop HF prior to the completion of chemotherapy, which may necessitate treatment termination and influence cancer-specific outcomes.

The median age of HF patients was 67 years compared with 54 years in non-HF patients. In other studies of adults with HF, the median age of HF diagnosis has ranged from 70 to 82.5 years.[19, 21-23] Our results suggest that cancer treatment might trigger the development of HF at an earlier age than typically observed.

In the HF group there were a greater proportion of patients with haematologic cancers relative to those with breast cancer, compared to the non-HF group. This may be due to different drug exposure, older age of patients with haematologic cancers, and additional treatments including radiotherapy.

During the study period the median number of hospitalisations (HF and chemotherapy admissions combined) and chemotherapy admissions were greater in the non-HF group. It is possible that the treatments were altered or prematurely ceased in some patients at the time of diagnosis of HF. This is supported by our observation that a high proportion of patients developed HF rapidly thereby resulting in fewer chemotherapy admissions. Furthermore, the number of hospitalisations and chemotherapy admissions may be less in the HF group due to the greater mortality of this population.

Survival time was lower in the HF group compared to the non-HF group, with the combination of cancer and HF being 67% more deadly than cancer alone (Figure 3). This maybe expected as other studies have shown patients with HF having poorer prognosis compared to most solid-organ cancers.[24]

In the HF group, all-cause mortality was 2.45 times greater than the non-HF group. Relative to the Australian population, those in the HF group had a fourfold higher mortality. Those in the non-HF group had a fivefold higher mortality than the overall Australian population. This is likely due to the age differences between groups with the SMR calculated for the non-HF group relative to a younger population.

In non-HF patients, increases in mortality were observed with increasing age. This was not observed in HF patients, with no differences in mortality between older and younger patients, suggesting that the increased risk of mortality with HF overrides the effect of age alone.

Other studies have shown median survival times after HF diagnosis ranging from 3.21 years in women and 5.39 years in men.[25] .

The non-HF group also showed a decrease in mortality risk with increasing number of chemotherapy treatments, until ≥17, but there was no additional effect on mortality risk with increasing number of chemotherapy admissions in the HF group. This may be due to the moderation of chemotherapy cycles in the HF patients in accordance with the cardiotoxicity treatment guidelines.[2] However, in the context of an observational study, there are numerous confounders that were unable to be considered.

The difference in trajectory for patients with cardiotoxicity compared to those with cancer or HF alone has been presented schematically in Figure 5.

Strengths and Limitations

The strengths of this study are the large sample size and the inclusion of 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, many of which are generic to this type of research. This study was one of the first from a newly established data linkage service, as such we could only access datasets that had custodian approval therefore we were unable to access information regarding cancer treatment including chemotherapy drugs, radiotherapy and pre-existing cardiovascular risk factors. Using the available data we included chemotherapy admissions as a surrogate for drug information and demonstrated differences in treatment regimes in patients who developed HF and those who did not.

The inclusion of breast cancer patients has resulted in an over-representation of female patients. Also, our sample was not representative of the Queensland rural population.

Approximately 52% of the residential population lived in rural areas,[26] however, in this study 13.7% of patients lived in rural Queensland, it appears that metropolitan contact details were while undergoing treatment. Thus, residence was excluded from the Cox Proportional Hazard Models of mortality.

With the inclusion of only HF hospitalisations and not other cardiovascular complications associated with cancer therapy, this study may be just the tip of the iceberg when describing the burden of cardiotoxicity on cancer patients.

Clinical Implications

This study showed that 69.9% of patients had an index HF admission within three years following cancer diagnosis; therefore monitoring should continue for a number of years following treatment. The European Society of Medical Oncology (ESMO) recommend that prior to undergoing chemotherapy, patients should be assessed for cardiovascular risk and vital signs should be monitored during chemotherapy infusion.[27] For children, adolescents and young adults, the American Heart Association recommends monitoring patients to allow for early detection of potential cardiac conditions and timely intervention to prevent, reverse or slow deterioration and also tailoring cancer therapies to decrease risk of cardiotoxicity.[28]

Given the emergence of new cancer treatments, we do not know how large the problem of cardiotoxicity associated with cancer treatment is likely to become. There are no accurate data to indicate the most likely stage of the cancer trajectory when HF develops, when intervention should begin, and how patients should be best-managed within the health system and in the community. Just as important, little has been published in regard to cancer survivors' perceived cardiac health care needs and concerns, or whether they understand the risk of HF.

Conclusion

Compared to HF in the non-cancer population after chemotherapy this group developed HF more rapidly (47% within one year and 69% in three years) at a younger age (67 years compared to 70 to 82.5 years). However, in both our population and the non-cancer population the prevalence was higher in males. There was a greater mortality risk in those with breast or haematologic cancer and HF compared to breast or haematologic cancer alone. Further research to understand predictors of cardiac risk in cancer patients is needed to develop strategies for patient management and risk mitigation.

References

1. Yeh ETH and Bickford CL. Cardiovascular Complications of Cancer Therapy: Incidence, Pathogenesis, Diagnosis, and Management. J Am Coll Cardiol. 2009;53:2231-2247.

2. Curigliano G, Cardinale D, Suter T, Plataniotis G, de Azambuja E, Sandri M, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. Ann Oncol. 2012;23(suppl 7):vii155-vii166.

3. Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, et al. Anthracycline-induced cardiomyopathyClinical relevance and response to pharmacologic therapy. J Am Coll Cardiol. 2010;55:213-220.

4. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, et al. Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev. 2012;4.

5. Senkus E and Jassem J. Cardiovascular effects of systemic cancer treatment. Cancer Treat Rev. 2011;37:300-311.

6. Wells QS and Lenihan DJ. Reversibility of left ventricular dysfunction resulting from chemotherapy: can this be expected? Prog Cardiovasc Dis. 2010;53:140-148.

7. Gagliardi G, Constine LS, Moiseenko V, Correa C, Pierce LJ, Allen AM et al. Radiation dose–volume effects in the heart. *Int J Radiat Oncol Biol Phys*. 2010;76:S77-S85.

8. Abhayaratna WP, Smith WT, Becker NG, Marwick TH, Jeffery IM and McGill DA. Prevalence of heart failure and systolic ventricular dysfunction in older Australians: the Canberra Heart Study. *Med J Aust*. 2006;184:151.

9. Singletary SE. Rating the risk factors for breast cancer. *Ann Surg*. 2003;237:474.

10. Chargari C, Kirov KM, Bollet MA, Magné N, Védrine L, Cremades S, et al. Cardiac toxicity in breast cancer patients: From a fractional point of view to a global assessment. *Cancer Treat Rev*. 2011;37:321-330.

11. Aapro M, Bernard-Marty C, Brain E, Batist G, Erdkamp F, Krzemieniecki K, et al. Anthracycline cardiotoxicity in the elderly cancer patient: a SIOG expert position paper. Ann Oncol. 2011;22:257-267.

12. Carver JR. Management of trastuzumab-related cardiac dysfunction. Prog Cardiovasc Dis. 2010;53:130-139.

13. Hsieh CC, Sprod LK, Hydock DS, Carter SD, Hayward R and Schneider CM. Effects of a supervised exercise intervention on recovery from treatment regimens in breast cancer survivors. Oncol Nurs Forum. 2008;35:909-915.

14. Sawyer DB, Peng X, Chen B, Pentassuglia L and Lim CC. Mechanisms of anthracycline cardiac injury: can we identify strategies for cardioprotection? Prog Cardiovasc Dis. 2010;53:105-113.

15. Australian Institute of Health and Welfare. Queensland Cancer Registry. Australian Institute of Health and Welfare. 2013. Retreived 06/10/2015 from http://www.aihw.gov.au/qld-cancer-registry/.

16. State of Queensland. Queensland Data Linkage Framework. Queensland Health. 2014.

17. Harron K, Wade A, Gilbert R, Muller-Pebody B and Goldstein H. Evaluating bias due to data linkage error in electronic healthcare records. BMC Med Res Methodol. 2014;14:36.

18. Centre for Health Record Linkage. Master Linkage Key (MLK) Quality Assurance. 2012. Retreived 22/10/2014 from: http://www.cherel.org.au/media/24160/qa_report_2012.pdf

19. Ho KKL, Pinsky JL, Kannel WB, Levy D and Pitt B. The epidemiology of heart failure: The Framingham Study. *J Am Coll Cardiol*. 1993;22:A6-A13.

20. Australian Institute of Health and Welfare. Cardiovascular disease: Australian facts 2011. *Cardiovascular disease series Cat no CVD 53*. 2011. Canberra, Australia.

21. Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. *Eur Heart J*. 2004;25:1614-1619.

22. Cowie MR, Wood DA, Coats AJS, Thompson SG, Poole-Wilson PA, Suresh V et al. Incidence and aetiology of heart failure; a population-based study. *Eur Heart J*. 1999;20:421-428.

23. Teng T-HK, Finn J, Hobbs M and Hung J. Heart Failure Incidence, Case Fatality, and Hospitalization Rates in Western Australia Between 1990 and 2005. *Circulation: Heart Failure*. 2010;3:236-243.

24. Stewart S, MacIntyre K, Hole DJ, Capewell S and McMurray JJV. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. *Eur J Heart Fail*. 2001;3:315-322.

25. Ho KK, Anderson KM, Kannel WB, Grossman W and Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation*. 1993;88:107-15.

26. Australian Bureau of Statistics. Population by Age and Sex, Regions of Australia. Catalouge Number: 3235.0. 2013.

27. Bovelli D, Plataniotis G and Roila F. On behalf of the ESMO Guidelines Working Group. Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines. Ann Oncol. 2010;21:v277-v282.

28. Lipshultz SE, Adams MJ, Colan SD, Constine LS, Herman EH, Hsu DT, et al. Long-term Cardiovascular Toxicity in Children, Adolescents, and Young Adults Who Receive

Cancer Therapy: Pathophysiology, Course, Monitoring, Management, Prevention, and Research Directions A Scientific Statement From the American Heart Association. *Circulation.* 2013;128:1927-1995.

29. Murray SA, Sheikh A. Care for all at the end of life. *BMJ*. 2008;336(7650):958-959.

Tables

Table 1: Demographics, Mortality, Hospitalization and Chemotherapy Rates for all chemotherapy receiving breast cancer and haematologic (Leukemias, Lymphomas and related disorders) cancer patients

Characteristics	**Heart Failure N=1,062 (6.6%)**	**Non-Heart Failure N=14,925 (93.4%)**	***P-value***
Age (at cancer diagnosis), years Median (IQR)	67.0 (58 – 75)	54.0 (44 – 64)	<0.001*
Age Group, years, n(%)			
< 20	32 (3.0)	820 (5.5)	<0.001*
20–29	14 (1.3)	470 (3.1)	
30–39	23 (2.2)	1,359 (9.1)	
40–49	71 (6.7)	3,199 (21.4)	
50–59	166 (15.6)	3,926 (26.3)	
60–69	322 (30.3)	3,054 (20.5)	
≥ 70	434 (40.9)	2,097 (14.1)	
Sex, n(%)			
Female	546 (51.4)	10,528 (70.5)	<0.001*
Male	516 (48.6)	4,397 (29.5)	
Marital Status, n(%)			
Married/De Facto	635 (59.8)	9,719 (65.1)	0.001*
Single/divorced/widowed	427 (40.2)	5,206 (34.9)	
Country of Birth, n(%)			
Australia	759 (71.5)	11,221 (75.2)	0.007*
All Other Countries	303 (28.5)	3,704 (24.8)	
Indigenous Status, n(%)			
Indigenous	15 (1.4)	233 (1.6)	0.784
Non-Indigenous	1,047 (98.6)	14,692 (98.4)	
Residence (Postcode), n(%)			
Metropolitan	916 (86.3)	12,954 (86.8)	0.609
Rural/Remote	146 (13.7)	1,971 (13.2)	
Cancer Morphology/Site, n(%)			
Breast	180 (16.9)	7,468 (50.0)	<0.001*
Hematologic	882 (83.1)	7,457 (50.0)	
All-cause Mortality			
Crude	728 (68.5)	4,166 (27.9)	<0.001*
SMR	4.19	5.27	
HF Related Mortality			
Crude	279 (17.4)	455 (3.0)	<0.001*
No of hospitalizations, Median (IQR)	7 (3 – 15)	8 (4 – 15)	0.100
No of chemotherapy admissions, Median (IQR)	5 (2 – 12)	7 (4 – 14)	<0.001*
No of chemotherapy admissions, quintiles			
1–3	392 (36.9)	3,067 (20.6)	<0.001*
4–6	213 (20.1)	4,040 (27.1)	
7–9	125 (11.8)	1,941 (13.0)	
10–16	179 (16.9)	3,050 (20.4)	
≥ 17	153 (14.4)	2,827 (18.9)	

IQR indicates interquartile range (25th–75th percentile); and SMR, standardized mortality ratio
Hematologic cancer= leukemias, lymphomas and related disorders
Hospitalisations are a combination of admissions for HF and for chemotherapy
* Significantly different at p≤0.05

Table 2: Adjusted time-varying Cox Proportional Hazard Models for all-Cause mortality between HF and non-HF. Data were adjusted for age, sex, marital status, country of birth, cancer site and number of chemotherapy admissions.

	HF Patients		Non-HF Patients	
Parameter	**HR (95% CI)**	***P-value***	**HR (95% CI)**	***P-value***
Age, years				
< 20	Referent		Referent	
20–29	1.98 (0.93-4.25)	0.078	1.83 (1.39-2.42)	< 0.001*
30–39	1.67 (0.81-3.45)	0.168	2.61 (2.09-3.27)	< 0.001*
40–49	1.35 (0.75-2.41)	0.314	2.99 (2.43-3.68)	< 0.001*
50–59	1.39 (0.81-2.37)	0.228	3.39 (2.77-4.15)	< 0.001*
60–69	1.64 (0.98-2.75)	0.062	4.75 (3.89-5.80)	< 0.001*
≥ 70	2.08 (1.25-3.47)	0.005*	8.71 (7.15-10.62)	< 0.001*
Sex				
Female vs Male	1.32 (1.11-1.55)	0.001*	1.26 (1.16–1.37)	< 0.001*
Marital status				
Married/de facto vs All other	1.16 (0.99-1.36)	0.073	1.18 (1.10–1.26)	< 0.001*
Country of birth				
All other vs Australia	0.77 (0.65-0.91)	0.002*	0.99 (0.93–1.06)	0.823
Cancer site				
Breast Cancer vs haematologic	1.41 (1.12-1.77)	0.003*	1.29 (1.18-1.40)	< 0.001*
Number of Chemotherapy admissions				
1–3	Referent		Referent	
4–6	0.99 (0.94-1.04)	0.711	0.87 (0.85-0.90)	< 0.001*
7–9	1.00 (0.95-1.06)	0.953	0.93 (0.90-0.96)	< 0.001*
10–16	0.99 (0.94-1.04)	0.640	0.93 (0.91-0.96)	< 0.001*
≥ 17	0.99 (0.93-1.04)	0.604	1.04 (1.02-1.06)	0.001*

HF indicates heart failure; HR, hazard ratio; and CI, confidence interval.
Hematologic cancer= leukemias, lymphomas and related disorders
* Statistically significant at $p \leq 0.05$

Figures

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

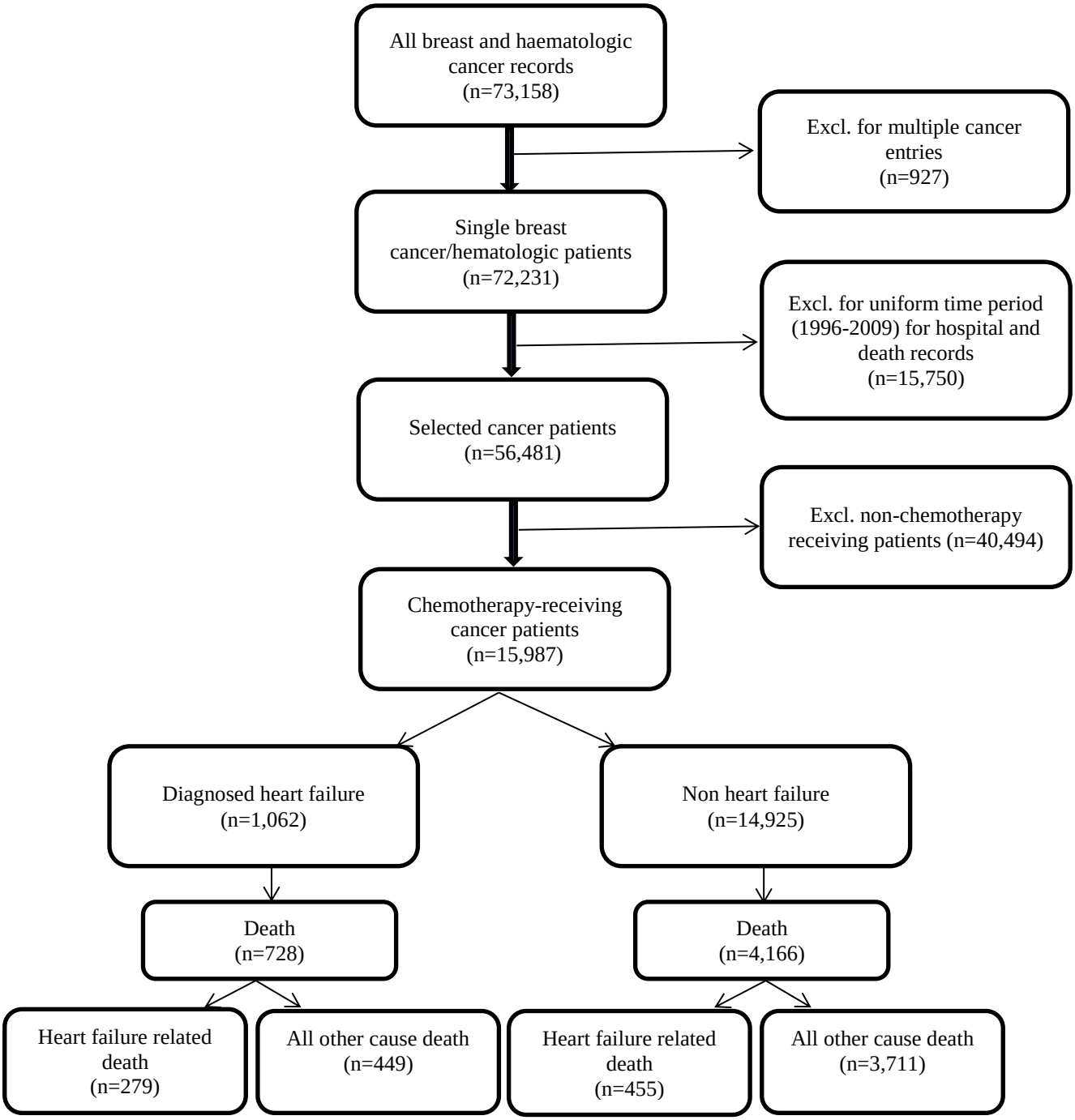


Figure 2. Time from cancer diagnosis to the first index heart failure admission in n=1062 patients who underwent chemotherapy treatment for breast or haematologic (leukemias, lymphomas and related disorders) cancer

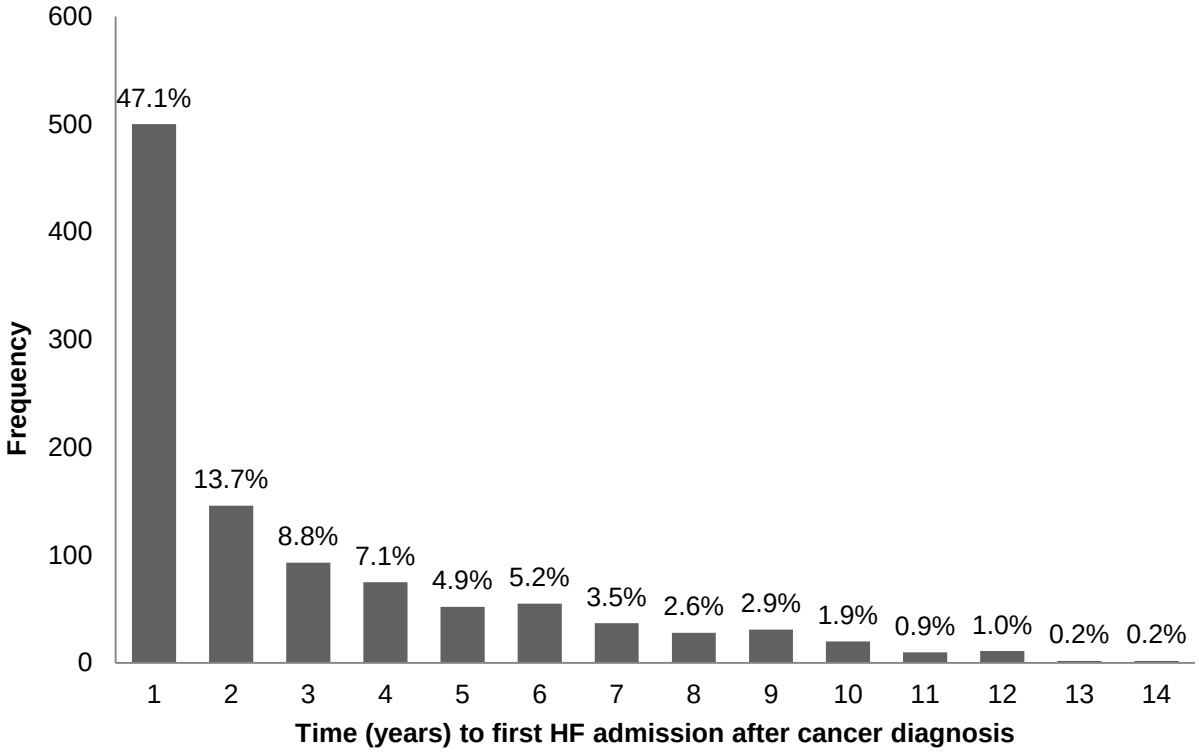
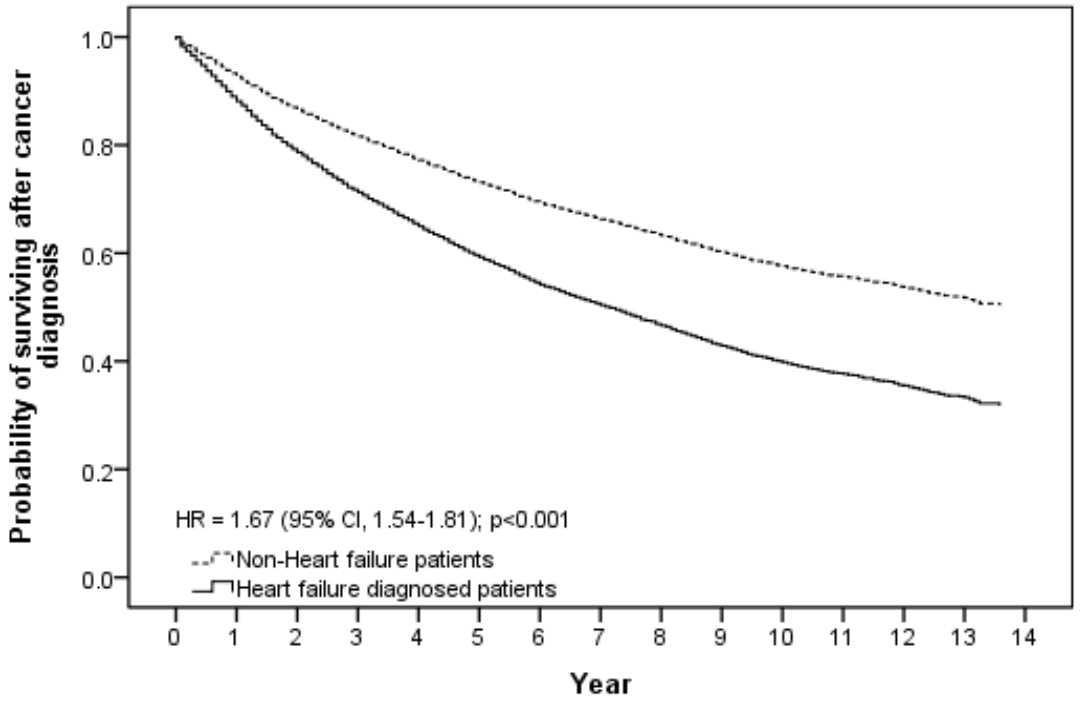


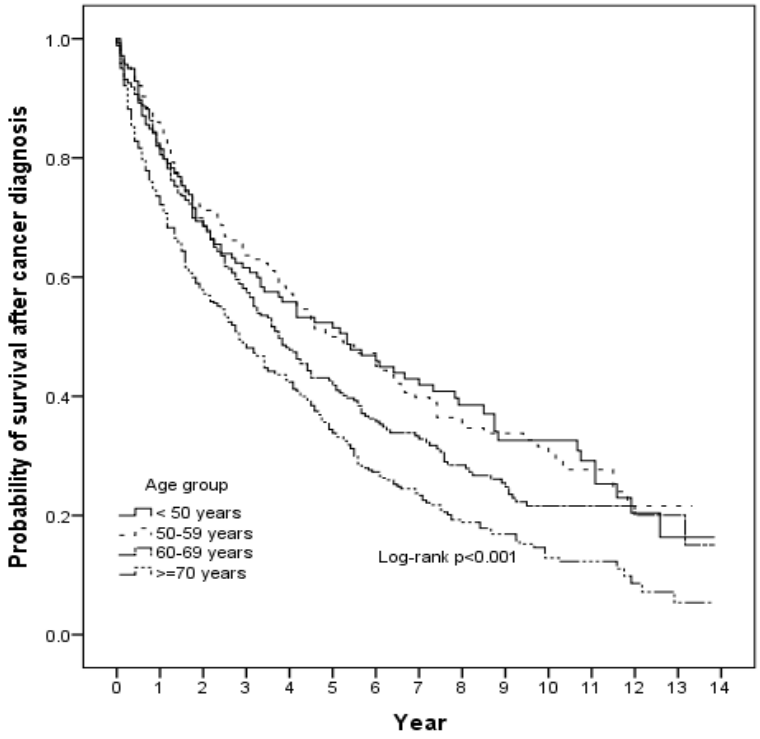
Figure 3: Survival curves for all-cause mortality of HF and non-HF chemotherapy-receiving cancer patients, adjusted by age, sex, marital status, country of birth, cancer site and number of chemotherapy admissions.



	Year													
	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Numbers at risk														
Non-HF	14925	12368	9892	8025	6759	5750	4882	4048	3284	2580	1957	1395	786	388
HF	1062	817	637	508	421	346	276	214	169	128	99	69	34	10

Figure 4. Probability of survival after treatment for cancer with chemotherapy in heart failure patients (unadjusted) by a) age, b) sex

A) Age



B) Sex

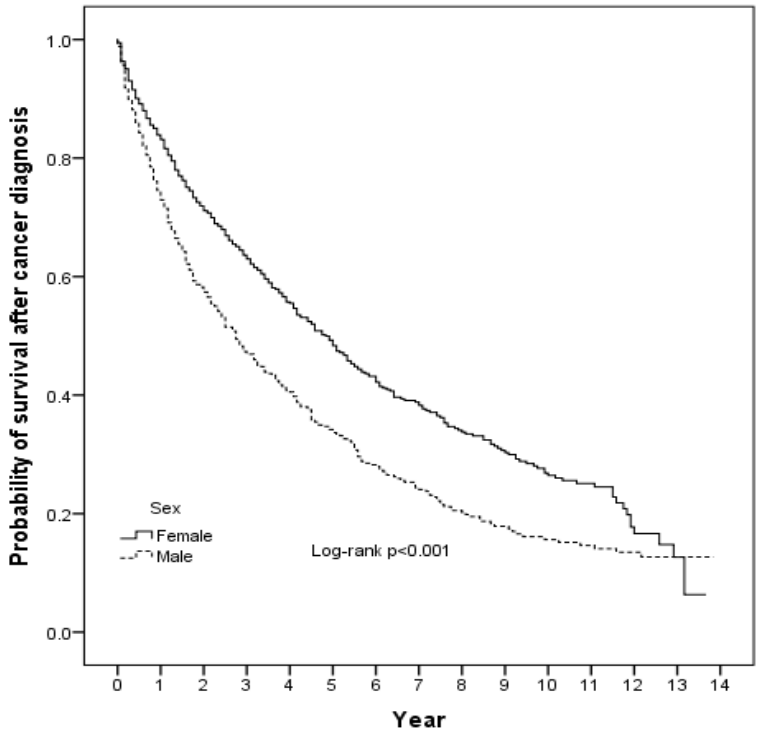


Figure 5. The differential in patient trajectory of physical function declines to mortality for Cancer, Cardiotoxicity, Organ failure and Physical and Cognitive frailty. Adapted from (Murray and Sheik 2008) [29]

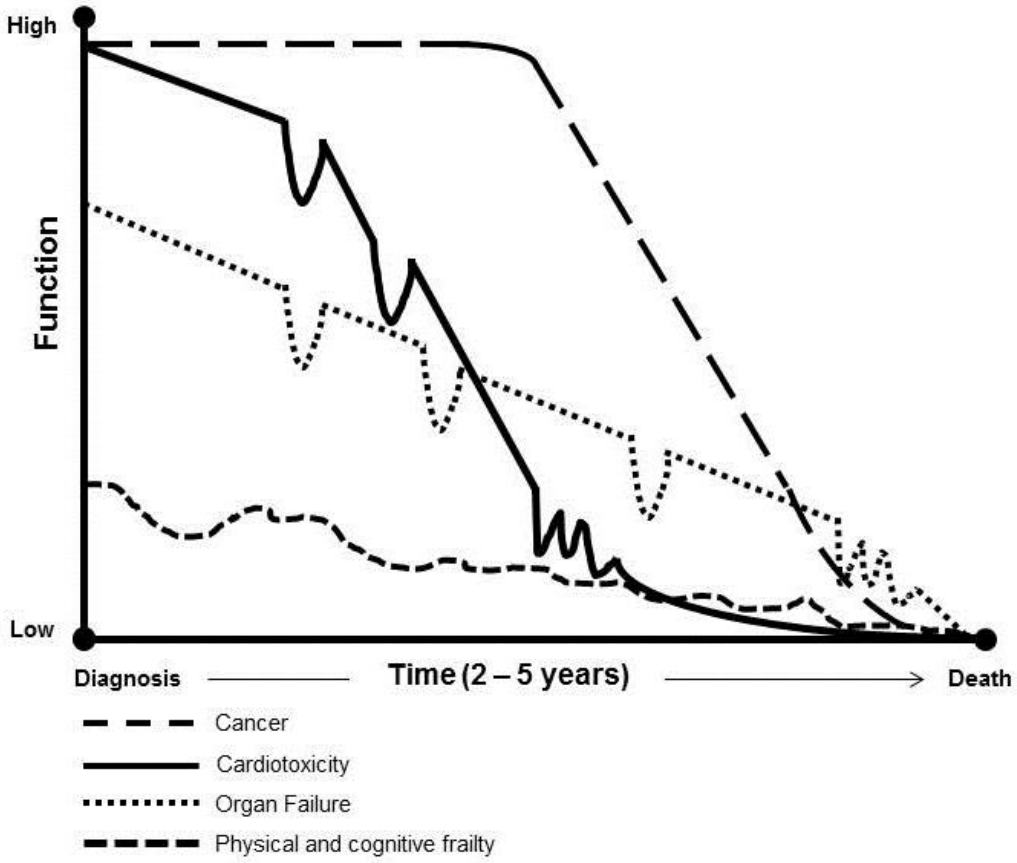


Figure Legends

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

Figure 2. Time from cancer diagnosis to the first index heart failure admission in n=1062 patients who underwent chemotherapy treatment for breast or haematologic (leukemias, lymphomas and related disorders) cancer

Figure 3: Survival curves for all-cause mortality of HF and non-HF chemotherapy-receiving cancer patients, adjusted by age, sex, marital status, country of birth, cancer site and number of chemotherapy admissions.

Figure 4. Probability of survival after treatment for cancer with chemotherapy in heart failure patients (unadjusted) by a) age, b) sex

Figure 5. The differential in patient trajectory of physical function declines to mortality for Cancer, Cardiotoxicity, Organ failure and Physical and Cognitive frailty. Adapted from Murray and Sheik (2008) [31]