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RESEARCH ARTICLE

Do patients have worse outcomes in heart failure than in cancer? A primary care-based cohort study with 10-year follow-up in Scotland

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Aims This study was designed to evaluate whether survival rates in patients with heart failure (HF) are better than those in patients with diagnoses of the four most common cancers in men and women, respectively, in a contemporary primary care cohort in the community in Scotland.

Methods and results Data were obtained from the Primary Care Clinical Informatics Unit from a database of 1.75 million people registered with 393 general practices in Scotland. Sex-specific survival modelling was undertaken using Cox proportional hazards models, adjusted for potential confounders. A total of 56 658 subjects were eligible for inclusion in the study. These represented a total of 147 938 person-years of follow-up (median follow-up: 2.04 years). In men, HF (reference group; 5-year survival: 55.8%) had worse mortality outcomes than prostate cancer [hazard ratio (HR) 0.61, 95% confidence interval (CI) 0.57–0.65; 5-year survival: 68.3%], and bladder cancer (HR 0.88, 95% CI 0.81–0.96; 5-year survival: 57.3%), but better outcomes than lung cancer (HR 3.86, 95% CI 3.65–4.07; 5-year survival: 8.4%) and colorectal cancer (HR 1.23, 95% CI 1.16–1.31; 5-year survival: 48.9%). In women, HF (reference group; 5-year survival: 49.5%) had worse mortality outcomes than breast cancer (HR 0.55, 95% CI 0.51–0.59; 5-year survival 77.7%), but better outcomes than colorectal cancer (HR 1.21, 95% CI 1.13–1.29; 5-year survival 51.5%), lung cancer (HR 3.82, 95% CI 3.60–4.05; 5-year survival 10.4%), and ovarian cancer (HR 1.98, 95% CI 1.80–2.17; 5-year survival 38.2%).

Conclusions Despite advances in management, HF remains as 'malignant' as some of the common cancers in both men and women.

Keywords Heart failure • Cancer • Mortality

Introduction

Cardiovascular disease is the most common cause of death globally, accounting for an estimated 17.5 million deaths in 2012, or around a third of all deaths worldwide.[1] Heart failure (HF) represents the end phenotype of many cardiovascular disorders and has a prevalence of around 1–2% in the general population, rising to >10% in individuals aged ≥70 years. Heart failure is also the most common cause of hospitalization in people aged >65 years.[2] Advances in pharmacological and intracardiac device-based therapies have reduced mortality rates in patients with HF by as much as 50% over the past decade, but both short- and long-term mortality

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rates remain significant.[3–5] The adverse outcomes associated with HF have drawn comparisons with those of cancer amongst many commentators, including international cardiological societies.[6]

Collectively, cancer in all its forms represents the second leading cause of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer-related deaths in 2012.[7] As with cardiovascular disease, improved treatments over recent decades have reduced mortality rates in many cancers.[5,8] A previous comparative analysis of patients with a first admission to hospital in Scotland in 1991 with HF or one of the four most common types of cancer specific to men and women, respectively, suggested that, with the exception of lung and ovarian cancer, HF had a similar or worse 5-year survival rate than the remaining cancers.[9] A comparable analysis of over 1.1 million hospital admissions in Sweden during 1998–2004 reported similar findings.[5]

Important limitations of these findings include the observation that a first hospital admission for many cancers frequently relates to elective surgery or investigations,[5] whereas that for HF often represents an acute HF syndrome. These differences will bias survival comparisons towards worse outcomes for HF. Furthermore, until now, there has been no attempt to adjust for co-morbidity burden,[5,9] which has been increasingly recognized as an important confounding factor in this patient population that may substantially affect survival.

Finally, although improved survival rates in patients diagnosed with HF and with many cancers have been reported over the past decade, these improvements may have occurred at different rates in the various diagnostic groups and past comparisons, therefore, may no longer hold. In view of the limitations of the previous studies highlighted above, it is possible that survival rates in patients with HF in the community are significantly better than those in patients with a diagnosis of cancer in contemporary practice, particularly when differences in co-morbid burden are taken into account. We report here an analysis of outcomes in patients in care cohorts derived from a national primary care database in Scotland with the aim of investigating whether the often quoted maxim 'heart failure is as malignant as cancer' still holds in contemporary practice.

Methods

Study design and setting

The data for this study were obtained from the Primary Care Clinical Informatics Unit (PCCIU).[10,11] In brief, the PCCIU was founded in 1999 to feed information about aspects of clinical care back to practices as part of the Royal College of General Practitioners Scotland Programme of Clinical Improvement and Effectiveness (SPICE). The work involved collecting anonymized clinical information bi-annually between 2000 and 2011 from 393 practices across Scotland, which together cared for about a third of the Scottish population, held data on 1.75 million patients and were representative of the Scottish population in terms of spread of age, gender, material deprivation and rurality.[12]

We carried out a retrospective analysis of the PCCIU cohort; our population consisted entirely of adults aged ≥16 years with an incident diagnosis of either HF or a cancer between 1 April 2002 and 31 March 2011 (the last date of update of the PCCIU dataset). The first 3 years of the PCCIU (1 April 1999 to 30 March 2002) were used to mitigate the risk for the inclusion of prevalent cases: patients with diagnosis codes for either HF or cancer in this period were excluded. Cancers were restricted to the four most common cancers by gender and included prostate, lung, colorectal and bladder cancer in men, and breast, colorectal, lung and ovarian cancer in women. The Read codes (the clinical coding system used in UK general practice to record patient diagnoses and procedures in health care IT systems) for these diagnoses are given in the supplementary material online (*Tables S1* and *S2*). The primary exposure was first entry of the diagnosis of HF or cancer type on the health care record, and the date of diagnosis was the index date. Patients with diagnoses of both HF and cancer were assigned to the cohort of patients associated with the diagnosis that had been made first. When possible, we based our morbidity definitions on Quality Outcomes Framework (QOF) (http://qof.digital.nhs.uk/) business rules[13] and Read code groups for long-term disorders [as defined by National Health Service (NHS) Scotland].[14] The QOF is the world's largest pay-for-performance programme. It was introduced for all family practices in 2004 and links up to 25% of family practitioners' income to performance for more than 100 publicly reported quality indicators relating to the management of chronic disease, organization of care and patient experience. A significant proportion of a family practitioner's income will depend on the maintenance of a register of patients with a particular diagnosis (such as HF and cancer diagnoses) and will also relate to the proportion of such patients who receive evidence-based care.

The primary outcome was survival time to all-cause mortality. Potential confounders accounted for included: age at index diagnosis (continuous variable); material deprivation (Scottish Index of Multiple Deprivation, in quintiles whereby 1 = least deprived and 5 = most deprived); rurality (urban–rural index in six levels, of which level 1 represents the most urban and level 6 the most remote and rural); smoking status, and co-morbidities (before index date only). These confounders were treated as ever/never terms (i.e. they were not time-varying). Co-morbidities were initially selected and derived from Read codes following Barnett *et al.*[10] A shortlist of these [hypertension, depression, asthma, coronary heart disease, diabetes, thyroid disease, rheumatoid arthritis, chronic obstructive pulmonary disease, stroke or transient ischaemic attack (TIA), chronic kidney disease, atrial fibrillation, peripheral vascular disease, epilepsy, dementia, schizophrenia, bronchiectasis, Parkinson's disease, multiple sclerosis, viral hepatitis, chronic liver disease, previous myocardial infarction] was then used for subsequent modelling. Co-morbidities diagnosed after the index date, and all medications for HF (diuretics, aldosterone receptor antagonists, beta-blockers, ACE inhibitors, angiotensin receptor blockers, anti-platelets and lipids) were not considered in multivariable models (supplementary material online, *Table S3*). Data cleaning included the removal of patients for whom information on deprivation and rurality was missing, and of those with logical conflicts in the dates of recorded events. Imputation of deprivation and rurality was considered but the proportion of patients for whom these fields were missing was low (1.94%) and it was felt reasonable to assume that these fields were missing completely at random. The majority of the clinical variables were binary indicators of presence of a clinical code; the associated condition or medication was assumed to be absent if the code was absent.

Statistical methods

Descriptive statistics were presented as means with standard deviations (SDs), or proportions; these were stratified first by gender and

then by primary exposure. These were compared between exposure groups using analysis of variance (ANOVA) (to compare means) or χ^2 tests (to compare proportions), with the *P*-values reported. Numbers of co-morbidities were compared between disease groups graphically; survival was compared between groups using Kaplan–Meier plots.

Sex-specific survival modelling was carried out using Cox proportional hazards models. Three models were considered: (i) a univariable model with the primary diagnosis only; (ii) a model corrected for demographic variables of age and deprivation; and (iii) a fully adjusted model that corrected for all confounders described above (i.e. age, deprivation, rurality, smoking status) and all of the co-morbidities described above that were diagnosed before baseline. Many of these confounders may be highly correlated, which may make their effect sizes and standard errors difficult to interpret. However, we do not make any inference about these. We did not correct for any medications because these may act as mediators. Continuous variables such as age were treated as linear. The proportional hazards assumption was checked using Schoenfeld residuals.[15] All analyses were carried out using R Version 3.0.2.[16]

Results

A total of 58 412 patients met the study inclusion criteria from a database of 1.75 million people registered with 393 medical practices in Scotland. A total of 1754 (3.0%) patients were excluded, including 1119 patients for whom deprivation data were lacking, and 635 patients for whom the date of death represented the date of diagnosis, or in whom the date of loss from follow-up could not be established. Thus, the final dataset comprised 56 658 patients. These included 28 064 men and 28 594 women, with a mean ± SD age at first diagnosis of 69.16 ± 12.76 years. The median follow-up was 2.04 years and the cohort represented a total of 147 938 person-years. Diagnoses in men included 6795 cases of prostate cancer, 4693 of lung cancer, 4239 of colorectal cancer, 2028 of bladder cancer, and 10 309 of HF. Among the women, 10 760 had breast cancer, 3610 had colorectal cancer, 3859 had lung cancer, 1234 had ovarian cancer, and 9131 had HF.

Descriptive sample characteristics are presented in *Table 1* for men and in *Table 2* for women. In men, ages at cancer and HF diagnoses were similar, whereas in women a diagnosis of HF occurred later in life than one of cancer. Patients with HF, both men and women, had more co-morbidities than those with cancer; only 5.5% of HF patients of either gender had no co-morbidity, compared with 20–38% of patients with a diagnosis of cancer. The mean number of co-morbid conditions was also greater in patients with HF compared with patients diagnosed with cancer. Male patients with HF had a mean ± SD of 2.62 ± 1.55 co-morbidities, whereas patients diagnosed with cancer had fewer (prostate cancer: 1.47 ± 1.38; lung cancer: 1.79 ± 1.56; colorectal cancer: 1.52 ± 1.49; bladder cancer: 1.71 ± 1.52). Similar observations were recorded in women, in whom a mean ± SD of 2.8 ± 1.61 co-morbidities were reported in patients with HF and lower numbers were recorded in the other diagnoses (breast cancer: 1.19 ± 1.31; colorectal cancer: 1.52 ± 1.46; lung cancer: 1.95 ± 1.60; ovarian cancer: 1.21 ± 1.32). Numbers of co-morbidities at index date in each disease and by gender are shown in *Figure 1*.

Crude mortality rates at 30 days, 1 year and 5 years are also presented in *Tables 1* and *2*. The highest crude mortality rates occurred in patients with lung cancer, with 8.7% of men and 9.3% of women dying within 30 days. The lowest crude mortality rates were recorded in women diagnosed with breast cancer (0.5%) and men diagnosed with prostate cancer (0.4%). In subjects diagnosed with HF, 30-day mortality rates were 1.5% in men and 2.2% in women, and 1-year mortality rates were 14.5% and 17.7% in men and women, respectively.

Kaplan–Meier plots for overall survival in years since diagnosis are presented in *Figure 2*. The main Cox proportional hazards model results are presented in *Table 3*. Men with prostate cancer [hazard ratio (HR) 0.61, 95% confidence interval (CI) 0.57–0.65; $P < 0.001$] or bladder cancer (HR 0.88, 95% CI 0.81–0.96; $P < 0.005$) had better survival than those with HF, whereas those with lung cancer (HR 3.86, 95% CI 3.65–4.07; $P < 0.001$) or colorectal cancer (HR 1.23, 95% CI 1.16–1.31; $P < 0.001$) generally fared worse. Women with breast cancer (HR 0.55, 95% CI 0.51–0.59; $P < 0.001$) had better survival than those with HF, whereas those with lung cancer (HR 3.82, 95% CI 3.60–4.05, $P < 0.001$), ovarian cancer (HR 1.98, 95% CI 1.80–2.17; $P < 0.001$) or colorectal cancer (HR 1.21, 95% CI 1.13–1.29; $P < 0.001$) fared worse.

All models showed some deviation from proportional hazards. Deviations still existed in the fully corrected models, but were minor and so should not affect the interpretation of the results (see supplementary material online, *Tables S4* and *S5*).

Discussion

Our analysis is the first to compare survival outcomes in a primary care setting in patients with diagnoses of HF or any of the four most common cancers in men and women, respectively, in a contemporary cohort of patients treated with current evidence-based practice that has changed dramatically over the two decades since the older studies first reported outcomes following first hospital admission with a diagnosis of HF or cancer. Despite advances in care, we found that men and women with a diagnosis of HF continue to have worse survival than patients with one of several common cancers. Our findings are particularly relevant given that the current analysis overcomes many of the limitations of previous work, particularly in relation to admission bias for different conditions and differences in co-morbid burden between patients with HF and those with cancer.

Advances in both medical and device-based treatments have been associated with improved survival rates in patients with HF in many[17–20] but not all national registry-based studies.[21] Age-standardized rates of death from HF are reported to have decreased by 40% in seven European countries from 1987 to 2008.[4] An analysis of all patients in Scotland hospitalized with a first episode of HF between 1986 and 2003 demonstrated relative declines in short- and medium-term case fatality rates of 40–50% in men and 20–25% in women; these changes are associated with significant increases in ACE inhibitor and beta-blocker use over this period.[17]

Table 1 Baseline characteristics and mortality data in men with prostate, lung, colorectal or bladder cancer or heart failure

	Prostate cancer	Lung cancer	Colorectal cancer	Bladder cancer	Heart failure
Cases, *n*	6795	4693	4239	2082	10 309
Age at diagnosis, years, mean ± SD	70.4 ± 9.1	69.1 ± 10.2	68.3 ± 11.3	70.2 ± 11.3	70.5 ± 12.2
Date of first diagnosis (median)	22/12/2005	13/02/2006	13/01/2006	23/11/2005	05/01/2005
Heart failure	95 (1.4%)	97 (2.1%)	81 (1.9%)	41 (2.0%)	
Cancer					226 (2.2%)
Urban–rural index, *n* (%)					
1 (most urban)	2151 (31.7%)	1749 (37.3%)	1429 (33.7%)	711 (35.1%)	3756 (36.4%)
2	2360 (34.7%)	1604 (34.2%)	1426 (33.6%)	722 (35.6%)	3255 (31.6%)
3	977 (14.4%)	654 (13.9%)	583 (13.8%)	288 (14.2%)	1374 (13.3%)
4	507 (7.5%)	269 (5.7%)	324 (7.6%)	100 (4.9%)	698 (6.8%)
5	481 (7.1%)	238 (5.1%)	278 (6.6%)	132 (6.5%)	686 (6.7%)
6 (most rural)	319 (4.7%)	179 (3.8%)	199 (4.7%)	75 (3.7%)	540 (5.2%)
Scottish Index of Multiple Deprivation, *n* (%)					
1 (least deprived)	1165 (17.1%)	551 (11.7%)	608 (14.3%)	332 (16.4%)	1266 (12.3%)
2	1419 (20.9%)	712 (15.2%)	784 (18.5%)	379 (18.7%)	1732 (16.8%)
3	1401 (20.6%)	939 (20%)	862 (20.3%)	394 (19.4%)	2162 (21.0%)
4	1608 (23.7%)	1190 (25.4%)	1102 (26.0%)	516 (25.4%)	2708 (26.3%)
5 (most deprived)	1202 (17.7%)	1301 (27.7%)	883 (20.8%)	407 (20.1%)	2441 (23.7%)
Non-smoker, *n* (%)	2085 (30.7%)	153 (3.3%)	942 (22.2%)	377 (18.6%)	2368 (23.0%)
Smoker, *n* (%)	913 (13.4%)	661 (14.1%)	430 (10.1%)	384 (18.9%)	1757 (17.0%)
Ex-smoker, *n* (%)	2283 (33.6%)	1033 (22.0%)	1345 (31.7%)	763 (37.6%)	4396 (42.6%)
Smoking data missing, *n* (%)	1514 (22.3%)	2846 (60.6%)	1522 (35.9%)	504 (24.9%)	1788 (17.3%)
Co-morbidities, mean ± SD	1.47 ± 1.38	1.79 ± 1.56	1.52 ± 1.49	1.71 ± 1.52	2.62 ± 1.55
No co-morbidity, *n* (%)	1949 (28.7%)	1116 (23.8%)	1278 (30.1%)	499 (24.6%)	562 (5.5%)
Hypertension, *n* (%)	2614 (38.5%)	1515 (32.3%)	1596 (37.7%)	801 (39.5%)	4711 (45.7%)
Depression, *n* (%)	603 (8.9%)	464 (9.9%)	358 (8.4%)	190 (9.4%)	1068 (10.4%)
Asthma, *n* (%)	491 (7.2%)	355 (7.6%)	286 (6.7%)	124 (6.1%)	788 (7.6%)
Coronary heart disease, *n* (%)	1303 (19.2%)	1091 (23.2%)	817 (19.3%)	488 (24.1%)	6295 (61.1%)
Diabetes, *n* (%)	688 (10.1%)	562 (12.0%)	611 (14.4%)	314 (15.5%)	2234 (21.7%)
Thyroid disease, *n* (%)	202 (3.0%)	139 (3.0%)	109 (2.6%)	68 (3.4%)	480 (4.7%)
Rheumatoid arthritis, *n* (%)	584 (8.6%)	358 (7.6%)	382 (9.0%)	187 (9.2%)	1209 (11.7%)
COPD, *n* (%)	611 (9.0%)	1241 (26.4%)	390 (9.2%)	237 (11.7%)	1707 (16.6%)
Stroke or TIA, *n* (%)	321 (4.7%)	445 (9.5%)	245 (5.8%)	112 (5.5%)	754 (7.3%)
Chronic kidney disease, *n* (%)	550 (8.1%)	473 (10.1%)	381 (9.0%)	220 (10.8%)	1560 (15.1%)
Atrial fibrillation, *n* (%)	238 (3.5%)	168 (3.6%)	162 (3.8%)	106 (5.2%)	552 (5.4%)
PVD, *n* (%)	388 (5.7%)	285 (6.1%)	250 (5.9%)	115 (5.7%)	2519 (24.4%)
Epilepsy, *n* (%)	295 (4.3%)	508 (10.8%)	231 (5.4%)	149 (7.3%)	1153 (11.2%)
Dementia, *n* (%)	78 (1.1%)	83 (1.8%)	57 (1.3%)	29 (1.4%)	172 (1.7%)
Schizophrenia, *n* (%)	82 (1.2%)	72 (1.5%)	47 (1.1%)	46 (2.3%)	230 (2.2%)
Bronchiectasis, *n* (%)	31 (0.5%)	60 (1.3%)	27 (0.6%)	14 (0.7%)	86 (0.8%)
Parkinson's disease, *n* (%)	32 (0.5%)	22 (0.5%)	15 (0.4%)	6 (0.3%)	54 (0.5%)
Multiple sclerosis, *n* (%)	50 (0.7%)	17 (0.4%)	22 (0.5%)	11 (0.5%)	100 (1.0%)
Viral hepatitis, *n* (%)	11 (0.2%)	3 (0.1%)	6 (0.1%)	2 (0.1%)	18 (0.2%)
Chronic liver disease, *n* (%)	2 (<0.1%)	4 (0.1%)	2 (<0.1%)	0 (0%)	3 (<0.1%)
Previous MI, *n* (%)	657 (9.7%)	563 (12.0%)	442 (10.4%)	261 (12.9%)	4448 (43.1%)
CABG, *n* (%)	416 (6.1%)	239 (5.1%)	233 (5.5%)	127 (6.3%)	1956 (19.0%)
Diuretics, *n* (%)	2406 (35.4%)	1279 (27.3%)	1402 (33.1%)	699 (34.5%)	8189 (79.4%)
Aldosterone receptor antagonists, *n* (%)	464 (6.8%)	114 (2.4%)	218 (5.1%)	130 (6.4%)	741 (7.2%)
Beta-blockers, *n* (%)	1819 (26.8%)	733 (15.6%)	1048 (24.7%)	580 (28.6%)	6307 (61.2%)
ACE inhibitors, *n* (%)	1352 (19.9%)	451 (9.6%)	704 (16.6%)	396 (19.5%)	3634 (35.3%)
Angiotensin receptor antagonists, *n* (%)	580 (8.5%)	165 (3.5%)	245 (5.8%)	149 (7.3%)	1727 (16.8%)
Anti-platelet agents	3014 (44.4%)	1565 (33.3%)	1600 (37.7%)	944 (46.5%)	7683 (74.5%)
Lipid-lowering agents, *n* (%)	2889 (42.5%)	1184 (25.2%)	1516 (35.8%)	903 (44.5%)	7143 (69.3%)
Death within 30 days post-diagnosis, *n* (%)	25/6759 (0.4%)	405/4647 (8.7%)	102/4196 (2.4%)	22/2017 (1.1%)	156/10 254 (1.5%)
Death within 1 year post-diagnosis, *n* (%)	439/5862 (7.5%)	2879/4255 (67.7%)	850/3671 (23.2%)	290/1786 (16.2%)	1343/9322 (14.4%)
Death within 5 years post-diagnosis, *n* (%)	1442/2829 (51.0%)	3707/3812 (97.2%)	1616/2181 (74.1%)	621/978 (63.5%)	3430/5508 (62.3%)
Death (ever recorded), *n* (%)	1586/6795 (23.3%)	3727/4693 (79.4%)	1671/4239 (39.4%)	655/2028 (32.3%)	3713/10 309 (36.0%)

CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PVD, peripheral vascular disease; SD, standard deviation; TIA, transient ischaemic attack.

Table 2 Baseline characteristics and mortality data in women with breast, colorectal, lung or ovarian cancer or heart failure

	Breast cancer	Colorectal cancer	Lung cancer	Ovarian cancer	Heart failure
Cases, *n*	10 760	3610	3859	1234	9131
Age at diagnosis, years, mean ± SD	61.3 ± 14.0	70.0 ± 13.1	69.7 ± 10.7	62.7 ± 14.3	76.4 ± 11.5
Date of first diagnosis (median)	30/11/2005	18/01/2006	20/04/2006	25/10/2005	25/01/2005
Heart failure, *n* (%)	85 (0.8%)	43 (1.2%)	61 (1.6%)	15 (1.2%)	
Cancer, *n* (%)					364 (4.0%)
Urban–rural index, *n* (%)					
1 (most urban)	3688 (34.3%)	1322 (36.6%)	1550 (40.2%)	432 (35.0%)	3354 (36.7%)
2	3694 (34.3%)	1162 (32.2%)	1311 (34.0%)	407 (33.0%)	2899 (31.7%)
3	1484 (13.8%)	475 (13.2%)	471 (12.2%)	168 (13.6%)	1168 (12.8%)
4	655 (6.1%)	256 (7.1%)	198 (5.1%)	83 (6.7%)	690 (7.6%)
5	727 (6.8%)	217 (6.0%)	199 (5.2%)	91 (7.4%)	573 (6.3%)
6 (most rural)	512 (4.8%)	178 (4.9%)	130 (3.4%)	53 (4.3%)	447 (4.9%)
Scottish Index of Multiple Deprivation, *n* (%)					
1 (least deprived)	1542 (14.3%)	486 (13.5%)	431 (11.2%)	197 (16.0%)	1197 (13.1%)
2	2135 (19.8%)	700 (19.4%)	595 (15.4%)	242 (19.6%)	1453 (15.9%)
3	2270 (21.1%)	748 (20.7%)	750 (19.4%)	271 (22.0%)	2042 (22.4%)
4	2626 (24.4%)	866 (24.0%)	954 (24.7%)	274 (22.2%)	2293 (25.1%)
5	2187 (20.3%)	810 (22.4%)	1129 (29.3%)	250 (20.3%)	2146 (23.5%)
Non-smoker, *n* (%)	4129 (38.4%)	1168 (32.4%)	140 (3.6%)	345 (28.0%)	3352 (36.7%)
Smoker, *n* (%)	1646 (15.3%)	328 (9.1%)	617 (16.0%)	145 (11.8%)	1027 (11.2%)
Ex-smoker, *n* (%)	2264 (21.0%)	700 (19.4%)	760 (19.7%)	189 (15.3%)	2536 (27.8%)
Smoking data missing, *n* (%)	2721 (25.3%)	1414 (39.2%)	2342 (60.7%)	555 (45.0%)	2216 (24.3%)
Co-morbidities, mean ± SD	1.19 ± 1.31	1.52 ± 1.46	1.95 ± 1.60	1.21 ± 1.32	2.80 ± 1.61
No co-morbidity, *n* (%)	4115 (38.2%)	1024 (28.4%)	769 (19.9%)	465 (37.7%)	500 (5.5%)
Hypertension, *n* (%)	3259 (30.3%)	1450 (40.2%)	1451 (37.6%)	364 (29.5%)	4984 (54.6%)
Depression, *n* (%)	1863 (17.3%)	511 (14.2%)	776 (20.1%)	224 (18.2%)	1642 (18.0%)
Asthma, *n* (%)	945 (8.8%)	296 (8.2%)	386 (10.0%)	95 (7.7%)	925 (10.1%)
Coronary heart disease, *n* (%)	839 (7.8%)	499 (13.8%)	718 (18.6%)	108 (8.8%)	4367 (47.8%)
Diabetes, *n* (%)	786 (7.3%)	425 (11.8%)	421 (10.9%)	89 (7.2%)	1708 (18.7%)
Thyroid disease, *n* (%)	1173 (10.9%)	465 (12.9%)	474 (12.3%)	133 (10.8%)	1532 (16.8%)
Rheumatoid arthritis, *n* (%)	613 (5.7%)	302 (8.4%)	392 (10.2%)	85 (6.9%)	1327 (14.5%)
COPD, *n* (%)	583 (5.4%)	275 (7.6%)	1118 (29.0%)	74 (6.0%)	1455 (15.9%)
Stroke, TIA, *n* (%)	445 (4.1%)	237 (6.6%)	382 (9.9%)	58 (4.7%)	1404 (15.4%)
Chronic kidney disease, *n* (%)	265 (2.5%)	179 (5.0%)	228 (5.9%)	37 (3.0%)	722 (7.9%)
Atrial fibrillation, *n* (%)	316 (2.9%)	158 (4.4%)	161 (4.2%)	25 (2.0%)	2370 (26.0%)
PVD, *n* (%)	238 (2.2%)	130 (3.6%)	274 (7.1%)	30 (2.4%)	740 (8.1%)
Epilepsy, *n* (%)	136 (1.3%)	39 (1.1%)	49 (1.3%)	23 (1.9%)	149 (1.6%)
Dementia, *n* (%)	190 (1.8%)	75 (2.1%)	98 (2.5%)	13 (1.1%)	448 (4.9%)
Schizophrenia, *n* (%)	96 (0.9%)	38 (1.1%)	36 (0.9%)	8 (0.6%)	103 (1.1%)
Bronchiectasis, *n* (%)	34 (0.3%)	13 (0.4%)	26 (0.7%)	1 (0.1%)	73 (0.8%)
Parkinson's disease, *n* (%)	39 (0.4%)	12 (0.3%)	13 (0.3%)	4 (0.3%)	63 (0.7%)
Multiple sclerosis, *n* (%)	50 (0.5%)	10 (0.3%)	10 (0.3%)	6 (0.5%)	19 (0.2%)
Viral hepatitis, *n* (%)	6 (0.1%)	3 (0.1%)	0 (0%)	0 (0%)	3 (<0.1%)
Chronic liver disease, *n* (%)	597 (5.5%)	261 (7.2%)	258 (6.7%)	76 (6.2%)	984 (10.8%)
Previous MI, *n* (%)	305 (2.8%)	207 (5.7%)	292 (7.6%)	48 (3.9%)	2665 (29.2%)
CABG, *n* (%)	88 (0.8%)	62 (1.7%)	94 (2.4%)	13 (1.1%)	690 (7.6%)
Diuretics, *n* (%)	3531 (32.8%)	1451 (40.2%)	1309 (33.9%)	422 (34.2%)	8010 (87.7%)
Aldosterone receptor blockers, *n* (%)	320 (3.0%)	114 (3.2%)	79 (2.0%)	24 (1.9%)	566 (6.2%)
Beta-blockers, *n* (%)	2165 (20.1%)	840 (23.3%)	550 (14.3%)	228 (18.5%)	4480 (49.1%)
ACE inhibitors, *n* (%)	1358 (12.6%)	489 (13.5%)	337 (8.7%)	93 (7.5%)	2881 (31.6%)
Angiotensin receptor antagonists, *n* (%)	805 (7.5%)	261 (7.2%)	174 (4.5%)	57 (4.6%)	1684 (18.4%)
Anti-platelet agents, *n* (%)	2493 (23.2%)	1056 (29.3%)	1218 (31.6%)	225 (18.2%)	6326 (69.3%)
Lipid-lowering agents, *n* (%)	2547 (23.7%)	1061 (29.4%)	994 (25.8%)	223 (18.1%)	5149 (56.4%)
Death within 30 days post-diagnosis, *n* (%)	57/10 666 (0.5%)	79/3577 (2.2%)	354/3826 (9.3%)	39/1224 (3.2%)	197/9065 (2.2%)
Death within 1 year post-diagnosis, *n* (%)	480/9235 (5.2%)	719/3101 (23.2%)	2241/3427 (65.4%)	295/1105 (26.7%)	1441/8121 (17.7%)
Death within 5 years post-diagnosis, *n* (%)	1582/4053 (39.0%)	1337/1867 (71.6%)	2920/3030 (96.4%)	596/736 (81.0%)	3448/5061 (68.1%)
Death (ever recorded), *n* (%)	1709/10 760 (15.9%)	1376/3610 (38.1%)	2941/3859 (76.2%)	611/1234 (49.5%)	3747/9131 (41.0%)

CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PVD, peripheral vascular disease; SD, standard deviation; TIA, transient ischaemic attack.

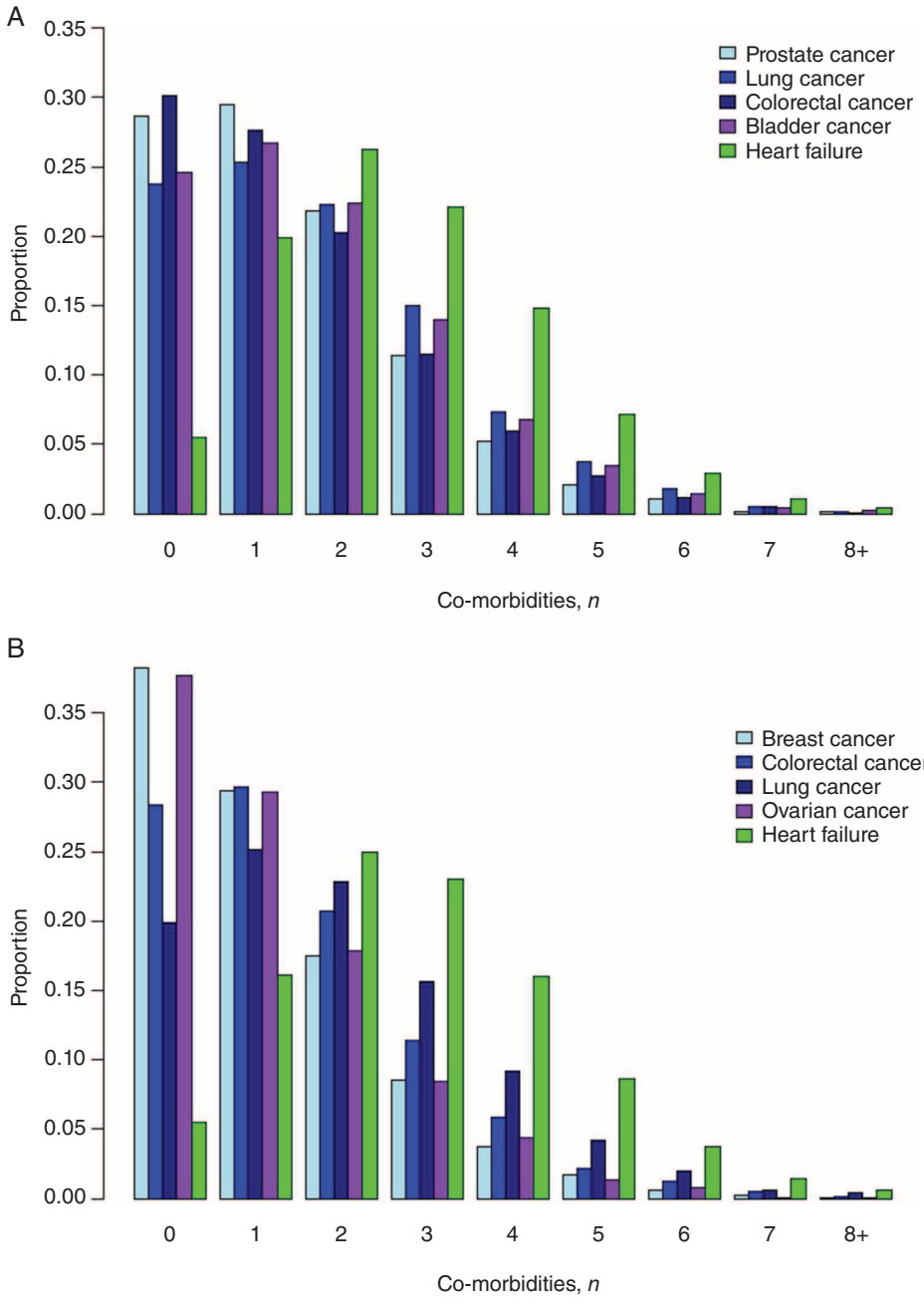
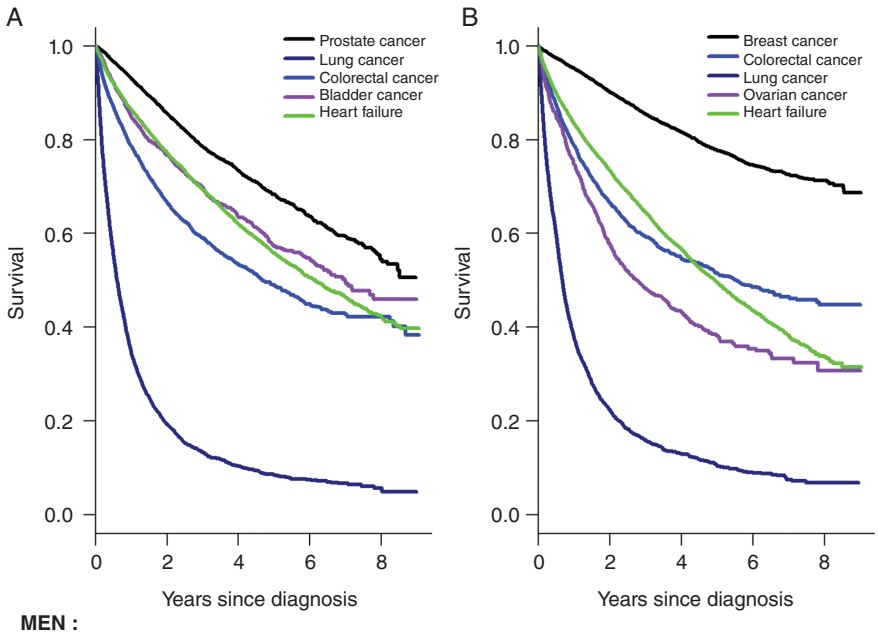


Figure 1 Numbers of co-morbidities by disease group in (*A*) men with prostate, lung, colorectal or bladder cancer, or heart failure and (*B*) women with breast, colorectal, lung or ovarian cancer, or heart failure.

There are limited data regarding longer-term outcomes of incident HF in the community. Our analysis suggests that mortality rates in patients with this condition remain significant. Our observed 1- and 5-year mortality rates of 14.4% and 62.3%, respectively, in males, and 17.7% and 68.1%, respectively, in females from time of first recorded diagnosis of HF are lower than mortality rates recorded following an acute admission to hospital for HF,[22,23] probably because the latter population represents a sicker cohort. Our mortality rates are greater than the 5-year mortality rate of 38% reported in a contemporary community cohort of subjects with new diagnoses of HF assembled in Ireland.[24] Similarly, the Echocardiographic Heart of England Screening Study (ECHOES) community-based study reported 5-year mortality rates of 38% in HF with preserved ejection fraction (HFpEF) and 47% in HF with reduced ejection fraction (HFrEF), although the study represented a cross-sectional analysis and did not report on survival from time of diagnosis.[25] Similarly, data derived from Olmsted County reported 5-year survival of 45%, but again referred to a



MEN :

	Prostate	Lung	Colorectal	Bladder	HF
Prob[alive after 30d]	99.6% [99.5,99.8]	91.3% [90.5,92.1]	97.6% [97.1,98.0]	98.9% [98.5,99.4]	98.5% [98.2,98.7]
Prob[alive after 1y]	93.1%* [92.1,93.7]	34.7% [33.3,36.2]	78.6% [77.3,79.9]	84.8% [83.2,86.4]	86.4% [85.7,87.0]
Prob[alive after 5y]	68.3%* [66.8,69.8]	8.4% [7.4,9.6]	48.9% [47.0,50.9]	57.3% [54.5,60.2]	55.8% [54.6,57.1]

WOMEN :

	Breast	Colorectal	Lung	Ovarian	HF
Prob[alive after 30d]	99.5% [99.3,99.6]	97.8% [97.3,98.3]	90.8% [89.9,91.7]	96.8% [95.9,97.8]	97.8% [97.5,98.1]
Prob[alive after 1y]	95.2%* [94.8,95.6]	78.7% [77.3,80.1]	37.7% [36.2,39.4]	74.8% [72.3,77.3]	83.4% [82.6,84.2]
Prob[alive after 5y]	77.7%* [76.7,78.8]	51.5% [49.4,53.6]	10.4% [9.1,11.8]	38.2% [34.9,41.9]	49.5% [48.2,50.8]

Figure 2 Kaplan–Meier curves for overall survival in (*A*) men with prostate, lung, colorectal or bladder cancer, or heart failure and (*B*) women with breast, colorectal, lung or ovarian cancer, or heart failure. HF, heart failure. *Correction added on 11 May 2017, after first online publication: missing percentages for prostate and breast cancer have been added.

cross-sectional survival analysis in which data were derived from the time of initiation of the study rather than from the time of diagnosis of HF, which may have introduced a degree of bias towards a poorer outcome.[26]

Survival rates in HF, and in many cancers, have improved over the past decade, but these improvements have occurred at different rates in HF and cancer populations. For example, an analysis of hospital admissions in Sweden conducted by Stewart *et al.* suggested that survival rates in HF admissions had improved by a greater margin each calendar year than had survival rates in the various cancers studied.[5] Although our analysis is not subject to many of the limitations of previous analyses, such as admission bias and failure to adjust for type and number of co-morbidities,[5,9] our findings are remarkably similar to those reported initially by Stewart *et al.*[9] and subsequently from hospital admission data derived from Sweden.[5] This suggests that even in a more contemporaneous cohort (by at least a decade), a diagnosis of HF remains as 'malignant' as that of some cancers. Our findings were broadly consistent when the data were stratified by co-morbid burden and age at diagnosis.

The burden of co-morbidity among patients with HF is significant.[27] Only 3.0% of patients with HF had no recorded co-morbidity, whereas up to a third of patients with a cancer diagnosis had no co-morbid conditions documented in their

Table 3 Results of Cox proportional hazards models, separated by gender

	HR (95% CI), *P*-value		
Disease	**Unadjusted HR**	**HR adjusted for age, deprivation**	**HR fully adjusted**
In men			
Heart failure	1.0 (ref)	1.0 (ref)	1.0 (ref)
Prostate cancer	0.64 (0.60–0.68), $P < 0.001$	0.64 (0.61–0.68), $P < 0.001$	0.61 (0.57–0.65), $P < 0.001$
Lung cancer	5.72 (5.46–6.00), $P < 0.001$	6.27 (5.98–6.58), $P < 0.001$	3.86 (3.65–4.07), $P < 0.001$
Colorectal cancer	1.34 (1.26–1.42), $P < 0.001$	1.45 (1.37–1.54), $P < 0.001$	1.23 (1.16–1.31), $P < 0.001$
Bladder cancer	0.96 (0.88–1.04), $P = 0.28$	0.97 (0.89–1.05), $P = 0.46$	0.88 (0.81–0.96), $P < 0.005$
In women			
Heart failure	1.0 (ref)	1.0 (ref)	1.0 (ref)
Breast cancer	0.34 (0.32–0.36), $P < 0.001$	0.58 (0.55–0.62), $P < 0.001$	0.55 (0.51–0.59), $P < 0.001$
Colorectal cancer	1.05 (0.99–1.12), $P = 0.12$	1.31 (1.23–1.40), $P < 0.001$	1.21 (1.13–1.29), $P < 0.001$
Lung cancer	4.22 (4.01–4.43), $P < 0.001$	5.64 (5.36–5.94), $P < 0.001$	3.82 (3.60–4.05), $P < 0.001$
Ovarian cancer	1.46 (1.34–1.59), $P < 0.001$	2.55 (2.33–2.78), $P < 0.001$	1.98 (1.80–2.17), $P < 0.001$

CI, confidence interval; HR, hazard ratio.

medical record. Numbers of co-morbidities in patients with HF appeared to be similar in both sexes despite the 6-year increase in average age at diagnosis in women with HF in comparison with men. Previous studies have also reported a significant co-morbidity burden in patients with HF, the presence of which is independently associated with increased mortality.[28,29] This burden appears to have increased over time.[29] In the Cardiovascular Research Network PRESERVE study, undertaken during 2005–08, fewer than 2% of HF patients had no co-morbid conditions.[30] Data derived from the Spanish National Heart Failure Registry suggest that only 15% of patients with HF have no co-morbidity.[28] Only 4% of individuals with HF in a Medicare dataset of 122 630 patients had no non-cardiac co-morbid conditions and 40% had five or more such co-morbidities.[31] It is not surprising that the burden of cardiovascular co-morbidities is greatest in patients with HF, given that many of these conditions, such as diabetes mellitus, hypertension and coronary artery disease, are risk factors for the future development of HF.[32] In contrast, studies of patients with cancer suggest that the co-morbid burden is significantly lower in this population. For instance, perhaps only half of all lung cancer patients have co-morbidities,[33] and even fewer patients with breast, ovarian or uterine cancers do so.[34]

Our data suggest that the burden of cardiovascular disease in patients with a diagnosis of cancer is also significant: 20% of men with a common cancer also have a diagnosis of coronary artery disease; 10–20% of both genders are diagnosed with diabetes; rates of previous strokes or TIAs are significant, particularly in men, and prevalences of hypertension vary between 30% and 45% in both genders. Previous registry-based studies have also reported significant rates of cardiovascular co-morbidity in patients with lung and prostate cancer.[35,36] Cardiovascular co-morbidity and estimated cardiovascular risk have been independently associated with worse outcomes in patients with lung and breast cancer.[35,37]

Our study is subject to several limitations. Firstly, we relied on primary care coding to identify the study cohort and did not validate the codes. Like all other observational research undertaken using data derived from electronic health care records, PCCIU research relies on clinicians' observations and the entry of relevant codes into electronic health care records, which may result in an incomplete or inaccurate representation of a patient's health. Whereas diagnoses of cancer are generally made by specialists based on imaging or biopsy information and hence are robust, diagnoses of HF may be clinical in the first instance and may be less robust, particularly in the presence of obesity or other conditions associated with dyspnoea and oedema. However, the diagnosis of HF is well recorded in UK primary care electronic health care records because it is an important part of the QOF pay-for-performance scheme, which requires the maintenance of a register of patients with a diagnosis of HF, and records the percentage of such patients with a diagnosis of HF confirmed by echocardiography or by specialist assessment at 3 months before or 12 months after entry to the register. In Scotland, the percentage of patients with a diagnosis of HF (diagnosed on or after 1 April 2006) as confirmed by echocardiography or by specialist assessment at 3 months before or 12 months after entry to the register exceeds 95%,[38] which suggests that the diagnosis of HF is robust. Furthermore, the associated risk factor profile and survival rates among the HF and cancer cohorts are in line with those reported in the literature for incident HF and cancer in the community. Secondly, although we were able to report on outcomes associated with a diagnosis of HF, we were unable to differentiate between heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Previous studies have suggested that patients with HFrEF have short- and long-term mortality outcomes similar[39] to or worse[40] than those in patients with HFpEF, and hence the comparisons of outcomes in HFrEF and HFpEF, respectively, with those in patients with a cancer diagnosis may differ. Thirdly, although our analysis captures the diagnosis of cancer in the primary care health record, it does not provide information relating to the stage of cancer, whether the cancer is in remission, whether the cancer has been 'cured', or what cancer-related treatments were given. Finally, in order to reduce

the risk for length of time bias and to exclude prevalent cases of HF or cancer, patients with diagnosis codes for either HF or cancer during the first 3 years of the PCCIU (1 April 1999 to 30 March 2002) were excluded and only patients who had been registered with the practice for at least 3 months prior to their index diagnosis date were included. Nevertheless, we cannot exclude the possibility that non-incident cases of either HF or cancer were included in the study cohort, although the numbers of these would be small.

In conclusion, the current report of over 147 938 person-years of observation is the first to compare survival outcomes in a primary care setting in patients with diagnoses of, respectively, HF and each of the four most common cancers in men and women separately. The study reveals that despite advances in management, HF remains as 'malignant' as some common cancers. Our results highlight the substantial multi-morbidity associated with HF that will represent a significant challenge to the delivery of health care in the future, particularly as the burden of HF continues to grow. Targeted management of the co-morbidities common in HF may be associated with better survival and quality of life in this patient population.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Read codes used in heart failure diagnosis.
Table S2. Read codes used in cancer diagnosis.
Table S3. Drug groups and search strings.
Table S4. Hazard non-proportionality for men.
Table S5. Hazard non-proportionality for women.

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Contributorship MAM and PKM conceived the study and developed study protocol and analysis plan in collaboration with PCCIU Academic Team (MW, CB, PM, PH), Data management team of PCCIU (KW, AC), Medical Statistics Group at University of East Anglia (ABC) and the Farr Institute (MS, IB). Record linkage was performed by KW & AC. MS analysed the data. MAM drafted the paper. All authors contributed in interpretation of results and in making an important intellectual contribution to the manuscript. PKM and MAM are guarantors.

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