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Trends in the prevalence of malignancy among patients admitted with acute heart failure and associated outcomes: a nationwide population-based study

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Abstract

Cancer is the second leading cause of death in the USA, and cardiovascular disease is the second leading cause of morbidity and mortality among cancer survivors. Cancer survivors share common risk factors for cardiovascular disease with non-cancer patients. With improved survival, cancer patients become susceptible to treatment-related toxicity often involving the heart. The impact of concurrent malignancy on outcomes particularly among heart failure patients is an area of active research. We studied the trends in the prevalence of a concurrent diagnosis of breast, prostate, colorectal, and lung cancer among admissions for acute heart failure and the associated trends for in-hospital mortality. Patients aged ≥ 18 years who were admitted with a primary diagnosis of "congestive heart failure" (CCS codes 99 and 108) from years 2003 to 2014 were included. We analyzed the rate of admission and in-hospital mortality among patients who had a concurrent diagnosis for either lung cancer, colorectal cancer, breast cancer (among females), or prostate cancer (among males). We performed a multivariate analysis to assess the role of a concurrent diagnosis of any cancer in predicting in-hospital mortality among HF admissions. From 2003 to 2014 across over 12 million HF admissions, ≈ 7% had a concurrent diagnosis of either lung, breast, colorectal, or prostate cancer. The prevalence was highest for breast cancer (2.3%) followed by prostate cancer (2.1%) and colorectal cancer (1.5%) and lowest with lung cancer (1.1%). The prevalence of cancer increased over the duration of study among all four cancer types with the largest increase in prevalence of breast cancer. Baseline comorbidities including hypertension, diabetes, smoking, chronic kidney disease, and coronary artery disease increased over time among patients with and without cancer. In-hospital mortality was higher among those with a diagnosis of lung cancer (5.9%) followed by colorectal cancer (4.0%), prostate cancer (3.5%), no diagnosis of cancer (3.3%), and breast cancer (3.2%). In-hospital mortality declined across HF admissions with and without a cancer diagnosis from 2003 to 2014. Decline in such mortality among heart failure was highest for patients with lung cancer (8.1 to 4.6% from 2003 to 2014; $p < 0.001$). Multivariate analysis showed that a concurrent diagnosis of cancer was associated with a marginally lower hospital mortality compared with controls (adjusted odds ratio 0.95, 95% confidence interval 0.94–0.96; $p < 0.001$). Among HF admissions, the prevalence of a concurrent cancer diagnosis increased over time for breast, lung, colorectal, and prostate cancer. Baseline in-hospital mortality was higher among HF admissions with either lung cancer, colorectal cancer, or prostate cancer and lower with breast cancer compared with controls without a cancer diagnosis. Adjusted analysis revealed no evidence for higher hospital mortality among HF admissions with any accompanying cancer diagnosis.

Keywords Cardiooncology · Cardiotoxicity · Heart failure · Inpatient mortality · Cancer · Malignancy

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Background

According to recent reports from the American Cancer Society, cancer mortality continues to decline, which has been largely attributed to prevention, early detection, and treatment [1, 2]. However, it is still the second leading cause of death in the USA for both sexes following heart disease [3]. Cardiovascular disease is the second leading cause of morbidity and mortality among cancer survivors [4]. The dynamic evolution of novel therapeutics has paved the way for

improved overall survival but carries a double-edged sword. Traditional cytotoxic chemotherapies (e.g., anthracyclines, antimetabolites, alkylating agents), targeted therapies (e.g., vascular endothelial growth factor inhibitors), and immunotherapies all have been reported to cause cardiotoxicity [5, 6]. The definition of cardiotoxicity is a moving target, and so is the monitoring, prevention, and treatment for such disease [7, 8]. Cardiotoxicity ranges from decrease in left ventricular ejection fraction (LVEF), congestive heart failure, arrhythmias, myocarditis, pericardial disease, coronary artery disease and valvular disease [9]. Currently, the mainstay for evaluation of cardiotoxicity is following LVEF through serial echocardiography [10].

Cancer survivors are susceptible to cardiovascular morbidity not only from the chemotherapeutic agents and history of radiation but also from other co-morbidities [11]. Furthermore, this subgroup of patients shares common risk factors with the general population at risk of developing cardiovascular disease such as older age, hypertension, dyslipidemia, diabetes, and smoking [12]. As of 2016, almost one-half of cancer survivors are 70 years and older, and it is projected that by 2026, more than 20 million Americans will be living with cancer [4]. The outcomes among patients with cancer who develop HF are an active area of research with several unknowns. The aim of our study was to examine trends in the prevalence of breast, prostate, lung, and colorectal cancer among patients admitted for acute HF. We performed additional analyses to assess trends in hospital mortality among HF admissions with a concurrent diagnosis of breast, prostate, lung, and colorectal cancer and among those without cancer.

Methods

Data source and study population

We conducted our analysis on weighted hospital discharge data from the Healthcare Cost and Utilization Project-Nationwide Inpatient Sample (HCUP-NIS) from 2003 through 2014. The NIS is the largest, publicly available, all-payer inpatient database in the USA. Annually, the NIS is composed of discharge-level data from roughly 8 million hospitalizations and approximates a stratified sample of 20% of community hospitals in the USA. Each hospitalization within the database contains clinical and resource-use information. Patients' diagnoses are documented in parallel, as both International Classification of Disease, 9th edition, Clinical Modification (ICD-9-CM) and clinically meaningful clusters of ICD-9-CMs, termed Clinical Classification Software (CCS) codes. Core hospital stay files contain details on patient demographics (e.g., age, sex, race); International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes (15–30, depending on the year) [13]; comorbidities; length of hospital stay; discharge status; in-hospital mortality; and total charges among other variables. A comprehensive synopsis on NIS data is available at http://www.hcup-us.ahrq.gov. Patients aged ≥ 18 years who were admitted with a primary diagnosis of "congestive heart failure" (CCS codes 99 and 108) were included in the study. Patients with missing mortality data and those transferred out of hospital were excluded from the analysis. We analyzed the trends in the prevalence of a concurrent secondary diagnosis of lung cancer (CCS codes 19 and 20), colorectal cancer (CCS code 14 and 15), breast cancer (CCS code 24, among females), and prostate cancer (CCS code 29, among males) among all HF admissions. Another study endpoint was in-hospital mortality, and its trends over time were studied within these study groups. For the multivariate analysis, we evaluated the role of a secondary diagnosis of any cancer (lung, colorectal, gastrointestinal, breast, prostate, and genitourinary cancer; leukemias; lymphomas; multiple myeloma; secondary cancers; metastatic disease; etc. and patients who received chemotherapy or radiation therapy: CCS codes 11 to 45, procedure CCS codes 211 and 224) in predicting in-hospital mortality compared with those without cancer.

Statistics

Demographics and baseline characteristics were summarized using descriptive statistics. Continuous data was expressed as mean ± one standard deviation and analyzed using Student's *t* test or analysis of variance. Pearson's chi-square test was used for analysis of categorical variables. Trend analyses were performed using the Mantel-Haenszel test of trend. We performed multivariate analysis in order to assess the role of a cancer diagnosis in predicting in-hospital mortality among HF admissions. The multivariate model adjusted for patients' demographics, patient characteristics, hospital characteristics, and several patient comorbidities (such as chronic kidney disease, acute renal injury, hypertension, diabetes, hyperlipidemia, previous myocardial infarction [MI], smoking, comorbidity score). Results were considered statistically significant for *p*-values < 0.05. IBM SPSS V23.0 (Armonk, NY) was used to perform data analysis.

Results

Over 12 million admissions with HF as the primary diagnosis were included in the study. Median patient age for admission was 74 years. In total, 71.1% admissions occurred in patients over the age of 65 years and 50.9% of the admitted patients were female. Mean length of stay was 5.3 days and overall inpatient mortality was 3.4% during this period.

HF with malignancies—baseline characteristics and demographics

From 2003 to 2014, ≈ 7% of all HF admissions had an associated diagnosis of lung, breast, colorectal, or prostate cancer. The prevalence was highest for breast cancer (2.3%) followed by prostate cancer (2.1%) and colorectal cancer (1.5%) and lowest with lung cancer (1.1%). Figure 1 trends the prevalence of these four malignancies over the 12-year period among patients admitted for HF. An uptrend in prevalence was noted in all four cancers being studied; however, it was most prominent in breast followed by prostate cancer. Median age at admission for lung, prostate, breast, and colorectal cancer patients was 72, 81, 80, and 82 years respectively. The largest proportion of admitted patients was 66 to 80 years old irrespective of the presence of a cancer diagnosis. Baseline comorbidities including hypertension, diabetes, smoking, chronic kidney disease, and coronary artery disease significantly increased over time among patients with and without cancer (Table 1, Supplementary table). Smoking was most common among patients with lung cancer whereas kidney disease, dyslipidemia, and coronary artery disease were most prevalent among HF admissions with a diagnosis for prostate cancer.

Impact of malignancy on HF outcomes

Among HF admissions without a cancer diagnosis, in-hospital mortality saw an overall decline from 2003 to 2014 (3.6 to 3.2%; $p<0.001$). Mortality was higher when HF admission was associated with an accompanying diagnosis of lung cancer (5.9%) followed by colorectal cancer (4.0%) and prostate cancer (3.5%) compared with those without a diagnosis of cancer (3.3%) as seen in Fig. 2. Hospital mortality associated with the presence of breast cancer was slightly lower than among HF admissions without cancer (3.2% vs. 3.3%; $p=0.01$). The decline in mortality among HF admissions with a cancer diagnosis was more prominent than those without a malignancy diagnosis. Reduction in hospital mortality among HF admissions was highest for patients with lung cancer from 2003 to 2014 (8.1 to 4.6%; $p<0.001$) followed by prostate, breast, and colorectal cancer. Figure 2 trends the inpatient mortality for HF admissions with and without malignancies. Mean length of stay also declined for all HF admissions, regardless of malignancy.

For the multivariate analysis, roughly 1.5 million patients (11.6%) had a concurrent diagnosis of at least one type of cancer within the total cohort. The multivariate analysis showed that a concurrent diagnosis of cancer was associated with a marginally lower hospital mortality compared with controls (adjusted odds ratio 0.95, 95% confidence interval 0.94–0.96; $p < 0.001$).

Discussion

The major findings from our study are (i) the prevalence of a concurrent cancer diagnosis increased over time for breast, lung, colorectal, and prostate cancer among HF admissions; (ii) hospital mortality declined over time across all HF admissions irrespective of cancer, and the decline was most prominent among patients with lung cancer; (iii) baseline in-hospital mortality was higher among HF admissions with either lung cancer, colorectal cancer, or prostate cancer and lower with breast cancer compared with controls without a cancer diagnosis; and (iv) adjusted analysis revealed association with a slightly lower hospital mortality among HF admissions with an accompanying cancer diagnosis.

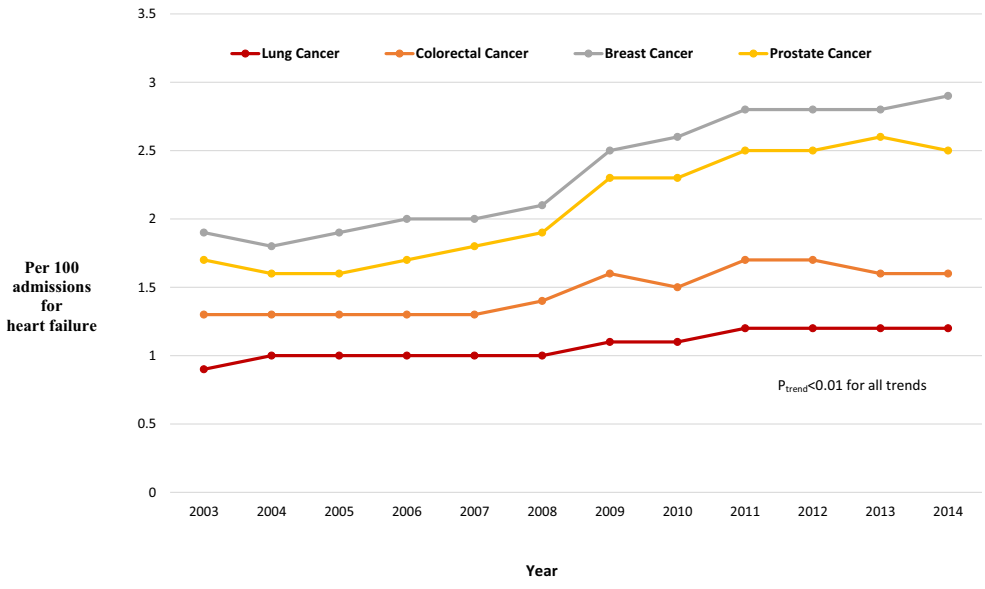

Fig. 1 Trends in the prevalence of lung, colorectal, breast, and prostate cancer for every 100 heart failure admissions within the USA

Table 1 Mean baseline characteristics of heart failure patients with and without cancer (2003–2014)

Variable	Lung cancer ($n = 136,372$)	Colorectal cancer ($n = 185,754$)	Breast cancer ($n = 293,369$)	Prostate cancer ($n = 264,757$)	No cancer ($n = 11.3$ million)	p value
Rate of hospitalization per 100 heart failure admissions	1.1	1.5	2.3	2.1	88.4	na
Age in years (median)	76	82	80	81	74	< 0.01
Age group ≤ 50 years (%)	1.0	0.8	2.4	0.2	8.9	
Age group 51–65 years (%)	14.2	8.1	12.8	5.7	21.6	
Age group 66–80 years (%)	52.8	35.3	35.3	40.5	36.2	
Age group > 80 years (%)	32.0	55.8	49.5	53.7	33.3	
Length of stay in days (mean ± SD)	5.3 ± 4.7	5.1 + 4.8	4.9 + 4.4	4.8 + 4.3	5.1 + 5.5	< 0.01
In hospital mortality (%)	5.9	4	3.2	3.5	3.3	< 0.01
Diabetes (%)	33.9	38.3	37.3	35.5	43.4	< 0.01
Hypertension (%)	58.0	64.2	64.7	64.1	62.5	< 0.01
Chronic kidney disease (%)	24.6	30.5	25	35.2	29.7	< 0.01
Acute kidney injury (%)	12.8	15	12.8	16.5	15.4	< 0.01
Coronary artery disease (%)	52.7	53.2	42.4	61.7	50.9	< 0.01
Smoking (%)	34.9	19.5	17	24.6	18.8	< 0.01
Dyslipidemia (%)	32.8	34.4	35.3	40.3	33.7	< 0.01
Prior myocardial infarction (%)	13.1	13.8	10.8	16.1	12.1	< 0.01
Cost of stay (in US dollars)	31,939	30,523	24,127	21,555	32,310	< 0.01

Our study demonstrated that there is a gradual increase in the rate of breast, prostate, lung, and colorectal cancer among HF hospitalizations within the USA over the last 12 years. In a Danish cohort by Banke et al., HF patients had a 1.24-fold incidence rate ratio of developing any type of cancer compared with patients without HF [14]. Their study evaluated 9307 outpatient HF patients longitudinally and found that HF patients were more likely to be diagnosed with de novo colorectal, hepatobiliary, lung, skin, breast, genitourinary, and lymph-/blood-based cancers. According to the 2018 US cancer statistics, breast and prostate cancers remain the commonest cancer in females and males, respectively [1]. The increase in prevalence of breast and prostate cancer in our study should be interpreted with caution as it may also be attributed to improved screening. We are also unable to differentiate between de novo, prior-treated, and active forms of cancer in our analysis. The incidence of de novo lung cancer outnumbers colorectal cancer within the general

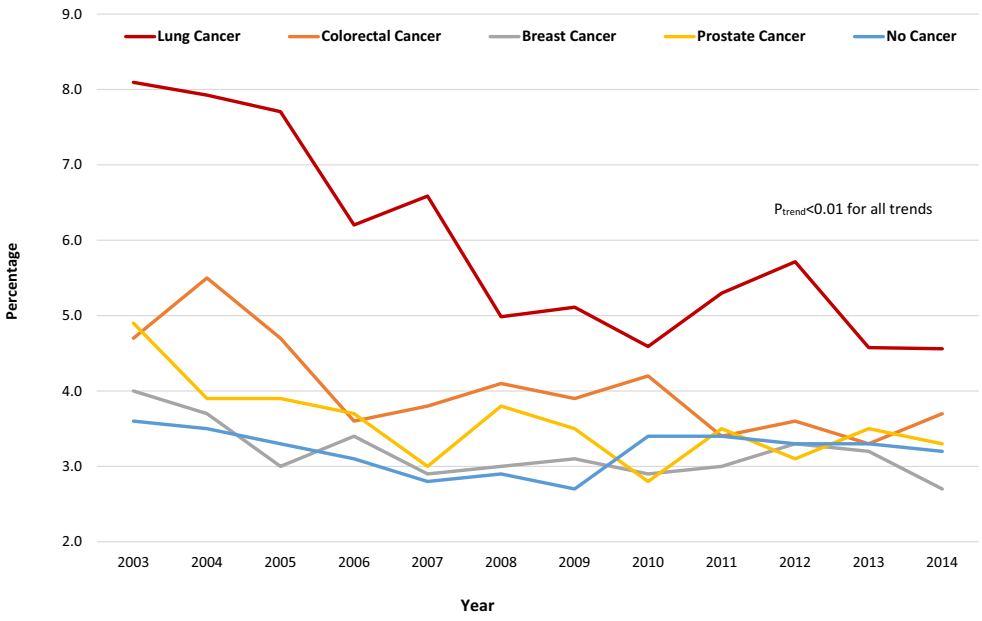

Fig. 2 Trends in hospital mortality among heart failure admissions based on the presence of an accompanying cancer diagnosis

population [1]. We found the prevalence of colorectal cancer to be higher among admitted HF patients, and there may be several hypotheses for this difference including but not limited to greater survival bias leading to admission in colorectal cancer patients. Changes in screening colonoscopy guidelines preceding lung cancer screening updates may have also contributed to this trend as the consequence of a lead time bias among others. Recently, tumorigenic proteins (serpinA3 and A1, fibronectin, ceruloplasmin, and paraoxonase 1) were found to be elevated in HF patients suggesting that a diagnosis of HF may be a risk factor for developing several different cancer types [15].

In this study, we noted an increased comorbidity burden across all HF patients. Considering that such findings were not isolated to cancer patients, it may be the result of better individual disease management, improved HF care, and greater survival, while not discounting the impact of upcoding in recent years. As previously mentioned, advances in cancer treatment directly impacts the prevalence of comorbidities as survivors tend to accrue these over time. Lung cancer is significantly associated with smoking and smoking-related morbidity such as chronic obstructive pulmonary disease and cardiovascular disease, which predisposes them to higher mortality [16–18]. Prostate cancer had the highest prevalence for coronary artery disease, hyperlipidemia, prior MI, acute kidney injury, and chronic kidney disease in our study, which can be explained by age-related increases in these conditions. According to a recent analysis, having a diagnosis of CHF was associated with less likelihood of receiving treatment for lung cancer [19] and prostate cancer [20]. Furthermore, neoadjuvant hormonal therapy for prostate cancer is also associated with increased mortality particularly in patients with a history of coronary artery-induced HF [21]. Regarding breast cancer, there is conflicting data on host-related (e.g., age, baseline EF) and chemotherapy-related factors contributing to mortality [22]. With improved treatment strategies, cardiomyopathy from anthracyclines has been shown to have a better prognosis than previously reported [23].

Hypertension is the most common comorbid condition in our study, and this can be attributed to the predominantly elderly age group of our cohort. In a Danish population-based case-control study, Jørgensen et al. identified chronic obstructive pulmonary disease, diabetes, and HF as the most common comorbidities in patients with breast, lung, colorectal, prostate, and ovarian cancer with similar median age group [17].

Multiple studies have demonstrated conflicting trends in mortality of HF patients with some showing lower and others showing a much higher mortality [24–28]. Data from studying cancer and HF so far seems to suggest that mortality is generally higher where these two diseases coexist [14]. In a Canadian cohort of 270,089 (cancer survivors and non-cancer) patients, cancer survivors had increased risk of mortality and HF after acute MI [26]. Studies by Stewart et al. (1988–2004) and Mamas et al. (2000–2011) have shown that, independent of each other, HF had similar "malignant" impact on the cancer patient population [29, 30]. We found that baseline hospital mortality was higher among HF admissions with lung, colorectal, and prostate cancer compared with controls but the adjusted analysis across all cancers found no signal for higher mortality. We believe that our study establishes that admitted HF patients with a diagnosis of cancer can now achieve comparable hospital mortality to other non-cancer-associated HF admission. It is certainly encouraging to publish such reassuring findings, and we believe strongly that appropriate medical therapies should not be withheld from HF patients with accompanying cancer in current times. HF management still poses a challenge within the cohort of cancer patients but it is important to recognize that morbidity from cardiovascular disease particularly HF significantly impairs their quality of life [31]. According to Cheung et al., advanced age was associated with underuse of preventive cardiovascular care among cancer survivors [16]. There is an opportunity to be vigilant in addressing primary and secondary prevention of shared risk factors of cardiovascular disease and cancer [12]. Cancer survivors remain a vulnerable population, and attention needs to be focused beyond simply cancer care where cardiovascular risk factors are not neglected [32]. A multidisciplinary approach may be key to avoid underuse of essential therapies from either the HF or cancer therapy standpoint [31].

Our study has several limitations due to the administrative nature of the database and its reliance on accuracy of coding. The findings of our study are limited to index stay and cannot be extrapolated to post-discharge events. Important factors relating to cancer such as cancer stage and corresponding treatment were not accounted for. However, these limitations are counterbalanced by the considerable sample size and presentation of contemporary real-world data. There is an unmet need for more prospective data as the pool of cancer patients needing help dealing with cardiovascular issues is expanding.

In summary among HF admissions, the prevalence of a concurrent cancer diagnosis increased over time for breast, lung, colorectal, and prostate cancer. Hospital mortality declined over time, particularly among HF admissions with a cancer diagnosis. Baseline in-hospital mortality was higher among HF admissions with either lung cancer, colorectal cancer, or prostate cancer and lower with breast cancer compared with controls without a cancer diagnosis. An accompanying cancer diagnosis was associated with a marginally lower hospital mortality, compared with HF admissions without cancer.

Author contributions The authors are solely responsible for the study design, conduct and analyses, drafting, and editing of the manuscript and its final contents. All authors had access to the data and a role in writing the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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